



CLINICAL STUDY PROTOCOL

Title: A Phase 2, Open-Label, Repeat-Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Proof-of-Concept of Intravenous ANX005 in Subjects with Warm Autoimmune Hemolytic Anemia

Protocol No: ANX005-wAIHA-02

Study Drug: ANX005

Development Phase: Phase 2

Sponsor: Annexon, Inc.
1400 Sierra Point Parkway, Building C, 2nd Floor
Brisbane, CA 94005

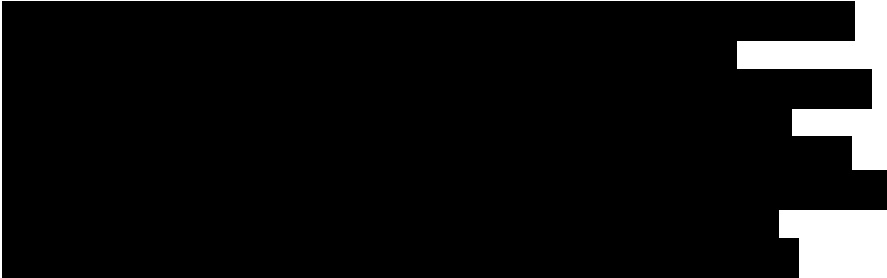
Medical Monitor: Contact information will be provided separately

Regulatory Agency IDs: IND 147936, NCT 04631570, EudraCT 2020-003675-18

Date of Protocol: Version 3.0: 23 March 2022
Version 2.0: 06 May 2021
Version 1.0: 17 June 2020

SYNOPSIS

Protocol Title	A Phase 2, Open-Label, Repeat-Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Proof-of-Concept of Intravenous ANX005 in Subjects with Warm Autoimmune Hemolytic Anemia
Protocol Number	ANX005-wAIHA-02
Development Phase	Phase 2
Sponsor	Annexon, Inc.
Study Centers	Multicenter
Patient Population	Patients with Warm Autoimmune Hemolytic Anemia
Number of Study Patients	Approximately 12 patients
Study Duration	Per patient duration (from screening through the end of the study): approximately 16 weeks
Study Objectives	The primary objectives of this repeat dose Phase 2 study are: - To evaluate the safety and tolerability of two once-weekly intravenous (IV) infusions of 100 mg/kg ANX005 in patients with Warm Autoimmune Hemolytic Anemia (wAIHA) - To evaluate the clinical effect of two once-weekly IV infusions of 100 mg/kg ANX005 in patients with wAIHA The secondary objectives of the study are: - To evaluate the pharmacokinetic (PK) profile of ANX005 in patients with wAIHA - To evaluate the effect of ANX005 on classical complement pathway inhibition as measured by complement system related biomarkers in patients with wAIHA
Study Endpoints	Primary: - Number and percent of patients experiencing treatment-emergent adverse events (TEAEs) - Change from baseline in hemoglobin over time up to Day 71 - Maximum absolute change in hemoglobin from baseline - Change from baseline in biomarkers of hemolysis (reticulocyte count, haptoglobin, lactate dehydrogenase [LDH], total and indirect bilirubin) over time up to Day 71 Secondary: - ANX005 plasma concentration profiles and PK parameters - Inhibition of classical complement activity as measured by serum CH50 from baseline over time up to Day 71 - Change and percent change from baseline in serum C4 concentrations over time up to Day 71 - Change and percent change from baseline in serum free C1q concentrations over time up to Day 71

Study Design	This is an open-label, repeat-dose, Phase 2 study in adult male and female patients with wAIHA. This study is designed to evaluate the safety, tolerability, PK, pharmacodynamics (PD), and clinical effect of ANX005 in patients with wAIHA. One cohort of up to approximately 12 patients with wAIHA will be enrolled in this study.  Study assessments for safety, PK/PD will also be performed on Day 4. Patients will check-in to the study center on Day 8 for the second dose of 100 mg/kg of ANX005 administered by IV infusion over approximately 4 hours. Patients will be observed for 4 hours after completion of the infusion and may be released once all required end of infusion procedures (eg, PK/PD samples and vital signs) have been conducted. Blood samples for serial PK/PD assessments will be collected following each dose of ANX005. The first three samples (pre-dose through 4 hours post-infusion) will be collected on site, and remaining samples may be collected either on site or via home visit. Patients will return to the clinic to have study assessments for safety, PK, and PD on Days 15, 22, 29, 36, 43, 50, 57, and 71. Any study visit in this timeframe, except for the end-of-study (Day 71 or early termination) visit, may be conducted at home by qualified site personnel or by a home health vendor if allowed by institution policy and regional guidelines. If a patient does not receive all scheduled infusions or discontinues prematurely from the study, additional patients may be enrolled to ensure a sufficient number of evaluable patients to assess the study endpoints. Up to 5 additional patients may be enrolled, at the discretion of the sponsor.
Safety Evaluations	Study personnel collect information on AEs and SAEs throughout the study. Patients are evaluated for the following: • Adverse events (AEs) • Serious AEs (SAEs) • Adverse events of special interest (AESI) • Discontinuation of participation due to an AE • Clinically significant laboratory or physical examination findings • Clinically significant ECG findings Safety and tolerability are evaluated via collection of AEs, vital signs, physical examination, electrocardiograms (ECGs) and clinical laboratory tests. Patients experiencing AEs are followed until resolution or stabilization of the AE.

	Immunogenicity will be assessed by analysis of serum samples for anti-drug (ANX005) antibodies (ADA) in validated screening, confirmatory and titer assays. Patients positive for ADA in the screening assay will be tested in a confirmation assay, run in the presence of high concentrations of drug, followed by an ADA titer assay.
PK Evaluations	ANX005 serum levels
PD and Preliminary Efficacy Evaluations	Blood samples to measure CH50 and C4, other complement biomarkers in blood (eg, [REDACTED]), disease-related biomarkers (eg, hemoglobin, LDH, indirect bilirubin, haptoglobin, reticulocytes), and [REDACTED] See Table 1 (Schedule of Assessments) for sampling timepoints.
Study Medication, Dose, and Route of Administration	100 mg/kg ANX005 will be administered via IV infusion on Day 1 and Day 8.
Study Population	Male and female patients ≥ 18 years of age diagnosed with wAIHA with a hemoglobin level ≤ 10.0 g/dL (pre-transfusion); evidence of classical complement pathway activation according to protocol-specified criteria (CH50 below the lower limit of normal and/or C4 level no greater than 1.5 times the lower limit of normal; and evidence of active hemolysis (LDH above the lower limit of normal and/or indirect bilirubin above the lower limit of normal and/or haptoglobin below the lower limit of normal). Patients with platelet count $< 30 \times 10^9/L$; history of isolated cold agglutinin disease, solid organ, bone marrow, or stem cell transplantation; or history of splenectomy within 90 days will be excluded. Rituximab (or other B cell depleting antibody) use within 90 days, IV immunoglobulin use within 90 days, and plasmapheresis or immunoadsorption treatments within 60 days are prohibited.
Statistical Methods	No formal statistical hypotheses are being tested in this study. Data will be summarized descriptively. The final analysis of all data will occur when the last patient completes the end-of-study visit (Day 71 or early termination). Final analysis will occur once all data from the study are in the database and the database is locked. The primary endpoint is the number and proportion of patients experiencing TEAEs which will be summarized by MedDRA SOC and PT. Similar summaries will be provided for related TEAEs, SAEs, CTCAE Grade 3 and higher AEs, related CTCAE Grade 3 and higher TEAEs, AESIs, and AEs leading to discontinuation of ANX005. Summaries will also be generated by maximum severity. Results and changes from baseline in hemoglobin and biomarkers of hemolysis (reticulocyte count, haptoglobin, LDH, total and indirect bilirubin) will be summarized over time up to Day 71. ANX005 plasma concentrations and corresponding PK parameters will be summarized descriptively.

	Inhibition of classical complement activity as measured by serum CH50 along with changes from baseline in C4 and free C1q concentrations in serum will be summarized over time up to Day 71. The statistical analysis plan will describe and serve as the final plan for all analyses and statistical considerations.
--	---

Table 1: Schedule of Assessments

Assessment	Screening			Treatment				Follow-up							
	Week -6 ≤42 Days Prior to Day 1	Week -2 ≤14 days Prior to Day 1	Re-screen 42 days before Day 1 visit until Day 1	Day 1 ^a	Day 2	Day 4	Wk 1 D8	Wk 2 D15	Wk 3 D22	Wk 4 D29	Wk 5 D36	Wk 6 D43	Wk 7 D50	Wk 8 D57	Wk 10 D71 EOS/ET
	±3 days	±3 days				±4 hours		±2 days	±2 days	±2 days	±2 days	±3 days	±3 days	±3 days	±3 days
Written Informed Consent	X														
ANA sample	X ^b	X ^b		X ^b						X					X
Inc/Exclusion Criteria	X		X												
Demographics	X														
Medical History	X														
Vaccinations ^c	X	X													
Vital Signs ^d	X			X	X	X	X	X	X	X	X	X	X	X	X
Weight	X														X
Height	X														
Physical Examination	X			X	X	X	X	X		X		X		X	X
ECG	X			X			X								X
Serology ^e	X														
SARS-CoV-2 (COVID-19) Screen ^f				X											
Pregnancy Test ^g	X			X						X				X	X
CBC, Differential and Reticulocytes	X			X	X	X	X	X	X	X	X	X	X	X	X
DAT	X			X											
Iron Studies ^h	X														X
Erythropoietin ^h	X														
Vitamin B12 and Folic Acid ^h	X														

	Screening			Treatment				Follow-up							
Assessment	Week -6 ≤42 Days Prior to Day 1	Week -2 ≤14 days Prior to Day 1	Re-screen 42 days before Day 1 visit until Day 1	Day 1 ^a	Day 2	Day 4	Wk 1 D8	Wk 2 D15	Wk 3 D22	Wk 4 D29	Wk 5 D36	Wk 6 D43	Wk 7 D50	Wk 8 D57	Wk 10 D71 EOS/ET
	±3 days	±3 days				±4 hours		±2 days	±2 days	±2 days	±2 days	±3 days	±3 days	±3 days	±3 days
IgM Cold Agglutinin	X														
Chemistry (Incl. LDH & Indirect Bilirubin)	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Haptoglobin	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation	X			X			X	X		X		X		X	X
Urinalysis (urine dipstick)	X			X	X	X	X	X	X	X	X	X	X	X	X
ADA Serum Sample				X ^j						X					X
PK and free C1q (serum) ^k				X	X	X	X	X	X	X	X	X	X	X	X
Flow Cytometry (whole blood) ^l	X			X	X	X	X	X	X	X	X	X	X	X	X
CH50, C4, 	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Other PD Biomarkers (serum) ^l				X	X	X	X	X	X	X	X	X	X	X	X
Other PD Biomarkers (plasma) ^l				X	X	X	X	X	X	X	X	X	X	X	X
Premedication ^m				X											
Infusion of ANX005 ⁿ				X			X								

	Screening			Treatment				Follow-up							
Assessment	Week -6 ≤42 Days Prior to Day 1	Week -2 ≤14 days Prior to Day 1	Re-screen 42 days before Day 1 visit until Day 1	Day 1 ^a	Day 2	Day 4	Wk 1 D8	Wk 2 D15	Wk 3 D22	Wk 4 D29	Wk 5 D36	Wk 6 D43	Wk 7 D50	Wk 8 D57	Wk 10 D71 EOS/ET
	±3 days	±3 days				±4 hours		±2 days	±2 days	±2 days	±2 days	±3 days	±3 days	±3 days	±3 days
Adverse Events ^o	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X		X	X	X	X	X	X	X	X	X	X	X	X

Notes:

- Non-dosing study visits (except for Screening and Week 35/EOS/ET visits) may be conducted at home by qualified site personnel or by a home health vendor if allowed by policy and regional guidelines.
- Refer to protocol [Section 7](#) for additional details and instructions on all assessments that will be conducted during this study.
- ^a Day 1 is the baseline visit. All procedures that require pre-exposure baseline results should be performed prior to infusion of ANX005. Subsequent visits should be conducted at the same time of day as the Day 1 visit.
- ^b ANA sample must be collected prior to administration of vaccinations (if applicable) or prior to the first administration of ANX005 on Day 1. The Day 1 sample will be used for immediate processing of ANA titers but also aliquoted and stored for evaluation of a panel of auto-antibodies as listed in [Section 7.3.5](#) and [Section 9.7](#). Post-baseline positive ANA titers ≥1:160 in the setting of signs and symptoms of a systemic autoimmune disorder may trigger additional autoantibody testing as recommended in [Section 7.3.5](#).
- ^c Applies only to patients without a documented history of vaccination within 5 years prior to screening. See protocol [Section 7.1.2](#) for additional details regarding vaccination and other acceptable prophylactic measures against infections with encapsulated bacteria.
- ^d Vital signs include heart rate, respiratory rate, blood pressure, and body temperature. Vital signs should be collected after 5 minutes rest in a seated upright position. On Day 1 and Day 8, vital signs should be collected 30 minutes prior to the start of the infusion (±5 minutes), every 4 hours during the infusion (±15 minutes), and within 1 hour (±15 minutes) after the end of the infusion. Vital signs may be collected at additional timepoints at the discretion of the investigator.
- ^e Serology includes HIV-1, HIV-2, hepatitis B, and hepatitis C.
- ^f Screening and testing for SARS-CoV-2 infection (COVID-19) will be conducted in accordance with local guidelines and should be performed during the Day 1 visit prior to the first administration of ANX005. Additional testing for SARS-CoV-2 throughout the duration of the study may also be performed at the investigator's discretion according to local guidelines.
- ^g Serum pregnancy test required at Screening for WOCBP as defined in [Section 6.3.1](#). Additional serum or urine pregnancy testing may be conducted per the investigator's discretion or as required by local regulation to establish the absence of pregnancy at any time during participation in the study.
- ^h Iron studies include iron, ferritin, transferrin, and total iron binding capacity. Iron studies, EPO, vitamin B12, and folic acid levels may be retested at the investigator's discretion if found to be below the lower limit of normal during screening.

- i [REDACTED]
- j On Day 1, collect blood sample for anti-drug antibodies (ADA) prior to infusion. Patients positive for ADA in the screening assay will be tested in a confirmation assay, run in the presence of high concentrations of drug, followed by an ADA titer assay.
- k On Day 1 and Day 8, PK and free C1q samples will be collected prior to the start of the infusion (within 30 minutes pre-dose), within 15 minutes after completing the infusion and again 4 hours (± 15 minutes) after the end of the infusion. Sample collection on non-dosing days should be completed at approximately the same time as the start of the Day 1 infusion (± 4 hours).
- l After screening, collect whole blood sample for flow cytometry, serum for CH50 and complement factors ([REDACTED] C4, and [REDACTED] plasma for [REDACTED] and plasma and serum for PD biomarkers. On Day 1 and Day 8, samples will be collected prior to the start of the infusion (within 30 minutes pre-dose) and within 15 minutes after completing the infusion. Collection on non-dosing days should be completed at approximately the same time as the start of the Day 1 infusion (± 4 hours).
- m Administer premedication for ANX005 as recommended in [Section 5.4](#) up to 2 hours prior to infusion of ANX005. Pre-medication may be repeated as needed per investigator discretion but is only required prior to the first ANX005 infusion.
- n For the first ANX005 infusion, the total duration is expected to be approximately 21 hours. The Day 8 infusion should occur over approximately 4 hours. Refer to the Pharmacy Manual for instructions on handling, storage, preparation, and administration. Sites must use the ANX005 Infusion Plan to calculate appropriate dose preparation for each infusion.
- o If a patient experiences an AE that is an IRR, additional samples for PK, free C1q, and ADA should be collected as close as possible to the onset of the IRR. In addition, vital signs should also be collected at the onset of the IRR (± 5 minutes), 15 minutes after the onset (± 5 minutes), and every 30 minutes (± 15 minutes) thereafter until vital signs are stabilized. Once vital signs are stabilized, vital signs should be collected every 4 hours (± 15 minutes) until the end of the infusion or the IRR is fully resolved. Refer to [Section 9.8](#) for additional information.

Abbreviations: ADA = antidrug antibodies; ANA = Anti-nuclear antibody; CBC = complete blood count; [REDACTED] D = day; DAT = direct antiglobulin test; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EOS = end of study; EPO = erythropoietin; ET = early termination; Exc = exclusion; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency; IgG = immunoglobulin G; IgM = immunoglobulin M; Inc = inclusion; IRR = infusion-related reaction; LDH = lactate dehydrogenase; PD = pharmacodynamic; PK = pharmacokinetic; RNA = ribonucleic acid; wAIHA = warm autoimmune hemolytic anemia.

TABLE OF CONTENTS

CLINICAL STUDY PROTOCOL	1
SYNOPSIS	2
TABLE OF CONTENTS	10
LIST OF TABLES	13
LIST OF ABBREVIATIONS AND DEFINITIONS	14
INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE	17
1. INTRODUCTION.....	18
1.1 Background	18
1.2 ANX005 Description and Mechanism of Action	20
1.3 Nonclinical	20
1.3.1 Nonclinical Pharmacology.....	21
1.3.2 Nonclinical Pharmacokinetics.....	21
1.3.3 Nonclinical Toxicology.....	21
1.3.4 Previous Human Experience.....	23
1.4 Potential Risks and Benefits.....	24
1.4.1 Potential Risks of ANX005.....	24
1.4.2 Potential Benefits of ANX005	25
1.4.3 Overall Benefit:Risk Conclusion	26
2. STUDY OBJECTIVES AND ENDPOINTS.....	26
3. INVESTIGATIONAL PLAN	27
3.1 Overall Study Design	27
3.2 Safety Review	28
3.3 Stopping Rules.....	28
3.4 Enrollment of Patients.....	29
3.5 Duration of Participation	29
3.6 End of Study Definition	29
4. STUDY POPULATION	30
4.1 Number of Patients	30
4.2 Eligibility Criteria.....	30
4.2.1 Inclusion Criteria	30
4.2.2 Exclusion Criteria	31
5. STUDY MEDICATION AND ADMINISTRATION.....	33
5.1 ANX005 Description	33

5.2	Packaging, Labeling, and Storage	33
5.3	Preparation of Study Medication	33
5.4	Dosage and Administration.....	33
5.5	Study Medication Accountability	35
5.6	Overdose	35
5.7	Missed Doses.....	35
6.	MEDICATIONS AND RESTRICTIONS	35
6.1	Permitted Medications.....	35
6.1.1	Rescue Medication	36
6.2	Prohibited Concomitant Medications, Procedures, and Supplements	36
6.3	Contraceptive Methods	37
6.3.1	Definitions.....	37
6.3.2	Contraceptive Guidance.....	37
6.4	Restrictions	38
7.	Study Assessments and Procedures.....	38
7.1	General Assessments.....	39
7.1.1	Screening and Informed Consent.....	39
7.1.2	Guidance for Prophylaxis Against Infections with Encapsulated Bacteria	39
7.1.3	Patient Identification Number	40
7.1.4	Rescreening Criteria.....	40
7.1.5	Demographics and Medical History.....	40
7.1.6	Screening Laboratory Assessments.....	41
7.2	Pharmacokinetic, Pharmacodynamic, and Other Efficacy Assessments	42
7.2.1	Pharmacokinetic Sampling for ANX005 Concentrations	42
7.2.2	Clinical, Pharmacodynamic, and Biomarker Sampling.....	42
7.2.3		43
7.3	Safety Assessments.....	43
7.3.1	Physical Examinations.....	43
7.3.2	Height and Weight	44
7.3.3	Vital Signs.....	44
7.3.4	Electrocardiograms.....	44
7.3.5	Safety Laboratory Assessments	44
8.	STUDY COMPLETION AND WITHDRAWAL	46
8.1	Patient Completion	46

8.2	Patient Withdrawal.....	46
8.3	Termination of the Study	47
9.	ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND REPORTING	47
9.1	Adverse Events	47
9.1.1	Definition	47
9.2	Severity and Causality Assessment	48
9.2.1	Severity Rating	48
9.2.2	Causality Rating.....	48
9.3	Documentation	49
9.4	Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions.....	51
9.4.1	Serious Adverse Event Definition.....	51
9.4.2	Suspected Unexpected Serious Adverse Reaction Definition.....	52
9.5	Reporting	52
9.5.1	Reporting for Disease Under Study.....	52
9.6	Clinically Significant Findings and Safety Monitoring	53
9.7	Monitoring for Infection and Autoimmunity	53
9.8	Infusion Reactions.....	55
9.8.1	Day 1 Dosing (Approximately 21-hour Infusion).....	56
9.8.2	Dosing Day 8 (Approximately 4-hour Infusion).....	56
9.8.3	Follow-up After Last Dose ANX005.....	57
9.9	Pregnancy	57
10.	STATISTICAL METHODS	57
10.1	Statistical Hypotheses	57
10.2	Sample Size Determination	58
10.3	Analysis Sets	58
10.4	Statistical Analyses.....	58
10.4.1	Timing of Analyses.....	58
10.4.2	General Considerations	59
10.4.3	Analysis of Primary Endpoints.....	59
10.4.4	Analysis of Secondary Endpoints	59
10.4.5	Analyses of Exploratory Endpoints.....	60
10.4.6	Other Safety Analyses.....	60
10.4.7	Other Analyses	61

11.	DATA MANAGEMENT	61
11.1	Data Collection and Management	61
12.	STUDY ADMINISTRATION	61
12.1	Ethical and Regulatory Considerations	61
12.2	Institutional Review Board/Independent Ethics Committee	62
12.3	Informed Consent	63
12.4	Protocol Amendments	63
12.5	Retention of Documents	64
12.6	Monitoring Procedures.....	64
12.7	Quality Control and Quality Assurance	65
12.8	Confidentiality.....	65
12.9	Publication	66
	REFERENCES.....	67
	INVESTIGATOR SIGNATURE PAGE.....	69
Appendix A	Adverse Event Severity Grading	70
Appendix B	Grading for Infusion-related Reactions.....	71
Appendix C	[REDACTED]	72

LIST OF TABLES

Table 1:	Schedule of Assessments	6
Table 2:	ANX005 Dosing Schedule.....	34

LIST OF ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
AESI	Adverse events of special interest
ADA	Antidrug (ANX005) antibodies
AIHA	Autoimmune hemolytic anemia
ANA	Anti-nuclear antibody
APL	Antiphospholipid antibody
AUC	Area under the curve
C1q	Component of C1 complement complex
C4a	Cleavage fragment of complement C4
CBC	Complete blood count
CAD	Cold agglutinin disease
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
Cmax	Maximum concentration
eCRF	Electronic case report form
████	████████████████████
CSF	Cerebrospinal fluid
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
CV	Coefficient variable
DAT	Direct antiglobulin test
DMP	Data management plan
DNA	Deoxyribonucleic acid
dsDNA	Double-stranded DNA antibody
EC ₅₀	Drug concentration that gives half-maximal response
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
EOS	End of study
EPO	Erythropoietin
ET	Early termination
████	██
GBS	Guillain-Barré Syndrome
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IB	Investigator's Brochure

ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive care unit
IEC	Independent ethics committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IgG4	Immunoglobulin gamma 4
INR	International Normalized Ratio
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IRB	Institutional review board
IRR	Infusion related reaction
IVIg	Intravenous immunoglobulin
IV	Intravenous
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
Men ACWY	Meningococcal vaccine to protect against disease caused by serogroups A, C, W, and Y
MenB	Meningococcal serotype B
MMF	Mycophenolate mofetil
NOAEL	No adverse effect level
PD	Pharmacodynamic or pharmacodynamics
PI	Principal investigator
PK	Pharmacokinetic or pharmacokinetics
PKAP	PK analysis plan
PP	Per Protocol
PT	Prothrombin time; preferred term
PTT	Partial thromboplastin time
RBC	Red blood cell
RNA	Ribonucleic acid
RNP	Ribonucleoprotein
RSI	Reference Safety Information
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SLE	Systemic lupus erythematosus
SOC	System organ class
SOP	Standard operating procedure
SUSAR	Suspected, unexpected, serious, adverse reaction
TEAE	Treatment-emergent adverse event

ULN	Upper limit of normal
Vd	Volume of distribution
wAIHA	Warm autoimmune hemolytic anemia
WBC	White blood cell
WHO-DD	World Health Organization Drug Dictionary
WOCBP	Women of child-bearing potential

INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE

Prior to beginning the study, the Principal Investigator (PI) must provide to a sponsor representative a current, signed curriculum vitae.

The clinical study is administered and monitored by representatives of Annexon, Inc. (the sponsor). Clinical research associates monitor the site on a periodic basis and perform verification of source documentation for each patient.

Sponsor representatives are responsible for the timely reporting of serious adverse events (SAEs) to appropriate regulatory authorities.

Clinical laboratory safety evaluations are performed at the central laboratory specified by the study sponsor.

1. INTRODUCTION

1.1 Background

Autoimmune hemolytic anemia (AIHA) is caused by autoantibodies that react with red blood cells (RBCs) resulting in RBC destruction. AIHA is classically divided into warm antibody hemolytic anemia (caused by polyclonal immunoglobulin G [IgG] antibodies that destroy blood cells at normal body temperature) and cold agglutinin disease (CAD; caused by clonal and polyclonal immunoglobulin M [IgM] antibodies that usually react with RBCs only at temperatures below normal body temperature). Patients with mixed AIHA have both warm and cold antibodies against RBCs. Warm autoimmune hemolytic anemia (wAIHA) usually produces extravascular hemolysis via the reticuloendothelial system and is the most common form of AIHA, accounting for approximately 70% to 85% of cases ([Michel 2014](#)). Mixed AIHA is much rarer and constitutes approximately 8% to 10% of AIHA patients ([Jager, 2020](#)).

Warm autoimmune hemolytic anemia can affect children (usually before the age of 5) and adults, although the mean age at diagnosis is around 50 years ([Michel 2014](#)). wAIHA in children is typically acute and transient, while in adults, wAIHA is a chronic condition that requires long-term therapy ([Bass 2014](#)). A mortality rate of 11% in adults and 4% in children has been reported ([Zanella 2014](#)).

Symptoms of wAIHA most often result from the anemia. If the disorder is severe, jaundice, dyspnea, chest pain, syncope, or heart failure may occur ([Bass 2014](#)). Other symptoms include mild splenomegaly and hemolysis (eg, decreased haptoglobin, elevated lactate dehydrogenase [LDH], elevated bilirubin, increased reticulocyte count); and microscopic examination of RBCs may show spherocytes ([Barcellini and Fattizzo 2015](#); [Bass 2014](#); [Michel 2014](#)).

wAIHA is diagnosed by detection of autoantibodies via the direct antiglobulin test (also known as the direct Coombs test) ([Bass 2014](#)). Anti-human antibody or anti-human C3d reagents (antiglobulin serum) are added to washed RBCs from the patient; agglutination indicates the presence of patient IgG and/or complement (C3d) bound to the RBCs, which is most often IgG in wAIHA. In general, the intensity of the direct antiglobulin test (DAT) correlates with the number of molecules of IgG or C3d bound to the RBC and, roughly, with the rate of hemolysis.

In approximately up to 50% of wAIHA patients, pathogenic IgG is not solely responsible for hemolysis, rather the complement system contributes to hemolysis and anemia, as evidenced by the finding of C3d on the RBCs. When RBCs are heavily coated with IgG, especially subclass IgG3, C1q can bind and activate the classical complement pathway, leading to deposition of C3b on the RBC and removal from the circulation by the mononuclear phagocytic system (extravascular hemolysis). Correlation between the extent of autoimmune hemolysis and the presence of complement on RBCs suggests that the presence and amount of C3 on RBCs in wAIHA patients is an important predictor of hemolysis and might act synergistically with IgG ([Wheeler 2004](#)).

In addition to the well-described role for IgG, it has been suggested that complement positivity on DAT may also be caused by difficult to detect warm-reactive autoantibodies of the IgM isotype that may be present in up to 15% of patients with wAIHA ([Meulenbroek 2015](#)). Upon complement activation in wAIHA, phagocytosis of C3b-opsonized erythrocytes by reticuloendothelial cells in the liver is responsible for most of the hemolysis ([Berentsen 2015](#)). Consequently, extravascular destruction of C3b- or IgG-coated RBCs is thought to be the primary mechanism of hemolysis in stable wAIHA.

The treatment of wAIHA is not evidence-based and relies on expert recommendations and physician experience ([Barcellini 2015](#)). Treatment outcomes are correlated with severity of wAIHA upon presentation; patients who present with more severe disease typically require more lines of therapy and have a poorer prognosis than patients who initially present with more mild disease. Approximately 40% of wAIHA patients require 2 or more types of therapy to achieve a response ([Barcellini 2015](#)).

At present, there are no FDA-approved treatments for wAIHA although corticosteroids are typically prescribed. Most patients have an excellent initial response to corticosteroids; however, a response sustained beyond 6 months is observed in only about one third of patients.

In patients with wAIHA who relapse after corticosteroid cessation or who are refractory to corticosteroids, second-line treatments include immunosuppressants, B cell depleting monoclonal antibodies (mAb), such as rituximab, or splenectomy. Splenectomy is used in approximately 10% to 15% of wAIHA cases, but it is ineffective in 30% of patients ([Barcellini 2015](#); [Jager 2020](#)). Patients may also relapse after a successful splenectomy ([Crowther 2011](#)). Splenectomy is associated with surgical complications, thrombotic complications, and a risk of serious and possibly fatal infections, which have been reported in 3% to 5% of cases with a mortality rate of 50% ([Barcellini 2015](#)).

The anti-CD20 mAb rituximab has been increasingly used as a second-line treatment over splenectomy for wAIHA. Much of the evidence for rituximab use in wAIHA is based on case reports and retrospective reviews; available studies demonstrate that approximately 70% to 80% of wAIHA patients respond to rituximab with a duration of response of 1 to 2 years ([Dierickx 2015](#); [Rodrigo 2015](#)).

Given the significant adverse effects of long-term use of high-dose corticosteroids, the potential long-term consequences of B-cell depletion with rituximab, and the subset of patients who do not respond to or relapse while receiving available therapies, there remains a significant unmet medical need for patients with wAIHA.

Consequently, inhibition of the classical complement pathway may provide a targeted treatment option for wAIHA patients who have had a suboptimal response to currently available treatments or have evidence of complement mediated wAIHA.

1.2 ANX005 Description and Mechanism of Action

ANX005 is a humanized IgG4 mAb that binds to and functionally inhibits human C1q, the initiating molecule of the classical complement cascade. Thereby, ANX005 can selectively block activation of the entire classical complement cascade. ANX005 is composed of two heavy chains of the IgG4 isotype and two light chains of the kappa isotype. ANX005 has a molecular weight of approximately 150K Da and binds to C1q with high affinity.

C1q has a critical role in autoimmune diseases as a key effector/amplification mechanism for pathogenic antibodies. The classical complement pathway has been shown to be involved in antibody-mediated autoimmune hemolytic anemias including warm and cold agglutinin disease (CAD) (Berentsen 2016, Kalfa 2016). In order to examine the potential benefit of ANX005 in patients with autoimmune hemolytic anemia, the activity of ANX005 was examined ex vivo using serum samples obtained from patients with CAD. Flow cytometry demonstrated that deposition of early complement components C1q, C4d and C3b on the surface of RBCs was inhibited by ANX005. In addition, ANX005 showed a dose-dependent inhibition of hemolysis, demonstrating that C1q inhibition can efficiently block activation of the late steps in the complement cascade in sera from CAD patients.

Plasma samples from CAD patients were evaluated for levels of complement proteins including C1q, C4, C2, C3 and C5. A significant decline in total complement proteins including C4, C2, and C3 was observed. In contrast, no significant changes were observed in C1q and C5. In addition, we observed a decline in activation markers for C4a, C2b, C3a, and C3d. These results demonstrate that cold agglutinin disease is characterized by consumption of complement proteins that drive the early steps in the complement cascade. The recovery of complement protein levels can serve as potential target-engagement biomarkers of classical complement cascade inhibition with ANX005 in human clinical trials.

Please refer to the Investigator's Brochure (IB) for a detailed description of these studies.

These results demonstrate that ANX005, a potent anti-C1q antibody, can inhibit both extravascular hemolysis (mediated by upstream components of the classical cascade) and intravascular hemolysis (mediated by C5 and downstream complement components), and support evaluation of ANX005 in a clinical trial to determine its benefit in AIHA patients.

1.3 Nonclinical

Pharmacology, pharmacokinetic (PK), and toxicology studies with ANX005 have been completed or are ongoing. This nonclinical program is consistent with the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use Harmonised Tripartite Guidelines S6(R1), M3(R2), and S5(R3). The IB provides more detailed and the most current information.

The IB provides the tables and figures displaying the data summarized below.

1.3.1 Nonclinical Pharmacology

C1q is a component of the C1 complex that initiates and drives the classical complement cascade as part of antibody-mediated immune responses. ANX005 is a humanized IgG4 monoclonal antibody that binds to human C1q as its antigen target and functionally inhibits the classical complement cascade both in vitro and in vivo.

ANX005 displays affinity for binding to human C1q (<10 pM), as measured by surface plasmon resonance, and in an in vitro binding assay for human C1q (drug concentration that gives half-maximal response $[EC_{50}] \sim 10$ ng/mL/70 pM).

ANX005 shows robust binding to C1q derived from multiple species, with equivalent affinity in humans, cynomolgus and rhesus monkeys, dogs, and rats. ANX005 also showed binding to serum-derived C1q and correspondingly robust inhibition of hemolysis in serum from humans, cynomolgus and rhesus monkeys, dogs, and rats with an EC_{50} of ~ 350 ng/mL (~ 2.5 nM).

1.3.2 Nonclinical Pharmacokinetics

Single-dose, intravenous (IV), PK, and pharmacodynamic (PD) studies in rats using anti-C1q antibody M1, repeat dose PK studies in rats with ANX005, and single-dose and repeat-dose PK studies with ANX005 in monkeys showed a robust PD effect consistent with the level of drug exposure, including reduction in free C1q levels in serum and inhibition of C1q functional activity in an ex vivo hemolysis assay.

In the 26-week repeat dose chronic toxicology study in cynomolgus monkeys at dose levels of 50, 100, and 200 mg/kg the increase in serum ANX005 exposure was approximately dose proportional with no clear gender differences. Concentration-time profiles were lower than expected in some animals, consistent with an ADA response. Following repeat administration of ANX005, serum concentrations observed at predose generally increased on Days 29, 57 and 64 and remained high in the subsequent timepoints for animals for which ADA was not evident, suggesting that steady state was achieved by Day 64. Systemic exposure increased on Days 85, 169, and 176 relative to Day 1 with mean accumulation ratios ranging from 2.64 to 7.98. The mean accumulation ratios decreased slightly with increasing dose levels. The terminal phase was well-characterized on Day 176 for the recovery animals where the individual $T_{1/2}$ ranged from 236 to 387 hours and clearance was between 0.0814 and 0.245 mL/hr/kg. The volume of distribution (V_d) ranged between 32.8 and 106 mL/kg, suggesting that ANX005 was not extensively distributed beyond the vasculature.

1.3.3 Nonclinical Toxicology

ANX005 shows equivalent potency for binding to C1q in serum from multiple species including humans, cynomolgus and rhesus monkeys, dogs, and rats. The binding affinity of ANX005 for mouse C1q was 2-fold lower than for other species, and no binding was observed to C1q derived from rabbit serum. ANX005 also showed strong inhibition of hemolysis in serum from humans, cynomolgus and rhesus monkeys, dogs, and rats; mouse

data showed 100x less potency than other species. These data supported the use of monkeys and rats in the nonclinical toxicology studies.

Repeat-dose toxicology studies were conducted in rats and cynomolgus monkeys, which are pharmacologically relevant species for testing ANX005. Pilot toxicology studies in rats and cynomolgus monkeys evaluated ANX005 following four weekly IV bolus doses of up to 100 mg/kg. No treatment-related toxicities were identified in these studies.

The following Good Laboratory Practice (GLP) studies have been completed:

The 4-week, GLP toxicology studies in rats and cynomolgus monkeys evaluated the potential toxicity of ANX005 following weekly IV bolus doses ([Charles River Laboratories, 2016](#); [Charles River Laboratories, 2017](#)). Standard toxicology endpoints included clinical signs, body weights, body-weight changes, food consumption, ophthalmic examinations, clinical pathology parameters (hematology, clinical chemistry, and urinalysis), toxicokinetic parameters (ANX005 levels in serum and cerebrospinal fluid [CSF]), antidrug antibodies (ADA; serum and CSF; samples archived for potential future analysis), gross necropsy findings, organ weights, and histopathologic examinations. In addition, in the 4-week cynomolgus monkey study, safety pharmacology endpoints included electrocardiography, respiratory and heart rates, blood pressure, and neurologic examination. No treatment-related toxicities were identified in the 4-week, GLP studies in rats and cynomolgus monkeys. The no-observed-adverse-effect level (NOAEL) was 200 mg/kg weekly, the top dose tested, in both rats and cynomolgus monkeys. Since results from the 4-week GLP toxicology studies in rats and cynomolgus monkeys were similar, the cynomolgus monkey was selected as the most appropriate species for use in the 26-week chronic repeat dose toxicology study [per ICHS6(R1)].

The 26-week GLP toxicology study in cynomolgus monkeys evaluated the potential toxicity of ANX005 following weekly IV bolus doses. Standard toxicology endpoints included clinical signs, body weights, ophthalmic examinations, clinical pathology parameters (hematology, clinical chemistry, and urinalysis), immunophenotyping, safety pharmacology endpoints (electrocardiography, respiratory and heart rates, blood pressure, and neurologic examination), toxicokinetic and pharmacodynamic parameters (ANX005 and C1q levels in serum and CSF), ADA, gross necropsy findings, organ weights, histopathologic examinations, and immunohistochemistry for the detection of immune complexes.

In the 26-week GLP monkey study, no treatment related toxicity was observed. All of the observed findings were related to the generation of ADA and included the following: infusion-related reactions (IRRs), associated clinical observations, clinical pathology changes, and histopathology (increased mononuclear cell infiltrates across groups, and micro hemorrhages in a single high-dose male). These findings were consistent with an ADA mediated response across dose groups (50, 100, 200 mg/kg), which was confirmed by ADA sample analysis. Two high dose (200 mg/kg) males were euthanized early; one was related to an acute IRR (Week 9) while the other was due to RBC depletion (Week 15); both of which were confirmed to be ADA-mediated. Granular deposits of immune complexes (monkey IgG, IgM, and/or C3 were detected either alone or co-localized with ANX005 in tissues) were detected in both animals by immunohistochemistry which was consistent with an

ADA-mediated response. ADA in serum was detected using two methods: a validated indirect assay and a non-validated direct enzyme-linked immunosorbent assay (ELISA) assay. While only the one male with an IRR euthanized in Week 9 was positive for serum ADA in the validated sandwich ELISA assay, both high dose males were positive for monkey IgG and/or IgM ADA against ANX005 as determined in the direct assay.

For the animals that did not develop adverse clinical signs of anti-drug antibody hypersensitivity, the NOAEL was considered to be 200 mg/kg/dose, the highest dose evaluated since there were no additional adverse toxicological findings in any parameter tested in the 26-week GLP toxicology study.

In conclusion, administration of ANX005 by once weekly slow-bolus intravenous injection for 26-weeks was well tolerated in cynomolgus monkeys up to 200 mg/kg/dose. The NOAEL was considered to be 200 mg/kg/dose.

A GLP tissue cross-reactivity study with cryosections from a full panel of human tissues (3 donors per tissue) showed specific ANX005 staining in all human tissues examined except blood. These results were expected and consistent with the fact that C1q is ubiquitously expressed throughout the body.

Results from developmental and reproductive toxicology studies in rats are provided in the Investigator's Brochure.

1.3.4 Previous Human Experience

For more detailed information on previous human experience, reference the ANX005 Investigator's Brochure.

1.3.4.1 ANX005 in Healthy Volunteers

A Phase 1 study (ANX005-CP-01) in healthy volunteers was initiated to evaluate the safety, PK, and PD of ANX005 by intravenous infusion. Study medication (ANX005 and placebo) was administered to healthy volunteers at single, ascending dose levels of 1, 3, and 10 mg/kg, with 6 subjects receiving ANX005 and 2 subjects receiving placebo per dose level. The study was discontinued by the Sponsor after 27 subjects were dosed with ANX005 or placebo in doses up to 8.2 mg/kg.

1.3.4.2 ANX005 in Guillain-Barré Syndrome (GBS) Patients

A Phase 1b study (ANX005-GBS-01), the first study conducted in patients, is a single-center, randomized, double-blind placebo-controlled ascending dose, single or 2 infusion study in patients recently diagnosed with GBS. The study objectives were to obtain information on the safety, tolerability, efficacy, PK, and PD of ANX005 administered as a single or two infusions to patients recently diagnosed with GBS. Cohorts completed (through 8 weeks of follow-up) include 3 patients who received ANX005 or placebo at 3 mg/kg (2:1), 4 patients at 9 mg/kg (3:1), 8 patients at 18 mg/kg (3:1), 8 patients at 36 mg/kg (3:1), 8 patients at 75 mg/kg (3:1), 11 patients at 2 x 75 mg/kg (75 mg/kg ANX005 dose, administered on Day 1

and Day 8, 3:1), and 8 patients at 100 mg/kg (3:1). At all doses tested, ANX005 has been shown to be safe and well tolerated as a monotherapy.

1.3.4.3 ANX005 in Cold Agglutinin Disease (CAD) Patients

A Phase 1b study (ANX005-CAD-01), the first clinical study conducted in AIHA, is an ongoing single-center, open-label study in 3 patients diagnosed with primary CAD. The effect of multiple intravenous doses of ANX005 on disease activity for at least 3 and up to 12 months. ANX005 has been shown to be safe and well tolerated. No infections with encapsulated bacteria or signs of symptoms of autoimmunity have been observed. Full C1q target engagement in blood during at least 3 months of dosing was seen. Maximum absolute change in hemoglobin ranged from 2.6 to 5.3 g/dL.

1.4 Potential Risks and Benefits

1.4.1 Potential Risks of ANX005

While ANX005 has to date been generally well tolerated, a potential risk of infection with encapsulated bacteria (eg, *Neisseria meningitidis*, including serogroup B meningococcus, *Haemophilus influenzae*, and *Streptococcus pneumoniae*) may exist due to its blockade of the classical complement pathway via inhibition of C1q. Since the other two initiator pathways of the complement cascade, the lectin and the alternative pathways, remain intact, patients receiving ANX005 may still possess alternative bacteriolytic capability to defend against infections. There have been no reported cases of infections with encapsulated bacteria (*Neisseria meningitidis*, including serogroup B meningococcus, *Haemophilus influenzae*, and *Streptococcus pneumoniae*) in vaccinated normal healthy volunteers and unvaccinated patients with an acute disease such as GBS treated with ANX005. For this study, patients will receive prophylaxis against infections with encapsulated bacteria prior to study entry via vaccination (or by demonstrating documented evidence of vaccination) and/or through the use of prophylactic antibiotics in accordance with local standards of practice and/or guidelines (see [Section 7.1.2](#)). Patients will be closely monitored for infections during study participation and will be instructed to report signs and symptoms that are consistent with an infection immediately.

Development of an autoimmune disease may be a potential risk of ANX005-mediated inhibition of C1q. Autoimmune diseases have developed in individuals with genetic C1q deficiency present at birth. Autoimmunity in individuals with inherited C1q deficiency (systemic lupus erythematosus [SLE]-like disease) typically occurs in mid-childhood or later, following many years of significant C1q deficiency.

[REDACTED]. Based on these observations, autoimmunity would not be expected following short-term suppression of C1q in this study.

IRRs are common adverse drug reactions that occur with the administration of monoclonal antibodies such as ANX005 and have the potential to cause local or systemic infusion

reactions ([ANX005 IB, 2021](#)). ANX005 can induce infusion-related reactions that are characterized as complement activation-related pseudoallergy (CARPA). An optimal dosing regimen and infusion management plan has been empirically established in 51 patients with GBS, which includes premedication that may delay or mitigate the IRR and a slow initial infusion rate that is increased over time. A safe initial infusion rate of 0.75 mg/kg/hr was established that did not lead to cardiovascular or other systemic adverse reactions. After the first dose of ANX005, drug/C1q complex formation and complement activation can no longer occur as long as C1q is fully saturated.

Refer to [Section 5.4](#) for details on recommended premedications and [Section 9.8](#) for further information on IRRs.

Please see the ANX005 IB for further details.

1.4.2 Potential Benefits of ANX005

We hypothesize that blockade of C1q with ANX005 in wAIHA will reduce downstream complement components and complement-mediated hemolysis of RBCs in patients with wAIHA.

The clinical safety profile of ANX005 to date demonstrated that single doses up to 100 mg/kg or two doses of 75 mg/kg administered 7 days apart was well tolerated in patients with GBS. In Huntington's disease, two doses of 75 mg/kg administered 5 to 6 days apart followed by 100 mg/kg every 2 weeks for 20 weeks was safe and well tolerated. In patients with CAD, 100 mg/kg administered on Day 1, 8, and 15 followed by every 2 weeks was well tolerated.

The nonclinical safety profile of ANX005 to date demonstrated that doses up to 200 mg/kg per week (the highest dose tested) for up to 26 weeks in cynomolgus monkeys and 4 weeks in rats have been well tolerated with no adverse effects; the 200 mg/kg weekly dose was the NOAEL in both species ([Section 1.3](#)). No drug-related adverse findings were noted in nonclinical studies, and all nonclinical findings were related to ADA formation and are not predicted to translate to humans. Importantly, no novel findings, other than ADA formation, emerged in the 26-week study in comparison to single dose or 4-week studies. Complete C1q suppression was observed in all animals other than those with confirmed or suspected ADA formation at the 50, 100, and 200 mg/kg weekly dose through the dosing duration of the 26-week cynomolgus monkey study.

Specific possible risks to patients are detailed in [Section 1.4.1](#). Off-target effects of ANX005 are unlikely given the specificity of this monoclonal antibody for its target of C1q. Immunogenicity with ANX005 is less likely due to the humanized monoclonal antibody property of ANX005 but will be monitored in this study.

The 100 mg/kg dose was selected for this study to maximize target saturation for as long as possible and to determine proof-of-concept in a chronic disease. The proposed treatment regimen is expected to provide complete C1q inhibition, which is required to completely suppress the complement pathway and potentially affect downstream biomarkers, for a period of at least 4 weeks.

1.4.3 Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize risk to patients participating in this study, the potential risks identified in association with ANX005 are justified by the anticipated benefits that may be afforded to patients with wAIHA. Based on data from completed and ongoing ANX005 studies, the benefit-risk profile remains favorable. For more detailed information on previous human experience, reference the ANX005 Investigator's Brochure.

2. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of two once-weekly intravenous infusions of 100 mg/kg ANX005 in patients with wAIHA	Number and percent of patients experiencing treatment-emergent adverse events (TEAEs)
To evaluate the clinical effect of two once-weekly intravenous infusions of 100 mg/kg ANX005 in patients with wAIHA	- Change from baseline in hemoglobin over time up to Day 71 - Maximum absolute change in hemoglobin from baseline - Change from baseline in biomarkers of hemolysis (reticulocyte count, haptoglobin, LDH, total and indirect bilirubin) over time up to Day 71
Secondary	
To evaluate the PK profile of ANX005 in patients with wAIHA	ANX005 plasma concentration profiles and PK parameters such as AUC, C_{max}, T_{max}, accumulation ratio, $t_{1/2}$, λ_z, CL and Vss
To evaluate the effect of ANX005 on classical complement pathway inhibition as measured by complement system related biomarkers in patients with wAIHA	- Inhibition of classical complement activity as measured by serum CH50 from baseline over time up to Day 71 - Change and percent change from baseline in serum C4 concentrations over time up to Day 71 - Change and percent change from baseline in serum free C1q concentrations over time up to Day 71

Objectives	Endpoints
Exploratory	

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design

This is an open-label, repeat-dose, Phase 2 study in adult male and female patients with wAIHA. This study is designed to evaluate the safety, tolerability, PK, PD, and clinical effect of ANX005 in patients with wAIHA.

One cohort of up to approximately 12 patients with wAIHA will be enrolled in this study.

Patients will be admitted to the study site to receive a 100 mg/kg dose of ANX005 administered by IV infusion on Day 1, which will be administered over approximately 21 hours. Patients will remain in clinic until after the Day 2 assessments have been completed. Patients will be observed for 4 hours after completion of the infusion and may be released once all required end of infusion procedures (eg, PK/PD samples and vital signs) have been conducted. All subsequent visits should be conducted at approximately the same time of day as the Day 1 visit.

Study assessments for safety and PK/PD will also be performed on Day 4.

Patients will check-in to the study center on Day 8 for the second dose of 100 mg/kg of ANX005 administered by IV infusion over approximately 4 hours. Patients will be observed for 4 hours after completion of the infusion and may be released once all required end of infusion procedures (eg, PK/PD samples and vital signs) have been conducted.

Blood samples for serial PK/PD assessments will be collected following each dose of ANX005. The first three samples (pre-dose through 4 hours post-infusion) will be collected on site, and remaining samples may be collected either on site or via home visit.

Patients will return to the clinic to have study assessments for safety, PK, and PD on Days 15, 22, 29, 36, 43, 50, 57, and 71. Any study visit in this timeframe, except for the end-of-study (Day 71 or early termination) visit, may be conducted at home by qualified site personnel or by a home health vendor if allowed by institution policy and regional guidelines.

Study assessments that will be performed in this study are listed in [Table 1](#).

3.2 Safety Review

The PI and the medical monitor will review safety data on an ongoing basis to evaluate the frequency and severity of the following events and findings:

- SAEs
- Discontinuation of treatment or participation due to an adverse event (AE)
- AEs
- Adverse events of special interest (AESI), such as hypersensitivity (eg, rash, angioedema, anaphylaxis, serum sickness reaction), and IRRs, evidence of an infection with encapsulated bacteria, or development of a systemic autoimmune disorder (see [Section 9.7](#) and [Section 9.8](#) for additional details on how such events will be monitored)
- New or worsening, clinically significant findings

See [Section 3.3](#) for a description of Stopping Rules.

3.3 Stopping Rules

Dosing of ANX005 on Day 1 will require patients to be on site for approximately 21 hours for IV infusion. It is expected that the 2nd (Day 8) IV infusion of ANX005 will be completed within approximately 4 hours. Individual patients will be monitored during study drug infusions and may experience study drug interruptions or discontinuation based on immediate observations (refer to [Section 5.4](#) and [Section 9.8](#) for information on study drug administration and management of IRRs). All patients will be followed for safety and with attention towards AESI as described in [Section 9.7](#) and [Section 9.8](#) which provide details for monitoring for infection and IRRs, respectively.

Stopping rules for this study include two or more occurrences of any of the following within a given category:

- Serious adverse events with signs, symptoms, and concurrent serologic evidence consistent with a systemic autoimmune disease considered related to study drug treatment.
- Serious adverse events of infection, including those with encapsulated bacteria, considered related to study drug treatment.
- Systemic life-threatening infusion-related or hypersensitivity reactions resulting in hospitalizations, admittance to the intensive care unit (ICU), or death considered related to study drug treatment.
- Other occurrences of the same or a similar SAE assessed as related to study drug treatment.

Causality of adverse events is determined by the study investigator ([Section 9.2.2](#)). The study may also be terminated if the Sponsor determine that any adverse event(s) are occurring that are intolerable or pose an unacceptable safety risk.

The study will continue to allow for patient follow-up visits as described and for safety observations in the event the study stopping rules are met.

3.4 Enrollment of Patients

Note: “Enrolled” means a participant's agreement to participate in a clinical study following completion of the informed consent process and screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.

If a patient does not receive all scheduled infusions of ANX005 or discontinues prematurely from the study for reasons unrelated to treatment prior to completing the Day 4 assessments, additional patients may be enrolled at the discretion of the sponsor in consultation with the PI to ensure a sufficient number of evaluable patients to assess the study endpoints. Up to 5 additional patients may be enrolled.

3.5 Duration of Participation

The total duration for individual participation in the study will be approximately 16 weeks. The patients are expected to follow the Schedule of Assessments ([Table 1](#)) through the EOS visit (Day 71).

3.6 End of Study Definition

The end of the study is defined as the date of the last visit (eg, Day 71 end-of-study or early termination visit) of the last patient in the study. Patient completion of the study is described in [Section 8.1](#).

4. STUDY POPULATION

The study population consists of male and female patients aged 18 and above, inclusive, at the time of consent with wAIHA with evidence of activation of the complement system. Patients will be primarily recruited from a non-interventional study (ANX-wAIHA-01), designed to establish the level of complement activation in a wide range of patients with wAIHA.

4.1 Number of Patients

Approximately 12 patients are expected to participate in the study.

4.2 Eligibility Criteria

4.2.1 Inclusion Criteria

Patients must meet **ALL** the following criteria to be eligible to participate in the study:

1. Male or female ≥ 18 years of age on the day of signing informed consent
2. Diagnosis of wAIHA at least 3 months prior to screening with a DAT ≥ 1 positive for IgG $\pm$ C3, or a diagnosis of mixed AIHA that is DAT positive for both IgG and C3, with a presence of a cold antibody with a thermal amplitude $\geq 30^{\circ}\text{C}$ (see [Section 7.1.6](#) for details)
3. Hemoglobin level ≤ 10.0 g/dL (pre-transfusion) in wAIHA-01 within 6 weeks of the Day 1 dosing day or during the wAIHA-02 Week -6 or rescreening visits
4. Evidence of classical complement pathway activation in wAIHA-01 within 6 weeks of the Day 1 dosing date or during the wAIHA-02 screening period (see [Section 7.1.6](#) for details):
 - a. Serum complement component 4 (C4) level no greater than 1.5 times the lower limit of normal and/or
 - b. CH50 below the lower limit of normal (LLN)
5. Evidence of active hemolysis at screening based on at least one of the following:
 - a. LDH above the upper limit of normal (ULN)
 - b. Indirect bilirubin above the ULN
 - c. Haptoglobin below the LLN
6. If on corticosteroids, patients must be receiving a stable dose ≤ 1 mg/kg prednisone or equivalent. Tapering of corticosteroids is permitted during the screening period, but the patient's dose must be stable for at least 14 days prior to ANX005 dosing and should not be increased after the screening visit that qualifies the patient. Enrolled patients should

remain on a stable prescribed dose throughout the study. Please refer to [Section 6.1](#) and [Section 6.1.1](#) for more details regarding corticosteroid use during the study period.

7. If on immunosuppressants (eg, azathioprine, mycophenolate mofetil, cyclosporine) must be on stable dose for at least 4 weeks prior to dosing. Please refer to [Section 6.1](#) and [Section 6.1.1](#) for more details regarding use of immunosuppressants during the study period.
8. Patients must have been previously vaccinated for encapsulated bacteria within 5 years prior to screening or be willing to receive prophylaxis against infections with encapsulated bacteria via vaccination and/or the use of prophylactic antibiotics in accordance with local standards of practice and/or guidelines. Please refer to [Section 7.1.2](#) for further details.
9. If female, must be either postmenopausal (no menses for at least 12 months without an alternative medical cause) or surgically sterilized (as described in [Section 6.3.1](#)); OR if a woman of childbearing potential (WOCBP), patient must use a highly effective (ie, failure rate of <1%) method of contraception (as described in [Section 6.3.2](#)) during the study and for 3 months after the last infusion with study medication.
10. If male, must agree to either abstain from heterosexual intercourse as the preferred and usual lifestyle (ie, abstinent on a long term and persistent basis) and agree to remain abstinent OR use a male condom during the study and for at least 3 months after the last infusion with study medication; and should also be advised of the benefit for a female partner to use a highly effective (ie, failure rate of <1%) method of contraception (as described in [Section 6.3.2](#))
11. Able to comply with the requirements of the study and complete the full sequence of protocol-related doses, procedures, and evaluations
12. Ability to understand and provide written informed consent

4.2.2 Exclusion Criteria

Patients must **NOT** meet any of the following criteria to be eligible to participate in the study:

1. Active lymphoma, lymphoproliferative disorder, or other malignancy requiring therapy and/or not clinically stable or in remission for at least 3 months prior to screening.
2. Elevated aspartate aminotransferase or alanine aminotransferase levels >2.5 times the upper limit of normal at screening unless associated with wAIHA
3. Platelet count <30 x 10⁹/L at screening
4. History of isolated cold agglutinin disease.
5. History of solid organ, bone marrow, or stem cell transplantation
6. History of splenectomy within the 90 days prior to screening

7. Received rituximab or other B cell depleting monoclonal antibody (eg, daratumumab) <90 days prior to screening
8. Clinically significant, ongoing illness or medical condition, including mental illness, suicide attempt, seizures, cardiovascular disease, malignancy, or a medical history that would jeopardize the safety of the patient, limit participation, or compromise the interpretation of the safety data derived from the patient
9. Signs and symptoms of or a diagnosis consistent with a chronic autoimmune disorder and/or an ANA titer $\geq 1:160$.
10. History of meningitis or septicemia within the past 2 years
11. Clinically significant infection (ie, viral, including symptomatic or asymptomatic SARS-CoV-2 [COVID-19], bacterial, fungal, or mycobacterial) that required medical intervention (not including antibiotic prophylaxis) within 1 month prior to screening
12. Known genetic deficiencies of the complement cascade system
13. Treatment with an investigational therapeutic agent within 30 days or five half-lives, whichever is longer, prior to screening
14. Active alcohol or substance abuse or any other reason that makes it unlikely that the patient will comply with study procedures
15. Females who are pregnant or breastfeeding.
Note: To be eligible, WOCBP (as defined in [Section 6.3.1](#)) must have a negative pregnancy test at screening (serum) and Day 1 (urine).
16. Hypersensitivity to ANX005 or any of the excipients in the ANX005 drug product
17. Hypersensitivity to or previous allergic reaction to the active substance or to any of the excipients in any of the immunizations required for this study
18. History of previous sensitivities or allergic or anaphylactic reactions to previous IV medication including, but not limited to, monoclonal antibodies
19. Positive serology for human immunodeficiency virus (HIV) 1 or 2 at screening
20. Evidence of hepatitis C virus (HCV) antibody at screening requires reflex testing for HCV ribonucleic acid (RNA). Patients with positive HCV RNA viral load at screening will be excluded. Patients with positive HCV antibody, but negative HCV RNA viral load are eligible but should be monitored throughout the study
21. Evidence of active or prior hepatitis B virus (HBV) infection. Patients with positive hepatitis B surface antigen (HBsAg) at screening are excluded from the study. Patients with positive HBV core antibody and deoxyribonucleic acid (DNA) viral load are excluded from the study
22. History of intravenous immunoglobulin (IVIg) treatment within 90 days prior to dosing
23. History of plasmapheresis or immunoadsorption treatment within 60 days prior to dosing
24. Received any complement inhibitor (eg, eculizumab, berinert) within 90 days or 5 half-lives, whichever is longer, prior to dosing
25. Body weight less than 50 kg or greater than 100 kg

5. STUDY MEDICATION AND ADMINISTRATION

ANX005 is the only study medication used in this study. Details on handling, storage, preparation, and administration of ANX005 are provided in the Pharmacy Manual. Sites must use the ANX005 Infusion Plan to calculate appropriate dose preparation for each infusion.

5.1 ANX005 Description

ANX005 is a recombinant, humanized, monoclonal antibody. The drug product composition is 20 mg/mL ANX005 and includes [REDACTED] as inactive ingredients.

ANX005 is a sterile, clear, colorless, preservative-free solution for IV administration, supplied with an ANX005 concentration of 20 mg/mL in sterile, single-use, 20 mL vials.

All study doses are based on patient body weight at baseline. No modification of the assigned dose is allowed.

5.2 Packaging, Labeling, and Storage

ANX005 packaging consists of supply cartons containing ANX005 vials. The cartons are tamper-seal protected for shipment. Labels are present on both the cartons and the vials.

Do not remove vials from their cartons prior to infusion preparation. Store ANX005 in a secure area with controlled access, under monitored refrigeration (2°C to 8°C) and protect from light. Excursions from these limits should be reported to sponsor representatives to determine whether the affected vials can be used. For this study, study drugs such as partially used study drug containers, vials, and syringes may be destroyed on site. Reference the study Pharmacy Manual for details.

Pharmacy records must document storage temperatures.

5.3 Preparation of Study Medication

ANX005 is diluted into normal saline to a total volume of 525 mL prior to IV infusion. Details for preparing ANX005 are provided in the Pharmacy Manual.

5.4 Dosage and Administration

Site personnel administer ANX005 via IV infusion following the sponsor-provided infusion plan such that each patient receives 100 mg/kg of ANX005. No modification of the assigned dose is allowed. The ANX005 Infusion Plan provides details on the preparation of ANX005 for infusion including drug concentrations, saline dilution, and infusion rates. The Day 1 infusion is expected to take approximately 21 hours to administer. The second (Day 8) infusion is expected to take approximately 4 hours to administer. The dosing schedule is detailed in [Table 2](#) below.

Table 2: ANX005 Dosing Schedule

Study Visit	Day 1	Day 8
Dose (mg/kg)	100	100
Infusion time (hours)	~21	~4

Monitor patients with a transcutaneous pulse oximeter continuously during each ANX005 infusion. Patients will be observed for 4 hours after completion of the infusion and may be released once all required end of infusion procedures (eg, PK/PD samples and vital signs) have been conducted.

Patients are allowed normal meals prior to and during the infusion of ANX005. Water use prior to, during, or after the infusion is unrestricted.

Patients are monitored closely for detection of IRRs during and following completion of the infusion of ANX005. If IRRs occur during the infusion, the infusion rate may be slowed or the infusion stopped temporarily until symptoms have resolved, or discontinued altogether as indicated depending on the severity of symptoms that develop during the infusion. See [Section 9.8](#) for details on monitoring for infusion reactions.

Premedication

During the initial ANX005 infusion, all patients should receive prophylactic treatment with an antihistamine and acetaminophen within 2 hours prior to the start of the infusion. The following medications should be administered prior to the first ANX005 infusion:

- Acetaminophen (500 mg) oral
- An H1 blocking antihistamine (10 mg cetirizine or equivalent) IV or oral
- An H2 blocking antihistamine (20 mg famotidine or equivalent) oral

During the first infusion of ANX005, the H1 blocking antihistamine should be administered every 8 hours and H2 blocking antihistamine 24 hours after the start of the infusion unless there are relative contraindications to doing so (eg, antihistamine side effects). The addition of diphenhydramine (25–50 mg IV or oral) may be given as needed in patients that develop pruritus (itching).

The Day 8 infusion can be expected to be completed over approximately 4 hours. Premedication is not expected to be needed for the Day 8 infusion of ANX005, but is not prohibited based on investigator discretion and after appropriate risk-benefit assessment (eg, considering IRRs during the first infusion).

Modification to the recommended medication guideline is acceptable based on individual patient condition and characteristics. Addition or substitution with alternative antihistamines, corticosteroid and/or other medication is acceptable based on investigator discretion. The PI

or medically qualified designee may choose to lower or omit doses of pre-medications if discussed with and approved by the medical monitor. Prophylactic medications may be repeated during the infusion of ANX005 at the discretion of the PI or medically qualified designee.

Please consult the relevant prescription drug labeling information (eg, USPI, SmPC, etc.) for potential drug-drug interactions (DDIs) between premedications and any other permitted medications (See [Section 6.1](#)) to be used concomitantly.

5.5 Study Medication Accountability

Site personnel must maintain adequate records of the receipt and disposition of all vials of ANX005. Records must include dates, lot numbers, quantities received, quantities dispensed, and the patient identification code associated with each infusion. Site personnel may destroy used vials of ANX005 per site standard operating procedures (SOPs).

5.6 Overdose

An accidental overdose is highly unlikely, because a pharmacist or qualified designee prepares ANX005 dilutions for infusion. In the event of an accidental overdose, contact the medical monitor immediately to discuss an appropriate course of action and follow-up. Based on nonclinical toxicology data, no adverse events are anticipated with overdoses of ANX005.

5.7 Missed Doses

If a patient does not complete the ANX005 infusions as planned (eg, failure to administer the scheduled dose in the specified interval or treatment is discontinued) the patient may not be rechallenged and should continue in the study with all scheduled visits and at a minimum return for the ET/EOS visit (Day 71) as discussed in [Section 8.2](#).

If a patient does not receive all scheduled infusions of ANX005 or discontinues prematurely from the study for reasons unrelated to treatment prior to completing the Day 4 assessments, up to 5 additional patients may be enrolled as described in [Section 3.4](#).

6. MEDICATIONS AND RESTRICTIONS

Record all medications on the concomitant medications electronic case report form (eCRF), including all medications taken from the screening visit through the final study visit.

6.1 Permitted Medications

Permitted concomitant medications include corticosteroids (stable dose for at least 2 weeks prior to dosing) and immunosuppressant therapy (eg, azathioprine, mycophenolate mofetil [MMF], or cyclosporine that has been at a stable dose for at least 4 weeks prior to dosing). wAIHA therapy must be maintained at stable doses throughout the study.

Concomitant therapy for iron, folic acid, and vitamin B12 deficiency is permitted and encouraged if deemed clinically necessary by the investigator.

Patients receiving a SARS-CoV-2 (COVID-19) vaccine are recommended to complete all vaccine doses at least 2 weeks prior to ANX005 dosing or after Day 71. If SARS-CoV-2 vaccination is being considered during the study period, please discuss with the Medical Monitor prior to vaccine administration. See [Section 7.1.2](#) for recommendations regarding other vaccinations.

6.1.1 Rescue Medication

The study site will provide rescue medication if deemed clinically necessary by the investigator due to worsening disease activity. It is also advised that investigators monitor for the possibility of rebound hemolysis following completion of ANX005 dosing. The following rescue medications may be used:

1. Corticosteroids
2. Immunosuppressants

Although the use of rescue medications is allowable at any time during the study, the use of rescue medications should be delayed, if possible, for at least 28 days following the administration of study intervention. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded. In cases where rescue therapy is warranted per the investigator's judgment, please discuss with the Medical Monitor whether the patient should continue participation in the trial.

6.2 Prohibited Concomitant Medications, Procedures, and Supplements

The following concomitant medications and procedures are not allowed during the study (ie, from Screening through Day 71/EOS/ET):

- B cell depleting monoclonal antibodies (eg, rituximab, daratumumab)
- Complement inhibitors other than ANX005 (eg, eculizumab, berinert)
- IVIg
- Plasmapheresis or immunoadsorption procedures
- Other investigational drugs
- Drugs of abuse

Of note, while concomitant use of corticosteroids (≤ 1 mg/kg prednisone or equivalent) and immunosuppressant medications at stable doses is permitted, modification of the dose or initiation of new treatment with these agents is prohibited. Please refer to [Section 6.1.1](#) for guidance regarding use of these agents as rescue therapy for worsening disease activity.

6.3 Contraceptive Methods

6.3.1 Definitions

Women of Childbearing Potential

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below)
 - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
 - Permanent sterilization methods (for the purpose of this study) include:
 - Documented hysterectomy
 - Documented bilateral salpingectomy
 - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should 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.

6.3.2 Contraceptive Guidance

Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female patients of childbearing potential and female partners of childbearing potential must agree to use a highly effective method of contraception during the study and for at least 3 months after the last infusion of study medication. Highly effective methods of contraception (ie, <1% failure rate when used consistently and correctly) include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)

- Vasectomized partner
- Sexual abstinence defined as complete absence of heterosexual intercourse

Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study medication.

6.4 Restrictions

Alcohol use is prohibited throughout the duration of the in-patient portion of the study (Day 1-2).

7. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Schedule of Assessments ([Table 1](#)). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the Schedule of Assessments ([Table 1](#)) is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients 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 time frame defined in the Schedule of Assessments ([Table 1](#)).
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Repeat laboratory testing is permitted at screening as well as during the study period.

7.1 General Assessments

7.1.1 Screening and Informed Consent

Prior to any screening evaluations or protocol-related activities, obtain informed consent from each potential patient in accordance with Good Clinical Practice (GCP) and local regulatory requirements. The format and content of the informed consent form (ICF) must be approved by the appropriate institutional research board/independent ethics committee (IRB/IEC) prior to implementation.

7.1.2 Guidance for Prophylaxis Against Infections with Encapsulated Bacteria

Complement activation results in the rapid clearance of bacteria by immune cells and direct bacterial killing via large pore forming terminal complement complexes. Long-term complement inhibition may increase the risk of infection with encapsulated bacteria, particularly *Neisseria meningitidis*, including serogroup B meningococcus, *Haemophilus influenzae*, and *Streptococcus pneumoniae*. While the overall risk of infection risk appears low with short-term and selective blockade of the classical complement pathway that leaves the immune function of the lectin and alternative pathways intact (eg, with ANX005 administration), an appropriate program of prophylactic procedures, including vaccinations or chemoprophylaxis will be instituted. Vaccination or chemoprophylaxis reduce but may not prevent the risk of infections and therefore patients must be advised to immediately report signs or symptoms (eg, fevers, severe cough, shortness of breath, sinusitis, intractable headache or neck stiffness, photosensitivity, etc.) that may be indicative of an active infection to the investigator. Patients who develop symptoms consistent with an infection due to encapsulated bacterial pathogens during the study period should have an appropriate medical workup to establish a diagnosis.

Patients who do not have a documented history of vaccination against encapsulated bacterial pathogens (*Neisseria meningitidis*, including serogroup B meningococcus, *Haemophilus influenzae*, and *Streptococcus pneumoniae*) within 5 years prior to screening must be willing to receive prophylaxis against infections with encapsulated bacteria via vaccination and/or the use of prophylactic antibiotics during first 6 weeks of treatment and follow-up or until complement activation returns as measured by CH50 in accordance with local standards of practice and/or guidelines.

The following vaccines are recommended for prevention of infection with encapsulated bacteria with the use of complement inhibitors:

- One dose of a meningococcal conjugate (MenACWY) vaccine
- Two doses of meningococcal serotype B (MenB) vaccine series
- One dose of a pneumococcal vaccine
- One dose of *Haemophilus influenzae* type b (according to investigator discretion)

Prophylaxis for infections with encapsulated bacteria should comply with local vaccination guidelines and standards of care. The following guidance is recommended, but should be discussed with the Medical Monitor if it conflicts with local vaccination guidelines and standards of care:

The first dose for each vaccine is recommended to be administered at least 14 days prior to dosing with ANX005. Both doses of the MenB vaccine will be administered during the screening period (eg, Week -6 and Week -2 visits). Chemoprophylaxis with antibiotics may be substituted for or be administered concomitantly with vaccinations at the investigator's discretion according to local guidance and standards of care, but should be discussed with the Medical Monitor.

The Week -2 visit is not required for patients who have a documented history of vaccination for *Neisseria meningitidis*, including serogroup B meningococcus, *Haemophilus influenzae*, and *Streptococcus pneumoniae* within 5 years prior to Screening. For these patients, the screening visit and associated procedures will be conducted at or during the 6-week screening period starting at Week -6, and all screening procedures described in both the Week -6 and rescreening visits in the Schedule of Assessments ([Table 1](#)) should be conducted during the screening period.

Guidelines for chemoprophylaxis against encapsulated bacteria for patients with asplenia and/or congenital complement deficiencies provide recommendations for the choice of antibiotics.

7.1.3 Patient Identification Number

Assign a unique, sequential number to each patient upon signature of an ICF. Patient numbers consist of 6 digits; the first 3 digits identify the study site, and the last 3 digits identify the patient screened at the site, in ascending order.

Patients who fail screening during the 6-week screening period are not considered enrolled in the study and must not be dosed with ANX005.

If an enrolled patient does not receive infusion of ANX005, do not reuse the same patient identification number for another patient.

7.1.4 Rescreening Criteria

Patients who do not meet all inclusion and exclusion criteria at Week -6 may rescreen twice during the 6-week screening period for eligibility criteria, using rescreening kits, if there is cause to believe that the patient will be eligible upon rescreen. Patients who are rescreened will retain their original patient identification number.

7.1.5 Demographics and Medical History

Demographics include age, sex, and self-reported race or ethnicity.

Medical history includes an assessment of past and present, clinically significant diseases and surgeries, as well as an assessment of current reproductive status. Record all medications (eg, prescription and over-the-counter medications, hormonal birth control, herbal or homeopathic remedies, and nutritional supplements) used by the patient within 3 months prior to the screening visit.

7.1.6 Screening Laboratory Assessments

The following laboratory assessments are performed during screening only ([Table 1](#)). Obtain blood samples for the following assessments and send to the laboratory specified by the sponsor for analysis to establish current health status or to determine eligibility for enrollment. Local laboratory results may be used to evaluate entry criteria in certain circumstances, in place of central laboratory results; please consult the study Medical Monitor. Refer to the Laboratory Manual for additional details.

- **DAT:** Polyspecific anti-IgG and anti-C3d
- **Evaluation for other causes of anemia:**
 - Iron studies will include iron, ferritin, transferrin, and total iron binding capacity.
 - Erythropoietin (EPO), folic acid, and vitamin B12 levels will also be evaluated.

Iron studies, EPO levels, vitamin B12, and folic acid levels may be retested at the investigator's discretion if found to be below the LLN during screening.
- **IgM cold agglutinin:** Includes thermal amplitude testing
- **Flow cytometry:** Collect whole blood sample to evaluate for complement deposition on the surface of blood cells.
- **Serology Tests:** HIV-1, HIV-2, hepatitis C, and hepatitis B test. A positive HCV antibody test at screening will trigger reflex testing for HCV RNA viral load. A positive HBV core antibody test with negative HBsAg and negative HBV surface antibody tests will trigger DNA viral load reflex testing. Reflex testing for HBV and HCV viral load should be performed consistent with local guidelines.
- **SARS-CoV-2 (COVID-19) Screen:** Screening and testing for SARS-CoV-2 infection (COVID-19) will be conducted in accordance with local guidelines and should be performed either during the screening period or during the Day 1 visit prior to the first administration of ANX005. Additional testing for SARS-CoV-2 throughout the duration of the study may also be performed at the investigator's discretion according to local guidelines.

Please note that C4, CH50, and Hemoglobin assessments obtained in the ANX-wAIHA-01 study to confirm a diagnosis of wAIHA with classical complement activity may be used to evaluate eligibility for participation in ANX005-wAIHA-02, provided that the samples from ANX-wAIHA-01 were collected within 6 weeks of dosing with ANX005 and the patient has not received any new wAIHA therapies (eg, steroids, immunosuppressants, immune-modulating therapy) or increased doses of any existing therapies while participating in ANX-wAIHA-01.

PK and PD laboratory assessments are described in [Section 7.2](#). Other laboratory assessments performed at screening and periodically throughout the study for safety are described in [Section 7.3.5](#).

7.2 Pharmacokinetic, Pharmacodynamic, and Other Efficacy Assessments

Obtain, process, aliquot, and freeze blood samples for the listed tests in preparation for shipment to a bioanalytical laboratory for analysis. When obtaining samples for PK and PD assessments, draw blood from the arm that was not used for the infusion of ANX005. Complete details pertaining to the collection, handling, and shipment of these samples are located in the Laboratory Manual.

7.2.1 Pharmacokinetic Sampling for ANX005 Concentrations

This test requires serum. On ANX005 dosing days ([Table 1](#)), PK samples will be collected prior to the start of the infusion (within 30 minutes pre-dose), within 15 minutes after completing the infusion and again 4 hours (± 15 minutes) after the end of the infusion. Sample collection on non-dosing days should be completed at approximately the same time as the start of the Day 1 infusion (± 4 hours).

Unscheduled samples may be drawn in the event of suspected ANX005-related toxicity or in the event of an IRR during ANX005 infusion (see [Section 9.8](#)).

7.2.2 Clinical, Pharmacodynamic, and Biomarker Sampling

Disease activity markers: Other disease-related activity biomarkers (eg, hemoglobin, LDH, total and indirect bilirubin, haptoglobin, reticulocytes) will be evaluated at the study visits indicated in [Table 1](#).

Free C1q: Analysis of free C1q in serum will be performed on the same samples collected for ANX005 PK. On ANX005 dosing days ([Table 1](#)), samples will be collected prior to the start of the infusion (within 30 minutes pre-dose), within 15 minutes after completing the infusion and again 4 hours (± 15 minutes) after the end of the infusion. Sample collection on non-dosing days should be completed at approximately the same time as the start of the Day 1 infusion (± 4 hours).

Unscheduled samples may be drawn in the event of an IRR during ANX005 infusion (see [Section 9.8](#)).

[REDACTED]

[REDACTED]

[REDACTED]

Other PD biomarkers:

[REDACTED]

[REDACTED]), samples will be collected prior to the start of the infusion (within 30 minutes pre-dose) and within 15 minutes after completing the infusion. Collection on non-dosing days should be completed at approximately the same time as the start of the Day 1 infusion (± 4 hours).

7.2.3

[REDACTED]

7.3 Safety Assessments

7.3.1 Physical Examinations

The physical examination includes a symptom-driven evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Record any abnormality identified prior to infusion of ANX005 as medical history.

Record any clinically significant, new or worsened abnormalities that occur after infusion of ANX005 as AEs ([Section 9](#)).

7.3.2 Height and Weight

Height and weight (for eligibility) will be collected as part of the physical examination at the specific timepoints indicated in the Schedule of Assessments ([Table 1](#)).

7.3.3 Vital Signs

Measure vital signs at the time points as indicated in the Schedule of Assessments ([Table 1](#)). Vital signs include body temperature, respiratory rate, heart rate, and blood pressure (systolic and diastolic). Heart rate, respiratory rate, and blood pressure should be measured after the patient has rested for at least 5 minutes in an upright seated position. Monitor patient with a transcutaneous pulse oximeter continuously during each ANX005 infusion (approximately 21 hours for Day 1 dosing and approximately 4 hours for Day 8).

7.3.3.1 Vital Signs and Dosing

Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) should be collected 30 minutes prior to the start of the infusion (± 5 minutes) and within 1 hour (± 15 minutes) after the end of the infusion. Vital signs may be collected at additional timepoints at the discretion of the investigator.

Should an IRR occur; vital signs should be collected at the onset of the IRR (± 5 minutes), 15 minutes after the onset (± 5 minutes), and every 30 minutes (± 5 minutes) thereafter until vital signs are stabilized. Once vital signs are stabilized, vital signs should be collected every 4 hours (± 15 minutes) until the end of the infusion or the IRR is fully resolved. See [Section 9.8](#) for additional information regarding IRRs.

7.3.4 Electrocardiograms

Perform electrocardiograms (ECGs) prior to infusion on dosing days after the patient has rested in a supine position for at least 5 minutes. Electrocardiograms may include ventricular heart rate; QRS duration; PR, RR, QT, QTcB, and QTcF intervals; QRS complex; and P and T waves. Record an evaluation of normal, abnormal (not clinically significant), or abnormal (clinically significant).

When the timing of these measurements coincides with blood collection, obtain the ECG prior to the nominal time of the blood collection, blood pressure, and heart rate.

7.3.5 Safety Laboratory Assessments

Obtain blood and urine samples for the following safety laboratory assessments according to the Schedule of Assessments ([Table 1](#)) and send to the laboratory specified by the sponsor for analysis to determine eligibility for enrollment or ongoing laboratory safety evaluation of the patients. Refer to the Laboratory Manual for additional details.

- **Hematology:** Hemoglobin, hematocrit, platelet count, red blood cell count, white blood cell (WBC) count, percent and absolute WBC differential count (neutrophils, eosinophils, lymphocytes, monocytes, basophils), percent and absolute reticulocyte count

- **Coagulation:** Prothrombin time, partial thromboplastin time (PTT), and derived measure international normalized ratio (INR)
- **Serum chemistries:** Chemistry panel including sodium, calcium, potassium, phosphorus, magnesium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, total and indirect bilirubin, albumin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total protein, uric acid, lactate dehydrogenase, gamma-glutamyl transferase, creatine phosphokinase (fractionated), and serum haptoglobin
- **Pregnancy test:** All women of childbearing potential ([Section 6.3](#)) must have a serum pregnancy test at screening. Additional pregnancy tests (serum or urine) must be done at time points outlined in the schedule of assessments. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

Note: 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 patient's participation in the study.

- **Urinalysis:** Urinalyses will be assessed by dipstick, including pH, specific gravity, protein, glucose, ketones, nitrites, bilirubin, urobilinogen, blood, and leukocyte esterase. Urine microscopy (leukocytes, erythrocytes, epithelial cells, casts, crystals, bacteria) is required at the screening and baseline (Day 1) visits. After the baseline (Day 1) visit, reflex microscopy should be performed when clinically significant abnormal urinalysis dipstick results are observed.
- **ANA (anti-nuclear antibody):** ANA samples will be obtained according to the Schedule of Assessments ([Table 1](#)). All ANA samples will be processed, however, the baseline sample for autoantibody testing (other than ANA) will be aliquoted and stored but not processed unless the following conditions apply:

If post-baseline ANA titers are $\geq 1:160$ and elevated from baseline by at least 2 dilutions or the patient has developed signs or symptoms of autoimmunity (eg, unexplained rash, arthritis, proteinuria, neurologic symptoms, recurring fever, swollen glands, new onset cytopenias), obtain an additional sample for autoantibody testing. In addition, the stored sample collected at baseline should be tested for ANA titers.

Additional autoantibody testing for both the baseline sample and subsequent collections should include:

1. ANA
2. Anti-double-stranded DNA antibody (anti-dsDNA)
3. Antiphospholipid antibody (APL) including lupus anticoagulant, anti-beta2 glycoprotein IgG and IgM, and anti-cardiolipin IgG and IgM
4. Ribonucleoprotein (RNP; also called nRNP and U1RNP) antibody
5. Smith antibody
6. SS-A/Ro antibody

7. SS-B/La antibody

- **ADA (Anti-ANX005 antibody):** This test requires serum. See the Schedule of Assessments ([Table 1](#)) for time points. Process and freeze samples in preparation for shipment to the bioanalytical laboratory at the request of sponsor representatives. Patients who test positive for ADA in the screening assay will be tested in a confirmation assay, run in the presence of high concentrations of drug, followed by an ADA titer assay. Unscheduled samples for analysis of ADA may be drawn in the event of an IRR during ANX005 infusion (see [Section 9.8](#)).

8. STUDY COMPLETION AND WITHDRAWAL

8.1 Patient Completion

Patients complete study visits as defined in [Table 1](#), culminating with the EOS visit (Day 71).

8.2 Patient Withdrawal

A patient may withdraw from the study at any time. Site personnel must make every effort to determine why a patient withdraws from the study early. Any patient who withdraws from the study with an ongoing AE that is considered related to ANX005 must be followed until the event is resolved or deemed stable. For patients who refuse further study visits, attempt to obtain an end-of-study evaluation at Day 71, with a total of 2 documented attempts of contact with the patient to review ongoing or new AEs that may have occurred since the infusion of ANX005.

The sponsor and/or investigator may choose to discontinue study treatment for patients who are determined to be at risk for continued treatment. If a patient does not complete the ANX005 infusions as planned (eg, failure to administer the scheduled dose in the specified interval or treatment is discontinued) the patient should continue in the study with all scheduled visits and at a minimum return for the ET/EOS visit (Day 71). Reasons for discontinuing treatment of individual patients may include:

- Patient withdraws consent
- Investigator or Sponsor considers that the patient will not benefit from further study drug administration
- Patient becomes pregnant
- Patient is unable to comply with the protocol requirements
- Adverse event

8.3 Termination of the Study

If the PI, the medical monitor, or other sponsor representatives become aware of conditions or events that suggest a possible hazard to patients if the clinical study continues, the clinical study may be terminated by the sponsor after appropriate consultation between the involved parties. The clinical study may also be terminated at the sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination of the clinical study include, but are not limited to the following examples:

- The discovery of an unexpected, relevant, or unacceptable risk to patients related to ANX005 enrolled in the clinical study
- Failure to fully enroll the study
- A decision of the sponsor to suspend or discontinue the study

Should the study be terminated, or the study site closed for any reason, all documentation pertaining to the study must be forwarded to sponsor representatives. The study physician must continue to assess and maintain patient safety as required, despite termination of the study by the Sponsor.

9. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND REPORTING

9.1 Adverse Events

9.1.1 Definition

An AE is any untoward medical occurrence in a patient who has been administered a pharmaceutical product. An AE does not necessarily have a causal relationship with the product and therefore can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a pharmaceutical product. An AE can arise with any use, route of administration, dose (including an overdose), or when used in combination with another pharmaceutical product.

Events occurring after signing the informed consent but prior to first administration of ANX005 should be documented as medical history unless the event is study procedure related, in which case it should be reported as an AE. Events observed during or following the first administration of ANX005 until the end of study visit, are to be recorded as AEs.

An AE includes any of the following:

- An exacerbation or an unexpected increase in frequency or intensity of a preexisting condition, including intermittent or episodic conditions
- New conditions or intercurrent illnesses detected or diagnosed after the first administration of ANX005

- A suspected drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either ANX005 or a concurrent medication
- Any clinically significant laboratory abnormality or physical examination finding that was not present prior to the first administration of ANX005

An AE does not include:

- Anticipated day-to-day fluctuations of any pre-existing conditions, including the disease under study (wAIHA)
- Medical or surgical procedure (eg, colonoscopy, hernia repair); the condition that leads to the procedure may be an AE, if not present in medical history
- Hospitalizations where an untoward medical occurrence did not occur (social or convenience admission to a hospital, such as the admission the night prior to an outpatient visit)
- Pre-existing diseases or conditions that were present before the start of ANX005 administration that do not worsen
- Overdose of either study drug or concomitant medication without any signs or symptoms

9.2 Severity and Causality Assessment

9.2.1 Severity Rating

The severity of each AE should be characterized and then classified according to National Cancer Institute Common Terminology Criteria for Adverse Events, (CTCAE v5.0), Adverse Event Severity Grading ([Appendix A](#)). For infusion related reaction severity grading please refer to [Appendix B](#).

9.2.2 Causality Rating

An event is considered related to ANX005 if there is a reasonable possibility that there is a causal relationship between the ANX005 and the event. Any AE judged by the PI or sponsor representatives as having a reasonably suspected, causal relationship to ANX005 qualifies as a related AE.

Adverse events are categorized as having one of the following causalities:

Not Related: The AE is not related to ANX005 if any of the following exists:

- An event that is considered part of natural history of wAIHA in intensity and frequency
- Another cause of the event is most plausible

- A clinically plausible temporal sequence is inconsistent with the onset of the event and the ANX005 administration
- A causal relationship is considered biologically implausible

Related: The AE is possibly or probably related if any of the following exists:

- The event is uncommon in the patient population and follows a reasonable, temporal sequence from administration of ANX005
- The event cannot readily have been produced by the clinical state of the patient, environmental factors, concomitant medication, or other modes of concomitant therapy
- The event improves on stopping ANX005 and reappears on subsequent exposure to ANX005

Relationship assessment for individual AEs is part of the PI responsibilities. Regardless of relationship, sponsor representatives review all AEs against cumulative experience of ANX005 to identify and communicate new safety findings to the PI and regulatory authorities, as applicable.

9.3 Documentation

An event that occurs after a patient signs the ICF, but prior to first administration of ANX005 should be documented as medical history, unless the event is study procedure related, in which case it should be reported as an AE. Any new event or worsening pretreatment event that occurs from the time of the first administration of ANX005 until the final study visit is recorded as an AE, irrespective of whether the event is considered to be related to ANX005.

Adverse events are reported at the maximum intensity experienced. If a previously recorded pretreatment condition increases in severity or frequency, it is recorded as a new AE. All AEs are considered ongoing until they have completely resolved or, in the case of a pretreatment condition, returned to baseline status recorded prior to administration of ANX005. At the time of the final study evaluation, all AEs should have a statement regarding resolution. Any AE that is assessed as related to ANX005 is followed until resolution or stabilization.

The following information is collected on all AEs experienced during this clinical study:

Event Term

- Whenever possible, report an AE as a specific diagnosis or syndrome using the most medically appropriate term rather than as signs or symptoms. If no specific diagnosis or syndrome can be identified, the AE symptoms should be recorded as separate and individual events.

Onset Date

- Report the date on which the AE was first experienced
- For AEs experienced during infusion of ANX005, report the date and time, using the infusion reaction eCRF page.

Resolution Date

- Report the date on which the AE was last experienced, completely resolved, or if for a pretreatment condition, returned to the baseline status

Severity

- Determine the worst grade as defined by NCI CTCAE v 5.0 ([Appendix A](#))

Seriousness

- Confirm whether or not the AE meets the definition of an SAE ([Section 9.4.1](#))

Causality

- Determine the relatedness of the AE to ANX005 ([Section 9.2.2](#))

Action Taken

- Report the action taken with ANX005 in response to the AE
 - Dose Not Changed (No action taken)
 - Drug Interrupted (infusion interrupted)
 - Drug Withdrawn (infusion discontinued)
 - Not applicable

Outcome

- Report the outcome of the AE
 - Ongoing
 - Fatal
 - Not recovered/not resolved
 - Recovered/resolved
 - Recovered/resolved with sequelae
 - Recovering/resolving
 - Unknown

Caused Discontinuation from Study

- Report whether the AE was the cause of the patient discontinuing from the study
- Record clinically significant, abnormal, laboratory, or physical examination findings discovered during the screening period on the Medical History eCRF as a diagnosis whenever possible.
- Record clinically significant, abnormal findings after the start of infusion of ANX005, throughout the study, until the final visit on the AE eCRF as a diagnosis.

9.4 Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions

The PI classifies each AE as serious or not serious.

The medical monitor determines the expectedness of AEs assessed as related to ANX005.

9.4.1 Serious Adverse Event Definition

An SAE is defined as any untoward medical occurrence that meets one or more of the following criteria:

1. Is fatal
2. Is life threatening (ie, patient was at risk of death at the time of the event)
3. Requires or prolongs in-patient hospitalization (unless related to an elective surgery, a routine procedure to treat a pre-existing condition that did not worsen or an admission for non-medical reasons such as respite care)
4. Results in persistent or significant incapacity or disability
5. Is a congenital anomaly/birth defect in the child of a patient exposed to ANX005 prior to conception, or during pregnancy
6. Is a medically important event (ie, events that may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition)

An SAE may also include any other event that the PI or the medical monitor judges to be serious or that suggests a significant hazard, contraindication, side effect, or precaution.

In addition, any event that occurs after the patient signs an ICF and the first infusion of ANX005 that is assessed by the PI as both serious and related to a protocol mandated procedure must be documented as an SAE.

9.4.2 Suspected Unexpected Serious Adverse Reaction Definition

A suspected, unexpected, serious, adverse reaction (SUSAR) is any AE for which there is evidence to suggest a causal relationship between the ANX005 and the AE, and which is both assessed as unexpected and serious. An unexpected adverse reaction (ie, any untoward and unintended response to the ANX005), is one for which the nature and severity is inconsistent with the applicable Reference Safety Information (RSI). The ANX005 Investigator's Brochure contains RSI that should be referenced for assessing expectedness of adverse events with ANX005 administration.

SUSARs are subject to expedited reporting to applicable regulatory authorities.

9.5 Reporting

Site personnel must provide patients with contact information for the PI and study physician for reporting SAEs.

The reporting period for SAEs begins from the time of infusion of ANX005 through study completion. If an ongoing SAE that is thought to be related to ANX005 remains unresolved at the conclusion of the study additional follow-up must continue until resolution or stabilization of the SAE.

All initial and follow-up information regarding SAEs including those related to protocol mandated procedures, must be reported by the PI or study physician immediately (within 1 day of discovery) to a sponsor representative. Reporting must not be delayed by waiting for additional information. Additional information can be reported in a follow-up report. Forms and instructions for completion and submission of SAE report forms are provided as part of the study instructions.

It is the responsibility of the medical monitor to assess expectedness and sponsor representatives report SUSARs to regulatory authorities within the time frames required by applicable regulations. It is the responsibility of the PI to notify the IRB/IEC of SAEs and any new and significant safety information. At a minimum, SUSARs must be brought to the attention of these review boards in accordance with regional regulations.

9.5.1 Reporting for Disease Under Study

The PI will assess if any worsening of wAIHA leading to prolongation of hospitalization that is considered part of natural history of wAIHA in intensity and frequency should be reported as an SAE.

An overnight stay in the hospital for social convenience the night prior to follow-up visits is not reported as an SAE.

Failure to respond to treatment for wAIHA is not reported as an SAE.

9.6 Clinically Significant Findings and Safety Monitoring

Sponsor representatives conduct an ongoing review of all study data, with particular attention given to laboratory findings, AEs, and concomitant medication data. Any significant trends in safety observations or other findings of significance that are considered related to ANX005 are reported to the PI and regulatory authorities.

Safety data include, but are not limited to, SAEs, AEs, physical examinations, vital signs, and laboratory data (protocol specified or ad hoc), as well as additional information provided by the PI.

9.7 Monitoring for Infection and Autoimmunity

Patients receiving the classical complement inhibitor ANX005 are potentially at risk of infections with encapsulated bacteria that are mainly, but not exclusively community -acquired. These pathogens include *Neisseria meningitidis*, including serogroup B meningococcus, *Haemophilus influenzae*, and *Streptococcus pneumoniae*. All patients enrolled in this study are required to receive prophylaxis via vaccinations and/or use of prophylactic antibiotics 6 weeks from the first dose of ANX005 for these pathogens or provide documented evidence of vaccination prior to enrolment. Although vaccination and prophylactic antibiotics against these bacteria is highly effective in reducing the risk of infections, it will not abolish the risk of any of these infections from occurring. Therefore, patients will be monitored for signs and symptoms of infection throughout the study.

As an additional precaution during the study, whether an in-patient or out-patient, patients must carry a detailed patient card describing the “alert” symptoms for infections at all times. The triggers for seeking immediate medical attention are any of the following symptoms:

- Fever
- Fever and a cough
- Flu like symptoms
- Sore throat
- Ear infection or pain
- Headache with nausea and vomiting
- Headache and fever
- Headache with a stiff neck or stiff back
- Fever and a rash
- Confusion
- Eyes sensitive to light

Any patient experiencing any of the above noted symptoms needs to follow the instructions displayed on the patient card and be seen by a physician as quickly as possible. Early

recognition of a bacterial infection with encapsulated bacteria and the identification of the causative pathogen by culture is important to optimize outcomes. After an initial work-up, instituting appropriate antimicrobial treatment and monitoring of the patient's condition is recommended.

Patients will have regular safety laboratory evaluations conducted ([Table 1](#)) with results assessed for signs and symptoms of potentially developing a systemic autoimmune disease including CBC with differential, urinalysis, and ANA.

Assessed at every visit where safety samples are collected:

- Treatment-emergent WBC $<4,000/\text{mm}^3$ OR
- Treatment-emergent absolute neutrophil count of $<1,500/\text{mm}^3$ OR
- Treatment-emergent lymphocyte count of $<1,000/\text{mm}^3$ OR
- Platelet count of $<100,000/\text{mm}^3$ in those with platelet counts above this threshold at baseline or platelet counts $<30,000/\text{mm}^3$ in those with platelet counts below $100,000/\text{mm}^3$ at baseline OR
- Urinalysis (including pH, specific gravity, protein, glucose, ketones, nitrites, bilirubin, urobilinogen, blood, and leukocyte esterase) will be used to assess for any significant changes from baseline. If urinalysis parameters show potentially new clinically significant abnormalities, reflex microscopy will be performed, and a determination of whether a clinically significant change from baseline based on reflex microscopy and clinical correlation will be made by the investigator. Specimens for spot urine protein-to-creatinine ratio assessment may also be collected and sent for evaluation at the investigator's discretion.

Assessed at baseline, Day 29, and Day 71:

- ANA titer $\geq 1:160$ and an increase from baseline of at least 2 dilutions

If any of the laboratory criteria (WBC, neutrophils, lymphocytes, platelets, or proteinuria) are met on 2 or more separate assessments in the absence of a known cause of the observed laboratory abnormalities, or an ANA titer $\geq 1:160$ with an increase from baseline of at least 2 dilutions is observed at 1 or more assessments, further autoantibody testing (see below and [Section 7.3.5](#)) will be conducted on the stored and current samples that will include:

- Antinuclear antibodies
- Anti-double-stranded DNA antibody (anti-dsDNA)
- Anti-B2GPI IgG and IgM
- Anti-cardiolipin IgG and IgM
- Lupus anticoagulant

- RNP (also called nRNP and U1RNP) antibody
- Smith antibody
- SS-A/Ro antibody
- SS-B/La antibody

At each visit, patients will also be assessed for signs and symptoms suggestive of an autoimmune disease such as SLE, including seizures, psychosis, pleuritis, pericarditis, persistent hypertension, or new onset arthritis. The development of any of these signs or symptoms or persistent mucocutaneous SLE symptoms (mucosal ulceration, alopecia, photosensitive rash, malar rash) or the presence of abnormal laboratory evaluations (eg CBC, proteinuria) will prompt further laboratory (autoantibody testing) work-up and a referral to a rheumatologist.

Treatment with ANX005 will be discontinued at this point for such patients and the occurrence of systemic autoimmunity should be recorded as an AE. If restoration of C1q function is deemed necessary, plasmapheresis with albumin or saline replacement may be utilized to eliminate ANX005. Fresh frozen plasma should not be given as a source of C1q in the presence of therapeutic levels of circulating ANX005; C1q levels will recover by endogenous production.

The [Investigator's Brochure](#) contains detailed information on the safety profile of ANX005.

9.8 Infusion Reactions

[REDACTED]

[REDACTED]

In the event of any AE of any grade, the investigator may stop the infusion, if the AE is viewed as a precursor or is indicative of developing anaphylaxis or hemodynamic instability. The patient should receive symptomatic treatment until complete resolution of symptoms

before attempting to resume the infusion. In case of a life-threatening event, including anaphylaxis, all appropriate standard measures, including full resuscitation medications and equipment should be used as clinically indicated.

After completion of the infusion of ANX005, the IV cannula or line should remain in situ for at least 1 hour, to facilitate administration of IV medications, if necessary, in the event of a delayed reaction. If no AEs occur during this period of time, the IV cannula or line may be removed. Patients will be observed for 4 hours after completion of the infusion and may be released once all required end of infusion procedures (eg, PK/PD samples and vital signs) have been conducted.

9.8.1 Day 1 Dosing (Approximately 21-hour Infusion)

Administration of premedication may reduce IRR symptoms and is required for Day 1 infusion ([Section 5.4](#)). For patients experiencing trace or mild macular rashes, or moderate maculo-papular rashes, and without systemic signs and symptoms, such as abnormal vital signs or any cardiac or respiratory symptoms, the infusion rate should continue as per the infusion plan.

For patients experiencing or developing any systemic signs or symptoms related to the infusion (ie, severe headache, fever, chills, syncope, seizure, hypertension, hypotension, tachycardia, vomiting, dyspnea, tachypnea, etc.), the ANX005 infusion should be immediately interrupted. Appropriate medical intervention with rescue medications as needed for IRR rescue management should be administered at the discretion of the investigator and institution's IRR and emergency management policies. A blood sample should be collected for PK, C1q, and ADA analysis at the onset of the first IRR, should it occur. In addition, vital signs will be collected at the onset of the IRR, 15 minutes after onset, and then every 30 minutes until vital signs are stabilized as described in [Section 7.3.3.1](#). Once the vital signs are stabilized, vital signs should be collected every 4 hours until the end of the infusion or the IRR is fully resolved. If mild or moderate headache is the only generalized sign/symptom, the infusion may be continued at the discretion of the investigator.

Upon resolution of the systemic adverse events the infusion may begin or resumed at half of the original rate, after a minimum of one hour hold, and be returned to normal rate slowly and in 1-to-2-hour steps (ie, 50%, 75%, 100%), only if symptoms do not worsen or recur during half rate infusion and IRR symptoms have improved or resolved. Prescribed target infusion rate may be reinstituted after at least 1 hour at half rate as long as signs and symptoms do not worsen or recur.

9.8.2 Dosing Day 8 (Approximately 4-hour Infusion)

Premedication is not expected to be needed for this infusion of ANX005 but is not prohibited based on investigator discretion and after appropriate risk benefit assessment.

For patients experiencing trace or mild macular rashes, or moderate maculo-papular rashes, and without systemic signs and symptoms, such as abnormal vital signs or any cardiac or respiratory symptoms, the infusion rate should continue as per the infusion plan.

For patients experiencing or developing any systemic signs or symptoms related to the infusion (ie, severe headache, fever, chills, syncope, seizure, hypertension, hypotension, tachycardia, vomiting, dyspnea, tachypnea, other), the ANX005 infusion should be immediately interrupted. Appropriate medical intervention with rescue medications as needed for IRR rescue management should be administered at the discretion of the investigator and institutions IRR and emergency management policies. A blood sample should also be collected for PK, C1q, and ADA analysis at the onset of the IRR. In addition, vital signs will be collected at the onset of the IRR, 15 minutes after onset, and then every 30 minutes until vital signs are stabilized as described in [Section 7.3.3.1](#). Once vital signs are stabilized, vital signs should be collected every 4 hours until the end of the infusion or until the IRR is fully resolved. If mild or moderate headache is the only generalized sign/symptom, the infusion may be continued at the discretion of the investigator.

9.8.3 Follow-up After Last Dose ANX005

It is anticipated that after the last dose of ANX005, restoration of classical complement activity, hemolysis, anemia and complement deposition on erythrocytes will occur some time during follow-up and before D71. This relapse of hemolytic anemia upon washout of ANX005 would confirm that C1q inhibition is necessary for the treatment of wAIHA and provides an additional opportunity to characterize the role of complement activation on macrophages that are involved in the phagocytosis of erythrocytes opsonized by auto-antibodies and complement. When, at any time during follow-up, a patient presents with return of hemolysis an unscheduled lab kit will be used to obtain a full safety lab panel ([Section 7.3.5](#)) as well as pharmacodynamic and complement biomarkers measurements listed in [Section 7.2.2](#).

9.9 Pregnancy

Pregnancies that occur in enrolled patients, or the partners of enrolled patients, while not considered AEs, must be reported by the PI to sponsor representatives within 24 hours of awareness, using the pregnancy report form provided in the study instructions. The pregnancy should be followed until there is a pregnancy outcome. Following delivery or termination of the pregnancy, the PI must report the pregnancy outcome within 1 business day of awareness, using the pregnancy report form. Any AEs observed during pregnancy or any abnormality in the newborn are evaluated for potential SAE reporting. Newborns should be followed for at least 6 months, whenever possible, for any potential, congenital anomalies. In the case of a partner pregnancy. Partner informed consent must be attained prior to collecting information on the pregnancy and outcome.

Sponsor representatives ensure due diligence to collect the outcome of the pregnancy (eg, term or preterm delivery, induced abortion, stillbirth, spontaneous abortion), details of the birth if available, and additional relevant information.

10. STATISTICAL METHODS

10.1 Statistical Hypotheses

No formal statistical hypotheses are being tested in this study.

10.2 Sample Size Determination

The sample size for this study is not based on providing statistical power for hypothesis testing. However, for an AE with a true rate of 10%, a sample size of up to 12 patients provides up to 72% likelihood that the event will be observed during the study.

10.3 Analysis Sets

For purposes of the analyses, the following analysis sets are defined:

- The Full analysis set (FAS) includes all patients who sign an ICF and meet all eligibility criteria as assessed by the investigator.
- A Per Protocol set (PP) includes all patients who completed all infusions of ANX005 and do not have major protocol violations. Major protocol violations may include, but are not limited to, violations of eligibility criteria, receipt of incorrect dose of ANX005, use of prohibited medications, and noncompliance with study assessments. A final determination of inclusion in the PP set will be made prior to database lock.
- The PP set analyses will be performed in patients with a historical diagnosis of wAIHA. A separate analysis will be performed in patients with mixed AIHA. A pooled analysis of the total population (wAIHA and mixed AIHA) and indication-specific subset analysis may be performed. Additional details will be provided in the Statistical Analysis Plan (SAP).
- The Safety analysis set (SAS) includes all patients who received any amount of ANX005.
- The Pharmacodynamic analysis set (PD) includes all patients who received at least 1 completed infusion of ANX005 and have at least one post infusion assessment.
- The Pharmacokinetic analysis set (PK) includes all participants who received any amount of ANX005 and have evaluable ANX005 concentration data.

10.4 Statistical Analyses

The SAP will be developed and finalized prior to database lock. The SAP will describe and serve as the final plan for all analyses and statistical considerations and will include a more technical and detailed description of the statistical analyses described in this section.

Below is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

10.4.1 Timing of Analyses

The PI and the medical monitor jointly monitor safety data for purposes of safety on an ongoing basis as described in [Section 3.2](#).

The final analysis of all data will be based on data from the complete study and will be performed after all patients have completed the study (End-of-Study visit on Day 71 or early termination) and all data from the study are in the database and the database is locked.

10.4.2 General Considerations

All statistical analyses will be performed using SAS[®] version 9.4 or higher.

All analyses will be descriptive in nature. Unless otherwise specified, categorical variables will be summarized with counts and percentages and continuous variables will be summarized with means, standard deviation (SD), medians, minimum and maximum values. Summaries may include 95% confidence intervals (CIs) for point estimates.

Unless otherwise specified, the baseline assessment will be the latest available assessment prior to the Day 1 infusion.

Further details of the analysis will be described in the SAP.

10.4.3 Analysis of Primary Endpoints

The primary endpoint that will evaluate the safety and tolerability of ANX005 in patients with wAIHA is the number and proportion of patients experiencing TEAEs. AE terms will be mapped to the appropriate system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA). A TEAE is defined as any AE with an onset on or after the day of infusion until the end of study visit. The number and percentage of patients experiencing TEAEs will be summarized by MedDRA SOC and PT. Similar summaries will be provided for related TEAEs, SAEs, CTCAE Grade 3 and higher AEs, related CTCAE Grade 3 and higher TEAEs, AESIs, and AEs leading to discontinuation of ANX005. Summaries will also be generated by maximum severity.

The following endpoints will evaluate the clinical effect of ANX005 in patients with wAIHA:

- Change from baseline in hemoglobin over time up to Day 71 (end of study visit)
- Maximum absolute change in hemoglobin from baseline
- Change from baseline in biomarkers of hemolysis (reticulocyte count, haptoglobin, LDH, total and indirect bilirubin) over time up to Day 71 (end of study visit)

Observed values, changes, and percent changes from baseline (if appropriate) will be summarized descriptively at each visit.

10.4.4 Analysis of Secondary Endpoints

To evaluate the PK profile of ANX005 in patients with wAIHA, ANX005 plasma concentrations will be tabulated descriptively, summarized by nominal sampling time, and will include number of patients, arithmetic mean, standard deviation, coefficient of variation (CV%), minimum, median, maximum, and geometric mean. Data will be displayed

graphically by visit and time point, as appropriate. Noncompartmental analyses on serial serum data will be applied as data allow.

PK parameters and analysis methods will be described in a separate PK Analysis Plan (PKAP). Parameters may include but are not limited to:

- Maximum observed serum concentration ($C_{\max}$)
- Observed time to $C_{\max}$ ($T_{\max}$)
- Area under the ANX005 serum concentration-time curve to the last sample (AUC_{0-t}) and extrapolated through infinity ($AUC_{0-\infty}$)
- Accumulation ratio
- Terminal half-life ($t_{1/2}$)
- Terminal elimination rate constant (λ_z)
- Clearance (CL)
- Volume of distribution (V_{ss})

To evaluate the effect of ANX005 on classical complement pathway inhibition as measured by complement system related biomarkers in patients with wAIHA, the following endpoints will be summarized descriptively:

- Inhibition of classical complement activity as measured by serum CH50 over time up to Day 71
- Change and percent change from baseline in C4 concentrations in serum over time up to Day 71
- Change and percent change from baseline in free C1q concentrations in serum over time up to Day 71

10.4.5 Analyses of Exploratory Endpoints

Analyses of exploratory endpoints will be described in the SAP.

10.4.6 Other Safety Analyses

In addition to adverse events, safety will be assessed by safety laboratory assessments (serum chemistry, hematology, urine analysis), ECG and vital signs.

Reported values and changes from baseline in vital signs, laboratory parameters and ECG parameters will be summarized descriptively.

10.4.7 Other Analyses

10.4.7.1 Immunogenicity to ANX005

Anti-ANX005 antibodies and ANX005 immune reactions will be presented in data listings. The number and % of patients with anti-ANX005 antibodies and ANX005 immune reactions will be summarized by visit.

11. DATA MANAGEMENT

11.1 Data Collection and Management

Clinical data are collected through an electronic data capture system. The handling and management of data, including data quality assurance, must comply with regulatory guidelines and are defined in a study specific data management plan (DMP). The DMP must include procedures for all aspects of the processing of the data from this study and, if clinical data management is outsourced, the responsibilities of sponsor representatives. In particular, the DMP includes a list of the SOPs that apply to this study.

Data collection processes and procedures are reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail is maintained of all data changes.

Adverse events and medications are coded using MedDRA and WHO-DD respectively. The DMP specifies the versions used.

The PI must ensure the accuracy, completeness, and timeliness of the data reported to a sponsor representative. Data reported on the eCRFs must be verifiable to source data, which necessitates access to all original recordings, laboratory reports and patient records as specifically related to the patient's participation in this study (ie, medical history, diagnosis of wAIHA, inclusion and exclusion criteria, adverse events, concomitant medications, study activities, and other pertinent medical information or procedures occurring during the study period). The PI and site personnel must cooperate with sponsor representatives for the periodic review of study documents, to ensure the accuracy and completeness of the data reported in the eCRFs.

12. STUDY ADMINISTRATION

12.1 Ethical and Regulatory Considerations

- This study will be conducted in accordance with the protocol and with the following:
 - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
 - Applicable ICH Good Clinical Practice (GCP) Guidelines
 - Applicable laws and regulations

- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study 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.
- The investigator will be responsible for the following:
 - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
 - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
 - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

12.2 Institutional Review Board/Independent Ethics Committee

The IRB/IEC must be constituted according to ICH and GCP requirements as well as the local laws and regulations of each participating country. Sponsor representatives supply relevant documents for the PI to submit to the IRB/IEC for review and approval. This protocol, the [Investigator's Brochure](#) and any relevant safety updates not contained in the Investigator's Brochure, the ICF template, and any other applicable documents must be submitted to an appropriate IRB/IEC by the PI. Written, unconditional, IRB/IEC approval must be obtained and submitted to sponsor representatives before commencement of the study (ie, shipment of ANX005 and activation of the study site). This approval must refer to the study by protocol title and sponsor protocol number whenever possible, identify the documents reviewed, and indicate the date of review and approval. Sponsor representatives must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the clinical study at each site.

Sponsor representatives provide appropriate updates and reports on the progress of the study to the PI and ensures that such are provided to the IRB/IEC in accordance with applicable local requirements and regulations. The PI must supply ongoing study progress reports to the IRB/IEC, per local requirements, such as updates on SAEs or SUSARs, protocol deviations and amendments, ICF revisions, relevant sponsor communication, enrollment updates, etc. In addition, the PI must notify the IRB/IEC at the closure of the study.

12.3 Informed Consent

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

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

Sponsor representatives provide a template ICF to site personnel for modification into the format required by the site SOPs. Site personnel must submit a draft ICF to and receive approval from sponsor representatives prior to submission to the IRB/IEC. Upon approval by the IRB/IEC, site personnel forward a copy of the ICF approved by the review board to sponsor representatives prior to performing any study specific procedures, including any copies of approved patient information sheets or ICFs translated to another language.

The ICF template documents the patient's informed agreement to participate. The Investigator or his/her representative must fully explain the content of the ICF and the study in layman's terms, including study goals, tests, anticipated benefits, and potential risks that participation might entail. The ICF must be appropriately signed and dated before the patient undergoes any study-related procedure. The original and any amended, signed, and dated ICFs must be retained in the patient's file at the study site, and a copy of each provided to the patient. Site personnel must also fully document the informed consent process in the patient's source documents.

The medical record must include a statement that written informed consent was obtained before the participant underwent any study procedures and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF. Patients must be re-consented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) must be provided to the participant.

Separate, additional ICFs may be required as part of the study to collect consent for optional protocol tests, or specific country or local requirements.

12.4 Protocol Amendments

This protocol must be followed as written. Any change or addition to this protocol requires a written protocol amendment that must be approved in writing by the IRB/IEC and any required regulatory authorities before implementation.

Sponsor representatives may decide to amend the protocol, or the PI may suggest protocol amendments. Sponsor representatives must notify the applicable regulatory authorities of all amendments to the protocol.

These requirements for amendment approval should in no way prevent any immediate action from being taken by the PI or by sponsor representatives in the interests of preserving the safety of an individual, or all patients included in the study. If an immediate change to the

protocol is deemed necessary by sponsor representatives or the PI and is implemented for safety reasons, the IRB/IEC as well as applicable regulatory agencies must be notified.

12.5 Retention of Documents

The PI must retain all study records required by the sponsor and by applicable regulations in a secure and safe location for as long as needed to comply with national and international regulations, but not less than 2 years after (1) the last approval of a marketing application in an ICH region, (2) there are no pending marketing applications, or (3) the discontinuation of a development plan for the ANX005.

Patient hospital records and source data must be kept for the maximum period required by the study site, but not less than 15 years.

The PI must consult sponsor representatives before disposal of any study records and must notify the sponsor of any change in the location, disposition, or change of custody. If the PI or study site is unable to continue maintenance of the study records for the full 15 years, the PI must notify sponsor representatives for assistance with retention.

Sponsor representatives notify the PI and study site when the retention of study related records is no longer required.

Study records include the following:

- Approvals by the IRB/IEC for the study protocol, ICF, and amendments
- All patient source documents, laboratory records, and applicable diaries, etc.
- Informed consent forms
- Essential documents such as curricula vitae, financial disclosure forms, and other local or national regulatory approvals
- All other pertinent study documentation

12.6 Monitoring Procedures

Sponsor representatives schedule monitoring visits to take place throughout the study at appropriate intervals as outlined in the monitoring plan.

These visits are to confirm that the study is conducted in compliance with the relevant GCP regulations and guidelines, verifying adherence to the protocol, and the completeness and accuracy of data entered on the source records, eCRF, and drug accountability forms. The study monitor verifies eCRF entries by comparing them with the source records, which must be available for this purpose. The PI must ensure adequate time and space availability for these visits. The PI and site personnel are responsible for being present or available for consultation during monitoring visits.

12.7 Quality Control and Quality Assurance

Prior to participation, sponsor representatives evaluate potential study sites and investigators for appropriate qualifications and ability to conduct the study. Study training must take place at each study site before any patients may be enrolled at that site. Study initiation visits and investigator meetings (if applicable) may include a review of GCP guidelines, study protocol and procedures review, management of AEs, preparation and administration of ANX005, and data collection and patient eligibility requirements.

All clinical work conducted under this protocol is subject to GCP regulations. This includes an inspection by sponsor and competent authority representatives at any time. The PI must agree to the inspection of study-related records by competent authority representatives and audits by sponsor representatives.

Sponsor representatives may conduct a quality assurance audit at a study site at any time before, during, or after completion of the study. Sponsor representatives inform the PI if an audit is to take place and advise him or her as to the scope of the audit. Representatives of regulatory agencies may also conduct an audit of the study site. If informed of such an inspection, the PI should notify sponsor representatives immediately. The PI must ensure that auditors have access to study supplies, site facilities, original source documentation, and all study records.

12.8 Confidentiality

All clinical study findings and documents are regarded as confidential. Study documents (protocols, investigator brochures, and other material) must be stored appropriately to ensure their confidentiality. The investigators, site personnel, and members of the IRB/IEC must not disclose such information without prior written approval from the sponsor, except to the extent necessary to comply with applicable regulatory requirements.

The anonymity of participating patients must be maintained per applicable local and national laws. Patients are specified on all documents by patient number and, whenever possible, initials, but not by name. Documents that identify the patient (eg, the signed ICF) must be maintained in confidence by site personnel.

Site personnel must obliterate patient names from study-required documents that identify the patient by name (eg, hospital records) prior to transmitting these documents to sponsor representatives.

Site personnel also acknowledge that United States securities law prohibits any party who receives material non-public information about the sponsor from purchasing or selling securities of the sponsor or from communicating such information to any other person under circumstances in which it is reasonably foreseeable that such person is likely to purchase or sell such securities in reliance on such information.

12.9 Publication

The data and information generated in this study are the exclusive property of the sponsor and are confidential. Written approval from the sponsor is required before disclosing any information relative to this clinical study, and no publications initiated by site personnel may be published until all protocol defined results are published in a manuscript. Publications of the results must be based on appropriate analyses and review of the complete data. Authorship may be determined based on enrollment of eligible patients or contribution to the design, conduct, or interpretation of the study.

Investigators agree to have their names listed as an investigator in any publication reporting the results from this study, whether or not they are an author on the publication.

The preparation and submittal for publication of manuscripts and presentations containing the study results shall be in accordance with a process determined by mutual written agreement between the sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws.

The details and processes of producing and reviewing reports, manuscripts and presentations based on the data from this study are described in the clinical trial agreement between the sponsor and the institution of the PIs.

REFERENCES

ANX005 Humanized Monoclonal Antibody Investigator's Brochure. Edition 7.0. Dated 26 April 2021.

Barcellini W, Fattizzo B. Clinical Applications of Hemolytic Markers in the Differential Diagnosis and Management of Hemolytic Anemia. *Dis Markers*. 2015;2015:635670.

Barcellini W. Current treatment strategies in autoimmune hemolytic disorders. *Expert Rev Hematol*. 2015;8(5):681-91.

Bass GF, Tuscano ET, Tuscano JM. Diagnosis and classification of autoimmune hemolytic anemia. *Autoimmun Rev*. 2014;13(4-5):560-4.

Berentsen S. Cold agglutinin disease. *Hematology*. 2016;2016(1):226-231. doi:10.1182/asheducation-2016.1.226

Berentsen S. Role of Complement in Autoimmune Hemolytic Anemia. *Transfus Med Hemother*. 2015;42(5):303-10

Charles River Laboratories, Inc. A 4-Week GLP Study of ANX005 by Intravenous Injection in Sprague Dawley Rats with a 4-Week Recovery Period. Audited Draft Report; Testing Facility No. 20094108; Sponsor Reference No. 2016-005-SDR-008; 03 January 2017.

Charles River Laboratories, Inc. A 4-Week GLP Study of ANX005 by Intravenous Injection in Cynomolgus Monkeys with a 4-Week Recovery Period. Audited Draft Report; Testing Facility No. 20094107; Sponsor Reference No. 2016-005-cyno-007; 15 December 2016

Crowther M, Chan YL, Garbett IK, Lim W, Vickers MA, Crowther MA. Evidence-based focused review of the treatment of idiopathic warm immune hemolytic anemia in adults. *Blood*. 2011;118(15):4036-40.

Dierickx D, Kentos A, Delannoy A. The role of rituximab in adults with warm antibody autoimmune hemolytic anemia. *Blood*. 2015;125(21):3223-9.

Jager U et. Al. Diagnosis and treatment of autoimmune hemolytic anemia in adults: Recommendations from the First International Consensus meeting. *Blood Reviews* 41 (2020) 100648.

Kalfa T. Warm antibody autoimmune hemolytic anemia. *Hematology*. 2016;2016(1):690-697. doi:10.1182/asheducation-2016.1.690

Meulenbroek EM, de Haas M, Brouwer C. Complement disposition in autoimmune hemolytic anemia is a footprint for difficult-to-detect IgM autoantibodies. *Haematologica*. 2015; 100(11):1407-14.

Michel M. Warm autoimmune hemolytic anemia: advances in pathophysiology and treatment. *Presse Med*. 2014;43(4 Pt 2):e97-e104.

Rodrigo C, Rajapakse S, Gooneratne L. Rituximab in the treatment of autoimmune haemolytic anaemia. *Br J Clin Pharmacol*. 2015;79(5):709-19.

Wheeler CA, Calhoun L, Blackall DP. Warm reactive autoantibodies: clinical and serologic correlations. *Am J Clin Pathol*. 2004;122(5):680-5.

Zanella A, Barcellini W. Treatment of autoimmune hemolytic anemias. *Haematologica*. 2014;99(10):1547-54.

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Phase 2, Open-Label, Repeat-Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Proof-of-Concept of Intravenous ANX005 in Subjects with Warm Autoimmune Hemolytic Anemia

Protocol Number: ANX005-wAIHA-02

Date: 23 March 2022

Declaration of the Principal Investigator

I have read this protocol and agree to conduct the study as outlined herein, in accordance with GCP and the Declaration of Helsinki, and complying with the obligations and requirements of clinical investigators and all other requirements listed in 21 CFR Part 312.

Principal Investigator

Print Name

Site Number

Signature

Date

APPENDIX A ADVERSE EVENT SEVERITY GRADING

Adverse event grading gives an assessment of the severity of an AE. The NCI-CTCAE provides a common system for AE grading, and is based on the guidelines shown in the table below.

<i>Grade</i>	<i>Description</i>
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. ^a
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. ^b
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE.

Source: NCI-CTCAE v 5.0

^a Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

^b Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Abbreviations: ADL = activities of daily living, AE = adverse event, NCI-CTCAE = National Cancer Institute's Common Terminology Criteria for Adverse Events

APPENDIX B GRADING FOR INFUSION-RELATED REACTIONS

An infusion-related reaction is a disorder characterized by an adverse reaction to the infusion of pharmacological or biological substances. The NCI-CTCAE provides a common system for grading infusion-related reactions, as shown in the table below.

<i>Grade</i>	<i>Description</i>
1	Mild transient reaction; infusion interruption not indicated; intervention not indicated.
2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.
3	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.
4	Life-threatening consequences; urgent intervention indicated.
5	Death.

Source: NCI-CTCAE v 5.0

Abbreviations: IV = intravenous, NCI-CTCAE = National Cancer Institute's Common Terminology Criteria for Adverse Events, NSAID = nonsteroidal anti-inflammatory drug.

APPENDIX C

