TITLE PAGE

Protocol Title:

Phase 2, Randomized, Double-Blind, Placebo-controlled, Parallel-Group, Multicenter Study to Evaluate the Safety and Efficacy of Tarperprumig in Adult Participants with Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis

Acronym: NA

Alexion Protocol Number: ALXN1820-ANCA-201

AstraZeneca D Code: D6722C00001

Version Number: 1.1 (EU)

Name of Study Drug (Active substance): Tarperprumig (ALXN1820)

Indication: CCI in ANCA-associated vasculitis

Brief Title:

Safety and Efficacy of Tarperprumig in Adult Participants with ANCA-Associated Vasculitis

Study Phase: 2

Sponsor Name: Alexion Pharmaceuticals, Inc.

Legal Registered Address:

121 Seaport Boulevard

Boston, MA 02210

Manufacturer:

NA

Regulatory Agency Identifier Number(s):

Registry	**Identification**
EU CT Number:	2025-521706-17-00
IND Number:	175174

Pediatric Investigational Plan Number:

NA

Approval Date: 24 Oct 2025

Sponsor Signatory:

This document has been e-signed. Please refer to the last page for signature details.

PPD	
PPD Clinical Development	

Medical Monitor Name and Contact Information

Will be provided separately

INVESTIGATOR'S AGREEMENT

I have read the study protocol and agree to conduct the study in accordance with this protocol, 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, 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.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Primary Site Address of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Version 1.1 (EU)	24 Oct 2025
Original Protocol (Version 1.0)	18 Jun 2025

Version 1.1 (24 Oct 2025)

This amendment is considered to be substantial based on the EU CTR 536/2014 Article 2, 2 (13).

OVERALL RATIONALE FOR THE AMENDMENT

The main purpose of this amendment is to address comments from a European Member State received during the original protocol review.

Summary of Changes (Protocol Version 1 to Version 1.1)

Section # and Name	Description of Change	Brief Rationale
Section 2.3 Benefit/Risk Assessment and Table 5 Study Risk Assessment	A reference to prescribing information for risks associated with prophylactic antibiotics has been added	In response to comments from a European Member State
Section 5.2 Exclusion Criteria	Exclusion criteria related to 1) participants with active infections within 14 days prior to Day 1 and 2) participants with any contraindications to rituximab	In response to comments from a European Member State
Section 6.9.2.1 Live Vaccines	Added restriction on live or live attenuated vaccines within 4 weeks prior to planned first dose and throughout the study	In response to comments from a European Member State
Section 9.9 Sample Size Determination	Further justification for sample size determination has been added	In response to comments from a European Member State

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LIST OF ABBREVIATIONS

Table 1: Abbreviations and Terms

Abbreviation or Term	Explanation
AAV-PRO	ANCA-Associated Vasculitis Patient-Reported Outcome
ACR/EULAR	American College of Rheumatology/European League Against Rheumatism
ADA	antidrug antibody
AE	adverse event
aHUS	atypical hemolytic uremic syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	anti-nuclear antibody
ANCA	anti-neutrophil cytoplasmic antibody
AP	alternative pathway
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AxMP	auxiliary medicinal product
CCI	CCI
CCI	CCI
BP	blood pressure
BVAS	Birmingham Vasculitis Activity Score
C3	complement component 3
CCI	CCI
CCI	CCI
C5	complement component 5
CCI	CCI
CCI	CCI
CAP	complement alternative pathway
CBP	childbearing potential
CCP	complement classical pathway
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences

Table 1: Abbreviations and Terms

Abbreviation or Term	Explanation
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
CLP	complement lectin pathway
CMH	Cochran-Mantel-Haenszel
CRO	contract research organization
CRP	C-reactive protein
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DtP	Direct to Patient
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EGPA	eosinophilic granulomatosis with polyangiitis
ELISA	enzyme-linked immunosorbent assay
EMLA	eutectic mixture of local anesthetics
EQ-5D-5L	EuroQol 5-dimension 5-level
ESKD	end-stage kidney disease
CCI	CCI
EU	European Union
EU CTR	European Union Clinical Trials Regulation
FAS	Full Analysis Set
fP	properdin/factor P
FSH	follicle stimulating hormone
GBM	glomerular basement membrane
GC	glucocorticoid
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GDP	Good Distribution Practice
GLP	Good Laboratory Practice
GPA	granulomatosis with polyangiitis

Table 1: Abbreviations and Terms

Abbreviation or Term	Explanation
HA	Health Authority
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HPF	high-power field
HR	heart rate
HRT	hormone replacement therapy
IAS	Immunogenicity Analysis Set
IB	Investigator's Brochure
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
iDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IF	immunofluorescence
Ig	immunoglobulin
IGRA	interferon γ release assay
I_{max}	maximum inhibitory effect
IMP	investigational medicinal product
IP	Intellectual property
IRB	Institutional Review Board
IRT	interactive response technology
ISR	injection site reaction
IV	intravenous
IVIG	intravenous immunoglobulin

Table 1: Abbreviations and Terms

Abbreviation or Term	Explanation
IVRS	interactive voice response system
IWRS	interactive web response system
KDIGO	Kidney Disease: Improving Global Outcomes
CCI	CCI
KOL	key opinion leaders
LAR	legally authorized representative; A LAR is an individual authorized (eg, by a court) to make decisions on behalf of another person
LDL	low-density lipoprotein
MCP-1	monocyte chemoattractant protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model for repeated measures
MPA	microscopic polyangiitis
MPO	myeloperoxidase
N/A	not applicable
NCBP	nonchildbearing potential
NET	neutrophil extracellular trap
NGAL	neutrophil gelatinase-associated lipocalin
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamic(s)
PE	physical examination
PDAS	Pharmacodynamic Analysis Set
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PhGA	Physician Global Assessment
PI	Principal Investigator
PK	pharmacokinetic(s)
PKAS	Pharmacokinetic Analysis Set
PML	progressive multifocal leukoencephalopathy
PNH	paroxysmal nocturnal hemoglobinuria
POCBP	participants of childbearing potential
PPD	purified protein derivative

Table 1: Abbreviations and Terms

Abbreviation or Term	Explanation
PR3	proteinase 3
PT	Preferred Term
CCI	CCI
QTcF	QT interval corrected using Fridericia's formula
CCI	CCI
RBC	red blood cell
RTSM	randomization and trial supply management
RTX	rituximab
SAP	statistical analysis plan
SAE	serious adverse event
SC	subcutaneous(ly)
SCD	sickle cell disease
CCI	CCI
SoA	schedule of activities
CCI	CCI
SOC	System Organ Class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
SS	Safety Set
TB	tuberculosis
CCI	CCI
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TNF	tumor necrosis factor
UACR	urine albumin-creatinine ratio
ULN	upper limit of normal
UPCR	urine protein-creatinine ratio
VDI	vasculitis damage index
VHH	variable heavy domain of heavy chain
WBC	white blood cell

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

Phase 2, Randomized, Double-Blind, Placebo-controlled, Parallel-Group, Multicenter Study to Evaluate the Safety and Efficacy of Tarperprumig in Adult Participants with Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis

Brief Title:

Safety and Efficacy of Tarperprumig in Adult Participants with ANCA-Associated Vasculitis

Regulatory Agency Identifier Number(s):

Registry	Identification
EU CT Number:	2025-521706-17-00
IND Number:	175174

Pediatric Investigational Plan Number:

NA

Rationale:

Tarperprumig (ALXN1820) is being developed for the treatment of diseases driven by the activation of the complement alternative pathway (CAP).

The aim of the study is to evaluate the safety and tolerability, efficacy, PK, PD, and immunogenicity of 2 different subcutaneous (SC) dose regimens of tarperprumig administered to participants with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, the granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) subtypes. Efficacy of tarperprumig as add on to CCI , ie, rituximab CCI CCI glucocorticoids [GCs] CCI compared to CCI will be evaluated for CCI of remission in participants with GPA and MPA.

Tarperprumig (ALXN1820) is being developed for the treatment of diseases driven by the activation of the CAP. Tarperprumig inhibits properdin, which stabilizes the CAP components, C3 and C5 convertases. CCI CCI

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of tarperprumig in participants with newly diagnosed or relapsing ANCA-associated vasculitis	• Incidence of TEAEs and TESAEs. • Changes from Baseline in safety assessments (vital sign measurements, physical examination, clinical laboratory tests, and ECG results).
Secondary	
• To evaluate the efficacy of treatment with tarperprumig on achieving disease remission, sustained remission, and preventing relapse in participants newly diagnosed or relapsing ANCA-associated vasculitis	• Achieving disease remission at Week 26.[a] • Achieving sustained remission at Week 52.[b] • Achieving BVAS = 0 at CCI , 26, and 52. • Relapse[c] after previously achieving disease remission at Week 26.[a] • Time to first relapse[c] after having achieved disease remission at Week 26.[a] • Change from Baseline in Vasculitis Damage Index (VDI) at CCI 26, and 52. • Time to first occurrence of BVAS = 0. • Change from Baseline in BVAS at all timepoints.
• To evaluate the efficacy of treatment with tarperprumig on kidney function and kidney damage in participants with newly diagnosed or relapsing ANCA-associated vasculitis	• Change from Baseline in eGFR (mL/min per 1.73 m^2) at CCI 26, and 52. • Change from Baseline in proteinuria based on spot UPCR (mg/g) and % change from Baseline at , 26, CCI and 52. • Change from Baseline in proteinuria based on spot UACR (mg/g) and % change from Baseline at CCI , 26, and 52. • Hematuria change from Baseline (RBCs/HPF) and % change from Baseline at CCI , 26, and 52.
Pharmacokinetics	
• To characterize the PK of tarperprumig in participants with newly diagnosed or relapsing ANCA-associated vasculitis	• Total tarperprumig serum concentrations over time. • PK parameters of total tarperprumig in serum over time.
Pharmacodynamics	
• To characterize the PD of tarperprumig in participants with newly diagnosed or relapsing ANCA-associated vasculitis	• Absolute values, change from Baseline, and % change from Baseline in total properdin, free properdin, and serum complement functional activity (CCP, CAP, and CLP), through the duration of the study.

Objectives	Endpoints
Immunogenicity	
• To assess the immunogenicity of tarperprumig in participants with newly diagnosed or relapsing ANCA-associated vasculitis	• Anti-tarperprumig antibody incidence, response categories, and titer for the duration of the study.

[a] Disease remission at Week 26 is defined BVAS of 0 at Week 26 and no prescribed GCs for treatment of ANCA-associated vasculitis within 4 weeks prior to Week 26.
[b] Sustained remission at Week 52 is defined as BVAS=0 at Week 26 without relapse to Week 52 and no prescribed GCs for treatment of ANCA-associated vasculitis within 4 weeks prior to Weeks 26 and 52.
[c] A relapse is defined as worsening of disease, after having previously achieved BVAS = 0, that involves: 1 or more major item in the BVAS, or 3 or more minor items in the BVAS, or 1 or 2 minor items in the BVAS recorded at 2 consecutive study visits.
Abbreviations: ANCA = anti neutrophil cytoplasmic antibody; BVAS = Birmingham Vasculitis Activity Score; CAP = complement alternative pathway; CCP = complement classical pathway; CLP = complement lectin pathway; ECG = electrocardiogram; GC = glucocorticoid; HPF= high-power field; RBC = red blood cell; UACR = urine albumin-creatinine ratio; UPCR = urine protein-creatinine ratio; VDI = Vasculitis Damage Index

The clinical question of interest with respect to efficacy at Week 26 is: What is the treatment effect of tarperprumig compared to placebo on achieving disease remission at Week 26 in adults with ANCA-associated vasculitis who are receiving the CCI

The estimand is described by the following attributes:

- Population: All adult participants diagnosed with ANCA-associated vasculitis and baseline eGFR ≥ 15 mL/min/1.73 m^2.
- Endpoint: Achieving disease remission at Week 26, defined as BVAS = 0 at Week 26 and no prescribed glucocorticoids for treatment of ANCA-associated vasculitis within 4 weeks prior to Week 26.
- Treatment of interest: Tarperprumig + CCI or placebo CCI Participants from the two tarperprumig treatment groups will be pooled for analysis.
- Handling of ICEs: The composite strategy will be used. Participants with ICEs occurring prior to the assessment time of the endpoint will be considered as not achieving the endpoint for the following ICEs:
  - death
  - kidney transplant and dialysis
  - use of rescue medication (eg, cyclophosphamide)
- Summary measure: Difference in the proportion of participants who achieve the efficacy endpoint between groups.

The clinical question of interest with respect to efficacy at Week 52 is: What is the treatment effect of tarperprumig compared to placebo on achieving sustained remission at Week 52 in adults with ANCA-associated vasculitis who are receiving the CCI ?

- The estimand attributes are the same as above except the endpoint is achieving sustained remission at Week 52, defined as BVAS = 0 at Week 26 without relapse to Week 52 and no prescribed GCs for treatment of ANCA-associated vasculitis within 4 weeks prior to Weeks 26 and 52.

Overall Design Synopsis:

This study is a Phase 2, double-blind, randomized, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of tarperprumig for CCI CCI in participants with ANCA-associated vasculitis GPA and MPA subtypes, on a background of treatment with rituximab and GC.

There will be 3 periods in this study: Screening Period, Double-Blind Treatment Period, and Safety Follow-up Period. Participants will be screened for eligibility for up to CCI during the Screening Period. Approximately 75 eligible participants will be randomized in a 1:1:1 ratio to receive one of the following during the Double-Blind Treatment Period:

- Treatment Group 1 (n = 25): Tarperprumig CCI SC CCI CCI SC CCI
- Treatment Group 2 (n =25): Tarperprumig CCI SC CCI CCI CCI
- Treatment Group 3 (n = 25): CCI SC CCI SC CCI

Randomization will be stratified based on the following factors using data at Screening:

- ANCA type (PR3-ANCA or MPO-ANCA)
- Disease status (newly diagnosed or relapsing ANCA-associated vasculitis)

Upon completing the last assessment of the 52-week Double-Blind Treatment Period, participants will continue into the CCI Safety Follow-up Period.

During the Safety Follow-up Period, participants will stop receiving tarperprumig but will continue with CCI treatment as needed.

Study Population:

Participants aged 18 to 80 years (inclusive) with ANCA-associated vasculitis GPA and MPA subtypes.

Study Intervention and Intervention Form:

- Experimental intervention
  - Tarperprumig or matching placebo (SC injection)
- Background intervention CCI)
  - Rituximab (IV infusion)
  - Glucocorticoids (oral)

- Prophylaxis
  - [redacted] for [redacted] (oral)

Number of Participants:

Approximately 75 eligible participants will be enrolled and randomized in a 1:1:1 ratio to the treatment groups below.

Treatment Groups and Duration:

The treatment groups are as follows:

Group title	Treatment Group 1	Treatment Group 2	Treatment Group 3
Group type	Experimental	Experimental	Control
[redacted]	Tarperprumig [redacted] SC, [redacted]	Tarperprumig [redacted] SC [redacted]	Tarperprumi [redacted] [redacted] SC [redacted]
[redacted]	Tarperprumig [redacted] SC, [redacted]	Tarperprumig [redacted] SC, [redacted]	Tarperprumi [redacted] [redacted] SC [redacted]
Safety Follow up	[redacted]	[redacted]	[redacted]

Abbreviations: [redacted] SC = subcutaneous; [redacted]

The duration of study participation will be as follows:

- Up to approximately 72 weeks: up to [redacted] in the Screening Period, 52 weeks in the Double-Blind Treatment Period, and [redacted] in the Safety Follow-up Period.

Data Monitoring Committee:

An iDMC, comprising experts in relevant fields with no direct relationship to the study, will be appointed by Alexion or designee. In this study, the iDMC will be responsible for review of safety and other relevant study data. The specific responsibilities of the iDMC and a schedule of meetings will be described in the iDMC Charter.

Ethical Considerations and Benefit-Risk Assessment

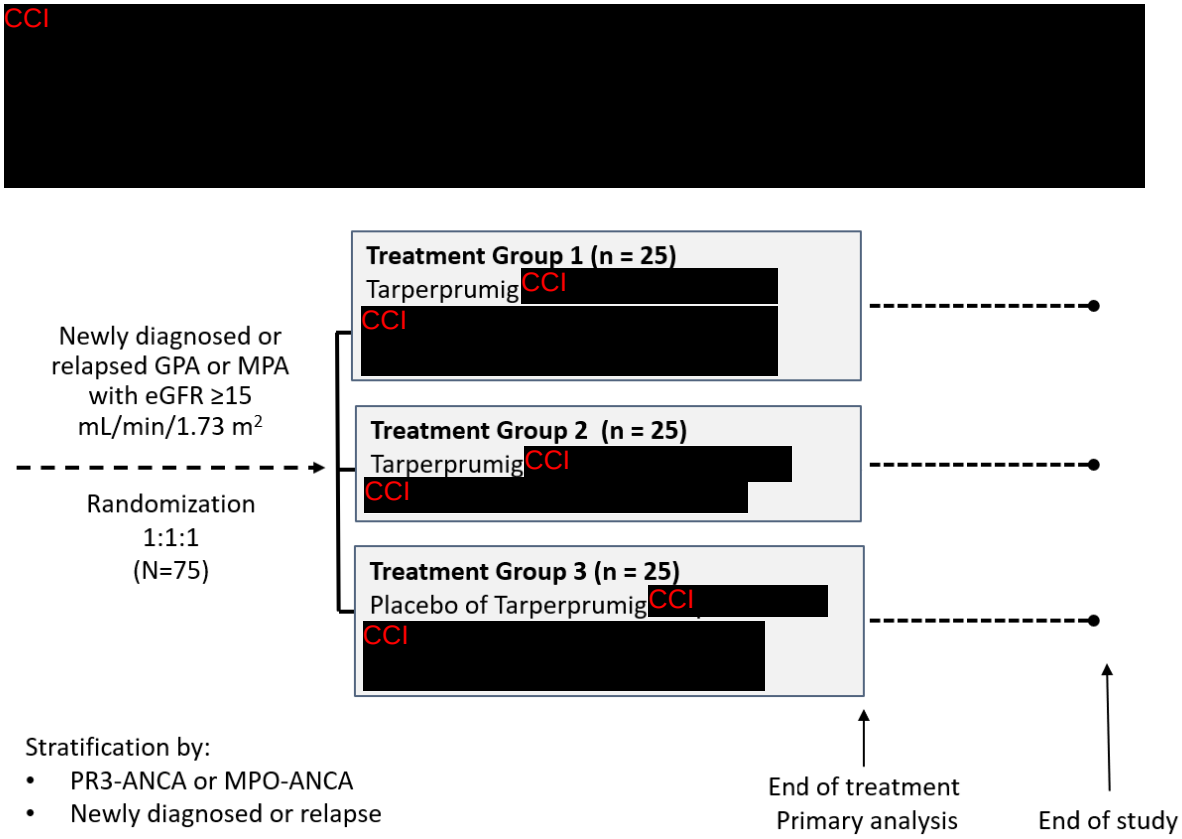
This study will be conducted as specified in this protocol and in accordance with the following:

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

A thorough benefit-risk assessment has been performed for tarperprumig and described in the protocol. Measures will be taken to minimize risks to study participants. The potential risks identified in association with tarperprumig are justified by the anticipated benefits that may be afforded to participants with ANCA-associated vasculitis.

1.2. Schema

Figure 1: Study Schematic



CCI will be administered throughout the study.
[a] Interim analyses optionally at CCI
[b] GCs up to CCI only
Abbreviations: ANCA = anti-neutrophil cytoplasmic antibody; D = day; eGFR = estimated glomerular filtration rate; GC = glucocorticoid; GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; MPO = myeloperoxidase; PR3 = proteinase 3; CCI; CCI; RTX = rituximab CCI); SC = subcutaneous; CCI; W (or w) = week(s)

1.3. Schedule of Activities (SoA)

The SoA tables provide an overview of the protocol visits, procedures, and assessments. SoA are provided as follows:

- Table 2 - Schedule of Activities – Screening and Double-Blind Treatment Period up to CCI
- Table 3 - Schedule of Activities – from CCI to CCI Safety Follow-up, and CCI Visit
- Table 4 - Sampling Schedule for PK, PD, Biomarkers, and Immunogenicity

When multiple assessments occur at a specific timepoint (eg, predose), the assessments should be conducted in the following order, if feasible:

1. PROs
2. Predose ECG, vital sign measurements
3. Predose urinalysis, PK/PD, and other blood sampling
4. Drug administration
5. Postdose PK/PD sampling

If the timepoint is not specified, the assessment should be performed predose. The same order of assessments is to be applied consistently across the study.

The Investigator is allowed to schedule visits (unplanned visits) in addition to those listed in the SoA tables to conduct evaluations or assessments required to protect the wellbeing of the participants.

Table 2: Schedule of Activities – Screening and Double-Blind Treatment Period up to CCI

CCI [redacted]

Informed consent	X																	Section 8.1.1
Inclusion/exclusion criteria	X	Review X																Section 5.1 Section 5.2; Section 8.1.3
Demographics	X																	Section 8.1.4
Medical history	X																	Section 8.1.6
Prior medications, including GC and meningococcal vaccinations	X																	Section 6.9
ANCA test (PR3-ANCA and MPO-ANCA)	X	X						X				X					X	Section 8.1.7
ANAs, anti-GBM antibodies, C3, C4, IgM, IgA, and IgG	X																	Section 8.1.8; See incl/excl in Section 5
IgG levels		X															X	Section 8.1.8
HBV, HCV, HIV tests (if not done within CCI before Screening)	X																	Section 8.1.10 and Table 12; Reactivation monitoring is allowed per national or local guidelines.
TB screening	X																	Section 8.1.9
Chest radiography (optional)	X	X										X					X	Section 8.1.9; can be done at any time
FSH test (only for NCBP)	X																	Table 12

Table 2: Schedule of Activities – Screening and Double-Blind Treatment Period up to CCI [redacted]

CCI [redacted]																		
Stratification and randomization		X																Section 6.3
Participant safety card dispensing (D1) and review		X	X	X		X		X		X		X		X		X		Section 8.3.7
Dosing diary dispense (D1) and review		X	X	X		X		X		X		X		X		X		Section 8.1.4
Complete PE/ Abbreviated PE	Comp X	Abbrev X	Abbrev X	Abbrev X		Abbrev X		Abbrev X		Abbrev X		Abbrev X		Abbrev X		Abbrev X		Comp X	Section 8.3.2
Vital signs, including height (Screening only) and body weight	X	X	X	X		X		X		X		X		X		X		X	Section 8.3.3
12-lead ECG (Triplicate predose)	X	X	X									X						X	Section 8.3.4
Hematology, clinical chemistry and coagulation panel	X	X		X		X		X		X		X		X		X		X	Section 8.3.5, Table 12
Urinalysis (spot urine)	X	X		X		X		X		X		X		X		X		X	Section 8.2.7, Table 12
CCI [redacted]		X						X				X						X	Table 12
eGFR (based on 2021 CKD-EPI equation)	X	X		X		X		X		X		X		X		X		X	Section 8.2.6; For serum and urine creatinine, refer to Table 12.
Birmingham Vasculitis Activity Score (BVAS)	X					X		X		X		X		X		X		X	Section 8.2.2; To be completed as early as possible at each Clinic Visit and when relapse occurs;

Table 2: Schedule of Activities – Screening and Double-Blind Treatment Period up to CCI [redacted]

CCI [redacted]																		
																		may be done remotely.
Pregnancy test (POCBP only)	X	X				X				X		X		X		X		Section 8.3.6; Serum test at Screening.
PK samples		X	X	X				X				X						X	Table 4; Section 8.5
PD samples		X	X	X				X				X						X	Table 4; Section 8.6
Immunogenicity samples		X	X	X				X				X						X	Table 4; Section 8.9
Biomarker samples CCI [redacted]	X	X	X	X				X				X						X	Table 4; Section 8.8
24-hour CCI [redacted] biomarker samples (optional)		During inpatient admissions at study sites, in agreement with participant																	Section 8.2.7
Record relapse events		Continuous monitoring																	Section 8.2.3. If relapse occurs, BVAS will be assessed.
VDI questionnaire	X											X						X	Section 8.2.4
PhGA		X																X	Section 8.2.5
EQ-5D-5L		X																X	Section 8.2.5; Questionnaires preferably completed by participant before seeing Investigator at each Visit.
AAV-PRO		X																X	
PGI-S		X																X	
PGI-C																		X	

Table 2: Schedule of Activities – Screening and Double-Blind Treatment Period up to CCI

CCI																		
Tarperprumig/ placebo SC administration CCI		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Table 7, Table 8, and Section 6.1.1 Administration body site to be recorded.
CCI		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3.9; Following each SC injection
GC CCI CCI		X	X	X		X		X		X		X		X		X		Section 6.1.2.
Rituximab IV administration[d]	CCI																	Table 7
CCI		Continuous administration																Section 6.9.3
CCI GC CCI CCI CCI		Continuous monitoring																Section 6.9
AEs and SAEs	Continuous monitoring from signing of the ICF																	Section 8.4
Medication error, abuse and misuse		Continuous monitoring																Section 8.4.5
Medical resource utilization		Continuous monitoring																Section 8.10
Genomics initiative (optional) exploratory genetic samples		X																Section 8.7.1, Section 10.7.1, and Section 10.7.2
CCI		CCI																

[a] See Table 3 for CCI and unscheduled visits.
[b] Screening tests will be done locally at the sites, unless otherwise specified. See Section 8.1.

Table 2: Schedule of Activities – Screening and Double-Blind Treatment Period up to CCI

[c] Remote visits may be performed by home health nurse/site staff per local regulations.
[d] Rituximab should not be administered on the same day of tarperprumig administration. See Section 6.1.3.
Abbreviations: AAV-PRO = ANCA-Associated Vasculitis Patient-Reported Outcome; AE =adverse event; ANA=anti-nuclear antibody; ANCA = anti-neutrophil cytoplasmic antibody; BVAS = Birmingham Vasculitis Activity Score; CKD-EPI = Chronic Kidney Disease-Epidemiology Collaboration; D = day; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EQ-5D-5L = EuroQol 5-dimension 5-level; FSH = follicle-stimulating hormone; GBM = glomerular basement membrane; GC = glucocorticoid; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; Ig =immunoglobulin; IV = intravenous; MPO = myeloperoxidase; NCBP = nonchildbearing potential; PD =pharmacodynamic; PE = physical examination; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PhGA = Physician Global Assessment; PK = pharmacokinetic; POCBP = participants of childbearing potential; PR3 = proteinase 3; SAE = serious adverse event; SC = subcutaneous CCI TB = tuberculosis; CCI VDI = Vasculitis Damage Index; W = week; WBC = white blood cell.

Table 3: Schedule of Activities – from CCI to CCI Safety Follow-up, and CCI Visit

CCI

ANCA test (ANCA-PR3 and ANCA-MPO)		X		X			X	X	X	Section 8.1.7
Participant safety card review	X	X	X	X	X	X	X	X	X	Section 8.3.7
Dosing diary review		X		X	X	X	X			Section 8.1.4
Complete PE /Abbreviated PE		Abbrev X		Comp X	Abbrev X	Abbrev X	Comp X	Abbrev X	Comp X	Section 8.3.2
Vital signs, including body weight		X		X	X	X	X	X	X	Section 8.3.3
12-lead ECG (Triplicate predose)		X		X			X	X	X	Section 8.3.4
Hematology, clinical chemistry, and coagulation panel		X		X	X		X	X	X	Section 8.3.5; Table 12
Urinalysis (spot urine)		X		X	X		X	X	X	Section 8.2.7
IgG levels				X					X	Section 8.1.8
CCI				X					X	Table 12
eGFR (based on 2021 CKD-EPI equation)		X		X	X	X	X	X	X	Section 8.2.6; For serum and urine creatinine, refer to Table 12.
Birmingham Vasculitis Activity Score (BVAS)	Clinic Visits as needed or when relapse occurs For participants in remission, every 3 months For participants not in remission, monthly until remission			X	Clinic Visits as needed or when relapse occurs For participants in remission, every 3 months For participants not in remission, monthly until remission			X	X	Section 8.2.2; To be completed as early as possible at each Clinic Visit. May be conducted remotely. Remission is BVAS = 0
Pregnancy test (only for POCBP)	X	X	X	X	X		X	X	X	Section 8.3.6; monthly
PK samples				X			X		X	Table 4; Section 8.5
PD samples				X			X		X	Table 4; Section 8.6
Immunogenicity samples				X			X		X	Table 4; Section 8.9
Biomarker samples CCI CCI				X			X		X	Table 4; Section 8.8
24-hour CCI biomarker samples (optional)	During inpatient admissions at study sites, in agreement with participant							X	X	Section 8.2.7

Table 3: Schedule of Activities – from CCI to CCI Safety Follow-up, and CCI Visit

CCI										
Record relapse events	Continuous monitoring								X	X	Section 8.2.3. If relapse occurs, BVAS will be assessed.
VDI questionnaire				X						X	Section 8.2.4
PhGA				X						X	Section 8.2.5
EQ-5D-5L				X						X	Section 8.2.5; Questionnaires preferably completed by participant before seeing Investigator at each Visit.
AAV-PRO				X						X	
PGI-S				X						X	
PGI-C				X						X	
Tarperprumig/ placebo SC administration CCI	Biweekly administration starting at W28, administered in-clinic or by a home nurse (other weeks). Administration body site to be recorded.										Table 7, Table 8, and Section 6.1.1
CCI	Following each SC injection.										Section 8.3.9
Rituximab IV administration[b]	CCI				CCI						Table 7
CCI	Continuous administration										Section 6.9.3
CCI CCI GCs CCI CCI	Continuous monitoring										Section 6.9
AEs and SAEs	Continuous monitoring										Section 8.4
Medical resource utilization	Continuous monitoring										Section 8.10
Medication error, abuse and misuse	Continuous monitoring										Section 8.4.5
CCI	CCI										

[a] Remote visits may be performed by home health nurse/site staff per local regulations.
[b] Rituximab should not be administered on the same day of tarperprumig administration. See Section 6.1.3.

Abbreviations: AAV-PRO = ANCA-Associated Vasculitis Patient-Reported Outcome; AE =adverse event; ANA=anti-nuclear antibody; ANCA = anti-neutrophil cytoplasmic antibody; BVAS = Birmingham Vasculitis Activity Score; CKD-EPI = Chronic Kidney Disease-Epidemiology Collaboration; CT = computed tomography; D = day; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; CCI EQ-5D-5L = EuroQol 5-dimension 5-level; ; GC = glucocorticoid; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; Ig =immunoglobulin; IV = intravenous; MPO = myeloperoxidase; NCBP = nonchildbearing potential; PD =pharmacodynamic; PE = physical examination; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PhGA = Physician Global Assessment; PK = pharmacokinetic; POCBP = participants of childbearing potential;

PR3 = proteinase 3; CCI SAE = serious adverse event; SC = subcutaneous; CCI TB = tuberculosis; CCI
VDI = Vasculitis Damage Index; W = week; WBC = white blood cell

Table 4: Sampling Schedule for PK, PD, Biomarkers, and Immunogenicity

CCI						
PK samples		X	X	X	X	Section 8.5
PD samples		X	X	X	X	Section 8.6
Biomarker samples CCI CCI	X	X		X	X	Section 8.8
Immunogenicity samples		X		X	X	Section 8.9 Immunogenicity samples to be collected predose. In case of a suspected SAE of hypersensitivity or anaphylaxis, 1 additional immunogenicity sample may be collected during or in proximity to the event.

Abbreviations: CCI PD =pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse event; W = week

2. INTRODUCTION

2.1. Study Rationale

Tarperprumig (ALXN1820) is being developed for the treatment of diseases driven by the activation of the complement alternative pathway (CAP).

The aim of the study is to evaluate the safety and tolerability, efficacy, PK, PD, and immunogenicity of 2 different subcutaneous (SC) dose regimens of tarperprumig administered in participants with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, the granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) subtypes. Efficacy of tarperprumig as add on to CCI ie, rituximab CCI GC CCI compared to CCI will be evaluated fo CCI CCI of remission in participants with GPA and MPA.

Tarperprumig inhibits properdin, which stabilizes the CAP components, C3 and C5 convertases. CCI CCI

2.2. Background

2.2.1. Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis

ANCA-associated vasculitis is characterized by inflammation and destruction of small- and medium-sized blood vessels and the presence of circulating ANCA. Patients with ANCA-associated vasculitis typically present with organ- or life-threatening disease, including kidney involvement, caused by progressive focal necrotizing glomerulonephritis, and/or pulmonary involvement (eg, alveolar hemorrhage). ANCA-associated vasculitis often results in deterioration of health-related quality of life caused by organ damage and/or toxicity from the medications used for disease management, including the long-term use of glucocorticoids (GC) (Benarous, 2017).

2.2.2. Tarperprumig

Tarperprumig is a recombinant, humanized variable heavy domain of heavy (VHH) chain bispecific antibody that binds to human properdin (or factor P, fP) and serum albumin (Tamburini, 2024). The anti-properdin VHH binds selectively and with high affinity to human properdin, a component of the CAP, preventing it from stabilizing the C3 and C5 convertases that cleave C3 and C5 into their activation products. The anti-albumin VHH binds serum albumin, which extends the circulatory half-life of the molecule.

2.3. Benefit/Risk Assessment

There may be potential benefits to participants with ANCA-associated vasculitis.

Identified and potential risks and potential risk mitigation strategies are described below. More detailed information about the known and expected benefits and risks and reasonably expected AEs of tarperprumig may be found in the IB. More detailed information about the risks associated with the use of glucocorticoid, rituximab, cyclophosphamide, and prophylactic antibiotics can be found in their respective full prescribing information.

2.3.1. Risk Assessment

Table 5: Study Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention		
Tarperprumig		
CCI [redacted]	CCI [redacted]	CCI [redacted]
Hypersensitivity	Treatment with any therapeutic biologic has the potential to induce an immune response. Potential clinical consequences may include hypersensitivity reactions, including anaphylaxis, or loss of efficacy.	Exclusion criteria added for participants with hypersensitivity to any ingredient contained in the study intervention. Monitoring of hypersensitivity to tarperprumig is in place as part of continuous AE monitoring as specified in the SoA (Section 1.3). Stop the medication in the event of any drug-related severe adverse events like systemic hypersensitivity or anaphylaxis.
Immunogenicity	Treatment with any therapeutic biologic has the potential to induce an immune response. Potential clinical consequences may include hypersensitivity reactions, including anaphylaxis, or loss of efficacy.	Monitoring for hypersensitivity and serious injection-related reactions will be conducted as part of safety assessments for this study (Section 8.3.8). In case of suspected SAEs of hypersensitivity or anaphylaxis, additional ADA samples may be collected during or in proximity of the event.
Study Procedures		
Phlebotomy	Multiple blood samples will be collected throughout the study period. Blood draw risks may include pain and bruising.	Limits for the number of samples to be collected and sample volumes are in place according to

Table 5: Study Risk Assessment

		local guidance.
Mode of Administration		
Injection site reactions (ISR)	SC administration may cause local ISR, such as erythema, pruritus (itch), pain, and bruising.	The incidence of ISR will be monitored as part of routine safety assessments for this study (see SoA in Section 1.3). To mitigate the risk of injection site reactions, participants will be advised to rotate the injection sites.
Other		
Exposure during pregnancy/lactation	No studies of tarperprumig have been conducted in pregnant women. There are no data available on the excretion of tarperprumig in breast milk.	Pregnant or nursing women are excluded from participating in this study. Monitoring for pregnancy in all participants of child-bearing potential is in place (SoA; Section 1.3). Negative urine pregnancy tests, as scheduled, are required prior to administrations of the study intervention. Participants and their spouses/partners must use a highly effective method of contraception during the study (see Section 10.5.2) If a pregnancy is reported during the study, safety follow-up will be performed (Section 8.4.6).

Abbreviations: ADA = antidrug antibody; AE = adverse event; SAE = serious adverse events; SoA = schedule of activities

2.3.2. Benefit Assessment

Despite the optimization of treatment algorithms over the years and the recent approval of CCI ANCA-associated vasculitis remains associated with a reduced quality of life and an increased risk of death when compared to the general population (Benarous, 2017; Sánchez Álamo, 2023).

In the US, between year 2002 to 2017, the mortality rate was 38.4 per 1000 person-years in a cohort of 484 patients with a mean diagnosis age of 58 years. The most common causes of death were cardiovascular disease (7.1%), malignancy (5.9%) and infection (4.1%) (Wallace, 2020). GC exposure is associated with a significant treatment toxicity such as diabetes, osteoporosis, psychiatric disorders, increased risk of infections and burden on patient's quality of life (Neumann, 2020). In the US, up to 38% of patients will progress to ESKD within 5 years (Cortazar, 2023) and between 21% and 89% will relapse within 5 years after diagnosis depending

on the CCI [redacted] regimens (Hogan, 2005; Salama, 2019; Smith, 2012; Smith, 2023; Stone, 2010).

There is a considerable unmet need in patients with ANCA-associated vasculitis for therapies that lessen the reliance on high-dose GC treatment and their associated toxicities. These therapies should also provide faster disease control, higher rates of remission, and lower risk of relapse.

Tarperprumig represents an appropriate candidate for investigation based on the broad nonclinical pharmacology, PK, PD, and toxicology data of tarperprumig, initial safety data for tarperprumig in healthy volunteers (Sandhu, 2025), and reported efficacy of tarperprumig in a passive transfer model of ANCA-associated vasculitis in mice. In the latter study, necrotizing and crescentic glomerulonephritis was induced by intravenous injection of mouse anti-mouse MPO (MPO-ANCA) IgG on Day 0. Control IgG or anti-factor P was administered at 1 mg/25 g body weight. Results of the urinalysis demonstrate that mice treated with the anti-factor P mouse surrogate (14E1 mAb) had significantly reduced proteinuria and leukocyturia compared to the control IgG. Kidney histology demonstrated significantly reduced formation of glomerular crescents in mice treated with 14E1 compared to the control IgG. These data provide nonclinical proof of concept that inhibition of properdin may be an appropriate target to treat ANCA-associated vasculitis.

2.3.3. Overall Benefit Risk Conclusion

ANCA-associated vasculitis is a severe systemic autoimmune disease that affects small-sized blood vessels in multiple organs, most frequently the kidney and the respiratory tract (Kitching, 2020). Current treatment regimens of ANCA-associated vasculitis include immunosuppressive and anti-inflammatory therapies that carry significant side effects and are not always efficacious in disease remission and preventing relapse (Neumann, 2020; Sánchez Álamo, 2023).

Study ALXN1820-HV-101 was a single and multiple ascending dose study in which tarperprumig was administered via SC and IV routes in 45 healthy adults. No SAEs, deaths, or TEAEs of CTCAE Grade 3 or above were reported during any part of the study, and no participants met the safety stopping criteria, with no safety concerns identified. Tarperprumig was safe and well tolerated under the conditions of the study (Sandhu, 2025).

Tarperprumig has also been studied in the Phase 2 Study ALXN1820-SCD-201 CCI [redacted] CCI [redacted] (Dai, 2022) CCI [redacted] CCI [redacted]

Study ALXN1820-ANCA-201 will be the third study with human exposure to tarperprumig. Study ALXN1820-ANCA-201 will be conducted in participants with ANCA-associated vasculitis, and dosing will be initiated based on review of safety, tolerability, and PK/PD data from Studies ALXN1820-HV-101 and ALXN1820-SCD-201. The doses administered in the current study are expected to produce exposure lower than the highest exposure tested in Study ALXN1820-HV-101, CCI [redacted] CCI [redacted]

CCI An iDMC will evaluate the available study data at prespecified time points for participant safety and make recommendations on continuation or termination of the study. CCI
CCI

Considering the high unmet need for treatments that lead to faster disease control, higher rates of remission, and lower risk of relapse and the safety data for tarperprumig based on studies in healthy volunteer and participants with SCD, the nonclinical studies, and the measures taken to minimize risk to participants in this study, the potential risks in association with tarperprumig are justified by the anticipated benefits that may be afforded to adult participants with ANCA-associated vasculitis.

More detailed information about the potential benefits and risks of tarperprumig may be found in the IB.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

The objectives and endpoints for this study are presented in Table 6.

Table 6: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of tarperprumig in participants with newly diagnosed or relapsing ANCA-associated vasculitis	• Incidence of TEAEs and TESAEs. • Changes from Baseline in safety assessments (vital sign measurements, physical examination, clinical laboratory tests, and ECG results).
Secondary	
• To evaluate the efficacy of treatment with tarperprumig on achieving disease remission, sustained remission, and preventing relapse in participants newly diagnosed or relapsing ANCA-associated vasculitis	• Achieving disease remission at Week 26.[a] • Achieving sustained remission at Week 52.[b] • Achieving BVAS = 0 at CCI 26, and 52. • Relapse[c] after previously achieving disease remission at Week 26.[a] • Time to first relapse[c] after having achieved disease remission at Week 26.[a] • Change from Baseline in Vasculitis Damage Index (VDI) at CCI 26, and 52. • Time to first occurrence of BVAS = 0. • Change from Baseline in BVAS at all timepoints.
• To evaluate the efficacy of treatment with tarperprumig on kidney function and kidney damage in participants with newly diagnosed or relapsing ANCA-associated vasculitis	• Change from Baseline in eGFR (mL/min per 1.73 m^2) at CCI 26, and 52. • Change from Baseline in proteinuria based on spot UPCR (mg/g) and % change from Baseline at CCI 26, and 52. • Change from Baseline in proteinuria based on spot UACR (mg/g) and % change from Baseline at CCI , 26, and 52. • Hematuria change from Baseline (RBCs/HPF) and % change from Baseline at CCI , 26, and 52.
Pharmacokinetics	
• To characterize the PK of tarperprumig in participants with newly diagnosed or relapsing ANCA-associated vasculitis	• Total tarperprumig serum concentrations over time. • PK parameters of total tarperprumig in serum over time.

Table 6: Objectives and Endpoints

Objectives	Endpoints
Pharmacodynamics	
• To characterize the PD of tarperprumig in participants with newly diagnosed or relapsing ANCA-associated vasculitis	• Absolute values, change from Baseline, and % change from Baseline in total properdin, free properdin, and serum complement functional activity (CCP, CAP, and CLP), through the duration of the study.
Immunogenicity	
• To assess the immunogenicity of tarperprumig in participants with newly diagnosed or relapsing ANCA-associated vasculitis	• Anti-tarperprumig antibody incidence, response categories, and titer for the duration of the study.
Exploratory	
• To evaluate the efficacy of treatment with tarperprumig on achieving disease remission and preventing relapse in participants newly diagnosed or relapsing ANCA-associated vasculitis	• Achieving disease remission at CCI [d] • Treatment response at CCI [e] • Achieving BVAS = 0 at CCI that is sustained without relapse through CCI • Relapse[c] after previously achieving BVAS = 0 at any time in the study. • Time to first relapse[c] after having achieved BVAS = 0 at any time in the study.
• To evaluate the efficacy of treatment with tarperprumig on kidney function and kidney damage in participants with newly diagnosed or relapsing ANCA-associated vasculitis	• Kidney function recovery at CCI • Time to first occurrence of UACR ≤ 300 mg/g. • Time to first occurrence of UPCR < 500 mg/g.
• To evaluate tarperprumig on key biomarker measures in participants with newly diagnosed or relapsing ANCA-associated vasculitis	• CCI •
• To assess the quality of life based on participant-reported outcomes in participants with newly diagnosed or relapsing ANCA-associated vasculitis based on treatment with tarperprumig	• Change from Baseline in EQ-5D-5L at CCI CCI • Change from Baseline in AAV-PRO at CCI CCI • Change from Baseline in PhGA at CCI • Change from Baseline in PGI-S at CCI

Table 6: Objectives and Endpoints

Objectives	Endpoints
	• PGI-C at CCI
• To assess medical resource utilization in participants with newly diagnosed or relapsing ANCA-associated vasculitis based on treatment with tarperprumig	• Number of inpatient admissions by CCI • Duration of hospitalizations by CCI • Number of outpatient medical encounters (including physician or emergency room visits) by CCI CCI
• CCI	• CCI
• To evaluate the effect of tarperprumig on CCI	• Change in CCI over time.

[a] Disease remission at Week 26 is defined BVAS of 0 at Week 26 and no prescribed glucocorticoids for treatment of ANCA-associated vasculitis within 4 weeks prior to Week 26.
[b] Sustained remission at Week 52 is defined as BVAS=0 at Week 26 without relapse to Week 52 and no prescribed GCs for treatment of ANCA-associated vasculitis within 4 weeks prior to Weeks 26 and 52.
[c] A relapse is defined as worsening of disease, after having previously achieved BVAS = 0, that involves: 1 or more major item in the BVAS, or 3 or more minor items in the BVAS, or 1 or 2 minor items in the BVAS recorded at 2 consecutive study visits.
[d] Disease remission at CCI is defined as BVAS = 0 and no prescribed glucocorticoids for treatment of ANCA-associated vasculitis within 4 weeks prior to CCI
[e] Treatment response at CCI s defined as at least 50% decrease in BVAS from Baseline with no worsening in any body system.
[f] Kidney function recovery is defined by an increase in eGFR from baseline of ≥ 15 mL/min per 1.73 m^2, which corresponds to a categorial change in CKD stage.
Abbreviations: AAV-PRO = ANCA-Associated Vasculitis Patient-Reported Outcome; ANCA = anti neutrophil cytoplasmic antibody; CCI CCI ; BVAS = Birmingham Vasculitis Activity Score CCI CAP = complement alternative pathway; CCP = complement classical pathway; CLP = complement lectin pathway; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EQ-5D-5L = EuroQol 5-dimension 5-level ; GC = glucocorticoid; HPF= high-power field; CCI ; MCP-1 = monocyte chemoattractant protein-1; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PhGA = Physician Global Assessment; RBC = red blood cell CCI CCI ; UACR = urine albumin-creatinine ratio; UPCR = urine protein-creatinine ratio; VDI = Vasculitis Damage Index

The clinical question of interest with respect to efficacy at Week 26 is: What is the treatment effect of tarperprumig compared to placebo on achieving disease remission at Week 26 in adults with ANCA-associated vasculitis who are receiving the CCI

The estimand is described by the following attributes:

- Population: All adult participants diagnosed with ANCA-associated vasculitis and baseline eGFR ≥ 15 mL/min/1.73 m^2.

- Endpoint: Achieving disease remission at Week 26, defined as BVAS = 0 at Week 26 and no prescribed glucocorticoids for treatment of ANCA-associated vasculitis within 4 weeks prior to Week 26.
- Treatment of interest: Tarperprumig + CCI or placebo CCI. Participants from the two tarperprumig treatment groups will be pooled for analysis.
- Handling of ICEs: The composite strategy will be used. Participants with ICEs occurring prior to the assessment time of the endpoint will be considered as not achieving the endpoint for the following ICEs:
  - Death
  - Kidney transplant and dialysis
  - Use of rescue medication (eg, cyclophosphamide)
- Summary measure: Difference in the proportion of participants who achieve the efficacy endpoint between groups.

The clinical question of interest with respect to efficacy at Week 52 is: What is the treatment effect of tarperprumig compared to placebo on achieving sustained remission at Week 52 in adults with ANCA-associated vasculitis who are receiving the CCI

- The estimand attributes are the same as above except the endpoint is achieving sustained remission at Week 52, defined as BVAS = 0 at Week 26 without relapse to Week 52 and no prescribed GCs for treatment of ANCA-associated vasculitis within 4 weeks prior to Weeks 26 and 52.

4. STUDY DESIGN

4.1. Overall Design

For a description of study intervention after the end of the study refer to Section 6.7.

This study is a Phase 2, double-blind, randomized, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of tarperprumig in participants with ANCA-associated vasculitis GPA and MPA subtypes, on a background of treatment with rituximab and GC.

There will be 3 periods in this study: Screening Period, Double-Blind Treatment Period, and Safety Follow-up Period. Participants will be screened for eligibility for up to CCI during the Screening Period. Approximately 75 eligible participants will be randomized in a 1:1:1 ratio to receive one of the following during the Double-Blind Treatment Period (see Section 6.1; Figure 1):

- Treatment Group 1 (n = 25): Tarperprumig CCI SC CCI CCI SC CCI
- Treatment Group 2 (n =25): Tarperprumig CCI S CCI CCI
- Treatment Group 3 (n = 25): CCI SC CCI SC CCI

Randomization will be stratified based on the following factors using data at Screening:

- ANCA type (PR3-ANCA or MPO-ANCA)
- Disease status (newly diagnosed or relapsing ANCA-associated vasculitis)

Upon completing the last assessment of the 52-week Double-Blind Treatment Period, participants will continue into the CCI Safety Follow-up Period.

During the Safety Follow-up Period, participants will stop receiving tarperprumig but will continue with CCI treatment as needed.

4.2. Scientific Rationale for Study Design

Tarperprumig is being developed for the treatment of diseases driven by the activation of the complement alternative pathway.

The purpose of this study is to evaluate the safety, tolerability, efficacy to induce and maintain remission in combination with rituximab and CCI GC CCI PK, PD, and immunogenicity of multiple weekly or every CCI SC doses of tarperprumig administered in participants with ANCA-associated vasculitis GPA and MPA subtypes. Patients with GPA and MPA are characterized by the loss of tolerance toward neutrophil proteins, most often leukocyte proteinase 3 (PR3) or neutrophil myeloperoxidase (MPO) (Kitching, 2020). Autoimmunity is documented clinically by serum ANCA to PR3 (PR3-ANCA) or MPO (MPO-ANCA), which are generally associated with the main syndromic ANCA presentations and relapse (Kitching, 2020).

The randomized, double-blind study design will minimize any potential bias introduced during study conduct to treatment effect evaluation. Randomization will be stratified by ANCA type

(PR3-ANCA or MPO-ANCA) and disease status (newly diagnosed or relapsing) using data at Screening to reduce any impact by the stratification factors to treatment.

Approximately 80% of patients with ANCA-associated vasculitis (60% of the GPA and 80% of MPA) have kidney involvement and these patients typically present with other organ manifestations (Kronbichler, 2024; Sachez-Alamo, 2024). Kidney function (eGFR) and kidney damage (proteinuria and hematuria) are objective outcomes to measure. Early kidney function changes in patients with ANCA-associated vasculitis were correlated with long-term ESKD (unpublished; in press) and survival (Sachez-Alamo, 2024). Given these reasons, changes in kidney function will be monitored in this trial.

A Double-Blind Treatment Period of 52 weeks was selected to assess disease remission at Week 26, and sustained remission at both Week 26 and Week 52 using BVAS, and to assess kidney function improvement. According to current guidelines, CCI of ANCA-associated vasculitis is administered at disease diagnosis or relapse (Hellmich, 2024; KDIGO, 2024), and usually lasts between 3 and 6 months. CCI starts after induction of remission and lasts between 18 months and 4 years (Chung, 2021; Hellmich, 2024; KDIGO, 2024). CCI

CCI

- CCI
- CCI

Additional safety and efficacy data will be collected during the Safety Follow-up Period.

CCI

[redacted]

Tarperprumig is being developed as add-on therapy to [redacted] that, in this study, will be [redacted] with rituximab plus [redacted] GC [redacted] The use of rituximab plus [redacted] GC [redacted] as [redacted] is continuously growing and is in line with the recent guidelines (Chung, 2021; Hellmich, 2024; KDIGO, 2024). GC treatment will be allowed before and during the Screening Period and will be tapered during the Double-Blind Treatment Period modified based on recommendation from the 2024 KDIGO guidelines for ANCA-associated vasculitis (referred to as [redacted] GC [redacted] in this document). The use of additional GC will be allowed under specified circumstances (Section 6.1.2.2). [redacted] The GC sparing effect of complement inhibitors has been demonstrated in the [redacted] studies (CLEAR (Jayne, 2017), ADVOCATE (Jayne, 2021) and eculizumab case studies in treatment of patients with ANCA-associated vasculitis (Huizenga, 2020; Ribes, 2019). In this study [redacted] However, non-study-supplied GC use is allowed in case of early resistance, worsening, and relapse. [redacted]

Use of GCs is detailed in Section 6.1.2.

Rituximab is used as the [redacted] for ANCA-associated vasculitis according to the recent guidelines (Chung, 2021; Hellmich, 2024; KDIGO, 2024). Currently, majority of the patients are treated with rituximab as [redacted] and this trend is continuously growing.

Cyclophosphamide will be allowed under specified circumstances (Section 6.9.1.1).

Properdin inhibition increases the risk of meningococcal infection in participants. [redacted]

A Safety Follow-up Period of [redacted] was chosen to make sure that all participants will be followed for at least 5 half-lives after the last treatment with tarperprumig. Based on Study ALXN1820-HV-101, the half-life of tarperprumig in healthy participants was approximately 24 days after multiple doses of tarperprumig.

4.2.1. Patient Input into Design

During protocol development, the study team met with 4 individuals living with ANCA-associated vasculitis along with 1 patient advocacy group leader to provide their input in the study. Participants represented various geographies in the US, the UK, and France. The team discussed with the participants the overall study design, study visit schedule, dosing instructions, and visit procedures to gain a better understanding if patients will be able to manage these aspects while they are participating in the study.

Based on patient input, the team is adding the following support services:

- Increase educational material content for patient advocacy groups and healthcare professionals to support the study and ANCA-associated vasculitis disease awareness
- Communication tools to support participants in their understanding of risks (specifically around steroids), need for clinical studies, and the requirements of participants with respect to study visit and study requirement adherence
- Increase home nursing availability to include more weekend opportunities
- Develop a mechanism to relay study results back to the participants
- Create a frequently asked question document for participants with common conversation topics with sites
- Supporting study participants with travel and expense reimbursement where allowed

4.3. Justification for Dose

The dose and the frequency of dosing is based on all available data including the overall safety, tolerability, pharmacometric analysis of Study ALXN1820-HV-101; and toxicology data from the GLP 6-week and 6-month studies in cynomolgus monkeys. A population PK/PD model was established based on data from the Phase 1 Study ALXN1820-HV-101 in healthy participants. This CCI model assumed monovalent tarperprumig binding to CCI CCI The relationship between free properdin and CAP activity was characterized by a CCI model. The model provided good fits to the observed data (tarperprumig, total and free properdin, and CAP activity) judged by the model diagnostics.

Results from the Phase 1 study showed that CAP activity inhibition of CCI % of baseline was achieved in healthy participants. This threshold was considered as complete CAP inhibition and used to identify the therapeutic dose. CCI CCI CCI To account for the potentially local increase of properdin released by activated neutrophil, a CCI increase of baseline properdin was assumed. Utilizing the population PK/PD model, simulations were conducted based on these assumptions CCI CCI

CCI

CCI

[redacted]

4.4. End-of-Study Definition

The end of the study is defined as the date of the last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the study globally.

A participant is considered to have completed the study if they have completed all periods of the study, including the last visit, as per the SoA (Section 1.3).

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

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

Age

1. Participants aged 18 to 80 years (inclusive) at the time of consent.

Type of Participant and Disease Characteristics

2. Newly diagnosed or relapsing ANCA-associated vasculitis, GPA and MPA subtypes consistent with the 2022 ACR/EULAR classification criteria for GPA and MPA for whom treatment with rituximab or cyclophosphamide is considered.
3. Positive test for antibodies to either PR3-ANCA or MPO-ANCA at Screening or in the past by a quantitative assay (for example, ELISA, bead assay, etc).
4. At least one major item, or at least 3 minor items, or at least 2 renal items in the BVAS.
5. Estimated glomerular filtration rate (eGFR) ≥ 15 mL/min/1.73 m^2 (calculated using the 2021 CKD-EPI equation without race coefficient) at Screening (Section 8.2.6).

CCI [redacted]

Weight

There is no weight restriction in this study.

Sex and Contraceptive/Barrier Requirements

7. All participants must agree to follow protocol-specified contraception guidance as outlined in the study protocol. Contraceptive use must be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

   a. Male participants:

   Participants are eligible to participate if they agree to the following during the study intervention treatment period and for at least CCI [redacted] after the last dose of study intervention:

   - Refrain from donating sperm
   - Be abstinent from intercourse where pregnancy can occur (abstinent on a long-term and persistent basis) and agree to remain abstinent

OR

Must agree to use contraception/barrier as detailed below

- Agree to use an external condom and should also be advised of the benefit for a partner of CBP to use a highly effective method of contraception as a condom may break or leak when having sexual intercourse with a partner able to give birth who is not currently pregnant
- Agree to use an external condom when engaging in any activity that allows for passage of ejaculate to another person.

b. Female participants:

A participant is eligible to participate if not pregnant or breastfeeding, and one of the following conditions applies:

- Is a woman of NCBP as defined in Section 10.5 Contraceptive and Barrier Guidance.
- Is of CBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), preferably with low user dependency, as described in Section 10.5 Contraceptive and Barrier Guidance during the study intervention treatment period and for at least CCI after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The Investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention.
- A CBP participant must have a negative highly sensitive pregnancy test (urine) as required by local regulations) within 24 hours before the first dose of study intervention, see Section 8.3.6 Pregnancy Testing.
  - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.6 Pregnancy Testing.
- The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a participant with an early undetected pregnancy.

Informed Consent

8. Willing and able to give written informed consent and to comply with the requirements of the study protocol.

Other Inclusion Criteria

Not applicable.

5.2. Exclusion Criteria

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

Medical Conditions

1. Other systemic diseases that, in the judgment of the Investigator, constitute the primary illness, including but not limited to: eosinophilic granulomatosis with polyangiitis (EGPA), systemic lupus erythematosus, IgA nephropathy and/or IgA-associated vasculitis with or without Henoch-Schönlein purpura, rheumatoid vasculitis, Sjögren's syndrome, anti-GBM disease, cryoglobulinemic vasculitis, autoimmune hemolytic anemia, or mixed connective tissue disease.
2. Alveolar hemorrhage requiring invasive pulmonary ventilation support at Screening.
3. Any diseases or conditions that, in the judgment of the Investigator, present a substantial clinical risk to participate in this study.
4. For patients with a previous diagnosis of CKD, patients known to have a stable eGFR for greater than 3 months prior to Screening and a decline less than 25% of previous eGFR at Screening will be excluded.
5. Known hypersensitivity to any ingredient contained in the study intervention.
6. History of serious *N meningitidis* infection.
7. Current and/or history (within the previous 5 years) of drug and/or alcohol abuse and/or dependence.
8. Evidence of active hepatitis B, hepatitis C, and/or HIV infection. Only participants with documented negative historical results (within CCI before Screening) for HBV, HCV, and HIV or a negative test by screening can be included into the study.

   Evidence of hepatitis B or hepatitis C infections will be according to the following criteria at Screening:

   - Testing positive for HBsAg, OR
   - Testing positive for HBcAb while having a negative HBsAb.
   - Positive hepatitis C antibody test result at Screening or within 3 months unless HCV RNA negative test is documented.

   Note: HBV DNA testing may be performed instead of HBsAb as per local standard practice.
9. Evidence of hepatic disease: AST, ALT, ALP, or bilirubin > 3 times the ULN at Screening.
10. Evidence of latent or active TB (Section 8.1.9).
11. History of complement deficiency.
12. History of splenectomy.

13. History of malignancy, lymphoproliferative, or myeloproliferative disorder within 5 years prior to Screening with the exception of nonmelanoma skin cancer or carcinoma in situ of the cervix that has been treated with no evidence of recurrence.

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15. Participants with an active systemic bacterial, viral, fungal, or parasitic infection, with the diagnostic assessment at the discretion of the investigator, that required use of intravenous antibacterials, antivirals, antifungals, or anti-parasitic agents within 14 days prior to Day 1.
16. Participants with any contraindication to rituximab per the locally approved product information, or any label warning/precaution that in the Investigator's judgment would prevent safe rituximab administration in this study.

Prior/Concomitant Therapy

17. Has received any of the following:
    a. A kidney transplant
    b. Dialysis or plasma exchange within CCI [redacted] before Screening
    c. Cyclophosphamide within CCI [redacted] before Screening
    d. Rituximab or other B cell or plasma cell-depleting agent within 12 months to > 14 days before Screening
    e. A cumulative dose of intravenous glucocorticoids greater than 3 g methylprednisolone equivalent within 4 weeks of Screening
    f. Oral daily dose of a glucocorticoid of > 10 mg prednisone equivalent for more than CCI [redacted] continuously prior to the Screening Visit
    g. CCI [redacted] or other complement inhibitors (eculizumab, ravulizumab, etc) within 30 days or 5 half-lives, whichever is longer, before Screening
    h. Anti-tumor necrosis factor treatment, abatacept, alemtuzumab, IVIG, antithymocyte globulin, or any other experimental or biological therapy within CCI [redacted] or 5 half-lives, whichever is longer, before Screening.

Prior/Concurrent Clinical Study Experience

18. Participation in a clinical study involving an investigational medical product or device within 30 days or 5 half-lives of the investigational drug, whichever is longer, before Screening

Diagnostic Assessments

19. The following abnormal laboratory findings at Screening:
    - IgG < 5 g/L (if rituximab treatment is initiated before Screening, then test results before initiation of rituximab and within 6 months of the Screening can be used)
    - WBC count less than 3500/µL or neutrophil count less than 1500/µL

Other Exclusions

20. Women who are pregnant (positive pregnancy test) or breastfeeding at study entry

5.3. Lifestyle Considerations

There are no lifestyle restrictions for this study.

5.4. Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently randomized to any dose regimen. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (eg, eligibility status), and all AEs (including any SAEs, and any AEs related to concomitant medication) occurring during the Screening Period.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened one time. Participants are allowed for rescreening only when there is delay due to assessment of eligibility criteria. Some examples include delay in reporting of a screening test or repeat of a screening test due to a temporary condition that is expected to be resolved quickly. See Section 8.1.2.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

Not applicable.

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY

6.1. Study Interventions Administered

Study interventions are all prespecified investigational and non-investigational medicinal products, and other interventions intended to be administered to the study participants during the study conduct.

Refer to Table 7 for a full list of study interventions to be administered in this study. Study interventions per treatment group are listed in Table 8. For blinding measures, see Section 6.4.

Table 7: Study Interventions Administered

Intervention name	Tarperprumig	Placebo of Tarperprumig	Rituximab	Glucocorticoids
IMP or AxMP	IMP	IMP	AxMP	AxMP
Type	Biologic	Matching placebo	Biologic	Small molecule
Dose formulation	Formulated as 150 mg/mL tarperprumig in 50 mM acetate buffer, 86.0 mg/mL sucrose, 1.5 mg/mL polysorbate 80, pH 5.4	50 mM acetate buffer, 86.0 mg/mL sucrose, 1.5 mg/mL polysorbate 80, pH 5.4	Sterile solution for infusion	As described in the label
Dosage level(s)	CCI	N/A	See Section 6.1.3 for dosing	See Section 6.1.2 for dosing
Route of administration	SC injection	SC injection	IV infusion	Oral
Use	Experimental	Experimental	Background intervention	Background intervention
Sourcing	Provided centrally by Alexion	Provided centrally by Alexion	Sourced by the clinical site using locally approved product or provided by the site by local vendors coordinated by Alexion, or provided centrally by Alexion	Sourced by the clinical site using locally approved product or provided by the site by local vendors coordinated by Alexion, or provided centrally by Alexion

Table 7: Study Interventions Administered

Intervention name	Tarperprumig	Placebo of Tarperprumig	Rituximab	Glucocorticoids
Packaging and labeling	Each 2-mL vial (150 mg/mL) will be packaged into a kit. There will be 1 vial per kit. Both vials and kits will be labeled according to the protocol and local regulatory requirements.	Identical to active drug	Provided centrally by Alexion or as locally approved product and labeled as required per country and site requirements	Provided centrally by Alexion or as locally approved product and labeled as required per country and site requirements
Additional trade names	N/A	N/A	Rituxan	N/A

Abbreviations: AxMP = auxiliary medicinal product; IMP = investigational medicinal product; IV = intravenous; N/A= not applicable; SC = subcutaneous

Table 8: Study Interventions per Treatment Group

Group title	Treatment Group 1	Treatment Group 2	Treatment Group 3
Group type	Experimental	Experimental	Control
CCI	Tarperprumig CCI SC, CCI	Tarperprumig CCI SC CCI	Tarperprumig CCI CCI , SC CCI
CCI	Tarperprumig CCI SC, CCI	Tarperprumig CCI SC, CCI	Tarperprumi CCI CCI , SC CCI
Safety Follow up	CCI	CCI	CCI

Abbreviations: CCI ; CCI SC = subcutaneous; CCI

6.1.1. Tarperprumig and Matching Placebo

Tarperprumig or matching placebo will be delivered SC using a manual push with syringe and needle (see the Pharmacy Manual).

The blinded study intervention will be administered at Clinic Visits by trained and delegated study site personnel. Outside of Clinic Visits, the study intervention will be administered by a trained home nurse, where allowed according to local legislation. For reference, see the Pharmacy Manual.

Administration sites will be rotated. After administration, the location of each injection site (ie, upper left abdomen, lower left abdomen, upper right abdomen, lower right abdomen, right thigh, left thigh, upper right arm, and upper left arm) will be recorded. See Pharmacy Manual for additional details.

6.1.2. Glucocorticoids

6.1.2.1. Study-Supplied Glucocorticoid Use

Participants will receive GCs (Table 7) according to CCI

CCI

CCI

CCI

6.1.2.2. Non- Study Supplied Glucocorticoid Use

Use of additional GCs not supplied as study intervention must be avoided as much as possible during the study. The following sections provide guidance for non-study-supplied GC use (as rescue therapy). Use of additional GCs will not be considered as treatment failure.

6.1.2.2.1. Before the Screening Period

Participants with severe ANCA-associated vasculitis will be allowed to have received IV GCs at a cumulative dose up to 3 g methylprednisolone equivalent in the 4-week period before screening.

Participants will also be allowed to have received oral GCs at any dose in the CCI period before Screening.

Participants will not be eligible for Screening if they received continuous treatment with oral moderate- or high-dose GCs continuously for more than CCI prior to the Screening Visit; moderate to high dose is defined as greater than 10 mg prednisone equivalent per day.

6.1.2.2.2. During the Screening Period

During the Screening Period of the study, IV GCs will be allowed for participants with severe ANCA-associated vasculitis, as long as the cumulative dose for the 4-week period before screening plus the IV dose(s) given during the Screening Period do not exceed 3 g methylprednisolone equivalent.

During the Screening Period of the study, oral GCs will be allowed for participants with severe ANCA-associated vasculitis.

6.1.2.2.3. During the Double-Blind Treatment and Follow-up Periods

All participants will take GC according to Section 6.1.2.

If GCs cannot be tapered to a dose of zero due to adrenal insufficiency, the AE of adrenal insufficiency and treatment administered must be recorded, along with the evidence supporting the diagnosis. Replacement GCs for adrenal insufficiency must not exceed 10 mg prednisone

equivalent per day; CCI must be reinitiated as soon as possible, and condition must be monitored consistent with Investigator judgment and local standards. The AE of adrenal insufficiency, and treatment for the event, must be recorded and updated as treatment is tapered.

For participants with exacerbation of asthma or other conditions requiring GC treatment, a short course of GC can be given after consulting with the Medical Monitor. The AE of asthma exacerbation (or other conditions) and treatment administered must be recorded in the eCRF.

Participants who experience a relapse of their ANCA-associated vasculitis during the study may be treated with IV GCs (typically 0.5 to 1 g methylprednisolone per day for 3 days) or oral GCs, tapered according to the participant's condition. A relapse is defined as worsening of disease, after having previously achieved BVAS = 0, that involves:

- 1 or more major item in the BVAS, or
- 3 or more minor items in the BVAS, or
- 1 or 2 minor items in the BVAS recorded at 2 consecutive study visits.

These participants may continue treatment with tarperprumig and should continue in the study.

Participants who experience worsening of disease during the study that involves a major item in the BVAS may be treated with IV GCs (typically 0.5 to 1 g methylprednisolone per day for 3 days) or oral GCs, tapered according to the participant's condition. Worsening not involving a major item in the BVAS may be treated with a short burst (ie, not more than CCI) of oral GCs, at a maximum dose of 20 mg prednisone equivalent. Participants experiencing worsening of disease may continue treatment with tarperprumig and should continue in the study.

Participants experiencing a relapse or worsening of disease may continue study drug treatment and should continue in the study. The study-supplied prednisone will be temporarily halted during the IV and/or oral course of glucocorticoids, and if the participant's condition stabilizes, the study-supplied prednisone may be restarted according to the original study visit schedule. The tarperprumig/matching placebo may also continue during and following the treatment for the relapse or worsening, at the discretion of the Investigator.

Participants who have one or more major items in the BVAS before study entry, and who do not show an improvement or stabilization of these major items within the first 4 weeks of the study, may receive additional IV or oral GCs, tapered according to the participant's condition. If the Investigator considers giving other medications, such as additional rituximab or cyclophosphamide, these medications should be discussed with the Medical Monitor. These participants may continue treatment with tarperprumig and should continue in the study.

In participants with early resistant disease, the study-supplied prednisone will be temporarily halted during the IV and/or oral course of GCs, and if the participants' condition improves, the study-supplied prednisone may be resumed according to the original visit schedule. The tarperprumig/matching placebo may also continue during the treatment for early resistance, at the discretion of the Investigator.

GC use at the time of rituximab infusions is allowed as indicated in Section 6.1.3.

6.1.3. Rituximab

Rituximab will be given as follows:

Rituximab should not be administered on the same day of tarperprumig administration to avoid potential confounding effects of infusion-related reactions that may or may not be related to tarperprumig.

It is recommended to premedicate before each infusion with acetaminophen and an antihistamine.

For the first rituximab infusion, 100 mg methylprednisolone, or equivalent can be given. GC premedication for the second, third, and fourth rituximab infusions is allowed.

For the first IV infusion, it is recommended to initiate the infusion at a rate of 50 mg/h.

In the absence of infusion toxicity, it is recommended to increase the infusion rate by 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h.

For subsequent infusions, it is recommended to initiate the infusion at a rate of 100 mg/h. In the absence of infusion toxicity, it is recommended to increase the rate by 100 mg/h increments at 30-minute intervals, to a maximum of 400 mg/h.

The start and end times of the IV rituximab infusions will be recorded. Participants will undergo observation post-infusion as per local requirements.

6.1.4. Rescue Therapies

For rescue medications, see Section 6.1.2.2 and Section 6.9.1.1.

6.2. Preparation, Handling, Storage, and Accountability

- The Investigator or designee must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.
- Only authorized site staff may supply, dispense, prepare, or administer study intervention.
- Only participants randomized in the study may receive the study intervention.
- All study interventions 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.

- The Investigator is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
  - 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 has been released for distribution to an end customer that affects the performance of such product.
  - The pharmacist or other designated individual will maintain records of study intervention delivered to the study site, the inventory at the study site, the distribution to and use by each participant, and the return of materials to the sponsor for storage or disposal/destruction of materials at the study site. These records should include dates, quantities, batch/serial numbers, expiration dates, in-clinic temperature log, and unique code numbers assigned to the study intervention and study participants.
  - The Investigator will maintain records that adequately document that the participants were administered the correct study treatment kits and reconcile the products received from the drug dispensing center. Investigational product will not be returned to the sponsor or disposed of until accountability has been fully monitored.
  - In order to limit the burden on study participants, a Direct to Patient (DtP) IMP delivery may be implemented, where applicable, following participant consent. A qualified home nurse delegated by the Investigator, from a pre-qualified vendor, will collect the IMP from the study site and transport it directly to the participant's home for administration, as well as ensure IMP return to the site. All activities related to the handling, transport, and administration of the IMP will be conducted in strict compliance with GCP/GDP guidelines, under the full oversight of the Investigator, to ensure patient safety, product quality, and data integrity. The procedure will be available for study visits after[redacted] see Section 1.3).
  - Further guidance regarding preparation, handling, storage, and accountability and information for the final disposition of unused study interventions provided by Alexion are provided in the Pharmacy Manual.

6.3. Assignment to Study Intervention

All participants will be centrally assigned to randomized study intervention using IVRS/IWRS. Randomization will be stratified by ANCA type (PR3-ANCA or MPO-ANCA) and disease status (newly diagnosed or relapsing) based on data from Screening.

6.4. Blinding

Measures are in place to ensure that treatment assignments remain blinded to participants, Investigators, and study staff, thus maintaining the integrity of the study design.

6.4.1. Blinding of Tarperprumig

Vials containing tarperprumig or placebo will be provided in identical study intervention kits and with identical labels for all participants in the Double-Blind Treatment Period. Blinding will take into account differences in color between active drug and placebo.

Additional details will be provided in the Pharmacy Manual.

6.4.2. Unblinding

Investigators will receive only blinded information unless unblinded information is judged necessary for safety reasons. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator may, at the Investigator's discretion, contact Alexion to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If unblinding is deemed necessary, the Investigator will be able to unblind the participant's intervention assignment using the IRT. If a participant's intervention assignment is unblinded, Alexion must be notified within 24 hours after breaking the blind.

Alexion safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to Investigators in accordance with local regulations and/or Alexion policy.

In the event of a suspected unexpected serious adverse reaction (SUSAR), reporting guidance in Section 8.4.4 must be followed. The blind will be maintained for persons responsible for the ongoing conduct of the study (eg, Monitors, Investigators) and those responsible for data analysis and interpretation of results.

Except for these emergency situations, unblinded information will only be accessible to those who are involved in safety reporting to Health Authorities, Independent Ethics Committees (IECs), and/or Institutional Review Boards (IRBs).

See Section 9.8 for details of the interim analyses.

6.5. Study Intervention Compliance

6.5.1. Tarperprumig Compliance

Participants will receive study intervention (tarperprumig or matching placebo) in clinic directly from the Investigator or designee, or outside of the clinic administered by a home nurse. The date and time of each dose administered will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing.

For additional information on study intervention compliance and management, refer to the Pharmacy Manual.

6.5.2. Glucocorticoids Compliance

GCs will be dispensed to the participants at the Clinic Visits, mostly to be taken at home at the specified dosing regimen (see Table 9). At each Clinic Visit, the site should ensure that the participant has sufficient drug supply until the next Clinic Visit. Participants will be instructed to record their GC intake in the dosing diary and bring back all unused drugs at each Clinic Visit for accountability.

6.5.3. Rituximab Compliance

The dose, date and time of each dose of rituximab administered in the clinic will be recorded in the source documents and the eCRF (refer to Section 6.1.3 for rituximab dosing regimen).

6.6. Dose Modification

Dose modification is not applicable to tarperprumig. For dose modifications of GCs and rituximab, refer to Section 6.1.2 and Section 6.1.3, respectively.

6.7. Continued Access to Study Intervention after the End of the Study

Not applicable.

6.8. Treatment of Overdose

In case of overdose of IMPs, general supportive measures are recommended. It is not known if IMPs can be removed by dialysis.

In the event of an overdose or suspected overdose, the Investigator will:

- Capture and forward the event, with or without associated AEs, to Alexion Global Patient Safety via email or facsimile (clinicalsae@alexion.com or + 1.203.439.9347) using the Alexion Clinical Study Overdose Report Form within 24 hours of awareness.
- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, if possible, whether study intervention should be interrupted.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
- Obtain a serum sample for PK analysis (and ADA sample, if applicable) if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration (start and stop dates) of the overdose.

6.9. Prior and Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements), vaccine, or other specific categories of interest that the

participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor must be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1. Allowed Medicine and Therapy

Medications described in this section are permitted. These medications will be used as prophylactic medicine or to treat relapses, worsening of disease, or non-responders.

6.9.1.1. Cyclophosphamide

Cyclophosphamide, which is not supplied as study intervention, may be used as a rescue therapy in combination with rituximab if participants show no improvement or worsening in BVAS score and/or kidney function at least 4 weeks after the first dose of study intervention. Addition of cyclophosphamide will be considered as treatment failure. The tarperprumig/matching placebo may continue with the addition of cyclophosphamide, at the discretion of the Investigator.

The following sections provide guidance for non-study-supplied cyclophosphamide use.

- For IV dosing, a dose of 15 mg/kg cyclophosphamide will be given unless a lower dose is required per instructions below. The maximum permitted IV dose is 1.2 g. The start and end time of the IV infusion should be recorded.
- For oral dosing, a dose of 2 mg/kg/day cyclophosphamide will be given unless a lower dose is required per instructions below. The maximum daily oral dose permitted is 200 mg. Cyclophosphamide doses will be rounded down to the nearest 25 mg (or 50 mg, if 25 mg dose units are not available).
- Mesna and antiemetic treatment will be given according to local practice.
- The cyclophosphamide dose will be determined by 4 factors:
  - participant age
  - eGFR
  - WBC count at the study visit
  - WBC count nadir in between dose pulses (where applicable)

The dose for oral and IV cyclophosphamide, based on age and eGFR, is provided in Table 10.

Table 10: Dose (mg/kg/day) for Oral or IV Cyclophosphamide Based on Age and eGFR

Cyclophosphamide Dose	Oral Cyclophosphamide Dose (mg/kg/day)		IV Cyclophosphamide Dose (mg/kg)	
Age/eGFR	> 30 mL/min/1.73 m^2	≤ 30 mL/min/1.73 m^2	> 30 mL/min/1.73 m^2	≤ 30 mL/min/1.73 m^2
< 60 years	2	1.5	15	12.5
60 – 70 years	1.5	1.25	12.5	10
> 70 years	1.25	1	10	7.5

Abbreviations: IV = intravenous; eGFR = estimated glomerular filtration rate

For those receiving IV cyclophosphamide, the dose should be reduced further based on the WBC count as follows:

- WBC count assessed just prior to the IV dose:
  - If ≥ 3.5×10^9/L, dosing according to Table 10 will be given;
  - If < 3.5×10^9/L, the dose will be postponed until the WBC count is ≥ 3.5×10^9/L and then the dose from Table 10 will be reduced by another 25%;
- WBC count nadir in between IV cyclophosphamide doses:
  - If > 3×10^9/L, dosing according to Table 10 will be given;
  - If 2 to 3×10^9/L, the dose according to Table 10 will be reduced by 20%;
  - If 1 to 1.9×10^9/L, the dose according to Table 10 will be reduced by 40%;
  - If < 1×10^9/L, the next dose will be withheld and further dosing will only be given if the WBC is > 3×10^9/L.

For those receiving oral cyclophosphamide, the dose should be reduced further based on the WBC count as follows:

- If WBC count is < 3.5×10^9/L, withhold dosing. When WBC count returns to ≥ 3.5×10^9/L for 2 consecutive tests, or ≥ 5×10^9/L on a single test, restart oral cyclophosphamide at 25 mg less than dose according to Table 10. Monitor WBC count weekly after this episode. If only 50 mg dose units are available, restart oral cyclophosphamide at 50 mg less than dose according to Table 10.
- If WBC count is < 1×10^9/L, or < 3.5×10^9/L for more than CCI withhold dosing. When WBC count returns to ≥ 3.5×10^9/L for 2 consecutive tests or ≥ 5×10^9/L on a single test, restart oral cyclophosphamide at 50 mg less than dose from Table 10. Monitor WBC count weekly after this episode. Consider giving G-CSF, fungal prophylaxis, or other precautions.

- If WBC count decreases markedly without overt leukopenia, eg, WBC count $< 6 \times 10^9$/L and at least 2×10^9/L lower than the previous count, weekly WBC count monitoring should be done and the oral cyclophosphamide dose from Table 10 reduced by 25 mg (or 50 mg if 25 mg dose units are not available) if the WBC count continues to decrease.

6.9.2. Disallowed Medicine and Therapy

The following medicines or procedures are prohibited:

- Other medications for ANCA-associated vasculitis:
  - Azathioprine
  - Mycophenolate
  - Methotrexate
  - Plasma exchange
- Anti-TNF treatment
- Abatacept
- Alemtuzumab
- IVIG
- Belimumab
- Tocilizumab
- Complement inhibitors:
  - Eculizumab
  - Ravulizumab
  - CCI
- Other experimental or immunosuppressive drugs

6.9.2.1. Live Vaccines

Live or live attenuated vaccines: Participants must not receive any live or live attenuated vaccine within 4 weeks (28 days) prior to the first planned dose of rituximab, and must not receive any live or live attenuated vaccine during the study period until 12 months after the last dose of rituximab or until immune recovery, as determined by the Investigator.

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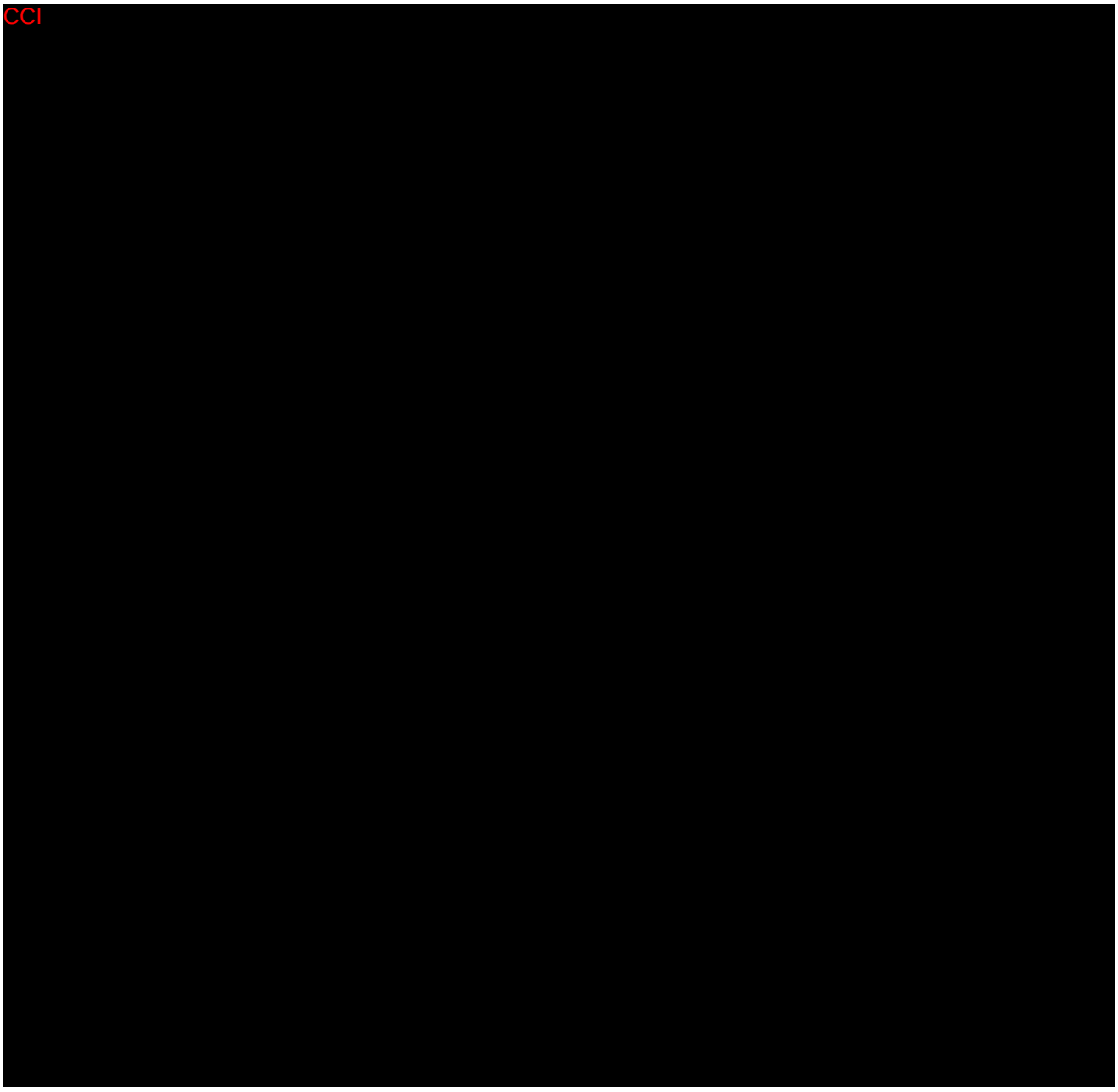
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7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1. Discontinuation of Study Intervention

7.1.1. Individual Stopping Criteria

Participants must be discontinued from the study intervention if they experience any of the following:

- Severe hypersensitivity reaction
- Pregnancy or planned pregnancy
- Use of disallowed medication
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator or Alexion, presents a substantial clinical risk to the participant with continued study intervention dosing.

Participants may discontinue the study intervention at any time but remain in the study. Following treatment discontinuation, the participant will enter the Safety Follow-up Period.

7.1.2. Study Stopping Criteria

The following events will be evaluated by the iDMC for whether they will be considered as study stopping rules:

- ≥ 2 Grade 4 hypersensitivity reactions (Section 8.3.8)
- ≥ 2 confirmed Hy's law cases (Table 12)

If the events are deemed to be related to the study drug, the study may be terminated at the recommendation of the iDMC. Continuation of the study would then require regulatory approval via a substantial amendment.

7.2. Participant Withdrawal from the Study

All efforts will be made to ensure participants are willing to comply with study participation prior to conducting the screening procedures.

- The study staff will notify Alexion and their site monitor of all study withdrawals as soon as possible. The reason for participant discontinuation must be recorded in the source documents and eCRF.
- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason) without any negative consequences.
- A participant who wishes to withdraw from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or Treating Physician, or information from medical records).

- Participants who withdraw consent must be asked by site staff if they agree to complete the CCI Visit (Section 1.3) as soon as possible, but no later than CCI after the last dose of study intervention.
- If a participant withdraws consent from the study, no further efforts may be made to collect data beyond the CCI Visit.
- A participant may be withdrawn at any time at the discretion of the Investigator.
- If the participant withdraws consent for disclosure of future information, Alexion may retain and continue to use any data collected before such a withdrawal of consent.
- If the participant withdraws from the study, Alexion may retain and continue to use any samples collected before such a withdrawal of consent for the purposes the participant originally consented unless the participant withdraws consent for use of samples already collected. If the participant specifically withdraws consent for any use of samples, it must be documented in the site study records by the Investigator and the Investigator must inform the Local and Global Study Team. Destruction of any samples taken and not yet tested should be carried out in line with documented sample withdrawal wishes in conjunction with what was stated in the informed consent and local regulation.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if the participant 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 participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered as lost to follow-up.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Alexion personnel will not be involved in any attempts to collect vital status information.

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.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- If a participant fails to return to the clinic, or is otherwise unavailable, for a scheduled visit within the acceptable visit window, the site study staff must make a reasonable attempt to contact the participant/participant's caregiver/LAR to determine the reason for missing the appointment. The participant/ participant's caregiver will be advised to return to the investigational site for evaluation, if an AE is suspected to have occurred. In this event, the investigational site will make a reasonable attempt to obtain all relevant medical records, and enter relevant data in the eCRF, as appropriate.
- Unscheduled visits that occur outside the protocol-specified visits are permitted at the discretion of the Investigator. Results for procedures, tests, and assessments conducted during unscheduled visits will be documented on the eCRF.
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by Alexion or the Investigator, as per local health authority/ethics requirements.
- Safety/laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- See Section 10.2 for a listing of clinical laboratory tests.
- The maximum amount of blood collected from each participant for the central laboratory over the duration of the study, including any extra assessments that may be required, can be found in the Laboratory Manual.
- Instructions for the collection and handling of human biological samples will be provided in the study-specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality.
- Planned timepoints for all assessments are provided in the SoA.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Administrative and General/Baseline Procedures

8.1.1. Informed Consent

The Investigator, or qualified designee, must obtain a signed and dated ICF from each participant prior to conducting any study procedures. All efforts will be made to ensure participants are willing to comply with study participation prior to conducting the screening procedures. In cases where a participant develops a need for a legally authorized representative (LAR) during the study, the LAR can sign potential reconsents, as needed. See Section 10.1.3.

8.1.2. Screening/Rescreening

Screening will occur within CCI before Day 1. Laboratory tests outside of the normal ranges can be repeated without rescreening if within the screening window. Rescreening is allowed one time. The eligibility criteria are listed in Section 5. All screening assessments are indicated in the SoA (Section 1.3).

The participant may be considered a screen failure if not enrolled CCI after Screening, as disease status may change dramatically during the first few weeks of disease onset.

8.1.3. Inclusion/Exclusion Criteria

All inclusion (Section 5.1) and exclusion (Section 5.2) criteria must be reviewed by the Investigator or qualified designee to ensure the participant qualifies for study participation. Tests to determine eligibility are listed in the SoA (Table 2) and will be done locally at the site. In addition to standard screening laboratory tests (Table 12), disease-specific tests (ie, TB screening, HBV/HCV/HIV, ANAs, anti-GBM antibodies, IgG, IgM, and IgA) will be performed as necessary to rule out medical conditions that precludes study participation.

8.1.4. Participant Dosing Diary

Participants will receive a dosing diary to record GC and CCI intake. Compliance with the study interventions will be assessed by reviewing the participant's entries in the diary during each Clinic Visit. The results of the review need to be recorded in the source documents. If required, site personnel can contact the participant remotely using telecommunication technologies such as phone calls as needed to query maintenance of the study interventions.

8.1.5. Demographics

Demographic parameters, including age, sex, race, and ethnicity will be collected at Screening. All demographic information provided will be documented in the eCRF.

8.1.6. Medical History and Indication/Disease History

The Investigator will review the participant's history and diagnosis and document the following at the Screening Visit:

- Medical history including all relevant medical/surgical history
- Additional information as applicable

Any changes to medical history occurring during the Screening Period and prior to first dose of study intervention on Day 1 will be documented.

8.1.7. ANCA Test

At Screening, tests for PR3-ANCA and MPO-ANCA will be performed at local laboratory for study eligibility, if no historical data are available. If performing these tests at local laboratories is not feasible, analysis by the central laboratory may be considered. For the rest of the study visits starting at Day 1, quantitative (for example, ELISA, bead assay, etc.) tests for anti-PR3 and anti-MPO antibodies will be performed at the central laboratory.

8.1.8. ANAs, Anti-GBM Antibodies, C3, C4, IgM, IgA, and IgG

These tests are not needed if historical results are available within the past 6 months pre-screening. IgG should be done before first rituximab dosing for[CCI].

At Screening, these tests will be performed at local laboratory for study eligibility, if no historical data are available. Results from prior tests must be recorded in the EDC system. After Screening, IgG test will be performed centrally to monitor hypogammaglobulinemia.

8.1.9. TB Screening and Optional Chest Radiography

TB screening will be performed at local laboratory using only one of the following: interferon γ release assay (IGRA), tuberculin purified protein derivative (PPD) skin test, or chest radiography (done within [CCI] prior to Screening or done during Screening). Monitoring of TB reactivation is allowed per national or local guidelines.

Optional chest radiography may be performed if the Investigator determines pulmonary disease involvement needing further assessments.

8.1.10. HBV, HCV, and HIV Screening

Tests will be performed at local laboratory, if no historical data within the past[CCI] prior to the Screening visit are available. Results from prior tests must be recorded in the EDC system. Monitoring of HBV, HCV, and HIV reactivation during the study is allowed per national or local guidelines.

8.2. Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3).

8.2.1. 2022 ACR/EULAR Classification Criteria for Microscopic Polyangiitis (MPA) and Granulomatosis with Polyangiitis (GPA)

The 2022 ACR/EULAR classification criteria should be applied to classify a patient as having MPA or GPA when a diagnosis of small- or medium-vessel vasculitis has been made (Robson, 2022; Suppiah, 2022). Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria. A copy of the 2022 ACR/EULAR classification criteria (Section 10.8) will be provided to the site separately. Confirmation of pauci-immune glomerulonephritis on biopsy will not be required.

8.2.2. Birmingham Vasculitis Activity Score (BVAS)

The BVAS is a validated, clinician-completed tool used for the comprehensive multisystem clinical assessment of disease activity in systemic vasculitis (Mukhtyar, 2009; Oxford University Innovation, 2023a; Suppiah, 2011). A copy of the BVAS questionnaire and completion manual will be provided to the site separately.

The BVAS form will be completed at the time points specified in the SoA (Section 1.3). Individual BVAS items will be entered by the Investigator or designee in the EDC. eGFR can be used in lieu of creatinine clearance for the BVAS renal item. BVAS data recorded by Investigators will be adjudicated, according to an adjudication charter, before data finalization and unblinding. The adjudicated data will be used in the interim and final analyses.

BVAS assessment may be performed remotely. If there are any skin involvement, participants will be asked to send photos of the impacted area.

8.2.3. Disease Relapse

A relapse is defined as worsening of disease, after having previously achieved remission (BVAS = 0).

Relapse is defined as the following:

- 1 or more major item in the BVAS, or
- 3 or more minor items in the BVAS, or
- 1 or 2 minor items in the BVAS recorded at 2 consecutive study visits.

Major items of BVAS are indicated in bold italics in the completion manual. Participants who experience a relapse during the study may be treated with glucocorticoids at a dose and regimen according to the participant's condition. Refer to Section 6.1.2 for detailed guidance. These participants should continue to be followed in the study if possible.

In participants experiencing a relapse, the study-supplied prednisone may be temporarily halted during the IV and/or oral course of glucocorticoids; if the participant's condition stabilizes, the study-supplied prednisone may be restarted according to the original study visit schedule. The tarperprumig/matching placebo may also continue during the treatment for the relapse, or restarted when interrupted, at the discretion of the Investigator.

Occurrence of relapse will be continuously monitored after participants achieved first remission.

All other cases of BVAS > 0 after achieving BVAS = 0 and not defined above will be summarized separately and may be used for further efficacy analysis.

8.2.4. Vasculitis Damage Index (VDI)

The VDI (Exley, 1997; Oxford University Innovation, 2023b) will be used to document those features of vasculitis which are due to persistent damage. A copy of the VDI questionnaire and completion manual will be provided to the site separately. The VDI form will be completed at the visits specified in the SoA (Section 1.3). VDI data will be recorded in the EDC. VDI data will be adjudicated before finalization and unblinding according to an adjudication charter. The adjudicated data will be used in the interim and final analysis.

8.2.5. Health-Related Quality of Life Assessments

The Treating Physician will complete the PhGA at visits specified in the SoA (Section 1.3) to measure the overall response to treatment.

The EQ-5D-5L, AAV-PRO, PGI-S, and PGI-C will be completed by study participants at visits specified in the SoA (Section 1.3) to measure health-related quality of life. Proven translations will be used for non-English speaking patients, whenever possible. An administrator will facilitate completion of the questionnaires by the patients but will not complete the forms for the patients. The administrator will establish a rapport with the patient, emphasize the importance of completing the form, and serve to answer questions and address concerns. The questionnaires should preferably be completed by participants before seeing the Investigator at the visit.

Refer to the health-related quality of life (HRQoL) assessments completion manual.

8.2.6. Estimated Glomerular Filtration Rate (eGFR)

The eGFR will be calculated from serum creatinine measurements at all applicable study visits using the 2021 CKD EPI equation without race coefficient (Inker, 2021).

$$\text{eGFR} = 142 \times \min(\text{standardized } S_{cr}/K, 1)^{\alpha} \times \max(\text{standardized } S_{cr}/K, 1)^{-1.200} \times 0.9938^{\text{Age}} \times 1.012 \text{ [if female]}$$

where:

eGFR = estimated glomerular filtration rate in mL/min/1.73 m^2

S_{cr} = serum creatinine in mg/dL

K = 0.7 (females) or 0.9 (males)

α = -0.241 (females) or -0.302 (males)

min = indicates the minimum of S_{cr}/K or 1

max = indicates the maximum of S_{cr}/K or 1

Kidney function recovery is defined by an increase in eGFR from baseline of ≥ 15 mL/min per 1.73 m^2, which corresponds to a categorial change in CKD stage.

8.2.7. Urinary Measurements

For spot urine, a clean catch midstream urine sample will be collected according to instructions provided separately. The screening urine sample may be sent to the local laboratory, instead of the central laboratory, for proteinuria assessment, as well as a microscopic examination for RBC casts and RBC count to determine patient eligibility.

Starting on Day 1, the urine samples will be sent to the central laboratory for analysis. The following analyses will be performed according to the SoA:

- Urinalysis including blood, protein, and nitrites;
- Quantitative protein, albumin and creatinine measurements to calculate the urinary protein:creatinine ratio (UPCR) and the urinary albumin:creatinine ratio (UACR);

- Urinary biomarkers related to inflammation, the complement system, and other biomarkers may also be performed.

If a urinary dipstick test is positive for blood, nitrite, or protein, a microscopic assessment for RBC casts and RBC count will be performed at the local or central laboratory.

When microscopy is performed, hematuria will be categorized as follows: None, Occasional (Occ), 1 - 2, 3 - 5, 6 - 9, 10 - 15, 16 - 29, 30 - 49, 50 - 75, and >75 RBCs per HPF.

Proteinuria will be assessed by measuring the total protein, albumin and creatinine concentrations and calculating the UPCR and UACR. Results will be expressed as mg protein/g creatinine or mg albumin/g creatinine.

During inpatient admissions, optional 24-hour[redacted] biomarker samples may be collected in agreement with the participant and according to instructions provided separately.

Inflammation, complement, and other biomarkers will be measured using validated assay methodology.

8.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.3.1. Blood Sampling Volumes

The following procedures for blood collection will be adhered to:

- Number of attempts: The number of attempts for sampling blood is limited to 3 times per day. This means that after 3 punctures for collection of blood have been performed and no or insufficient blood could be collected, no other puncture will be done on the same day.
- Volume of blood samples: See details in the laboratory manual.
- EMLA (eutectic mixture of local anesthetics) cream/plaster: To minimize the possible pain and discomfort due to collection of blood, the Investigator may apply an EMLA cream/plaster at the puncture site.

8.3.2. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the general appearance, head, ears, eyes, nose, and throat, neck, lymph nodes, chest, heart, abdominal cavity, limb, CNS and musculoskeletal system. An abbreviated physical examination will include a body-system relevant examination based upon Investigator's (or qualified designee) judgment and participant symptoms. At least 1 body system must be checked for an abbreviated examination.
- The Investigator must pay special attention to clinical signs related to previous serious illnesses. For consistency, the physical examination should preferably be performed by the same qualified study staff at each visit.

8.3.3. Vital Signs

- Body temperature, HR, respiratory rate, and BP will be recorded (before blood collection for laboratory tests).
- BP and pulse measurements will be assessed 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 (sitting position) for the participant in a quiet setting without distractions (eg, television, cell phones). Ideally, the same arm for each participant should be used for measurements.
- For BP measurements, 3 consecutive BP readings will be recorded at intervals of at least 1 minute. The average of the 3 BP readings will be recorded.
- Height (at Screening only) and weight will also be measured and recorded.

8.3.4. Electrocardiograms

- Triplicate 12-lead ECG(s) will be obtained predose as outlined in the SoA (Section 1.3) using preferably an ECG machine that automatically calculates the heart rate and measures PR, RR, QRS, QT, and QTcF intervals.
- At each timepoint at which triplicate ECGs are required, 3 individual ECG tracings will be obtained as closely as possible in succession but no more than 2 minutes apart.

8.3.5. Clinical Safety Laboratory Tests

- See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE in the AE section of the eCRF. The laboratory results must be retained with source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during the study will be repeated until the values return to normal or baseline, or are no longer considered clinically significant by the Investigator, or the end of the Safety Follow-up Period, whichever comes first.
  - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator and the Medical Monitor, the etiology will be identified, and Alexion notified.
  - All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.3).
  - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are

considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be documented.

8.3.6. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria. Serum tests will be performed at Screening. All pregnancy tests will be performed locally.
- Pregnancy testing (urine or serum as required by local regulations) will be conducted for POCBP at time points specified in the SoA (Section 1.3).
- Pregnancy testing (urine or serum as required by local regulations) will be conducted at the end of relevant systemic exposure and correspond with the time frame for female participant contraception in Section 5.1 Inclusion Criteria.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3.7. Participant Safety Card

On Day 1 predose, participants will receive a Participant Safety Card that they must carry with them at all times until end of study. The Safety Card is provided to increase participant awareness of the risk of meningococcal infection, promote quick recognition and disclosure of any potential signs or symptoms of such an infection during the study, and to inform participants about actions that must be taken if they are experiencing these symptoms or signs.

At each Clinic Visit throughout the study, the study staff will ensure that the participant has the Participant Safety Card with them and review the information provided on the card.

8.3.8. Injection-Associated Reactions

Injection-associated reactions are a potential risk with the use of therapeutic protein products; these reactions can be nonimmune or immune mediated (eg, hypersensitivity reactions). Signs and symptoms injection-associated reactions may include headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, hypertension, lightheadedness, hypotension, palpitations, and somnolence. Signs and symptoms of hypersensitivity or allergic reactions may include hives, swollen face, eyelids, lips, or tongue, or trouble with breathing.

All injection-associated reactions will be reported to the Investigator and qualified designee. The Investigator and qualified designee are responsible for detecting, documenting, and recording events that meet the definition of AE or SAE and remain responsible for following up events that are serious, considered related to the study drug or study procedures, or that caused the participant to discontinue tarperprumig.

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

8.3.9. Injection Site Reactions

Injection site reactions (ISR) may occur with any agent administered SC. Monitoring for ISRs will be part of the routine safety assessments for this study. Injection-site reactions may include erythema, pruritus (itch), pain and bruising at the site of the administration of the study intervention. These local reactions are typically observed during or shortly after an injection but may occur with a delay of up to 2 or 3 days. Information on ISRs will be collected but only those that are judged by the Investigator to be clinically significant will be reported as AEs.

8.4. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Section 10.3.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs OR AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention/study (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's LAR).

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

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

All AEs will be collected from the signing of the ICF until the follow-up visit at the timepoints specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

All SAEs will be recorded and reported to Alexion or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3.4. The Investigator will submit any updated SAE data to Alexion within 24 hours of it being available.

The Investigator is not obligated to actively seek new information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has concluded participation in the study, and the Investigator considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify Alexion.

8.4.2. 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 nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.4.4. Regulatory Reporting Requirements for SAEs and Other Events

- Notification by the Investigator, within 24 hours of the Investigator becoming aware of the event, to Alexion of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention 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 a study intervention under clinical investigation. Alexion will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.
- Alexion is required to submit individual SUSAR reports (defined in Section 10.3.4) in the format of MedWatch 3500 or CIOMS I Form to health authorities and Investigators as required.
- In the EU, Alexion will comply with safety reporting requirements and procedures as described in the EU CTR 536/2014. All SUSARs to IMP will be reported to the EudraVigilance database within the required regulatory timelines.
- 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 participant safety.
- If the Investigator receives a safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from Alexion, they will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Alexion policy.

8.4.5. Medication Error, Abuse, and Misuse

Medication error, abuse, and misuse will be collected from the date when consent was obtained through the last visit or the last scheduled procedure shown in the SoA (Section 1.3).

8.4.5.1. Timelines

If an event of medication error, abuse, or misuse occurs during the study, the Investigator or other site personnel will report to Alexion or designee immediately but no later than 24 hours of when they become aware of it.

The full definitions and examples of medication error, abuse, and misuse can be found in Section 10.4.

8.4.5.2. Medication Error

Alexion defines a medication error as an unintended failure or mistake in the treatment process for an IMP or Alexion AxMP that either causes harm to the participant or has the potential to cause harm to the participant.

8.4.5.3. Medication Abuse

Alexion defines medication abuse as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or Alexion AxMP for a perceived reward or desired non-therapeutic effect.

8.4.5.4. Medication Misuse

Alexion defines medication misuse as the intentional and inappropriate use of IMP or Alexion AxMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or Alexion AxMP, outside the intended use as specified in the protocol, including deliberate administration of the product by the wrong route.

8.4.6. Exposure during Pregnancy and Breastfeeding

- Details of all pregnancies in participants able to give birth, if indicated, participants' partners able to give birth, or breastfeeding infants will be collected after the start of study intervention and until CCI after the last dose of study intervention.
- If a pregnancy or breastfeeding is reported, the Investigator will record pregnancy or breastfeeding information on the "Pregnancy/Breastfeeding Reporting and Outcome Form" and must submit it to Alexion GPS (within 24 hours) of learning of the participant or participant's partner (after obtaining the necessary signed informed consent from the participant's partner) pregnancy or infant's breastfeeding by email (ClinicalSAE@alexion.com) or facsimile (1-203-439-9347).
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication, abnormal pregnancy outcomes, or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE:
  - Female participant: any pregnancy-related AE or SAE will be reported in the eCRF and in the pregnancy form to Alexion GPS
  - Female partner of male participant: any pregnancy-related AE or SAE will only be reported in the pregnancy form to Alexion GPS
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs for both participants able to give birth and participant's partner able to give birth and will be reported as above.
- When the outcome of the pregnancy becomes known, the pregnancy form will be updated and submitted to Alexion GPS. The Investigator will collect follow-up information on the participant/pregnant partner, the pregnancy outcome, and the neonate at 3 months postpartum, and the information will be forwarded to Alexion.

- Any poststudy pregnancy-related SAE in the mother or SAE in the newborn, if considered reasonably related to the study intervention by the Investigator, will be reported to Alexion GPS as described above. While the Investigator is not obligated to actively seek this information in former study participants/pregnant partners, the Investigator may learn of an SAE through spontaneous reporting.
- Any participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.
- Any suspected adverse reactions which occur in infants during relevant exposure/following exposure to a medicinal product from breastmilk will be reported to Alexion GPS as described above using the "Pregnancy/Breastfeeding Reporting and Outcome Form" via email or facsimile.

8.5. Pharmacokinetics

- Serum samples will be collected for the determination of tarperprumig concentrations in serum as specified in the SoA (Section 1.3), according to applicable regulations.
- Additional samples may be collected at additional timepoints during the study, contingent upon the Investigator's discretion and Alexion's consent. The sampling schedule may be adjusted throughout the study in response to emerging data, such as to obtain data closer to the time of peak serum concentrations, to ensure optimal monitoring.
- Instructions for the collection and handling of biological samples will be provided in the laboratory manual. The actual date and time (24-hour clock time) of each sample will be recorded.
- All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, on inpatient dosing days samples obtained greater than ± 6 minutes of the nominal time for collections < 1 hour from dosing and >10% of the nominal time for collections ≥ 1 hour from dosing (eg, greater than 6 minutes of a 1-hour sample) will be captured as a protocol deviation. Samples collected on non-dosing days during the inpatient period will have a ± 2 hours collection window. For PK collections during an outpatient period, an hour-based collection window is not applicable. A protocol deviation will result when the exact date and time of PK sample collection is not recorded.
- Information pertaining to the concentration of study intervention that may compromise the study's blinding will not be disclosed to investigative sites or blinded personnel until the study has been completed and unblinded.
- For storage, handling, reuse, and destruction of biological samples, refer to Section 10.6 and/or the laboratory manual, as applicable.

8.6. Pharmacodynamics

- Serum samples will be collected for the measurement of specified PD markers (total properdin, free properdin, and serum complement functional activity [CCP, CAP, and CLP]) as outlined in the SoA (Section 1.3), according to applicable regulations.

- Additional samples may be collected at additional time points during the study, contingent upon the Investigator's determination and Alexion's concurrence.
- Instructions for the collection and handling of biological samples will be provided in the laboratory manual. The actual date and time (24-hour clock time) of each sample will be recorded.
- All efforts will be made to obtain the PD samples at the exact nominal time relative to dosing. A protocol deviation will occur when the exact date and time of PD sample collection is not recorded.
- Samples collected for analyses of tarperprumig (serum) concentration may be utilized for research purposes or to assess safety or efficacy aspects during or after the study.
- Results that may potentially unblind the study will not be disclosed to investigational sites or blinded personnel until the study has been fully unblinded.
- For storage, handling, reuse, and destruction of biological samples, refer to Section 10.6 and/or the laboratory manual, as applicable.

8.7. Genetics

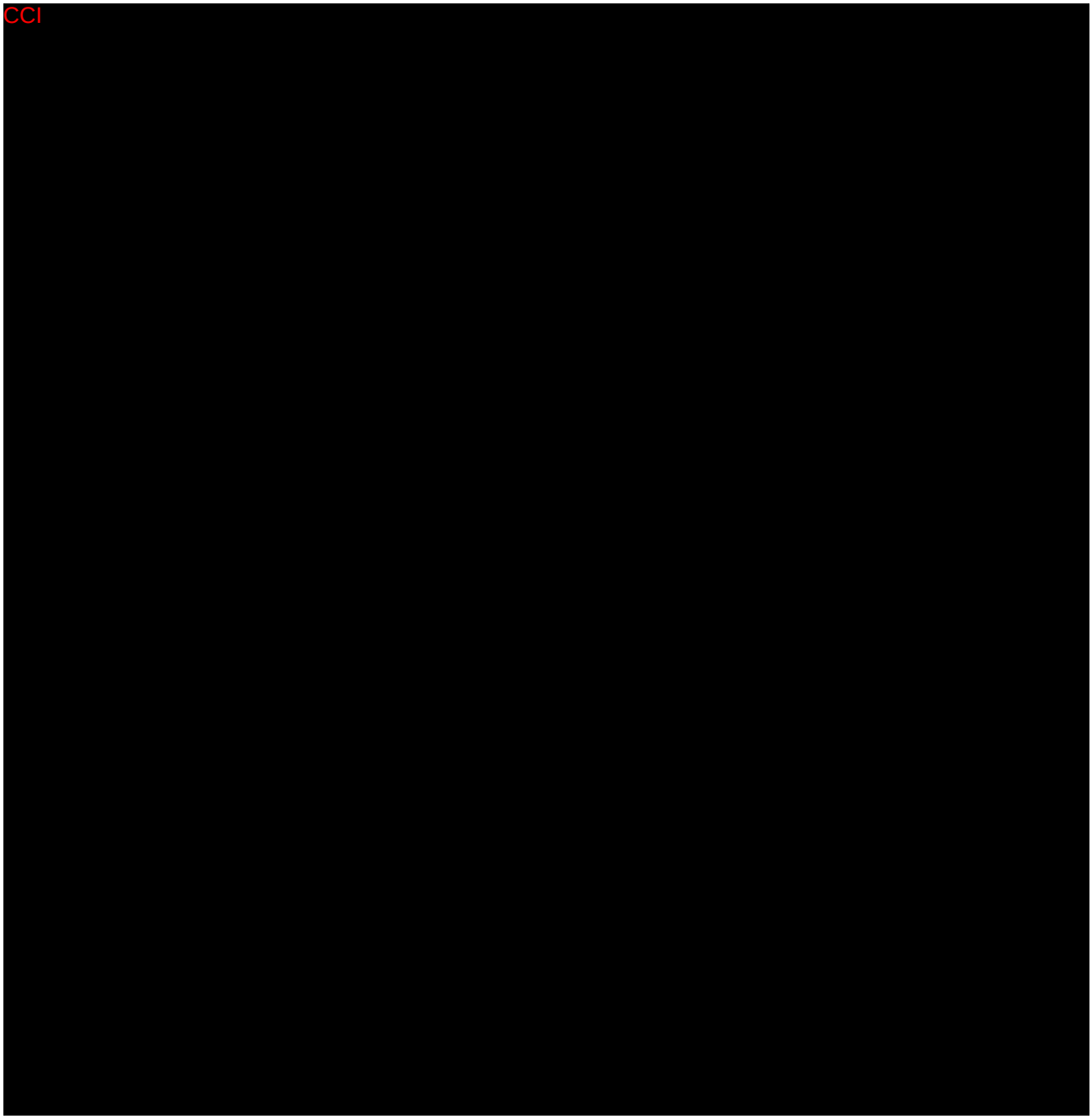
8.7.1. Optional Genetics Initiative

Collection of optional samples for Genomics Initiative research is also part of this study as specified in the SoA and is subject to participant agreement in the Optional Genetic ICF addendum.

Blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in genetic research may still participate in the study.

See Section 10.7 for inclusion criteria and information regarding the Genomics Initiative genetic samples including storage and destruction. Details on processes for collection and shipment and destruction of these samples can be found either in the appendices of this protocol or in the Laboratory Manual.

CCI



8.9. Immunogenicity Assessments

Serum samples for ADA analysis will be collected at timepoints according to schedule of activities (Section 1.3), All efforts will be made to obtain the immunogenicity samples at the exact nominal time relative to dosing. A protocol deviation will result when the exact date and time of immunogenicity sample collection is not recorded.

The detection and characterization of ADA to tarperprumig will be performed using a validated assay method by or under the supervision of Alexion. Antibodies to tarperprumig will be evaluated in serum samples collected from all participants according to the SoA (Section 1.3).

ADA positive samples will be further characterized for antibody titer. Samples may be stored as outlined in Section 10.6. Additional analyses may be performed on collected ADA samples for further analysis or characterization.

ADA results that may unblind the study will not be reported to investigational sites or blinded personnel until the study has been unblinded.

For storage, handling, reuse, and destruction of biological samples, refer to Section 10.6 and/or the laboratory manual, as applicable.

8.10. Medical Resource Utilization and Health Economics

Medical resource utilization associated with medical encounters, will be collected in the eCRF by the Investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected will be used to conduct exploratory economic analyses and will include the following:

- Number of inpatient admissions by 26 and 52 weeks
- Duration of hospitalizations by Week 52
- Number of outpatient medical encounters (including physician or emergency room visits) by 26 and 52 weeks

9. STATISTICAL CONSIDERATIONS

Statistical methods for this study will be further detailed in a separate SAP. This section is a summary of the planned statistical analyses of the most important endpoints. The study unblinding will occur when all participants complete the 52-week Double-Blind Treatment Period.

9.1. General Considerations

Summary statistics will be computed and displayed by treatment group and by visit, where applicable. Descriptive statistics for continuous variables will minimally include the number of participants, mean, 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.

9.1.1. Decision Criteria/Statistical Hypotheses

The primary objective is safety and tolerability of tarperprumig. All safety endpoints will be summarized descriptively on the Safety Set (SS) from all three treatment groups. No statistical inference will be performed for safety endpoints.

9.1.2. Multiplicity Adjustment

No multiple testing adjustment is performed for this study.

9.2. Analysis Sets

The analysis sets are defined in Table 11.

Table 11: Analysis Sets

Population	Description
Screened Set	All consented participants.
Enrolled Set	All consented participants excluding screen failures.
Safety Set (SS)	All randomized participants who receive at least 1 dose (full or partial) of study intervention. Participants will be analyzed according to the study intervention received.
Full Analysis Set (FAS)	All randomized participants who receive at least 1 dose (full or partial) of the study intervention. Participants will be analyzed as randomized.
Pharmacokinetic Analysis Set (PKAS)	All randomized participants who receive at least 1 dose (full or partial) of the study intervention and who have at least 1 measurable PK value.
Pharmacodynamic Analysis Set (PDAS)	All randomized participants who receive at least 1 dose (full or partial) of the study intervention and who have at least 1 measurable PD value.
Immunogenicity Analysis Set (IAS)	All participants who receive at least 1 dose (full or partial) of study intervention and have at least 1 reportable postdose result in the ADA assay. Participants will be analyzed according to the study intervention received.

Abbreviations: ADA = antidrug antibody; PD = pharmacodynamic(s); PK = pharmacokinetic(s)

9.3. Statistical Analyses Supporting Primary Objective(s)

9.3.1. Primary Endpoints

Safety and tolerability of tarperprumig in participants with ANCA-associated vasculitis will be evaluated as the primary objective for the study. All safety analyses will be performed on the SS in all 3 treatment groups. Safety endpoints will include all TEAEs, ECGs, clinical laboratory tests, physical examinations, and vital sign measurements. In addition, all concomitant medication will be coded using the World Health Organization Drug Dictionary and summarized using descriptive statistics.

9.3.1.1. Adverse Events

TEAEs are defined as those AEs with onset or existing events that worsen in severity from the initiation of study intervention dosing through 5 half-lives after last dose. AEs occurring from time of consent up to prior to dosing will be analyzed as predosing AEs. All AEs will be coded using the latest available version of MedDRA at the time of analysis and will be summarized overall, by SOC and PT, by severity, and by relationship to study interventions (ie, IMPs as well as AxMPs).

The incidence of TEAEs, TEAEs by relationship and severity, TEAEs leading to withdrawal from the study, TEAEs leading to study intervention discontinuation, and TESAEs will be summarized by treatment group and overall. Detailed by-participant listings of TEAEs, TESAEs, related TEAEs, and TEAEs leading to withdrawal from the study will be provided. Participants having multiple AEs within a category (eg, overall, SOC, PT) will be counted only once in that category. For severity tables, a participant's most severe event within a category will be counted.

9.3.1.2. Vital Signs

Observed values and changes from baseline in vital signs will be summarized descriptively by treatment group at baseline and postbaseline timepoints wherever applicable.

9.3.1.3. Clinical Laboratory Tests

Observed values and changes from baseline in clinical chemistry and hematology will be summarized descriptively by treatment group at baseline and at each postbaseline timepoint. For laboratory results that can be classified as normal, low, or high based on normal range values, shifts from baseline in classification will be summarized for all study visits.

9.3.1.4. 12-lead ECG

The ECG parameters will be measured at the specified time points, including heart rate, PR, RR, QRS, QT, and QTcF intervals. The average of the triplicate ECG readings at the time points collected will be calculated, and changes from baseline values will be assessed by treatment group.

An outlier analysis will be performed that will summarize the absolute count, frequency and percentage of participants who meet any of the following outlier criteria at each visit by treatment group:

- QT, QTcF interval > 450 msec

- QT, QTcF interval > 480 msec
- QT, QTcF interval > 500 msec
- QT, QTcF interval increases from baseline > 30 msec
- QT, QTcF interval increases from baseline > 60 msec

Analysis of drug-related QT/QTc interval changes relative to serum PK concentrations may be conducted on all dose regimens.

9.3.1.5. Physical Examination

Adverse changes from baseline in physical examination findings will be classified as AEs and analyzed accordingly.

9.4. Analyses Supporting Secondary Objectives

All secondary objectives are for efficacy evaluation. All statistical inferential analyses will be based on the pooled FAS from Treatment Group 1 and Treatment Group 2 (referred to as tarperprumig +CCI versus Treatment Group 3 (referred to as placebo +CCI . All summary tables with descriptive statistics will be based on the 3 treatment groups individually. Only nominal p-values will be reported.

BVAS and VDI data recorded by Investigators will be adjudicated according to an adjudication charter (Section 10.1.6), before data finalization and unblinding. The adjudicated data will be used in the final analysis.

9.4.1. Estimand for Achieving Disease Remission at Week 26

The clinical question of interest with respect to efficacy at Week 26 is: What is the treatment effect of tarperprumig compared to placebo on achieving disease remission at Week 26 in participants with ANCA-associated vasculitis who are receiving theCCI ?

The estimand is described by the following attributes:

1. Population: All adult participants meeting the inclusion and exclusion criteria in Section 5.
2. Endpoint: Achieving disease remission at Week 26, defined as BVAS=0 at Week 26 and no prescribed GCs for treatment of ANCA-associated vasculitis within 4 weeks prior to Week 26).
3. Treatment of interest: Tarperprumig +CCI or placebo +CCI (for details please refer to Section 6). Participants from the two tarperprumig treatment groups will be pooled for analysis.
4. Handling of ICEs. The composite strategy will be used. ICEs include death, use of rescue medication (eg, cyclophosphamide), kidney transplant, and dialysis. Participants with the ICEs occurring prior to Week 26 will be considered as not achieving disease remission at Week 26.
5. Summary measure: Difference in the proportion of participants who achieve disease remission at Week 26 between tarperprumig +CCI and placebo CCI.

The treatment difference in the proportion of participants who achieve disease remission at Week 26, between tarperprumig + CCI and placebo + CCI will be estimated using the Mantel-Haenszel estimator with strata defined by stratification factors at randomization. The 95% confidence interval (CI) and Wald test statistic will be constructed using Sato (Sato, 1989) variance estimate. The 95% Wald confidence interval for the proportion of participants who achieve disease remission at Week 26 for each treatment group will be based on the sample variance.

9.4.2. Estimand for Achieving Sustained Remission at Week 52

The clinical question of interest with respect to efficacy at Week 52 is: What is the treatment effect of tarperprumig compared to placebo on achieving sustained remission at Week 52 in participants with ANCA-associated vasculitis who are receiving the CCI ?

The attributes for this estimand and the analytical method are the same as the estimand in Section 9.4.1, except that the endpoint is achieving sustained remission at Week 52, defined as BVAS = 0 at Week 26 without relapse to Week 52 and no prescribed GCs for treatment of ANCA-associated vasculitis within 4 weeks prior to Weeks 26 and 52.

9.4.3. Other Secondary Endpoints

For the following binary endpoints, descriptive summary statistics will be presented by treatment groups.

- Achieving BVAS = 0 at CCI 26, 52.
- Relapse after previously achieving disease remission at Week 26.

For continuous endpoints of BVAS, VDI, eGFR, UPCR, UACR and hematuria, the observed value, change from Baseline and % change from Baseline, if appropriate, will be summarized using descriptive statistics by treatment group at all scheduled visits.

For time to first relapse after having achieved disease remission at Week 26, and time to first occurrence of BVAS = 0, participants without the event will be censored at the last follow-up date. Missing data will not be imputed. The number of participants with events and participants who are censored will be presented. Kaplan-Meier method will be used to estimate the 25th percentile, median and 75th percentile time to event for the treatment groups.

9.5. Exploratory Endpoint Analysis

All exploratory endpoints will be summarized for the treatment groups at all designated visits. The exploratory analyses will be descriptive in nature and will be based on the FAS. Full details for exploratory analysis are included in the SAP.

9.6. Safety Analyses

Refer to Section 9.3.1.

9.7. Other Analyses

Not applicable.

9.7.1. Pharmacokinetic and Pharmacodynamic Analyses

The PK and PD analyses will include all data in the PKAS and PDAS, respectively.

Graphs of mean serum tarperprumig concentration-time profiles and graphs of serum concentration-time profiles for individual participants will be provided. Descriptive statistics will be calculated for serum concentration data at each sampling time, as appropriate.

The PD effects of tarperprumig will be evaluated by the absolute values and changes and percentage changes from Baseline, as appropriate. Descriptive statistics will be calculated for the PD data at each sampling time, as appropriate.

9.7.2. Immunogenicity Analyses

All immunogenicity analyses will be performed on the IAS. Immunogenicity variables include ADA status categories, ADA response categories, ADA incidence; and ADA titer will be summarized over the duration of the study. Definitions of the ADA status and response categories will be provided in the SAP. ADA status and ADA response categories as listed below will be summarized as absolute occurrence (n) and percentage of all participants.

- ADA status categories
  - ADA negative
  - ADA positive
- Participants who are ADA positive will be further categorized into ADA response:
  - Pre-existing immunoreactivity
  - Treatment-emergent ADA responses
  - Treatment-boosted ADA responses
- Participants with a treatment-emergent or treatment-boosted ADA response will be further categorized as follows:
  - Persistent responses
  - Indeterminate responses
  - Transient responses

9.7.3. Subgroup Analyses

Subgroup analyses will be conducted for the first 2 secondary efficacy endpoints, ie, ‘achieving disease remission at Week 26’, and ‘achieving sustained remission at Week 52’. Subgroup factors will include (but not limited to) the following:

- Age at Study entry: ≤ 55 or > 55 years
- Sex: female or male
- ANCA-associated vasculitis type: GPA or MPA
- ANCA type: PR3-ANCA or MPO-ANCA
- Disease status: newly diagnosed or relapsing

- Disease location at Baseline: any renal involvement vs only non-renal
- BMI: < 30 or ≥ 30 kg/m^2
- Baseline eGFR: < 50 or ≥ 50 mL/min/1.73 m^2
- Baseline UACR: < 30, ≥ 30 to ≤ 300, or > 300 mg/g
- Baseline hematuria: < 10 RBCs/HPF or ≥ 10 RBCs/HPF
- Baseline BVAS: < 15 or ≥ 15

Given that the number of participants in some subgroups may be limited, subgroup categories may be combined or redefined as appropriate. Otherwise, the subgroup analysis may not be performed if deemed infeasible based on sample size. Forest plots will be used to present the estimated treatment effect on subgroups and the associated 95% CIs for the secondary endpoints, when appropriate. A full list of subgroups and further details on the statistical analysis will be provided in the SAP.

9.8. Interim Analyses

Two optional interim analyses are planned for the study. Investigators, participants, and the study team who are involved in the conduct of the study will remain blinded to individual treatment assignments until the end of the 1-year Double-Blind Treatment Period. Enrollment will not be paused during the interim analyses.

CCI [redacted]

CCI [redacted] An independent iDMC (Section 10.1.6) and a separate unblinded review committee (independent from the study team) will evaluate safety, PK/PD, plasma, and urine complement inhibition data.

CCI [redacted]

9.9. Sample Size Determination

The sample size for this study is based on safety and tolerability consideration. The planned sample size of approximately 75 eligible participants will be enrolled and randomized in a 1:1:1 ratio into 3 treatment groups (25 per arm). A sample size of 25 per arm is considered adequate to characterize safety and tolerability. The sample size per arm provides a reasonable level of precision for estimating incidences of adverse events. Using a binomial confidence interval method (e.g., the Wilson score approach), a sample size of 25 participants per arm is expected to yield 95% confidence interval half-widths of approximately ± 10% at an event rate of 5% and ±18% for event rates of 40%.

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 with 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, revised protocol, ICF, Investigator's Brochure, 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.
- Any substantial amendments to the protocol impacting study design will require IRB/IEC and applicable regulatory approval before implementation, except for changes necessary to eliminate an immediate hazard to study participants.

  Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

  Alexion will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with Alexion.
- The Investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures per local regulations
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, EU CTR 536/2014 for clinical studies conducted in the EU, EU MDR 2017/745 for clinical device research, and all other applicable local regulations
- Reporting of serious breaches:
  - A "serious breach" means a deviation of the approved version of the protocol or GCP that is likely to affect the safety, rights of a participant and/or the data reliability and robustness to a significant degree in the clinical study.

- All parties (Alexion, Service Provider, Investigator, Site Staff) involved in the conduct of the clinical study:
  - are responsible for immediately identifying and documenting any actual or potential serious breach.
  - must have a process in place to ensure that they are able to identify the occurrence of a (actual/potential) serious breach.
  - must report to Alexion (or delegated party) without delay, through the contacts (email address or telephone number) provided by Alexion.

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 informed consent from all study participants prior to performing any study-related procedures including screening assessments.
- The Investigator or designee will explain the nature of the study (including but not limited to the study objectives, potential benefits and risks, inconveniences, and the participant's rights and responsibilities) to the participant, defined according to local and country regulations where the study is taking place, and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, EU General Data Protection Regulation (GDPR), ICH GCP guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The participant's medical record must include a statement that signed informed consent was obtained before the participant was enrolled in the study and the date the consent was obtained. The authorized person obtaining the informed consent must also sign the ICF form(s).
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the signed informed consent documentation (ie, a complete set of participant information sheets and fully executed signature pages) must be provided to the participant or their legal guardian/LAR, as applicable. This document will require translation into the local language. Original signed consent forms must remain in each participant's study file and must be available for verification at any time.

A participant who is rescreened is not required to sign another ICF (unless a new version is available since their initial screening) if the rescreening occurs within 30 days from the previous ICF signature date.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature may be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4. Recruitment Strategy

Participants will be identified by qualified research staff. This may be done through a review of medical records, external referrals or using databases. Recruitment strategies may include study posters, referral letters, recruitment brochures, advertisements, social media posts, and websites, where permitted by local regulations. All recruitment materials will be submitted to local IRB/IEC as required, for review and approval for use.

10.1.5. Data Protection

- Participants will be assigned a unique identifier by Alexion or designee. Any participant records or datasets that are transferred to Alexion will contain the identifier only; participant names, initials, full date of birth, or any information which would make the participant identifiable will not be transferred.
- Participants must be informed about the uses of their personal study-related and coded (pseudonymized) data, who will have access to their personal data, how and how long it will be used, and that it will be used by Alexion in accordance with local data protection law. In addition, multiple local laws require that participants must also be informed of any individuals rights they may have with regard to their personal data.
- Participants will be informed about how their personal study-related data will be disclosed and are provided with the appropriate legal basis for which a controller processes their personal data. The level of disclosure, the security controls used to protect their data, and information regarding any transfer of their personal data outside of their country or region must also be explained to the participant.
- Participants 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, any third parties acting on behalf of Alexion, and by inspectors from regulatory authorities.
- Alexion and the site as a data controller has implemented privacy and security controls designed to help protect participant personal data, including information security controls, firewalls, incident detection, and secure transfer measures.
- The contract between Alexion and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.

- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- The EU GDPR defines pseudonymization as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organizational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.
- Appropriate safeguards will be implemented to protect coded data during and after the study that include:
  - Access to the coded data will be limited to specific individuals subject to confidentiality obligations (including the obligation to not attempt to re-identify individuals/decode the clinical data).
  - The coded data will be protected with security measures to avoid data alteration, loss, and unauthorized accesses and further de-identification techniques may be applied.
  - A data protection impact assessment (DPIA), where required, will apply to identify and mitigate privacy risks, if any, associated with each scientific research.
  - The coded data will not be shared for direct marketing purposes or other purposes that are not legal duties or are not considered scientific research according to the applicable data protection legislation. In particular, it will not be used to make decisions about future services available to the participant, such as insurance.
- In addition to having the participants' data and biosamples coded, the data are also protected by high-standard technical security means, such as strong access control and encryption.
- Participants are also protected legally by the following means if the level of disclosure of the coded data includes sharing of the latter with other third parties, as the participants will be explained in the ICF:
  - The participants' coded data are protected by contractual arrangements, Codes of Conduct, or certifications that set the rules for personal information protection to those available in European countries or other alternatives set forth in the law, as well as any supplementary technical and organizational measures that may result out of conducted transfer impact assessments.
- Reporting of personal data breaches:
  - A "personal data breach" means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data transmitted, stored or otherwise processed.

  - Alexion must be notified of any data breach (including if a data breach compromises the integrity, confidentiality, or availability of the personal data of participants) within 24 hours of the Investigator becoming aware of the event.

- In certain regions/countries, Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
- The Investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the Investigator/institution are able to identify the occurrence of a personal data breach.
  - A data breach is reported to Alexion or delegated party, through the contacts (email address or telephone number) provided by Alexion, within 24 hours of the Investigator becoming aware of the event.
  - Alexion and the site have taken all necessary steps to avoid personal data breaches and have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining, and keeping systems and information technology (IT) security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).
  - Both Alexion and the study site have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
  - In compliance with applicable laws, the data controller for the processing activity where the personal data breach occurred (Alexion or respectively the study site) will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
  - If participants need to be notified of a personal data breach, the notification is done by the site for the data breaches that occurred within the processing activities for which the site is the data controller. For data breaches that occur within the processing activities of Alexion as the data controller, the notification is done in collaboration with the site and is performed by the site and/or Investigator, acting on behalf of Alexion, so that Alexion has no access to the identifying personal information of the participants. The site and/or Investigator shall conduct the notification by contacting the participants using the information that they gave for communication purposes in clinical research.
  - If a personal data breach occurs in a processor's systems, engaged by Alexion, the processor under contractual obligations with Alexion promptly and in due course after discovering the breach notifies Alexion and provides full cooperation with the investigation. In these cases, to the extent Alexion is the data controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to participants. If the personal data breach needs to be notified to the participants, the notification to participants is done in collaboration with the site and is performed by the site

and/or Investigator, acting on behalf of Alexion, so that Alexion has no access to the identifying personal information of the participants.

  - If a personal data breach involving an Alexion's representative device (eg, Study Monitor laptop, the Alexion representative will provide Alexion with all of the information needed for notification of the breach, without disclosing data that allows Alexion directly or indirectly to identify the participants. The notification will be done by Alexion solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of reidentification of the participants. If the data breach must be notified to the data participants, the notification will be done directly by the Study Monitor in collaboration with the site and/or Investigator, acting on behalf of Alexion, so that Alexion has no access to the identifying personal information of the participants. The contract between Alexion and the Study Monitor shall expressly specify these conditions.
  - The contract between the study site and Alexion for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and participants, where applicable.

- The Coordinating Investigator will be identified among the enrolling Investigators during the course of the study and will be responsible for reviewing the CSR and confirming that it accurately describes the conduct and results of the study.

10.1.6. Committees Structure

An iDMC, comprising experts in relevant fields with no direct relationship to the study, will be appointed by Alexion or designee. In this study, the iDMC will be responsible for review of safety and other relevant study data. The specific responsibilities of the iDMC and a schedule of meetings will be described in the iDMC Charter.

An Adjudication Committee, comprising experts in relevant fields with no direct relationship to the study, will be appointed by Alexion or designee. In this study, the Adjudication Committee will be responsible for adjudication of BVAS and VDI data recorded by the Investigators. The specific responsibilities of the Adjudication Committee and a schedule of meetings will be described in the Adjudication Committee Charter.

10.1.7. Dissemination of Clinical Study Data

Study participants will be provided the option of receiving their individual study data after the end of the study. Management of dissemination and process for providing this option may be found in the study data management or individual participant data return plan in accordance with Alexion policies, laws, and regulations.

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. However, posting of study results per local regulations may be deferred to a later date for one of the following reasons:

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

10.1.8. Data Quality Assurance

- All participant 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 physically or electronically signing the eCRF.
- Guidance on completion of eCRFs will be provided in the eCRF Completion Guidelines.
- 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 documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- Alexion or designee is responsible for the data management of this study, including quality checking of the data.
- Alexion assumes accountability for actions delegated to other individuals (eg, CRO).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator as per country-specific requirements after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Alexion. No records may be transferred to another location or party without written notification to Alexion. Clinical study documents and records required as part of the Trial Master File (TMF) are archived and stored by Alexion for at least 30 years.

10.1.9. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site. The Investigator or designee will prepare and maintain adequate and accurate source documents (eg, medical records, ECGs, AE and concomitant medication reporting, raw data collection forms) designed to record all observations and other pertinent data for each participant.

- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. eCRF s must be completed by the Investigator or designee as indicated in the site delegation log. Source documents are filed at the investigational site. The Investigator may need to request previous medical records or transfer records, depending on the study and per local regulations, if applicable. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the Monitoring Plan.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Alexion or designee will perform source data verification for a sample of sites, participants, and data, which will be selected in a risk-based fashion as per the Medical Oversight Plan(s), to confirm that data entered into the eCRF by authorized site personnel are verifiable from source documents.
- Alexion or designee will perform ongoing source data review as per the Monitoring Plan to confirm that data in source are accurate and complete; that the safety and rights of participants 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.
- 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.

10.1.10. Study and Site Start and Termination/Closure

Study Start

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site activation and will be the study start date.

Study/Site Termination

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected 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 or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
- Total number of participants included earlier than expected

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 the study intervention to participants enrolled or continuing in the study
- Alexion decision to suspend or discontinue testing, evaluation, or development of the study intervention

If the study is prematurely terminated or suspended, Alexion shall inform the Investigators, the IECs/IRBs, the 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, within 24 hours. The Investigator shall inform the participant within 24 hours of study termination and will assure appropriate participant therapy and/or follow-up.

10.1.11. Publication Policy

Alexion strives to publish results from all research studies regardless of whether the findings are positive, negative, or inconclusive, or whether the product is investigational, licensed, or has been discontinued or withdrawn from the market. The minimum commitment is to all Phase 2 and Phase 3 clinical studies. Alexion also commits to publish other studies of significant scientific or medical importance including, but not limited to Phase 1 clinical studies, discovery, research, epidemiology, and health economics and outcomes research.

- For registration studies, journal submission of primary manuscripts must be within 12 to 18 months of study completion. Study completion is defined as data availability for primary endpoints following completion of the clinical study as defined in the protocol. In the case of early phase studies and research studies involving investigational products, submission may be delayed to protect intellectual property. In the case of discontinued investigational programs, study completion is defined as the time of data availability following termination of the program.
- 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 IP. All publications describing the results of Alexion sponsored studies (including Investigator-led analyses, as well as Investigator-initiated studies) shall be reviewed by the IP team at advanced draft stage in order to ensure IP protection.

- 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, the ICMJE (www.icmje.org) recommendations, and per the Alexion/AstraZeneca 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 ICMJE authorship guidelines as well as journal- and congress-specific guidelines and requirements (as applicable) and per the Alexion/AstraZeneca Publication Policy. Authors must meet all four ICMJE authorship criteria to qualify for authorship. The relative order of authors will be determined by consensus among the authors.
- Alexion will make reasonable efforts to publish Plain Language Summaries of abstracts of selected manuscripts and poster presentations based upon accepted criteria, and include participants and/or caregivers as reviewers for readability and understanding of lay person language.
- No compensation shall be provided to external Authors for authorship of publication, including drafting or revising a publication. Alexion may reimburse the presenting Author of an Alexion-supported publication for travel, lodging, and registration to present a poster or oral presentation at scientific meeting, consistent with the Alexion Global Procurement and Sourcing Procedure, the Alexion Antibribery Anticorruption Policy, and the Alexion Global Travel and Expense Policy.
- Fair market value compensation may be provided for needed preidentified services, such as statistical analyses, additional research or professional medical writing support, provided by Alexion pursuant to an executed contract.
- Authors must disclose financial or personal affiliations that could be considered a conflict of interest in the publication.
  - Investigators who participate as authors in manuscripts derived from Alexion sponsored studies will agree to the prerequisites as outlined in the Alexion Author Letter of Agreement prior to engaging in manuscript development.
- More details are provided in the Alexion/AstraZeneca Publication Policy.
- Medical publications are developed free of commercial influence. Publications cannot be developed with the intent to promote off-label use of a product or to unduly influence prescribers.

- Proposed publications should not be duplicative or redundant with prior publications unless there is a compelling medical/scientific need to reanalyze, reinterpret, or translate the prior publication.

10.2. Clinical Laboratory Tests

Table 12: Laboratory Tests

Laboratory Tests	Parameters	
Hematology	Platelet count	
	Red blood cell (RBC) count	
	RBC indices	• Distribution width • Mean corpuscular volume • Mean corpuscular hemoglobin • Percentage of reticulocytes
	White blood cell (WBC) count with differential:	• Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
	CCI [redacted]	
	Hemoglobin	
	Hematocrit	
	Haptoglobin	
	Coagulation panel	• International normalized ratio (INR) • Prothrombin time • Activated partial thromboplastin time (aPTT)

Table 12: Laboratory Tests

Laboratory Tests	Parameters	
Clinical chemistry[a]	• Alanine aminotransferase • Albumin • Alkaline phosphatase • Aspartate aminotransferase • Bicarbonate • Blood urea nitrogen • Calcium • Chloride • C-reactive protein • Gamma-glutamyltransferase	• Glucose • Lactate dehydrogenase • Magnesium • Phosphorus • Potassium • Creatinine and eGFR calculated using CKD-EPI formula • Sodium • Total and direct bilirubin • Total protein • Uric acid • Cholesterol/HDL ratio • HDL-C • LDL-C
Routine urinalysis (spot urine, refer to Section 8.2.7)	• Appearance • Bilirubin • Blood • Color • Creatinine • Glucose • Ketones	• Nitrite • pH • Protein • Albumin • Protein creatinine ratio • Albumin creatinine ratio • Specific gravity • Urobilinogen • Microscopic examination (if blood or protein is abnormal)
Other study specific tests	• ANAs, anti-GBM antibodies, C3, C4, IgM, IgA, IgG • ANCA test (PR3-ANCA and MPO-ANCA) • Serum or urine human chorionic gonadotropin pregnancy test (as needed for CBP participants)[b] • Follicle-stimulating hormone (as needed in NCBP participants only) • TB monitoring by one of the following methods: interferon γ release assay (IGRA), tuberculin purified protein derivative (PPD) skin test, or chest radiography • HIV antibody, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBcAb), HBV DNA (if required), HCV antibody, and HCV PCR viral load, as needed • All study-required laboratory tests will be performed by a central laboratory (unless otherwise specified), and with the exception of tests for Screening which would be done locally at the site (see Section 8.1.2).	

Table 12: Laboratory Tests

[a] All events of ALT or AST ≥3 × upper limit of normal (ULN) and total bilirubin ≥2 × ULN (> 35% direct bilirubin) or ALT or AST ≥3 × ULN and international normalized ratio (INR) > 1.5 (if INR measured), which may indicate severe liver injury (possible Hy's law), must be reported to Alexion in an expedited manner (excluding studies of hepatic impairment or cirrhosis)

[b] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Abbreviations: ANA = anti-nuclear antibody; ANCA = anti-neutrophil cytoplasmic antibody; C = complement; Ig = immunoglobulin; CBP = childbearing potential; CKD-EPI = Chronic Kidney Disease-Epidemiology Collaboration; eGFR= estimated glomerular filtration rate; HBV= hepatitis B virus; HCV= hepatitis C virus; HDL= high-density lipoprotein; LDL = low-density lipoprotein; MPO = myeloperoxidase; NCBP = nonchildbearing potential; PR3 = proteinase 3

10.3. AEs and SAEs: 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 clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

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, or more severe than expected for the participant's condition).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention 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 will be reported regardless of sequelae.
- 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 clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events not Meeting the AE Definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- 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).
- 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.
- Pregnancy itself is not an AE. However, any pregnancy complications, abnormal pregnancy outcomes, or elective termination due to medical reasons will be reported as an AE or SAE. Cases of pregnancy that occur during maternal or paternal exposure to study intervention are to be reported within 24 hours of Investigator/site awareness. Data on fetal outcome and breastfeeding will be collected for regulatory reporting and safety evaluation.
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- 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.
- "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 clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil 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, meets one or more of the criteria listed:

a. Results in death

b. Is life-threatening

The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (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 will be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant 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) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment will be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events will 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, convulsions not resulting in hospitalization, or development of drug dependency or medication abuse.

Definition of SUSAR

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

An event that is serious, that has at least a reasonable possibility as being related to the IMP as assessed by the Investigator and/or Alexion, and is not listed in the appropriate Reference Safety Information (IB).

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 regional, national, and local regulatory reporting requirements, as applicable.

10.3.3. Recording and Follow-up of AE and/or SAE

10.3.3.1. AE and SAE Recording

- 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 participant'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 participant identifiers, with the exception of the participant 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.

10.3.3.2. 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 5 categories from National Cancer Institute Common Terminology Criteria for Adverse Events (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

10.3.3.3. Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship as either "related" or "not related."
  - **Related:** Causality of "related" is made if following a review of the relevant data, there is evidence for a "reasonable possibility" of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.
  - **Not related**: The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as "not related."
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessment, the Investigator will also consult the IB and/or product information, for marketed products.
- The Investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. 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 their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.3.4. 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 healthcare professionals.
- If a participant 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 submitted documents.
- 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

- The primary mechanism for reporting an SAE to Alexion will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE Report Form to report the event to Alexion GPS within 24 hours.
  - The Investigator must complete, sign, and date the SAE pages, verify accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy via email or facsimile to the contact information provided below.
  - All paper forms and follow-up information submitted to Alexion must be accompanied by a cover page signed by the Investigator.
  - Contacts for paper SAE reporting:
    - Email: clinicalSAE@alexion.com or Fax: +1.203.439.9347
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form as described above.

10.4. Medication Error, Abuse, and Misuse

Medication Error

Alexion defines medication error as an unintended failure or mistake in the treatment process for an IMP or Alexion AxMP that either causes harm to the participant or has the potential to cause harm to the participant.

Any events of medication error, with or without associated AEs, are to be captured and forwarded to Alexion Global Patient Safety via email or facsimile (clinicalsae@alexion.com or + 1.203.439.9347) using the Alexion Clinical Study Medication Error Report Form.

A medication error is not lack of efficacy of the study intervention, but rather a human or process related failure while the intervention is under the control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Medication name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant
- Medication not administered as indicated, eg, wrong route or wrong site of administration
- Medication not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Medication not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong participant received the medication
- Wrong medication administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which led to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed medication dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose [refer to Section 6.8 for information on overdose])
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Medication Abuse

Alexion defines medication abuse as the persistent or sporadic intentional, nontherapeutic excessive use of IMP or Alexion AxMP for a perceived reward or desired nontherapeutic effect.

Any events of medication abuse, with or without associated AEs, are to be captured and forwarded to Alexion Global Patient Safety via email or facsimile (clinicalsae@alexion.com or + 1.203.439.9347) using the Alexion Clinical Study Drug Misuse or Drug Abuse Report Form. This form will be used both if the medication abuse happened in a study participant or if the medication abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of medication abuse include but are not limited to:

- The medication is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The medication in the form of a tablet is crushed and injected or snorted with the intent of getting high

Medication Misuse

Alexion define medication misuse as the intentional and inappropriate use of IMP or Alexion AxMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or Alexion AxMP, outside the intended use as specified in the protocol, including deliberate administration of the product by the wrong route.

Events of medication misuse, with or without associated AEs, are to be captured and forwarded to Alexion Global Patient Safety via email or facsimile (clinicalsae@alexion.com or + 1.203.439.9347) using the Alexion Clinical Study Drug Misuse or Drug Abuse Report Form. This form will be used both if the medication misuse happened in a study participant or if the medication misuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of medication misuse include but are not limited to:

- The medication is used with the intention to cause an effect in another person
- The medication is sold to other people for recreational purposes
- The medication is used to facilitate assault in another person
- The medication is deliberately administered by the wrong route
- The medication is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the medication

10.5. Contraceptive and Barrier Guidance

10.5.1. Definitions

Childbearing Potential (CBP) Participants or Partners

Individuals in the following categories are considered CBP (fertile):

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (refer to definition of NCBP below)

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

Nonchildbearing Potential (NCBP) Participants or Partners

Individuals in the following categories are considered NCBP:

3. Premenopausal individual with permanent infertility due to one of the following:
    a. Documented hysterectomy
    b. Documented bilateral salpingectomy
    c. Documented bilateral oophorectomy
    d. For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion will be applied to determining study entry.

NOTE: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

4. Postmenopausal individual
    a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in individuals not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
        - Individuals on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2. Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency: *Failure rate of < 1% per year when used consistently and correctly.*
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)[c]
Bilateral tubal occlusion
Azoospermic partner (vasectomized or due to a to medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the CBP participant and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* NOTE: Documentation of azoospermia for a participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods That Are User Dependent: *Failure rate of < 1% per year when used consistently and correctly.*

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • Oral • Intravaginal • Transdermal • Injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] • Oral • Injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from sexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. External condom and internal condom should not be used together (due to risk of failure with friction).

[a] Contraceptive use should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

[b] Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

[c] External condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Abbreviation: CBP = childbearing potential

10.6. Handling of Human Biological Samples

All research and biological samples, including those for possible future research, are subject to national regulations and will only be collected in a specified country if approved in that country.

Handling, storage, and shipment of biological samples are detailed in the laboratory manual.

10.6.1. Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator keeps full traceability of collected biological samples from the participants while in storage at the site until shipment or disposal (where appropriate) and records relevant processing information related to the samples while at the site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

Alexion or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the Alexion-assigned biobanks or other sample archive facilities and will be tracked by the appropriate Alexion team for the remainder of the sample life cycle.

All appropriately consented samples will be retained for a maximum of 25 years from study completion.

If required, Alexion will ensure that remaining biological samples are returned to the site according to local regulations or destroyed at the end of the retention period, whichever is sooner.

10.6.2. Withdrawal of Informed Consent for Donated Biological Samples

Alexion ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, Alexion is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures the participant's withdrawal of informed consent to the use of donated samples is communicated immediately to Alexion or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and Alexion are informed about the sample disposal.

Alexion ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, the action is documented, and study site is notified.

10.7. Genetics Research

10.7.1. Use/Analysis of DNA

- Alexion intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medicinal product.
- This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care, and to the discovery of new diagnostics, treatments, or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant's DNA, ie, the entire genome.

- The results of genetic analyses may be reported in a separate study summary.
- Alexion will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

10.7.2. Genetic Research Plan and Procedures

Selection of Genetic Research Population

- All participants will be asked to participate in this genetic research, and if a participant declines to participate, there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion Criteria

- For inclusion in this genetic research, participants must fulfil all of the inclusion criteria described in the main body of the protocol and: Provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

- Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
  - Previous allogeneic bone marrow transplant
  - Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Withdrawal of Consent for Genetic Research

- Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the main protocol.

Collection of Samples for Genetic Research

- The blood sample for this genetic research will be obtained from the participants after randomization (predose) on Day 1. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn at Day 1, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics research during the study.

Coding and Storage of DNA Samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years from the date of last participant last visit, after which they will be destroyed. DNA is a finite resource that will be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (Alexion employee or designated organizations working with the DNA).
- The link between the participant enrollment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

- The principles for ethical and regulatory requirements for the study, including this genetic research component, are outlined in Section 10.1.1.

Informed Consent

- The genetic component of this study is optional and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study the participant must sign and date both the consent form for the main study and for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the participant and the originals filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely, and that the participant understands that they may freely withdraw from the genetic aspect of the study at any time.

Participant Data Protection

- Alexion will not provide individual sequencing, genotype results to participants, any insurance company, any employer, their family members, or general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an Alexion Physician or an Investigator might know a participant's identity and also have access to their genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data management

- Any genetic data generated in this study will be stored at a secure system at Alexion and/or designated organisations to analyse the samples.
- Alexion and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations, or drug- or health-related companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results, but they will not be able to see individual participant data or any personal identifiers.
- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

10.8. Classification Criteria for Microscopic Polyangiitis (MPA) and Granulomatosis with Polyangiitis (GPA)

Below is the classification criteria for MPA (Table 13) and GPA (Table 14) based on the 2022 ACR/EULAR classification criteria (Robson, 2022; Suppiah, 2022).

Considerations when applying these criteria

- These classification criteria should be applied to classify a participant as having MPA or GPA when a diagnosis of small- or medium-vessel vasculitis has been made
- Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria.

Table 13: Classification Criteria for Microscopic Polyangiitis

Clinical criteria	
Nasal involvement: bloody discharge, ulcers, crusting, congestion, blockage or septal defect/perforation	-3
Laboratory, imaging, and biopsy criteria	
Positive test for perinuclear antineutrophil cytoplasmic antibodies (pANCA) or antimyeloperoxidase (anti-MPO) antibodies ANCA positive	+6
Fibrosis or interstitial lung disease on chest imaging	+3
Pauci-immune glomerulonephritis on biopsy	+3
Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies	-1
Blood eosinophil count $\geq 1 \times 10^9$/L	-4

Sum the scores for 6 items, if present. A score of ≥5 is needed for classification of MPA.

Table 14: Classification Criteria for Granulomatosis with Polyangiitis

Clinical criteria	
Nasal involvement: bloody discharge, ulcers, crusting, congestion, blockage or septal defect/perforation	-3
Cartilaginous involvement (inflammation of ear or nose cartilage, hoarse voice or stridor, endobronchial involvement, or saddle nose deformity)	+2
Conductive or sensorineural hearing loss	+1
Laboratory, imaging, and biopsy criteria	
Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies	+5
Pulmonary nodules, mass, or cavitation on chest imagining	+2
Granuloma, extravascular granulomatous inflammation, or giant cells on biopsy	+2
Inflammation, consolidation, or effusion of the nasal/paranasal sinuses, or mastoiditis on imagining	+1
Pauci-immune glomerulonephritis on biopsy	+1
Positive test for perinuclear antineutrophil cytoplasmic antibodies (pANCA) or antimyeloperoxidase (anti-MPO) antibodies	-1
Blood eosinophil count $\geq 1 \times 10^9$/L	-4

Sum the scores for 10 items, if present. A score of ≥5 is needed for classification of GPA.

10.9. Country-specific Requirements

Not applicable.

10.10. Protocol Amendment History

DOCUMENT HISTORY	
Document/Type of Amendment (Global or Country-specific)/Date	**Overall Rationale for the Amendment**
Version 1.1 (EU)/ 24 Oct 2025	The main purpose of this amendment is to address comments from a European Member State received during the original protocol review.
Original (Version 1)/18 Jun 2025	Protocol followed nomenclature of SOP-0118068 v12 effective 08 May 2025
Original Protocol/19 May 2025 (obsolete)	Protocol followed nomenclature of SOP-0118068 v11. Protocol was finalized but not submitted to any IEC or HA.

DOCUMENT HISTORY	
	Editorial and formatting changes and rearrangement of content were implemented.

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