



CLINICAL STUDY PROTOCOL

A Phase 2, Multicenter, Randomized, Parallel-Group, Double-Masked, 4-Arm, Sham-Controlled Study of the Efficacy, Safety, and Tolerability of ANX007 Administered by Intravitreal Injection in Patients with Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration (AMD)

The ARCHER Study

Protocol Number: ANX007-GA-01

Study Medication: ANX007

Brief Title A Study Investigating the Efficacy and Safety of Intravitreal Injections of ANX007 in Patients with Geographic Atrophy (ARCHER)

Study Phase: Phase 2

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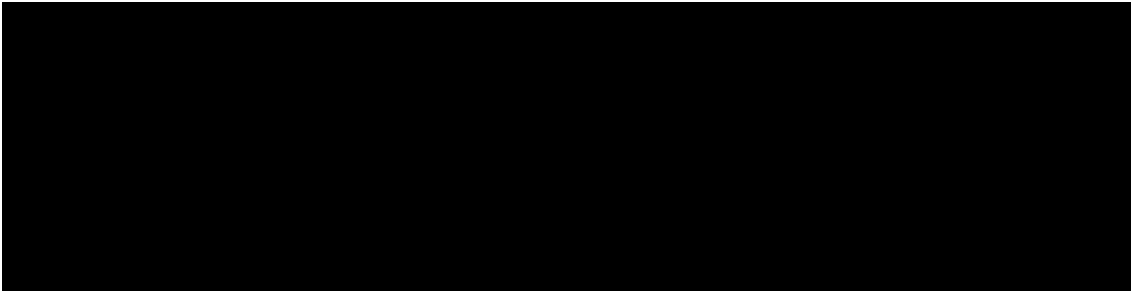
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LIST OF ABBREVIATIONS AND ACRONYMS

ADA	Antidrug antibodies
AE	Adverse event
AESI	AE of special interest
AICC	A version of Akaike information criterion
AMD	Age-related macular degeneration
ANA	Antinuclear antibodies
BCVA	Best corrected visual acuity
CI	Confidence interval
CNV	Choroidal neovascularization
CRA	Clinical Research Associate
CRO	Clinical Research Organization
DMP	Data Management Plan
DSMC	Data Safety Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EFD	Embryo fetal development
EM	Every month
EOM	Every other month
ET	Early termination
ETDRS	Early Treatment Diabetic Retinopathy Study
Fab	Antigen-binding fragment
FAF	Fundus autofluorescence
FEED	Fertility and early embryonic development
GA	Geographic atrophy
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IOP	Intraocular pressure
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
IVFA	Intravenous fluorescein angiography
IVT	Intravitreal
IWRS	Interactive Web Response System
LL-BCVA	Low-luminance BCVA

LL-VD	Low-luminance visual acuity deficit
LME	Linear Mixed Effect model
LS Means	Least Squares Means
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MMRM	Mixed-effect model for repeated measures
Near IR	Near infrared fundus reflectance
NOAEL	No observed adverse effect level
OCT	Optical coherence tomography
OCT-A	Optical coherence tomography angiography
PD	Pharmacodynamic or pharmacodynamics
PK	Pharmacokinetic or pharmacokinetics
PP	Per protocol
PPE	Personal Protective Equipment
PT	Pregnancy test
QMS	Quality Management System
QTLs	Quality tolerance limits
RPE	Retinal pigment epithelium
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SD-OCT	Spectral domain optical coherence tomography
SE	Standard error
SIV	Site Initiation Visit
SoA	Schedule of Activities
SoC	Standard of care
SOP	Standard operating procedure
SUSAR	Suspected, unexpected, serious, adverse reaction
T _{1/2}	Half-life
TEAEs	Treatment-emergent AEs
VEGF	Vascular endothelial growth factor
WOCBP	Women of child-bearing potential

INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE

Prior to beginning the study, the Investigator must provide to a Sponsor representative a current curriculum vitae.

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators and sub-Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

The clinical study is administered and monitored by representatives of Annexon, Inc. (the Sponsor). Clinical research associates monitor records at the study 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 a central laboratory.

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A Phase 2, Multicenter, Randomized, Parallel-Group, Double-Masked, 4-Arm, Sham-Controlled Study of the Efficacy, Safety, and Tolerability of ANX007 Administered by Intravitreal Injection in Patients with Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration (AMD)

Brief Title:

A Study Investigating the Efficacy and Safety of Intravitreal Injections of ANX007 in Patients with Geographic Atrophy (ARCHER)

Rationale:

C1q, the initiating molecule of the classical complement cascade, has been implicated in the initiation and propagation of GA. C1q is present in drusen, a key pathological feature of GA. In addition, early classical complement component C4 and downstream C3 deposition is observed on photoreceptor outer segments and edge of atrophic lesions in patients with GA ([Katschke et al 2018](#)). These results support the role for the classical complement cascade as a key initiator of the disease process in GA and supports clinical evaluation of a C1q inhibitor in GA. ANX007 is a C1q complement inhibitor that has been shown to inhibit free C1q for at least 29 days in aqueous humor following single 2.5 and 5 mg intravitreal (IVT) injections (Study ANX007-GLA-02). Repeat IVT injections (2 injections separated by 4 weeks) up to 5 mg were safe and well tolerated in patients with glaucoma.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To compare the GA lesion growth rate from once monthly and once every other month IVT injections of 5 mg ANX007 for 12 months with Sham control	Rate of change (slope) in GA lesion area from baseline to Month 12 as assessed by fundus autofluorescence (FAF)
Secondary	
To compare the GA lesion growth from once monthly and once every other month IVT injections of 5 mg ANX007 for 12 months with Sham control	Change from baseline in GA lesion area at Month 12 as assessed by FAF
To assess the safety and tolerability of IVT injections of ANX007	Incidence and severity of ocular and systemic treatment-emergent adverse events (AEs)
To evaluate effects of IVT injections of ANX007 on visual function and visual acuity	Change from baseline to Month 12 in Best Corrected Visual Acuity (BCVA) as assessed by the Early Treatment Diabetic

Objectives	Endpoints
	Retinopathy Study (ETDRS) chart at a starting distance of 4 m at each study visit • Change from baseline to Month 12 in low-luminance BCVA (LL-BCVA) • Change from baseline to Month 12 in low-luminance visual acuity deficit (LL-VD)
Exploratory	
• To assess the systemic pharmacokinetic exposure and pharmacodynamics (PD) of ANX007	• Serum ANX007 and C1q concentrations
• To evaluate the immunogenicity of ANX007	• Number and percentage of patients with anti-ANX007 antibodies (ADA) in serum

Overall Design:

Intervention Model:	Parallel group
Primary Purpose:	Treatment
Study Phase:	2
Number of Arms:	4
Masking:	Patient, evaluating physician, outcome assessor (Central Reading Center), Sponsor
Health Measurement/Observation:	GA lesion area
Intervention Name:	ANX007
Intervention Form:	Solution for IVT injection
Patient Sex:	Male and female
Patient Age Range:	≥50 years
Condition/Disease:	Patients with GA secondary to age-related macular degeneration (AMD)

Brief Summary:

This study is being conducted in patients with GA secondary to AMD. The purpose of the study is to determine if IVT injections of ANX007 once every month (EM) or once every other month (EOM) for 12 months reduces GA lesion growth rate. The results from this study will be used to guide further development of ANX007 in patients with GA.

The study consists of a 30-day screening period and a 12-month treatment period, followed by a 6-month (off treatment) follow-up period. The total duration of patient participation is 19 months. Patients will visit the clinic each month during the 12-month treatment period for treatment and/or safety assessments.

ANX007 is not available through an expanded use access (EUA) program.

Number of Patients:

Approximately 270 patients are planned to be enrolled and randomly assigned to one of 4 treatment arms so that approximately 231 patients are evaluable at Month 12 for the primary analysis (primary analysis is based on intent-to-treat population [ITT]). [REDACTED]

Note: “Enrolled” means the patient (or their legally acceptable representative) agrees to participate in the clinical study following completion of the informed consent process and has been randomized. Potential patients who are screened for the purpose of determining eligibility for the study, but are not randomized, are not considered enrolled.

Intervention Groups and Duration:

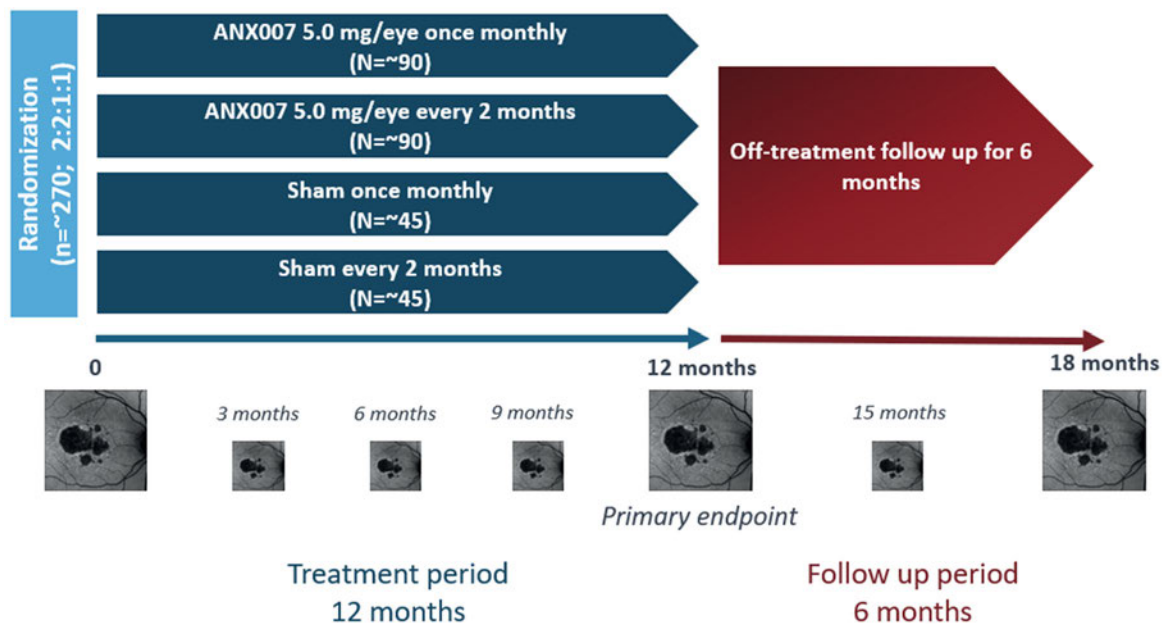
Study intervention assignment will be based on randomization (2:2:1:1). Patients will be assigned to one of the following treatment arms. Dose level is fixed and will not be modified.

- Arm 1 = ANX007 5.0 mg/eye (0.10 mL) once every month (EM) for 12 months (12 doses)
- Arm 2 = ANX007 5.0 mg/eye (0.10 mL) once every other month (EOM) for 12 months (6 doses)
- Arm 3 = Sham injection EM for 12 months (12 Sham injections)
- Arm 4 = Sham injection EOM for 12 months (6 Sham injections)

Data Monitoring/Other Committee: Yes (Data Safety Monitoring Committee [DSMC])

1.2 Schema

Figure 1 Study ANX007-GA-01 Schema



1.3 Schedule of Activities (SoA)

Table 1 Schedule of Assessments

Assessment	Screening Day -30 to -1	12-Month Treatment Period ^a													Off Treatment		
		Day 1	(±5-day visit window)												(±5-day visit window)		
			(Wk 2)	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12/ET	M15	M18
		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16
Informed Consent	X																
Incl/exclusion ^b	X	X															
Demographics	X																
Med Hx & PE	X														X		
Urine PT (WOCBP) ^c	Serum	X													X		
Vital Signs	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clin Labs ^d	X					X			X			X			X		
Genetic testing ^h	X																
Randomization		X															
Drug Admin		Once monthly or every other month IVT injection (study eye)															
EM dose		1		2	3	4	5	6	7	8	9	10	11	12			
EOM dose		1			2		3		4		5		6				
Ophthalmic Examinations (study eye only unless otherwise noted)																	
Pre-IVT tonometry	X**	Prior to each dose confirm IOP is ≤ 21 mmHg prior to injection (study eye) Measure IOP at every visit for both groups, including non-dosing visits for EOM													X**		X**
Post-IVT assessments		Immediately after each dose assess hand motion vision or central retinal artery perfusion visualization (study eye)															
Post-IVT tonometry		30 min after each dose and every 15 min thereafter (if elevated) until IOP < 25 mmHg (study eye)															
BCVA (ETDRS)	X**	X		X	X	X	X	X	X	X	X	X	X	X	X**	X	X**
LL-BCVA		X**							X						X**	X	X**
Slit-lamp bio-microscopy	X**	X		X	X	X	X	X	X	X	X	X	X	X	X**	X	X
Dilated fundus	X**	X		X	X	X	X	X	X	X	X	X	X	X	X**	X	X
Imaging (study eye only unless otherwise noted)																	
SD-OCT	X**	X**			X**	X**	X**		X**		X**	X**	X**		X**	X**	X**
OCT-A (select sites)		X													X		
Color fundus photos	X**								X**						X**		X**

Assessment	Screen- ing Day -30 to -1	12-Month Treatment Period ^a													Off Treatment		
		Day 1	(±5-day visit window)												(±5-day visit window)		
			(Wk 2)	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12/ET	M15	M18
		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16
Near IR	X**	X**				X**			X**			X**			X**	X**	X**
FAF (GA lesion)	X**	X**				X**			X**			X**			X**	X**	X**
IVFA	X**																
Blood for PK & PD ^e		X							X				EOM	EM			
Blood (serum) for ADA & ANA ^f		X	ADA			X			X			X	EOM	EM	X		X
Follow-up call ^g		←----- 4 days after each dose -----→															
Adverse Events		X	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	X	X	X

** Indicates procedure should be performed and recorded for both the study eye and the fellow eye.

Note: Unscheduled visits may occur as described in [Section 8.5.6](#).

- ^a Assessments should be conducted prior to IVT/sham administration, unless otherwise specified. Visits should be scheduled on approximately the same calendar day each month ±5 days. Dosing should be separated by at least 14 days.
- ^b Lesion eligibility will be confirmed by the Central Reading Center during Screening. Confirmation of inclusion/exclusion criteria on Day 1 does not include re-confirmation of lesion eligibility by the Central Reading Center.
- ^c Serum PT is required at Screening. On Day 1 and Month 12/ET, if urine PT is positive, collect serum PT to confirm (see [Section 8.5.4](#)). Additional PT should be conducted as required by local regulations.
- ^d Collect blood and urine samples for clinical laboratory assessments (eg, hematology, chemistry, coagulation, urinalysis) as outlined in [Appendix B](#).
- ^e Serum samples for PK and PD on dosing days: Pre-injection (up to 4 hours before dosing) and 3 hours (±15 min) post-injection. The 3-hour post-injection samples are optional and may be collected at home health visits. The Month 10 samples should be collected for EOM patients only, and the Month 11 samples should be collected for EM patients only.
- ^f Serum sample for ADA/ANA: On dosing days, obtain pre-injection. A serum sample for ADA should also be collected at Week 2 and may be collected as site visit or home health visit. The Month 10 samples should be collected for EOM patients only and the Month 11 samples should be collected for EM patients only.
- ^g Conduct follow-up phone calls 4 days after each injection (±2 days) to evaluate adverse events, concomitant medications, and necessity for patient evaluation.
- ^h Blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study (see [Section 8.7](#)). Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

Abbreviations: ADA = antidrug (anti-ANX007) antibodies; ANA = antinuclear antibodies; BCVA = Best Corrected Visual Acuity; Clin Labs = clinical laboratory tests; EM = every month; EOM = every other month; ET = early termination; ETDRS = Early Treatment Diabetic Retinopathy Study; FAF = fundus autofluorescence; IOP = intraocular pressure; IVFA = intravenous fluorescein angiography; IVT = intravitreal; LL-BCVA = low-luminance BCVA; M = month; Med Hx = medical history; Near IR = near-infrared fundus reflectance; OCT-A = optical coherence tomography angiography; PE = physical examination; PD = pharmacodynamics; PK = pharmacokinetic; PT = pregnancy test; SD-OCT = spectral domain optical coherence tomography; WOCBP = women of child-bearing potential

2 INTRODUCTION

2.1 Background

Age-related macular degeneration (AMD) is a leading cause of blindness globally. A systematic review and meta-analysis by Wong and colleagues in 2014 projected 196 million people worldwide to have AMD by 2020, with a projected increase to 288 million in 2040 (Wong et al 2014). Geographic atrophy (GA), also known as atrophic age-related macular degeneration or advanced dry AMD, is an advanced form of age-related macular degeneration resulting in the progressive and irreversible loss of central retinal photoreceptors, retinal pigment epithelium, and choriocapillaris, leading to vision loss. The prevalence of GA is estimated to be more than 5 million worldwide and 1 million in North America (Friedman et al 2004). Currently, there are no approved treatments for GA.

Complement appears to be genetically linked to AMD with polymorphisms identified in 6 distinct proteins that can alter complement pathway activity (Tan et al 2016, Csincsi et al 2017, Mohlin et al 2017, Chirco & Potempa 2018). The complement cascade is a critical component of innate immunity and can be activated through 3 distinct pathways: the classical, lectin, and alternative pathways. All 3 pathways lead to the activation of complement component C3, which ultimately leads to immune cell recruitment, inflammation, membrane lysis through the membrane attack complex, and cell death. By binding C1q, as with ANX007, the activity of the classical pathway can be modulated, leaving the lectin and alternative pathways intact. The C1q/classical complement pathway mediates elimination of unwanted synapses in development (Stevens et al 2007, Schafer et al 2012). In adults, C1q accumulates on synapses with age and disease and can aberrantly trigger synapse elimination, neuroinflammation and degeneration (Stephan et al 2013). Inhibition of C1q is protective in numerous models of neurodegeneration (Hong et al 2016, Lui et al 2016).

C1q, the initiating molecule of the classical complement cascade, has also been implicated in the initiation and propagation of GA. C1q accumulates with age in two separate and important GA-associated disease processes - on photoreceptor neuron synapses in the outer plexiform layer and on drusen (Annexon data on file). Recently, it has been shown that both classical and alternative complement pathway activation is evident on photoreceptor outer segments and drives retinal atrophy in GA (Katschke et al 2018). Aberrant C1q / classical pathway activity is associated with loss of photoreceptors in a photodamage induced mouse model of GA (Jiao et al 2018). Local C1q produced by retinal microglia/macrophages has been demonstrated as an instigator of inflammasome activation and inflammation. Retinal C1q inhibition with ANX007 in this model slowed retinal atrophy, reduced photoreceptor loss, increased retinal thickness, and preserved retinal function. ANX007 provides a novel approach for the treatment of complement-mediated retinal degenerations including GA (Jiao et al 2018).

2.2 ANX007 Description and Mechanism of Action

ANX007 is the antigen binding fragment (Fab) of a humanized recombinant monoclonal antibody and is composed of a single heavy chain of the IgG1 isotype and a single light chain

of the kappa isotype. ANX007 has a molecular weight of approximately 48 KDa. ANX007 binds to the globular heads of C1q, inhibiting C1q's ability to bind to its target and blocks the downstream activation of the classical complement cascade. ANX007 specifically inhibits the classical pathway without any impact on the lectin or alternate complement pathways.

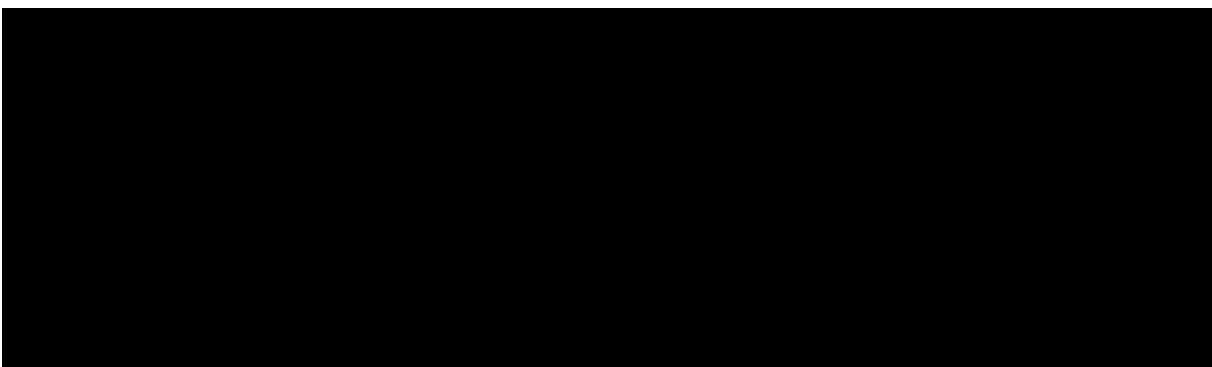
ANX007 provides retinal neuroprotection in a mouse model of photoreceptor loss by preventing activation of the classical complement cascade. Preclinical data highlight the potential of C1q inhibition in preventing photoreceptor degeneration in geographic atrophy patients for whom there is currently no treatment.

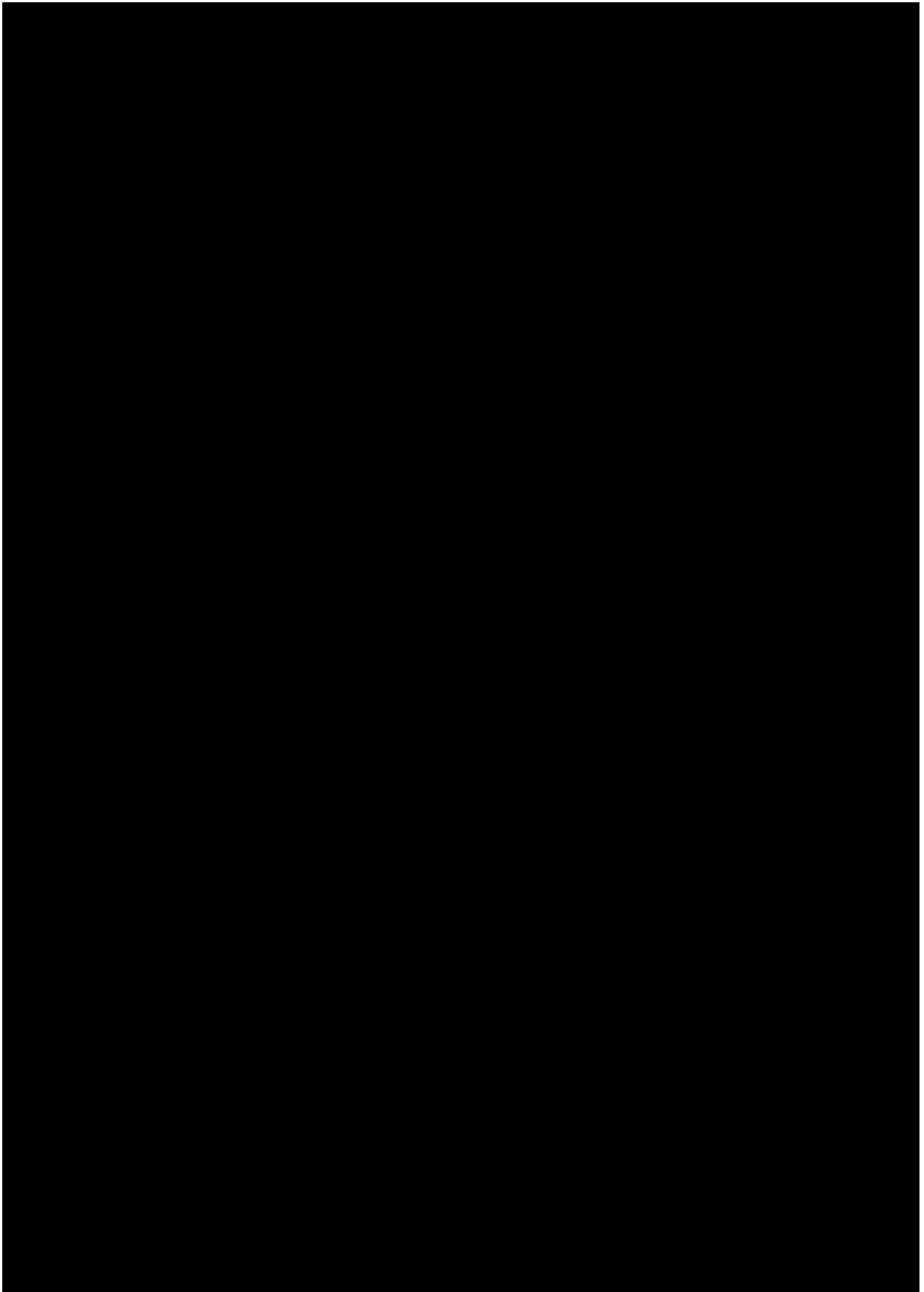
2.3 Nonclinical

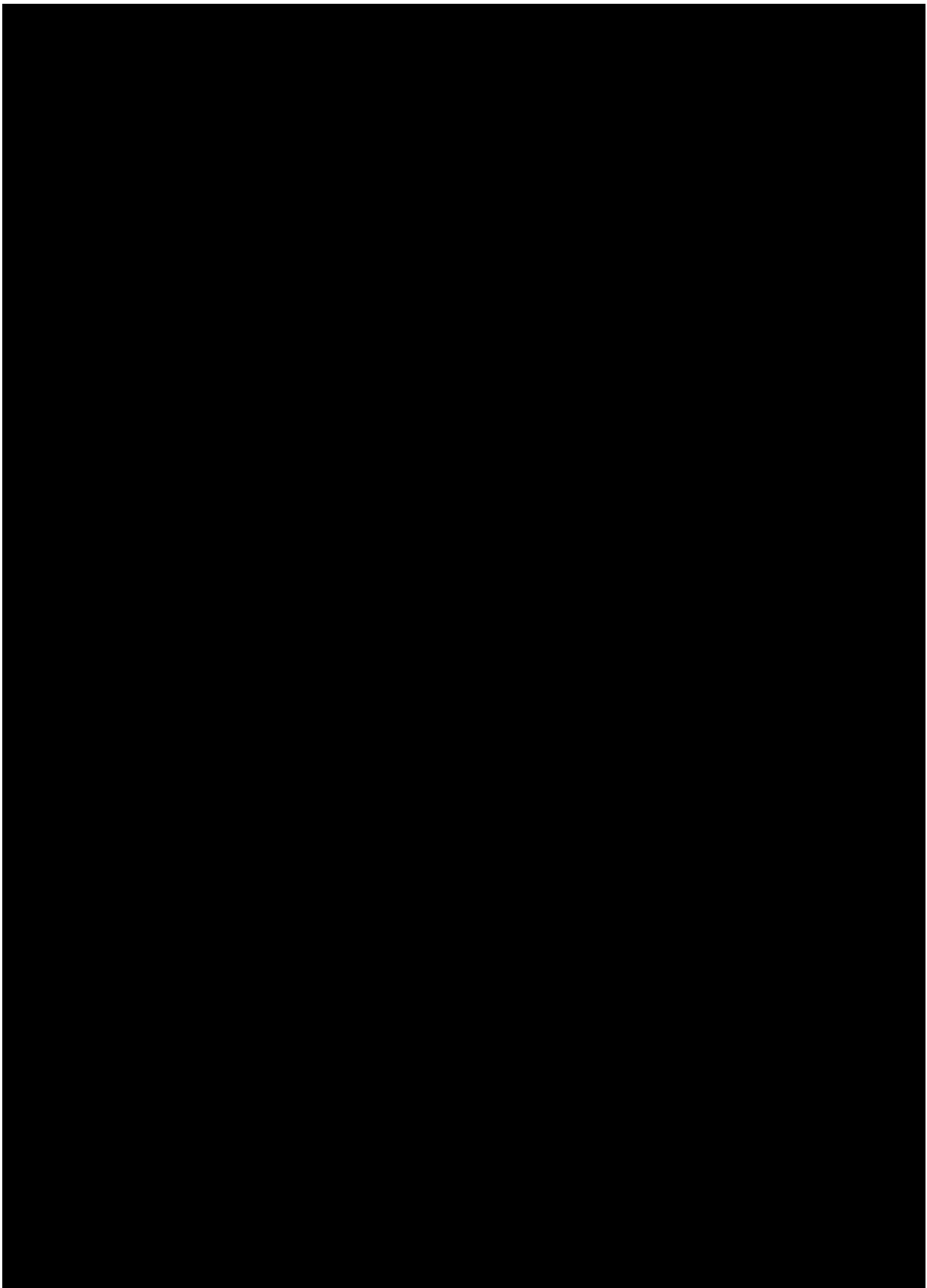
The ocular pharmacokinetics (PK) and toxicology of ANX007 following IVT administration has been characterized in rats and cynomolgus monkeys, and both are considered pharmacologically relevant species. In addition, pharmacology, PK, and toxicology studies with ANX005 (full-length antibody) and its Fab (ANX-Fab), ANX007, and other precursor molecules have been completed or are ongoing. Systemic toxicity by the IV route has been conducted in rats and cynomolgus monkeys with ANX005, the full-length IgG4 anti-C1q antibody, which has the same binding region or variable domain and complementarity-determining regions (CDR) sequences as ANX007. Therefore, ANX005 is expected to bind to the same targets as ANX007 in vivo and would support the evaluation of on-target and any potential off-target or unanticipated effects. Additionally, embryofetal development and fertility and early embryonic development studies have been conducted in rats dosed IV with ANX005. The IV route of administration achieves higher systemic exposures than the IVT route of administration and is thus an appropriate route to study toxicological effects. Lastly, ANX007 systemic toxicity by the subcutaneous (SC) route of administration has been evaluated in cynomolgus monkeys.

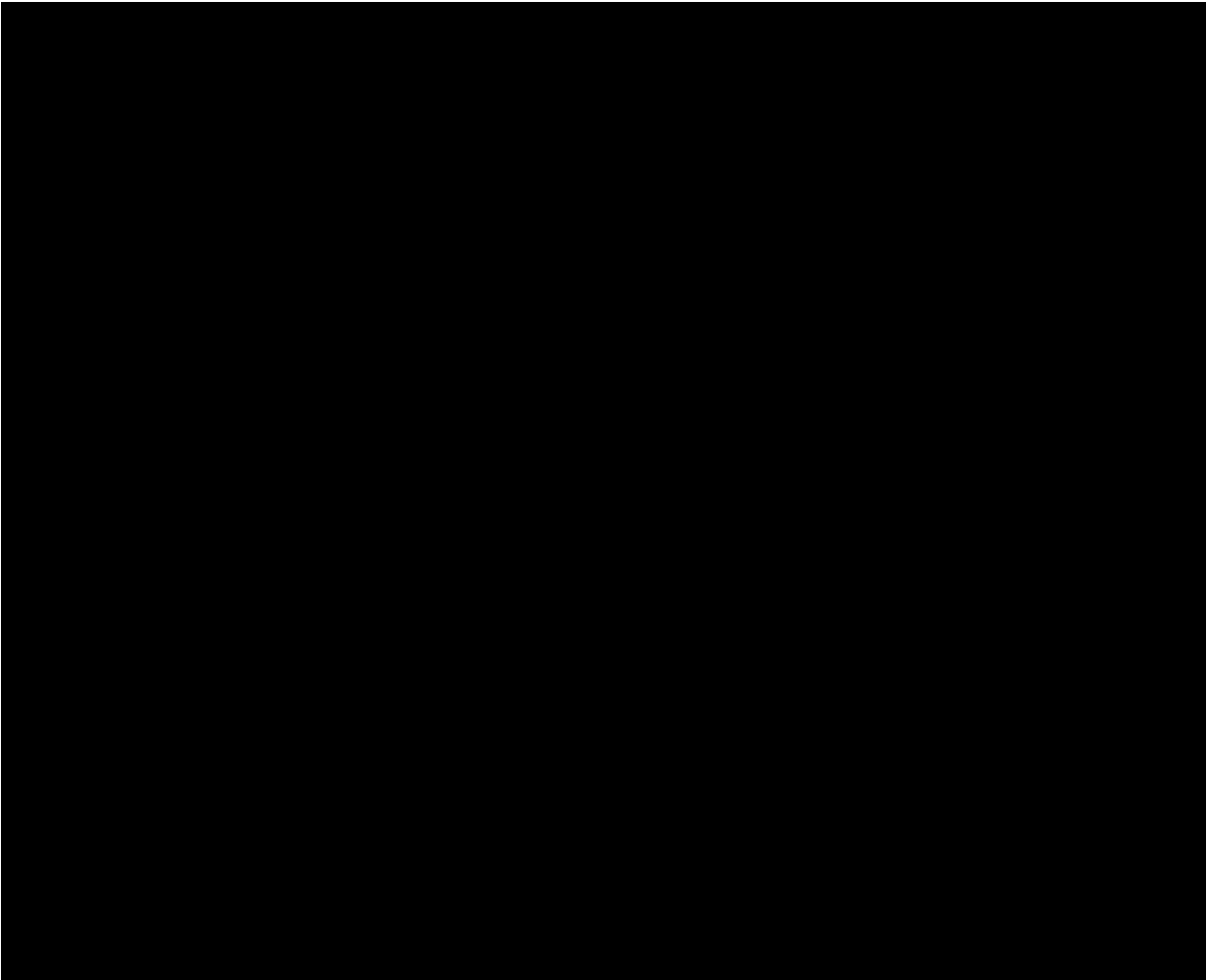
This nonclinical program is consistent with regulations and guidelines established by the Food and Drug Administration, European Medicines Agency, and International Council for Harmonisation (ICH) Harmonized Tripartite Guidelines S6(R1) and M3(R2). Additionally, all pivotal Good Laboratory Practice (GLP) nonclinical studies with ANX005 and ANX007 were conducted at Charles River Laboratories in the United States or Canada, both of which are OECD member countries.

The ANX007 Investigator's Brochure (IB) provides more detailed information.









2.4 Previous Human Experience

This is the third ophthalmic study to be conducted in humans with IVT injections of ANX007. Two Phase 1 clinical studies have been completed in patients with glaucoma and a total of 20 patients have been exposed to ANX007.

A Phase 1, open-label, single-dose, dose-escalation study (ANX007-GLA-01) evaluating the safety and pharmacokinetics of single doses of 1.0 mg, 2.5 mg, and 5.0 mg ANX007 IVT injections in 9 patients with primary open-angle glaucoma is completed. Overall, single injections of ANX007 up to 5 mg were well tolerated in this study; there were no serious or significant AEs. Ocular AEs included conjunctival hyperemia, conjunctival hemorrhage, and eye irritation and only occurred in the treated eye. There was only one systemic AE (sinusitis). Intraocular pressure (IOP) returned to normal (within 5 mm Hg of baseline) within 30 minutes of the IVT injection for all patients (see IB Section 5.4.1).

A Phase 1b, randomized, double-masked, sham-controlled study (ANX007-GLA-02) evaluating the safety of repeat doses of ANX007 (2.5 mg and 5.0 mg IVT) in 17 patients with primary, open-angle glaucoma is completed. Patients received two injections of ANX007 (or Sham injection) 4 weeks apart. Overall, 2 injections of ANX007 up to 5 mg were well tolerated in stable glaucoma patients; there were no serious or significant AEs.

Ocular AEs in patients treated with ANX007 included conjunctival hyperemia, conjunctival hemorrhage, and eye irritation and were only reported in the treated eye. Ocular AEs in patients in the Sham group included eye pain, foreign body sensation in eyes, ocular hyperemia, and vision blurred. The only systemic AEs reported with ANX007 in this study were bronchitis, viral conjunctivitis, and animal scratch in 1 patient each; none of which were considered related to ANX007. IOP returned to normal (< 21 mm Hg) for 16/17 patients within 30 minutes of the IVT injection and within 45 minutes for the remaining patient (see IB Section 5.4.2).

Overall, in the Phase 1 studies no safety signals with ANX007 were observed. In these studies, 8 patients received at least one 5.0-mg dose of ANX007.

Single IVT injections of 2.5 mg and 5 mg ANX007 inhibited free C1q for at least 29 days in aqueous humor (Study ANX007-GLA-02) (see ANX007 IB Section 5.2).

ANX007 was generally not detectable in systemic circulation after single or repeat IVT injections at any dose level studied in either of these studies. There were no changes in circulating free C1q and no anti-drug antibodies were detected in either study.

For additional details regarding clinical studies, see the ANX007 Investigator's Brochure (IB Section 5).

2.5 Study Rationale

C1q, the initiating molecule of the classical complement cascade, has been implicated in the initiation and propagation of GA. C1q is present in drusen, a key pathological feature of GA. In addition, early classical complement component C4 and downstream C3 deposition is observed on photoreceptor outer segments and edge of atrophic lesions in patients with GA ([Katschke et al 2018](#)). These results support the role for the classical complement cascade as a key initiator of the disease process in GA and supports clinical evaluation of a C1q inhibitor in GA. ANX007 is a C1q complement inhibitor that has been shown to inhibit free C1q for at least 29 days in aqueous humor following single 2.5 and 5 mg IVT injections (Study ANX007-GLA-02, Section 2.4). Repeat IVT injections (2 injections separated by 4 weeks) up to 5 mg were safe and well tolerated in patients with glaucoma.

This study is being conducted as a proof-of-concept study. The purpose of the study is to determine if IVT injections of 5 mg ANX007 once monthly or once every other month for 12 months reduces GA lesion growth rate. The results from this study will be used to guide further development of ANX007 in patients with geographic atrophy.

2.6 Benefit/Risk Assessment

2.6.1 Risk Assessment

Overall, single and repeat-dose IVT injections of ANX007 in Phase 1 studies in glaucoma patients were well tolerated as described in [Section 2.4](#). Potential risks of participating in this study and mitigation strategies are described in [Table 2](#).

Table 2 Potential Risks and Mitigation Strategy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention (s)		
Choroidal neovascularization (CNV)	Patients with GA are at risk of developing CNV as part of the natural history of AMD. This risk of developing CNV may be higher in eyes injected with some but not all complement inhibitors.	Patients will be monitored clinically at each visit and by spectral domain optical coherence tomography (SD-OCT) as specified in Table 1 for the development of new CNV. Those who develop new CNV will be treated with standard of care therapy while remaining on assigned study treatment (see Section 6.6).
Endophthalmitis	Endophthalmitis can occur with any IVT injection. Inhibiting the complement pathway may increase the risk of infection in the eye.	Patients will receive a follow-up call following every study injection and will be carefully examined at each study visit.
Hypersensitivity	Biologic drugs have the potential to cause allergic hypersensitivity reactions. Such reactions have not been observed with use of ANX007 in clinical studies to date.	Patients will be monitored for signs of hypersensitivity reactions during this study. Hypersensitivity may manifest as intraocular inflammation (see Appendix C).
Study Procedures		
Increase in IOP with IVT injections	Transient increases in IOP can occur with any IVT injection. In patients with glaucoma, IOP returned to normal within 30 minutes of administration in nearly all patients, and within 45 minutes for 1 patient (see Section 2.4).	IOP will be carefully monitored in this study prior to and following IVT injections (as described in Appendix D).
“Floaters” in the eye	Some syringes are known to contain silicone oil as a lubricant to decrease the syringe plunger glide force and initiation force. The potential hazard is deposition of silicone oil droplets in the vitreous. The potential harm could be symptomatic “floaters” in the patient’s field of vision, which normally are tolerable and resolve over a few months. However, if sufficiently bothersome, floaters may lead to a vitrectomy for their removal.	Patients will be monitored for evidence of floaters by ophthalmic examination and inquired about adverse event occurrences.

AMD = age-related macular degeneration; CNV = choroidal neovascularization; GA = geographic atrophy; IOP = intraocular pressure; IVT = intravitreal; SD-OCT = Spectral domain optical coherence tomography

There is potential for an immune response with biologics such as ANX007. Immune response could manifest as hypersensitivity reactions or loss of treatment response. Immune responses have not been observed with use of IVT injection of ANX007. No ADA were detected in ANX007-GLA-01. In ANX007-GLA-02, ADA positivity was detected in treated and Sham patients both pre- and post-dose, suggesting an unclear relationship between ADA measurement and ANX007 dosing. In this study, patients will be monitored for intraocular inflammation immediately following drug administration (see [Appendix A](#)) and for development of anti-ANX007 antibodies at the times specified in the Schedule of Activities (SoA, [Table 1](#)).

Patients systemically deficient in C1q have an increased risk of autoimmune disease. Since systemic exposure from IVT injections of ANX007 has been low, brief, and has not been shown to suppress serum C1q in clinical studies to date ([Section 2.4](#)), autoimmunity with ANX007 is not expected. Patients in this study will be monitored for autoimmunity (serum antinuclear antibodies [ANA]).

As this study will be initiated during the COVID-19 pandemic, the Sponsor is providing personal protective equipment (PPE) to trial participants and is offering clean transport between home and sites for scheduled study visits. Sites will follow local regulations and requirements. At home health care visits may be conducted by personnel educated and qualified to collect blood samples and/or assessments if necessary. Any procedural changes or protocol deviations due only to COVID-19 will be documented.

2.6.2 *Benefit Assessment*

Potential benefits of receiving ANX007 in this study include slowing the progression of GA. Patients in this study contribute to the process of developing a new therapy for a condition in which there is no approved drug. Patients may also benefit from the thorough medical evaluations to detect the development of neovascular AMD or any other ophthalmic condition.

2.6.3 *Overall Benefit: Risk Conclusion*

Based on the low risk to patients and measures to minimize risk to patients in this study, the potential risks identified in association with ANX007 are minimal and justified by the anticipated benefits that may be afforded to patients with GA. Risks of participating in this study need to be weighed against the benefits for the **individual patient**.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of ANX007 may be found in the ANX007 IB.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To compare the GA lesion growth rate from once monthly and once every other month IVT injections of 5 mg ANX007 for 12 months with Sham control	Rate of change (slope) in GA lesion area from baseline to Month 12 as assessed by fundus autofluorescence (FAF)
Secondary	
To compare the GA lesion growth from once monthly and once every other month IVT injections of 5 mg ANX007 for 12 months with Sham control	Change from baseline in GA lesion area at Month 12 as assessed by FAF
To assess the safety and tolerability of IVT injections of ANX007	Incidence and severity of ocular and systemic treatment-emergent adverse events (AEs)
To evaluate effects of IVT injections of ANX007 on visual function and visual acuity	- Change from baseline to Month 12 in Best Corrected Visual Acuity (BCVA) as assessed by the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at a starting distance of 4 m at each study visit - Change from baseline to Month 12 in low-luminance BCVA (LL-BCVA) - Change from baseline to Month 12 in low-luminance visual acuity deficit (LL-VD)
Exploratory	
To assess the systemic pharmacokinetic exposure and pharmacodynamics (PD) of ANX007	Serum ANX007 and C1q concentrations
To evaluate the immunogenicity of ANX007	Number and percentage of patients with anti-ANX007 antibodies (ADA) in serum

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is a Phase 2, multicenter, randomized, double-masked, sham-controlled study of intravitreal injections of ANX007. Eligible patients will receive ANX007 5 mg or Sham IVT injections once monthly or once every other month during the 12-month treatment period (either 6 or 12 injections over 12 months) and followed off-treatment for an additional 6 months. Patients in this study are adults (≥ 50 years of age) with geographic atrophy secondary to AMD macular degeneration. Approximately 40 to 60 study sites are planned for this study.

Approximately 270 patients are planned to be enrolled and randomly assigned (2:2:1:1) to study intervention (90 per group: ANX007 EM, ANX007 EOM, and pooled Sham) so that approximately 231 patients (~ 77 per group) are evaluable at Month 12 for the primary analysis (primary analysis is based on intent-to-treat [ITT]). Only one eye per patient will be selected as the study eye (see [Section 6.4.1](#)).

Treatment arms include:

- Arm 1 = ANX007 5.0 mg/eye (0.10 mL) once every month (EM) for 12 months (12 doses)
- Arm 2 = ANX007 5.0 mg/eye (0.10 mL) once every other month (EOM) for 12 months (6 doses)
- Arm 3 = Sham injection EM for 12 months (12 Sham injections)
- Arm 4 = Sham injection EOM (6 Sham injections)

Randomization is performed after the patient is deemed eligible and the independent Central Reading Center has confirmed lesion eligibility. Randomization will be stratified by lesion location (subfoveal or not), lesion size ($< 7.5 \text{ mm}^2$ or $\geq 7.5 \text{ mm}^2$), and history of or presence of CNV in the fellow eye (yes/no). [REDACTED]

At least two study physicians are required at each study site. A masked evaluating physician conducts routine study visits, which include safety assessments and eye examinations. An unmasked injecting physician performs all injections (ANX007 and Sham) and the immediate post-injection management. The unmasked injecting physician has no other role in the study and does not discuss any study-related observations with the masked members of the team.

Duration of Patient Participation: The total duration of patient participation is 19 months. The study consists of a 30-day screening period and a 12-month treatment period, followed by a 6-month (off treatment) follow-up period (see [Section 1.2](#)). Patients will visit the clinic each month during the 12-month treatment period for treatment and/or safety assessments. In

addition, all patients will visit the clinic on Week 2 (or have a home health visit) to have blood drawn to assess ADA.

Month 12/Early Termination: All patients return to the clinic at Month 12 for safety and efficacy follow-up assessments. Patients who discontinue from the treatment prior to completing the assigned treatment regimen will be encouraged to continue in the study and return to the clinic for follow-up assessments as scheduled.

Off-Treatment Follow-up: All patients return to the clinic 3 months (Month 15) and 6 months (Month 18) after the end of the 12-month treatment period for efficacy and safety follow-up assessments.

Masking: All patients, study site personnel (except for those performing/assisting the IVT injections), the evaluating physician, the Sponsor and Sponsor representatives (eg, Contract Research Organization [CRO]), and the independent Central Reading Center personnel will be masked to treatment assignment (ANX007 or Sham control); treatment regimen (EM or EOM treatment) is not masked in this study. The pharmacy and injecting physician are not masked to treatment assignment or regimen.

4.2 Data Safety Monitoring Committee

An independent Data Safety Monitoring Committee (DSMC) will be established to provide an ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of patients in the study. The structure and responsibilities of the DSMC will be described in the DSMC Charter.

The DSMC will review all available data after the first 30 patients have completed 3 months of treatment (ie, 3 injections for EM and 2 injections for EOM) ([Section 13.6](#)). The DSMC will provide ongoing periodic review as established in a DSMC charter.

4.3 Scientific Rationale for Study Design

Geographic atrophy (GA) is age-related, occurring primarily in people older than 50 years of age, and manifests as sharply demarcated areas of loss of the retinal pigment epithelium (RPE), choriocapillaris, and overlying photoreceptors that develop primarily in the macular retina and expand over time. In the absence of RPE, photoreceptors become nonviable and therefore areas of GA that are identified using imaging techniques correspond to scotomas in the visual field. FAF is the current standard imaging technology for the morphological assessment of GA. Sham controlled, dose-comparison intravitreal injection studies are well established.

GA lesion enlargement is the most widely used and reproducible assessment of GA progression and can result in substantial visual disability. Because lesions typically do not affect the fovea initially, testing BCVA may inadequately assess functional impairment in individual with preserved foveal function despite loss of pericentral macula. Other measures, including low-luminance visual acuity, reading speed, microperimetry, and patient-reported outcomes, might assess impairment of visual function in patients with GA, but these measures were not extensively used in earlier GA trials. Although some studies have

suggested that the square root transformation of the GA lesion area could potentially remove the correlation of baseline size and the growth rate of GA lesion, it is unclear whether the measurement transformation results in the best fit in modeling the growth curve and in assessing the treatment effect. Stratifying in randomization along with adjusting in the analysis model by baseline lesion size, using the GA lesion area in its original/untransformed scale would be more viable. In this study, the growth in GA lesion using the square root transformed measure will also be analyzed as a supportive analysis of the primary endpoint.

The rate of progression of GA can vary based on the size of the lesion and location of the lesion. GA lesion growth is generally linear, except for very large and very small GA lesions. The growth rate of smaller lesions is slower than that of larger lesions (Holz et al 2007, Sunness et al 2007). To minimize differences in the treatment arms due to baseline lesion size, randomization is stratified by lesion size ($< 7.5 \text{ mm}^2$, $\geq 7.5 \text{ mm}^2$). The lesion size of 7.5 mm^2 was selected for stratification based on the median lesion size reported in other GA studies (Holz et al 2018). Foveal lesions grow at a slower rate than non-foveal lesions (Schmitz-Valckenberg et al 2016). To minimize differences in the treatment arms due to lesion location, randomization is stratified by lesion location (subfoveal or not). In addition, AMD patients with a presence of CNV in one eye have a higher risk of developing CNV in the contralateral eye (Maguire et al 2013). To minimize differences in the treatment arms due to CNV risk, randomization is stratified by history of or presence of CNV in the fellow eye; history of or presence of CNV is not allowed in the study eye.

4.4 Justification for Dose

The 5 mg dose level was selected for this study based on a previous Phase 1b study, as described above (Section 2.4), where repeat doses ANX007 5 mg IVT (2 injections 4 weeks apart) were well tolerated. In the Phase 1b study, single doses of ANX007 at 2.5 mg and 5 mg inhibited free C1q in aqueous humor for at least 29 days. The 5 mg dose level was selected to support the once monthly and once every other month frequencies evaluated in this study, maximizing the pharmacodynamic effect in a larger patient population and supporting testing of the less frequent dosing interval.

4.5 End of Study Definition

The end of the study is defined as the date of the last scheduled procedure (eg, ophthalmic examinations, imaging, AEs) shown in the Schedule of Activities (Table 1) has been completed for the last patient in the trial at Month 18.

A patient is considered to have completed the Treatment Period of the study if he/she has completed all phases of the study up to the Month 12 visit and has not discontinued from treatment earlier.

A patient is considered to have completed the study if he/she has completed all phases of the study including the 6-month follow-up period (ie, completes the last scheduled procedure shown in the SoA up to Month 18).

5 STUDY POPULATION

The study population consists of men and women diagnosed with GA secondary to AMD.

5.1 Eligibility Criteria

5.1.1 Inclusion Criteria

Patients must meet ALL the following criteria to be eligible to participate in this study. An independent Central Reading Center will confirm lesion eligibility.



Age

1. Patient must be at least 50 years of age at the time of signing the informed consent.

Type of Patient and Disease Characteristics of the Study Eye

2. Diagnosis of geographic atrophy of the macula secondary to age-related macular degeneration as determined by the Investigator and confirmed by the Central Reading Center.
3. The GA lesion must have the following characteristics as determined by the independent Central Reading Center based on assessment of FAF imaging at screening:
 - a. Well-demarcated GA with a total area (baseline lesion size) $\geq 2.5 \text{ mm}^2$ and $\leq 17.5 \text{ mm}^2$.
 - b. If GA is multifocal, at least 1 focal lesion must measure $\geq 1.25 \text{ mm}^2$ with the overall aggregate area of GA as specified above in 3a.
 - c. Presence of hyper autofluorescence, any pattern, in the junctional zone of the GA. Absence of hyper autofluorescence (ie, pattern = none) is exclusionary.
 - d. The entire GA lesion must be completely visualized on the macula centered image and must be able to be imaged in its entirety and not contiguous with any peripapillary atrophy.
4. Normal luminance best corrected visual acuity (BCVA) of 24 to 83 letters, inclusive, using Early Treatment Diabetic Retinopathy Study (ETDRS) charts (20/25 to 20/320 Snellen equivalent, inclusive).

After the safety of ANX007 IVT injections for 3 months (3 injections for EM and 2 injections for EOM) has been evaluated in 30 patients by the DSMC, patients with better than 83 letters (better than 20/25 Snellen equivalent) may be enrolled.

Sex and Contraceptive/Barrier Requirements

5. Male or female
 - a. Female patients:

- A female patient is eligible if she is not pregnant or breastfeeding, and one of the following conditions applies:
 - Is a woman of non-childbearing potential.
- OR
- Is a women of child-bearing potential (WOCBP) using a contraceptive method that is highly effective, with a failure rate of $< 1\%$, as described in [Appendix F](#), during the study intervention period and for at least 30 days after the last dose of study intervention.
- WOCBP must have a negative pregnancy test within 24 hours before the first dose of study intervention, see [Section 8.5.4](#) Pregnancy Testing.
- The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

6. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.1.2 Exclusion Criteria

Patients are excluded from the study if **ANY** of the following criteria apply.

Medical Conditions

1. Geographic atrophy due to other causes than AMD such as Stargardt disease, cone-rod dystrophy, pathologic myopia, or toxic maculopathies (eg, plaquenil maculopathy) in either eye.
2. Any evidence of choroidal neovascularization (CNV) in the study eye:
 - a. Any history of CNV of any cause based on medical history.
 - b. Evidence of prior or active CNV or related findings (eg, retinal pigment epithelial rips or tears) based on FAF, SD-OCT imaging, IVFA and color fundus photo as assessed by the Central Reading Center.
3. Spherical equivalent of -8.00 diopters (D) myopia or higher in the study eye.
4. Uncontrolled glaucoma in the study eye (IOP > 25 mmHg despite treatment with anti-glaucoma medication) or history of neovascular glaucoma.
5. History of glaucoma filtration surgery, minimally-invasive glaucoma surgery involving an implant, or vitrectomy surgery, or other procedure in the study eye that could affect drug distribution and/or clearance.
6. History of uncomplicated cataract surgery less than 3 months prior to dosing in the study eye.

7. Any ophthalmic condition that may require surgery during the study period in the study eye.
8. Ocular trauma in the study eye within the preceding 6 months.
9. Any active ocular/intraocular infection or inflammation in either eye (eg, blepharitis, infectious conjunctivitis, keratitis, scleritis, endophthalmitis, uveitis).
10. History of idiopathic or autoimmune-associated uveitis in either eye.
11. Any current or prior ocular disease, other than geographic atrophy, that in the opinion of the Investigator could interfere with the conduct of the study including, but not limited to, insufficient pupil dilation, retinal or optic nerve disease, media opacity, or aphakia in the study eye.

Prior/Concomitant Therapy

12. History of any prior IVT treatment for any indication in the study eye.
13. Any prior treatment for AMD in the study eye (eg, surgical, radiation, thermotherapeutic, or laser intervention), except oral supplements or minerals.

Prior/Concurrent Clinical Study Experience

14. Previous participation in any studies of investigational medications within 3 months or 5 half-lives of the active ingredient (whichever is longer) prior to the start of study treatment.

Note: Clinical trials solely involving observation, over-the-counter vitamins, supplements, or diets are not exclusionary.

Other Exclusions

15. Known hypersensitivity to ANX007 or any of the excipients in the ANX007 solution (as described in the ANX007 IB Table 1) or other ANX molecules (eg, ANX005).
16. Known hypersensitivity to fluorescein.
17. Active alcohol or substance abuse/dependence or any other reason that makes it unlikely that the patient will comply with study procedures.
18. History of current systemic medical or psychiatric conditions or any other reason, including laboratory findings, that may, in the opinion of the Investigator, contraindicate the use of an investigational medication, affect interpretation of study results, preclude adherence to the study visit schedule, or safe participation in the study.

6 STUDY MEDICATION AND ADMINISTRATION

Refer to the Pharmacy Manual for additional information.

6.1 ANX007 Description

ANX007 is a recombinant, humanized, antigen -binding fragment (Fab) of a monoclonal antibody, composed of one VH and CH1 segment of an IgG1 heavy chain, covalently linked to 1 kappa light chain.

ANX007 is a sterile, isotonic, liquid for IVT injection. ANX007 is supplied as a 50 mg/mL solution in a 2-mL glass vial with a [REDACTED].

6.2 Sham Control

The sham injection is achieved by mimicking all the preparatory steps as with the ANX007 injection, except that instead of injection the physician is applying pressure to the eye at the location of a typical IVT injection using the blunt end of a syringe without a needle.

6.3 Packaging, Labeling, and Storage

ANX007 is provided as sterile, single-use vials for IVT injection. ANX007 vials must remain frozen at $-20^{\circ}\text{C}\pm 5^{\circ}\text{C}$ upon receipt and until prepared for use (details are provided in the Pharmacy Manual). Excursions from temperature limits must be reported to Sponsor representatives to determine whether or not the affected vials can be used. Store ANX007 in a secure area with limited access. Vials should be protected from direct sunlight.

Medication records must document storage temperatures.

6.4 Dose and Administration

A minimum of 2 study physicians are required at each study site.

Investigators are assigned as either an injecting physician or evaluating physician. Once the role is determined for each physician, the roles must remain the same for the duration of the study.

When masking is required, safety assessments and eye examinations are conducted by the evaluating physician, who is masked to treatment assignment. The injections (ANX007 and Sham) and immediate post-injection management are performed by the injecting physician, who is a qualified ophthalmologist with expertise in IVT injections, and who is not masked to the treatment assignment. The injecting physician has no other role in the study and does not discuss any study-related observations with masked members of the team. The roles and responsibilities of the injecting and evaluating physicians are defined in [Appendix C](#).

The preparation and post-injection care for the Sham injection is identical to the actual injection.

6.4.1 Pre-Injection

A single eye of each patient is selected as the study eye prior to the first injection. If both eyes are eligible, the study eye will be determined by the evaluating physician in consultation with the patient.

Prior to ANX007/Sham injection, the evaluating physician completes all protocol-specific safety assessments (including ophthalmic examinations and imaging) to ensure that no conditions exist that would preclude injection of ANX007 (see [Section 8.4.1](#) and [Appendix D](#)).

The injecting physician confirms IOP is ≤ 21 mmHg before proceeding with the injection; if IOP is > 21 mmHg, reschedule the injection or manage the IOP until IOP is ≤ 21 mmHg.

Note: For participants randomized to the EOM group, IOP will be assessed at each visit (monthly) during the 12-month treatment period (ie, for both dosing and non-dosing visits). For non-dosing visits, this will be a single IOP assessment.

6.4.2 Injection

ANX007/Sham administration is completed by the injecting physician using aseptic technique. Syringes and needles required for the IVT injections are provided by the study Sponsor.

All patients randomized to ANX007 will receive 5.0 mg/eye IVT (at a fixed volume of 0.10 mL) once every month or once every other month for 12 months. The procedure for drug administration is described in [Appendix D](#).

Sham is administered as described in [Section 6.2](#).

6.4.3 Post-Injection

Immediately following drug administration, the injecting physician will assess hand motion vision or central retinal artery perfusion visualization. If necessary, rule out other causes of vision loss such as vitreous hemorrhage. If needed, perform digital massage, and administer topical/oral IOP lowering medications, until hand motion vision or central retinal artery perfusion is observed.

IOP (tonometry) will be evaluated in the study eye only, 30 minutes after drug administration and, if elevated, every 15 minutes thereafter until IOP < 25 mmHg.

6.5 Masking

This study is masked. All patients, study site personnel (except the injecting physician and those assisting), the evaluating physician, Central Reading Center personnel, Sponsor, and Sponsor representatives involved in the conduct of the study are masked to treatment assignment (ANX007 or Sham control). Treatment regimen (EM or EOM treatment) is not

masked in this study. Once a masked physician performs unmasked study evaluations (eg, for emergency safety reasons) she/he cannot continue in the masked role.

In addition to the injecting physician, the following personnel are unmasked: site pharmacy team and injection assistants, drug reconciliation clinical research associate (CRA), Interactive Web Response System (IWRS) support staff, personnel generating the randomization code, DSMC, and Clinical Pharmacologist. A list of the names and roles of the unmasked individuals is maintained in the study files.

Treatment-revealing data, including PK and PD results, are not provided to the masked team until patient data have been cleaned (up to Month 12) and the study is unmasked for the primary analysis ([Section 11.4.1](#)). The Sponsor and Sponsor representatives involved with the analysis of the results will be unmasked after all patients complete the Month 12/ET visit and the data have been cleaned for the primary analysis. The masked individuals involved with the conduct of the study will remain masked until after the final analysis and the full database is locked and unmasked.

Unmasking for Patient Management

The Investigator or study staff may unmask in the event of an immediate medical emergency, where knowledge of the patient's treatment identity (ANX007 or Sham) must be known to provide adequate medical treatment.

If unmasking is necessary for patient management (eg, in the case of an SAE for which patient management might be affected by knowledge of treatment assignment), the Investigator will be able to break the treatment code by contacting the IWRS. Treatment codes should not be broken except in emergency situations. In these situations, the breaking of the patient's treatment identity must be reported to the Sponsor within 24 hours.

If the Investigator wishes to know the identity of the study treatment for any other reason, she/he must contact the Sponsor's Medical Monitor directly for approval before unmasking. The Investigator should document and provide an explanation for any premature unmasking (eg, accidental unmasking or unmasking due to SAEs).

If unmasking for a particular patient is necessary, the unmasking of the personnel should be documented in writing.

For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected suspected adverse reactions that are considered by the Investigator or Sponsor to be related to study drug.

Sponsor pharmacovigilance representatives may be unmasked to the intervention assignment for any patient with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the patient's intervention assignment, may be sent to Investigators in accordance with local regulations and/or Sponsor policy.

6.6 Development and Treatment of Neovascular AMD (Wet AMD) in the Study Eye

If, during the course of the study, the patient develops neovascular AMD (wet AMD) in the study eye, the patient may continue to receive ANX007 intravitreal injections and standard of care (SoC) treatment intravitreal injections for neovascular (wet) AMD. If conversion to wet AMD is suspected, CNV should be confirmed by SD-OCT, IVFA, and color fundus photos. If treatment is initiated, then imaging (SD-OCT, IVFA, and color fundus photos) will be provided to the Central Reading Center to confirm CNV, but the results are not required before treating wet AMD.

Treatment will be with one of the following SoC treatments for neovascular (wet) AMD for the duration of the study and should be administered according to the package insert:

1. LUCENTIS (ranibizumab injection) 0.5 mg (0.05 mL) administered by intravitreal injection-once a month (approximately 28 days)
OR
2. EYLEA (aflibercept) 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)

Treatment with SoC intravitreal injections for neovascular (wet) AMD may occur on the same day of the scheduled visit for study intervention and should be administered prior to ANX007/Sham. If the study treatment is delayed due to the SoC treatment for neovascular AMD, it should be administered within the allowed visit window (± 5 days). SoC treatments should be given by the unmasked injecting physician. Please see [Appendix D](#) and [Appendix E](#) for more information on injection procedures and SoC IVT injections for neovascular (wet) AMD.

6.7 Dose Modification

Fixed doses are administered in this study. No dose modifications are allowed.

6.8 Study Intervention Compliance

Study patients are dosed at the site and study intervention will be administered by the injecting physician.

The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention, study patient identification, and study eye will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.9 Accountability of ANX007

Pharmacy personnel must maintain adequate records of the receipt and disposition of all vials of ANX007. Records must include dates, lot numbers, quantities received, quantities dispensed, and the patient identification code associated with each injection. Site personnel may destroy used vials of ANX007 per site standard operating procedures (SOPs) and guidelines, following review and reconciliation of ANX007 inventory and pharmacy records by Sponsor representatives.

6.10 Treatment Overdose

An accidental overdose is highly unlikely. In the event of an accidental overdose, contact the Medical Monitor immediately to discuss an appropriate course of action and follow-up.

7 CONCOMITANT MEDICATIONS AND OTHER RESTRICTIONS

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

7.1 Permitted Medications

Record all medications on the Concomitant Medications case report form, including all medications taken within 30 days prior to the screening visit and through the final study visit. Permitted concomitant medications include all vitamins, herbal remedies, nutritional supplements, and over-the-counter and prescription medications, unless listed as a prohibited medication below.

7.2 Prohibited Medications

Prohibited medications include the following:

- Intravitreal medications in the study eye (per exclusion criteria) unless anti-vascular endothelial growth factor (VEGF) therapy for new onset choroidal neovascularization (see [Section 6.6](#)).

Patient must discontinue any investigational medications within 3 months or 5 half-lives of the active ingredient (whichever is longer) prior to the start of study treatment.

7.3 Restrictions

There are no meal or dietary restrictions or other lifestyle restrictions in this study.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities ([Table 1](#)).

The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 200 mL.

8.1 Screening

Written informed consent must be obtained prior to performing any study-specific activities or screening assessments. 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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) prior to implementation as described in [Section 13.3](#).

All inclusion criteria must be met, and none of the exclusion criteria may apply. An independent Central Reading Center will assess GA lesion eligibility. All results from the screening evaluations must be available before determining patient eligibility.

The entire screening period (ie, from the date of the first screening procedure until Day -1 [day prior to the first dose]), should not exceed 30 days for any given patient.

8.1.1 Patient Identification Number

A unique, sequential, ascending screening number will be assigned to each patient after signing the ICF. The patient screening number will consist of 3 digits that identify the study site followed by 3 digits that identify the patient in sequential screening order (eg, 100-001). This screening number will be used to identify the patient throughout the study.

Patients who are randomized are assigned a 4-digit randomization number; however, patients will be identified by their screening number for all study related data.

8.1.2 Screen Failures and Rescreening Criteria

Screen failures are defined as patients who consent to participate in the study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once if there is cause to believe that the patient may be eligible upon rescreen. If more than 4 weeks have elapsed since the initial screening, repeat all screening procedures, except informed consent. If a revised ICF has been issued, the patient should be reconsented.

8.2 Randomization

All patients will be centrally assigned to randomized study intervention using an Interactive Web Response System (IWRS). Before the study is initiated, the log in information and directions for the IWRS will be provided to each site. An IWRS randomizes patients upon confirmation of eligibility.

Patients will not be randomized until the Central Reading Center has confirmed lesion eligibility and CNV status.

Patients will be randomly assigned in a 2:2:1:1 ratio to receive ANX007 5.0 mg once every month (EM), ANX007 5.0 mg once every other month (EOM), Sham EM, or Sham EOM. Randomization will be stratified by lesion location (subfoveal or not), lesion size ($< 7.5 \text{ mm}^2$ or $\geq 7.5 \text{ mm}^2$), and history of or presence of CNV in the fellow eye (yes/no).

8.3 Medical History and Demographic Characteristics

Medical history includes an assessment of past and present history, and clinically significant diseases and surgeries, including ophthalmic history. Record all medications, used by the patient within 30 days prior to the screening visit. Demographic data include age, sex, and self-reported race or ethnicity.

8.4 Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA ([Table 1](#)).

8.4.1 Ophthalmic Examinations and Imaging

Ophthalmic examinations will be conducted by the masked evaluating physician as described in the SoA ([Table 1](#)). SD-OCT may be performed more frequently if needed at the discretion of the Investigator.

Ophthalmic examinations provide measurable parameters for determining efficacy and safety measurements throughout the study and should be performed in the following order or according to standard practice:

- BCVA and LL-BCVA as assessed by ETDRS
- Slit lamp biomicroscopy
 - Eyelid
 - Cornea (with fluorescein staining)
 - Conjunctiva
 - Anterior Chamber
 - Iris
 - Lens

- IOP / tonometry
- Dilation
 - phenylephrine 2.5% and tropicamide 1%

Post Dilation

- Slit lamp biomicroscopy
 - Vitreous
 - Retina
 - Macula
 - Choroid
 - Optic nerve and cup-disc ratio
 - Dilated fundus (indirect ophthalmoscopy)
 - Peripheral vitreous
 - Peripheral retina
- SD-OCT
- OCT-A (at select sites)
- Color fundus photos
- Near-infrared fundus reflectance (Near IR)
- FAF
- IVFA

Additional information on obtaining SD-OCT, color fundus photos, FAF, Near IR, and OCT-A imaging is included in the Imaging Manual (provided by the Central Reading Center).

8.5 Safety Assessments

Planned time points for all safety assessments are provided in the SoA ([Table 1](#)).

8.5.1 *Physical Examinations*

The physical examination includes height (screening only), body weight (without shoes, in kg) and an 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 the first dose of study drug as medical history.

Record any clinically significant, new, or worsened abnormalities that occur after first dose of study drug as AEs.

8.5.2 *Vital Signs*

Measure vital signs at all visits. Vital signs include body temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressures after the patient has rested (at least 5 minutes in seated position).

On dosing visits, vital signs should be measured prior to injection.

8.5.3 *Clinical Safety Laboratory Assessments*

Obtain blood and urine for the following safety laboratory assessments according to the SoA ([Table 1](#)). See [Appendix B](#) for a list of clinical laboratory tests to be performed. Clinical laboratory testing will be performed at a central laboratory.

- Hematology
- Serum chemistry
- Coagulation
- Pregnancy (for WOCBP only)
- Urinalysis

Additionally, samples for autoimmunity testing (serum ANA) are collected pre-injection on dosing days during the site visits specified in the SoA ([Table 1](#)) to monitor patients for autoimmunity (see [Section 2.6.1](#)).

8.5.4 *Pregnancy Testing (for WOCBP Only)*

Women of child-bearing potential (as defined in [Appendix F](#)), including those who have had tubal ligation, must have a negative serum pregnancy test during Screening and a negative pregnancy test (urine or serum) within 24 hours before drug administration on Day 1. Urine PT will be performed at Baseline (Visit 1) and at the Month 12/ET visit. If the urine PT is positive, collect a serum pregnancy sample and forward to the central laboratory for testing. If the serum pregnancy test is positive, do not administer the study treatment.

- Refer to [Section 5.1.1](#) Inclusion Criteria for pregnancy testing entry criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or as required by local regulation, to establish the absence of pregnancy at any time during the patient's participation in the study.

8.5.5 *Adverse Events*

Local and systemic adverse events will be monitored throughout the study as described in [Section 10](#). As described in the SoA ([Table 1](#)), all adverse events that have occurred to date will be reviewed at each visit and reported/updated accordingly.

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in [Section 10](#).

8.5.6 *Unscheduled Visits*

Additional visits to evaluate possible AEs/SAEs may occur at any time and may include ophthalmic examinations and/or imaging of one or both eyes; physical examination; vital signs; clinical laboratory blood or urine samples; and re-evaluation of medical history.

8.6 Pharmacokinetics, Pharmacodynamics, and Immunogenicity

Blood samples for PK (ANX007 serum concentrations) and PD evaluations (serum C1q concentrations) will be collected within 4 hours before dosing and 3 hours (± 15 min) after dosing at the visits specified in the SoA ([Table 1](#)). The 3-hour post-injection samples are optional and may be collected at home health visits.

Samples for immunogenicity testing (ADA) are collected pre-injection on dosing days during the site visits specified in the SoA ([Table 1](#)). Additionally, a sample for ADA will be collected at Week 2 at the site or a home health visit.

Detailed instructions for the collection and handling of biological samples will be provided by the Sponsor. The nominal and actual date and time (24-hour clock time) of each sample will be recorded. The volume of blood to collect at each visit is described in detail in the Laboratory Manual.

Refer to the Laboratory Manual for details pertaining to the collection, handling, and shipment of these samples.

Pharmacokinetics: This test requires serum. Blood samples will be collected for measurement of serum concentrations of ANX007.

Pharmacodynamics: This test requires serum. Serum concentrations of C1q will be analyzed.

Immunogenicity: This test requires serum. Immunogenicity is assessed by analysis of serum anti-drug (ANX007) antibodies (ADA).

8.7 Genetics

A 10-mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See [Appendix G](#) for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the Laboratory Manual.

9 DISCONTINUATION OF STUDY INTERVENTION AND PATIENT WITHDRAWAL

9.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a patient to permanently discontinue study intervention. If study intervention is permanently discontinued, the patient should be encouraged to remain in the study to be evaluated for, at a minimum, the Month 12 FAF imaging assessment, but preferably all non-injection-related assessments through Month 18. See the SoA ([Table 1](#)) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Note: If a patient develops CNV (wet AMD) in the study eye, assigned study treatment should be continued while SoC treatment for CNV is initiated (see [Section 6.6](#)).

9.2 Patient Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- At the time of withdrawal from the study, if possible, an early withdrawal visit should be conducted and should include the Month 18 assessments as described in the SoA ([Table 1](#)).
- The participant will be permanently withdrawn from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

Site personnel must make every effort to determine why a patient withdraws from the study prematurely. Any patient who withdraws from the study with an ongoing AE that is considered related to study intervention must be followed until the event is resolved or deemed stable.

9.3 Lost to Follow-Up

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

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

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

9.4 Termination of the Study

If the Sponsor's 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 including the DSMC. The clinical study may 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 a relevant or unacceptable risk to patients enrolled in the clinical study
- Failure to enroll patients at the required rate
- 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 the Sponsor representatives. Site personnel must continue to assess and maintain patient safety as required, despite termination of the study by the Sponsor.

10 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND REPORTING

10.1 Adverse Events

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

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in [Section 10.6](#)), will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up.

10.1.1 Definition

By definition, an AE is any untoward medical occurrence in a clinical study participant 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 (new or exacerbated) temporally associated with the use of a pharmaceutical product. An AE can arise with any use, route of administration, formulation, dose (including an overdose), or when used in combination with another pharmaceutical product.

An AE includes any of the following:

- An exacerbation or an unexpected increase in frequency or intensity of a pre-existing condition, including intermittent or episodic conditions.
- New conditions or intercurrent illnesses detected or diagnosed after the first injection procedure even if they may have been present before randomization.
- A suspected interaction with study intervention.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of study intervention.
- Any clinically significant laboratory finding that was not present prior to the first injection procedure or worsens from baseline.
- “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

An AE does not include any of the following:

- Anticipated day-to-day fluctuations of any pre-existing conditions, including the disease under study (GA)

- Medical or surgical procedure (eg, colonoscopy or hernia repair). The condition that led 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)
- Pre-existing diseases or conditions that were present before the injection of ANX007 that do not worsen

10.2 Severity and Causality Assessment

10.2.1 *Classification of Adverse Events by Intensity/Severity*

All AEs should be graded on a 3-point scale (mild, moderate, or severe) for intensity/severity. Unless otherwise defined in the protocol or protocol-specific manual, the definitions are as follows:

- Mild:** An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate:** An event that causes sufficient discomfort to interfere with normal everyday activities; minimal or no medical intervention/therapy required.
- Severe:** An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

There is a distinction between the severity and the seriousness of an AE. Severity is a measurement of intensity; thus, a severe reaction is not necessarily an SAE. For example, a headache may be severe in intensity, but would not be serious unless it met one of the criteria for SAEs (see [Section 10.4.1](#)).

10.2.2 *Causality Rating*

An event is considered related if there is a reasonable possibility that there is a causal relationship between event and the study intervention. Any AE judged by the Investigator or Sponsor representatives as having a reasonably suspected, causal relationship to the study intervention qualifies as a related AE. In addition, this study collects information on AEs that are related to the intervention procedure (ie, IVT/Sham injection procedure).

The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

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

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

- Another cause of the event is most plausible
- A clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention
- A causal relationship is considered biologically implausible

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

- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The event is uncommon in the general population and follows a reasonable, temporal sequence from study intervention
- The event cannot readily have been produced by the clinical state of the patient, environmental factors, concomitant medications, or other modes of concomitant therapy
- The event improves on stopping study intervention and reappears upon subsequent injection of study intervention

Relationship assessment for individual AEs is part of Investigator responsibilities. Regardless of relationship, Sponsor representatives review all AEs against cumulative experience of ANX007 to identify and communicate new safety findings to Investigators and regulatory authorities, as applicable.

There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data.

10.3 Documentation

An adverse event that occurs after a patient signs an ICF but prior to the first dose of study intervention 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 study intervention until the final study visit is recorded as an AE, irrespective of whether the event is considered to be related to study intervention.

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 study intervention. Ocular AEs should include study eye and/or non-study eye. At the time of the final study evaluation, all AEs should have a statement regarding resolution. Any AE that is assessed as related to study intervention is followed until resolution or stabilization.

Record clinically significant, abnormal laboratory or physical examination findings discovered during the screening period on the Medical History electronic case report form (eCRF) as a diagnosis whenever possible. Similarly, record clinically significant abnormal findings occurring after the first dose of study intervention, throughout the study, until the final visit on the Adverse Event eCRF as a diagnosis.

10.4 Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions

The Investigator classifies each AE as serious or not serious.

10.4.1 *Serious Adverse Event Definition*

An SAE is defined as any untoward medical occurrence that meets 1 or more of the following criteria:

1. Results in death.
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). Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.
4. Results in persistent or significant incapacity or disability where a substantial disruption of a person’s ability to conduct normal life functions occurs (does not include relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma [eg, sprained ankle] which may interfere with or prevent everyday life functions but do not constitute a substantial disruption).
5. Is a congenital anomaly or birth defect in the child of a patient exposed to ANX007 prior to conception, or during pregnancy.
6. Is a suspected transmission of any infectious agent via an authorized medicinal product.
7. 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 Investigator or Medical Monitor judges to be serious or that suggests a significant hazard, contraindication, side effect, or precaution.

10.4.2 *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 study intervention and the AE, and which is assessed as both unexpected and serious. An unexpected adverse reaction (ie, any untoward and unintended response to the study intervention) is one for which the nature and

severity is inconsistent with the applicable reference safety information (per the Investigator's Brochure).

SUSARs are subject to expedited reporting to applicable regulatory authorities.

10.5 Time Period and Reporting of AE and SAE Information

All AEs/SAEs will be collected from the start of intervention until the follow-up visit at the time points specified in the SoA ([Table 1](#)). Events occurring after signing the Informed Consent Form (ICF) but prior to first dose 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 injection procedure until the final study visit, are to be recorded as AEs.

Site personnel must provide patients with Investigator contact information for reporting SAEs.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours. The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool. If the electronic system is unavailable, then the site will use the paper SAE data collection tool to report the event within 24 hours.

If an ongoing SAE that is assessed as related to study intervention 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 or SUSARs, including those related to protocol-mandated procedures, must be reported by the Investigator immediately (within 24 hours 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 Investigator's responsibility 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.

It is the responsibility of Sponsor representatives to report SUSARs to regulatory authorities within the time frames required by applicable regulations.

10.6 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious or serious adverse events of special interest (AESIs) are required to be reported by the Investigator to the Sponsor immediately (ie, no more than 24 hours after learning of the event; see [Section 10.5](#) for reporting instructions). AESIs for this study apply to the study eye only and include:

1. Choroidal neovascularization
2. Endophthalmitis
3. Retinal vasculitis
4. Retinal vascular occlusion
5. AEs resulting from medication error, including but not limited to overdose, incorrect dose, incorrect route, incorrect drug, or incorrect administration.
Note: The primary event term should reflect the AE that occurred as a result of the medication error and identify it in “other suspected causes of SAE/AE” data field as a medication error.
6. Sight-threatening AEs that meet one or more of the following criteria (which should also be reported as serious events, listing the underlying cause [if known] of the event as primary event term):
 - a. It causes a decrease of ≥ 30 letters in BCVA score (compared with the last assessment of visual acuity prior to the most recent assessment) lasting more than 1 hour
 - b. It requires surgical intervention (ie, conventional surgery, vitreous tap, or biopsy with intravitreal injection of anti-infectives, or laser or retinal cryopexy with gas) to prevent permanent loss of sight
 - c. It is associated with severe intraocular inflammation (ie, 4+ anterior chamber cell/flare or vitreous haze score of 5; see [Appendix A](#) for intraocular grading scales)
 - d. In the opinion of the Investigator, it may require medical intervention to prevent permanent loss of sight

10.7 Pregnancy

Pregnancies that occur during study participation, while not considered AEs, must be reported by the Investigator 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 Investigator must report the pregnancy outcome within 24 hours 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.

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

11 STATISTICAL CONSIDERATIONS

11.1 Statistical Hypotheses

The null and alternative hypotheses for this study are:

$$H_0: \mu_S = \mu_{AM} \text{ vs } H_A: \mu_S \neq \mu_{AM}, \text{ and}$$

$$H_0: \mu_S = \mu_{AEOM} \text{ vs } H_A: \mu_S \neq \mu_{AEOM}$$

Note: here μ indicates each group's respective mean rate of change from baseline to Month 12 in GA lesion area for the comparison of the primary endpoint and the indexes S, AM, and AEOM indicate the pooled Sham control arm, ANX007 once monthly arm, and ANX007 once every other month arm, respectively.

Unless specified otherwise, all hypothesis tests for the purpose of signal seeking will be 2-sided and at an α level of 0.1. To adjust for multiplicity of having two ANX007 arms and multiple secondary endpoints, a Type-I error control plan will be specified in the Statistical Analysis Plan before the unmasked 12-month primary analysis.

11.2 Sample Size Determination

Approximately 270 patients are planned to be enrolled and randomly assigned to study intervention (90 per group: ANX007 EM, ANX007 EOM, and pooled Sham) so that approximately 231 patients (~77 per group) are evaluable at Month 12 for the primary analysis.

The primary analysis of the primary endpoint is based on a ITT data set (see [Section 11.3](#)).

The growth rate in GA lesion area is expected to be linear for the control during the first 12 months. Without explicit assumptions for the effect of ANX007 on the growth trend, study power is approximated by comparing the difference in mean growths at Month 12 between arms. The actual power for comparing the difference in growth rates (slopes) is expected to be higher than the approximated study power in most scenarios. The annual growth rate in GA lesion area for the Control arm is expected to be 2.1 mm² with a standard deviation (SD) of 1.3–1.4 mm² ([Holekamp et al 2020](#), [Liao et al 2020](#)). The assumptions made are that the ANX007 treated arms have the same variability as the Control and ANX007 has an effect of 30% in reducing the GA lesion growth rate (ie, it reduces the growth in GA lesion area by 0.63 mm² at Month 12).

Using a simple two-sample t-test on the growth at Month 12 to approximate the study power, $n = 77$ per arm at Month 12 (ie, a total of 231 evaluable patients) will yield a power of 91.1% to detect a difference between one of the ANX007 arms and the Sham control at a 2-sided α level of 0.1 for a common SD of 1.3 mm² (or 87.1% power for SD = 1.4 mm²).

Adjusting for a dropout rate of 15%, the study will randomize approximately 270 patients.

Note: “Enrolled” means the patient (or their legally acceptable representative) agrees to participate in the clinical study following completion of the informed consent process and has been randomization. Potential patients who are screened for the purpose of determining eligibility for the study, but are not randomized, are not considered enrolled.

11.3 Analysis Sets

Data from the study will be summarized based on the following key analysis sets.

Patient Analysis Set	Description
Intent-to-treat (ITT)	This set includes all randomized patients. The analysis will group patients based on the treatment arm they are assigned to.
Modified intent-to-treat (mITT)	This is a subset of the ITT set excluding patients with no post-baseline data for GA lesion area.
Per protocol (PP)	This is a subset of the ITT analysis set. Patients with any major protocol deviations that impact key efficacy outcomes will be excluded from this set. All protocol deviations will be reviewed and classified prior to study unmasking to determine patients’ inclusion/exclusion from this analysis set. Some protocol deviations impact only measurements assessed henceforth of the incidents. An alternative version of defining the per-protocol set excluding only impacted data points instead of the patients will be considered for sensitivity analyses.
Safety	All randomized patients who receive at least one ocular injection of ANX007 or Sham. Patients will be analyzed according to the treatment they actually received.

Patient disposition, demographics, and baseline characteristics will be summarized using the ITT set. The ITT, mITT, and PP sets will be used when analyzing efficacy outcome measures. The Safety set will be used to summarize safety, PK, PD, and immunogenicity outcomes.

11.4 Statistical Analyses

The statistical analysis plan will be finalized prior to un-masking for the 12-month primary analysis and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

11.4.1 General Considerations and Timing of Analyses

Timing of Analyses: Analyses planned for the study include:

1. A primary analysis after all patients have completed the 12-month treatment period through the Month 12 visit or have withdrawn from the study. Analyses will be performed once all data up to the Month 12/ET visit for all patients have been entered into the database and cleaned.

2. Analysis of the complete dataset after all patients have completed the 6-month follow-up period (Month 18) or have withdrawn from the study. Analyses will be performed once all data have been entered into the database, cleaned, and the database has been locked.

Unless specified otherwise, the baseline value will be the last assessment prior to the first dose on Day 1. For measurements not assessed at Day 1, the value at Screening will be the baseline.

The study includes two sham-injection arms (once monthly and once every-other-month) to ensure a proper masking of ANX007 administrations versus sham-injections. Patients in either EM or EOM sham arms will not receive an actual IVT injection. Therefore, the 2 sham arms will be pooled to form a single Sham control arm for the comparative analyses.

Unless specified otherwise, descriptive summary will be provided and will include N, mean, standard deviation, median, minimum, and maximum for continuous variables and N, counts and percentages for categorical outcomes. For key endpoints, a confidence interval (CI) of an estimate (such as mean, least square [LS] means, difference in means/LS means, percentages and differences in percentages) will be provided at both 90% and 95% levels.

Unless explicitly noted, the key stratification factors incorporated in analysis models will be categorized as follows: lesion location (subfoveal or not), lesion size ($< 7.5 \text{ mm}^2$ or $\geq 7.5 \text{ mm}^2$), and history of or presence of CNV in the fellow eye (yes/no).

All statistical analyses will be performed using SAS[®] version 9.4 or higher. All comparisons will be at a 2-sided α level of 0.1.

11.4.2 Statistical Analysis of Primary Endpoint(s)

GA Lesion Area

The primary efficacy endpoint is the rate of change (slope) from baseline to Month 12 in GA lesion area as assessed by fundus autofluorescence (FAF) imaging. GA lesion area will be assessed by an independent Central Reading Center.

The primary analysis is the comparison of the rate of change (slope) from baseline to Month 12 GA lesion area (mm^2) between each ANX007 arm and the pooled Sham control arm. The analysis using the square root transformed measure will also be performed. The primary analysis of the primary endpoint will be analyzed using the ITT set.

- ANX007 5 mg IVT EM compared with pooled Sham control
- ANX007 5 mg IVT EOM compared with pooled Sham control

A linear mixed-effect model (LME) will be used to analyze the longitudinal assessments of GA lesion area in the study eye from baseline to 12 months. The model will have the fixed effects of treatment, timepoint (in actual years relative to the first study treatment administration [or date of randomization for subjects not receiving the study treatment]), treatment-by-timepoint interaction, baseline GA, lesion location, CNV in fellow eye, and

baseline GA-by-time interaction, as well as the random effects across eyes of intercept and slope over timepoint. The baseline GA-by-time interaction, assessing the impact of baseline value on the growth rate, may be removed from the final model if the interaction term has a p-value of > 0.1 and removing the term improves the model's goodness of fit (as assessed by the fit statistics AICC [a version of Akaike information criterion]).

The mean slope, standard error (SE), and CI will be derived for each arm from the model. The difference in mean slopes between each of the ANX007 arms and the pooled Sham control and the SE and CI (at both 90% and 95% levels) of this difference will also be provided. An ANX007 arm is considered to have a significant reduction on GA lesion growth rate over the 12 months versus the Sham control if comparing the corresponding difference in mean slopes against 0 yields a p-value < 0.1 .

The primary analysis of the primary endpoint will include observed data up to the Month 12 visit. That is, data collected after the Month 12 visit for earlier enrollers will not be included in the main LME model. After study completion, the LME will be repeated to include all data to assess GA lesion growth rate post 12 months.

The main model used for the primary analysis assumes missing at random for missing data. To evaluate the robustness of the primary analysis, sensitivity analyses based on difference analysis sets (eg, PP set) and/or various approaches in handling missing data will be performed.

11.4.3 *Statistical Analyses of Secondary Endpoint(s)*

Continuous secondary endpoints that are assessed repeatedly over multiple post-baseline visits will be analyzed using MMRM. Fisher's Exact tests and Cochran-Mantel-Haenszel tests stratified by strata defined by GA lesion size, lesion location and CNV in the fellow eye will be applied for dichotomous endpoints.

GA Lesion Area

The change from baseline in GA lesion area using FAF to other time points will also be assessed. will be analyzed by a MMRM model including fixed effects of treatment, visit, treatment-by-visit interaction, baseline GA lesion (as a covariate), baseline-by-visit interaction, lesion location, and CNV in fellow eye. An unstructured variance-covariance matrix will be used, unless the model does not converge, in which case a compound symmetry variance-covariance matrix will be utilized.

The LS mean change from baseline at each visit will be estimated from the model for each arm. SE and CI (at both 90% and 95% levels) of the LS means will be provided. The difference in LS means between each of the ANX007 arms and the pooled Sham control and the SE and CIs of the difference will also be computed at each visit. An ANX007 arm will be considered to have a significantly lower GA lesion growth at 12 months than the Sham control if the corresponding comparison for the difference in LS means yields a P value < 0.1 .

Visual Function and Acuity

The change from baseline to Month 12 in BCVA, LL-BCVA, and LL-VD will be summarized and compared between treatment groups using an approach similar to that for the endpoint of GA lesion area. LL-VD will be derived by subtracting LL-BCVA from BCVA.

In addition, the change from baseline to other time points will also be summarized.

11.4.4 Statistical Analyses of Exploratory Endpoint(s)

Pharmacokinetics and Pharmacodynamics

Pharmacokinetic and pharmacodynamic analyses will be based on the Safety analysis set as data allow and will mainly be summarized descriptively.

Immunogenicity

Any patients who develop anti-ANX007 antibodies (ADA) will be presented in data listings. The number and percentage of patients who develop ADA will be summarized, if possible.

11.4.5 Safety Analyses

The Safety analysis dataset will be used for all safety analyses. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

Treatment emergent AEs (TEAEs) are defined as those AEs that develop (ie, emerge during and after treatment, having been absent pretreatment) or worsen on or after the date of first dose. TEAEs will be summarized by MedDRA coding terms (System Organ Class and Preferred Term) and by treatment arms.

The number and percentage of patients reporting each AE term will be provided. Separate summaries will be prepared for systemic (non-ocular) and ocular AEs, with events in the study eye and non-study eye summarized separately. Separate tabulations will be produced for all TEAEs, related adverse events (those considered by the Investigator as drug related), serious adverse events and discontinuations due to adverse events. In addition, TEAEs will also be summarized by severity.

Vital sign data and findings from physical and ophthalmologic examinations (eg, slit-lamp biomicroscopy, dilated fundus/indirect ophthalmoscopy, tonometry [IOP]) will be tabulated for changes over time on study. Laboratory parameters will be summarized for changes across study by using descriptive statistics.

11.4.6 Other Analysis

Data on the Fellow eye will be summarized descriptively. Of the patients with bilateral GA, statistical models utilizing the data on Fellow eyes may be explored to assess the contralateral effect on the GA lesion growth over time.

11.5 Interim Analysis

No formal interim analysis of efficacy outcomes, before unmasking for the primary analysis, is planned for the study.

Patient safety will be reviewed by a DSMC as described in [Section 13.6](#).

12 DATA MANAGEMENT

12.1 Data Collection and Management

Clinical data are collected through an electronic data capture (EDC) 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 includes 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 Medical Dictionary for Regulatory Activities and World Health Organization Drug Dictionary, respectively. The DMP specifies the versions used.

The Investigator must ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data reported on the electronic eCRF must be verifiable to source data, which necessitates access to all original recordings, laboratory reports, and patient records. The Investigator 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 electronic eCRF.

13 STUDY ADMINISTRATION

13.1 Ethical and Regulatory Considerations

The study is conducted in accordance with the protocol and the following:

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

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

13.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

The IRB/IEC must be constituted according to ICH and GCP requirements as well as the local laws and regulations of the country. Sponsor representatives supply relevant documents for the Investigator 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 Investigator. Written, unconditional, IRB/IEC approval must be obtained and submitted to Sponsor representatives before commencement of the study (ie, shipment of study intervention 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 Investigator and ensure that such are provided to the IRB/IEC in accordance with applicable local requirements and regulations. The Investigator 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 Investigator must notify the IRB/IEC at the closure of the study.

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.

13.3 Informed Consent

Site personnel obtain a properly written and executed ICF from each patient prior to commencing any screening procedures, in accordance with ICH GCP guidelines (ICH E6(R2)) and other applicable local regulations.

Sponsor representatives provide a template ICF to site personnel for modification into the format required by study 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 IRB/IEC 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. Site personnel 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.

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

13.4 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 and any required regulatory authorities before implementation.

Sponsor representatives may decide to amend the protocol, or the Investigator may suggest protocol amendments to the Sponsor. 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 Investigator 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 Investigator, and is implemented for safety reasons, the IRB as well as applicable regulatory agencies must be notified.

13.5 Retention of Documents

The Investigator 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 any one of the following conditions:

1. The last approval of a marketing application in an ICH region

2. There are no pending marketing applications
3. The discontinuation of a development plan for ANX007

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

The Investigator 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 Investigator or study site is unable to continue maintenance of the study records for the full 15 years, the Investigator must notify Sponsor representatives for assistance with retention.

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

Study records include the following:

- Ethics committee approvals for the study protocol, ICF, and amendments
- All patient source documents, laboratory records, applicable diaries, etc.
- eCRF/CRF copies
- Informed consent forms
- Other essential documents such as curricula vitae and other local or national regulatory approvals
- All other pertinent study documentation

13.6 Early Safety Data Review and Data Monitoring Committee

- Participant safety will be continuously monitored by the Sponsor's Medical Monitor, which includes safety signal detection at any time during the study.
- In addition, an early aggregated safety data review will be performed, the goal of which is to allow for a cautious, stepwise approach to ANX007 administration. An initial safety review for this study is planned after the first 30 participants who are dosed have provided safety data through Month 3.
- All safety data including AESIs collected will be summarized and reviewed by the Sponsor's independent DSMC for agreement of next steps.
- Additional ad hoc meetings of the DSMC can be requested by the Sponsor's Medical Monitor as needed.

13.7 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 for the purpose of confirming 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 study medication accountability forms. The CRA verifies eCRF entries by comparing them with the source records, which must be available for this purpose. The Investigator must ensure adequate time and space availability for these visits. The Investigator and site personnel are responsible for being present or available for consultation during monitoring visits.

13.8 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. The Site Initiation Visit (SIV) may include a review of ICH/GCP guidelines, study protocol and procedures review, management of AEs/SAEs, storage, preparation and injection of study intervention, and data collection processes and patient eligibility requirements.

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

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

- All patient data relating to the study will be recorded using printed or electronic eCRF forms unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Guidance on completion of eCRF will be provided in the Completion Guidelines.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) of all study related metrics will be pre-defined in the Quality Management System (QMS) to identify systematic issues that can impact patient

safety and/or reliability of study results. These pre-defined parameters/metrics will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals or companies (eg, Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a minimum 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor and written approval from the Sponsor.

13.9 Confidentiality

All clinical study findings and documents are regarded as confidential. Study documents (protocols, Investigator's Brochures, and other material) must be stored appropriately to ensure their confidentiality. The Investigator, 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 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 the Investigator.

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.

13.10 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 Investigators 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 study agreement between the Sponsor and the institution of the Investigator.

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APPENDIX A STANDARDIZATION OF NOMENCLATURE FOR UVEITIS

Uveitis Nomenclature Working Group Grading Scheme

Anterior Chamber Cells

Grade	Cells in Field [†]
0	< 1
0.5+	1–5
1+	6–15
2+	16–25
3+	26–50
4+	> 50

[†] Field Size is a 1 mm by 1 mm slit beam.

Source: Standardization of Uveitis Nomenclature (SUN) ([Jabs et al 2005](#))

Anterior Chamber Flare

Grade	Description
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

Source: Adapted from [Hogan et al \(1959\)](#)

Vitreous Haze

Score	Description	Clinical Findings
0	Nil	None
0.5+	Trace	
1	Minimal	Posterior pole clearly visible
2	Mild	Posterior pole details slightly hazy
3	Moderate	Posterior pole details very hazy
4	Marked	Posterior pole details barely visible
5	Severe	Fundal details not visible

Source: Adapted from [Nussenblatt et al \(1985\)](#)

APPENDIX B CLINICAL LABORATORY ASSESSMENTS

Hematology

HGB	Mean corpuscular HGB
Hematocrit	RBC count
Platelet count	WBC count
Mean corpuscular volume	WBC percent and absolute differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils)
Mean cell HGB concentration	

Chemistry

Sodium	Glucose (non-fasting)	Creatine phosphokinase
Calcium	Blood urea nitrogen	Albumin
Potassium	Creatinine	Aspartate aminotransferase
Phosphorous	Total bilirubin	Alanine aminotransferase
Magnesium	Uric acid	Alkaline phosphatase
Chloride	Lactate dehydrogenase	Total protein
Carbon dioxide (bicarbonate)	Gamma-glutamyl transferase	

Coagulation

International normalized ratio
Activated partial thromboplastin time

Pregnancy

Serum human chorionic gonadotropin

Urinalysis

pH	Nitrites	Reflex microscopy, if abnormal:
Specific gravity	Bilirubin	WBC
Protein	Urobilirubin	RBC
Glucose	Blood	Epithelial cells
Ketones	Leukocyte esterase	Casts
		Bacteria

Abbreviations: HGB = hemoglobin; RBC = red blood cell, WBC = white blood cell

APPENDIX C RESPONSIBILITIES OF THE INJECTING AND EVALUATING PHYSICIANS

The unmasked injecting physician performs the following procedures and assessments:

- Eye preparation procedures prior to injection
- Administration of ANX007/Sham
- Post-injection management (including paracentesis, if required)
- Completion of injection procedure source documents (maintained separately from other source documents)

The masked evaluating physician or designee remains masked and performs the following procedures and assessments:

- Clinical evaluations
- Ocular assessments
- Assessment and evaluation of safety concerns and reporting of AEs

APPENDIX D PROCEDURE FOR INTRAVITREAL INJECTION

Preparation of ANX007

Withdraw the entire volume of ANX007 (approximately 0.3 mL) from the sterile vial of ANX007, using a sterile 1.0 cc syringe with a 19-gauge × 1–1/2 inch, 5 micron, filter needle.

Replace the filter needle with a 30-gauge × 1/2 inch injection needle. Expel the excess volume of ANX007 from the syringe just prior to injection, leaving only the required injection volume in the syringe.

The dose volume of ANX007 is fixed at 0.10 mL once every month (EM) for 12 months (12 doses) or once every other month (EOM) for 12 months (6 doses). Additional information will be provided in the Pharmacy Manual.

Preparation for Intravitreal Injection

1. Verify the study eye.
2. Measure and record the pre-op intraocular pressure (IOP) in the study eye before injection. Perform tonometry on study eye only. The IOP must be ≤ 21 mmHg to proceed. If > 21 mmHg, reschedule the injection of ANX007 and manage the IOP at the Investigator's discretion.
3. Apply 1 drop of topical phenylephrine hydrochloride ophthalmic solution 2.5% to the study eye 30 minutes before the injection to allow visualization of the posterior pole after the injection, if necessary.
4. Immediately before injection:
 - Have the patient lie back in the examination chair with the neck well supported.

Intravitreal Injection

1. Hand-washing, sterile gloves, and surgical mask are required for the injection.
2. Apply topical proparacaine 0.5% to the study eye.
3. Apply povidone-iodine 10% to the eyelashes and eyelid margins. Avoid extensive massage of the eyelids either pre- or post-injection to avoid meibomian gland expression.
4. Retract the eyelids away from the intended injection site for the duration of the procedure. Use of a speculum is recommended.
5. Apply povidone-iodine 5% to the conjunctival surface, including the intended injection site.
6. For injection with ANX007: Insert the needle perpendicular to the sclera, 3.5 to 4 mm posterior to the limbus, between the vertical and horizontal rectus muscles. Apply a sterile cotton-tip applicator over the injection site immediately following removal of the needle to reduce vitreous reflux.
7. Sham injection: The preparation and post-injection care for the sham injection is identical to injection with ANX007. The sham injection is performed by applying

pressure to the eye at the location of a typical intravitreal injection using the blunt end of an empty syringe without a needle.

Post-Intravitreal Injection

1. Patients are to remain in the clinic after injection for ocular evaluations and safety follow-up.
2. Assess hand motion vision or central retinal artery perfusion immediately and rule out other causes of vision loss such as vitreous hemorrhage. Perform digital massage and administer topical/oral IOP lowering medications until hand motion vision or central retinal artery perfusion is observed, if no other cause is found.
3. Obtain IOP measurement in the study eye only at 30 minutes post-injection and, if elevated, every 15 minutes until IOP < 25 mmHg. Intraocular pressure in excess of 30 mmHg for more than 15 minutes should be treated at the physician's discretion.
4. Topical antibiotics are not required.

APPENDIX E PROCEDURE FOR THE STANDARD OF CARE ANTI-VEGF INTRAVITREAL INJECTION FOR WET AMD IN THE STUDY EYE

The Standard of Care Anti-VEGF Intravitreal Injection will be administered at least 30 minutes prior to the administration of ANX007 intravitreal injection or Sham.

Procedure for LUCENTIS (ranibizumab injection): Please see LUCENTIS (ranibizumab injection) label for diagrams and additional information.

Preparation for Administration (from LUCENTIS (ranibizumab injection) label):

To prepare LUCENTIS for intravitreal administration, please adhere to these instructions for use. Read all the instructions carefully before using the prefilled syringe.

How to store LUCENTIS:

1. LUCENTIS should be refrigerated at 2°C to 8°C (36°F-46°F). Do not freeze.
2. Do not use beyond the expiration date stamped on the label.
3. Protect LUCENTIS prefilled syringes from light and store in the original carton until time of use.
4. Do not open the sealed tray until time of use.

The prefilled syringe is for single use only. The prefilled syringe is sterile.

Do not use the product if the packaging is damaged or has been tampered with.

The opening of the sealed tray and all subsequent steps should be done under aseptic conditions.

For the intravitreal injection, a 30-gauge x ½ inch sterile injection needle should be used (not provided).

Note: the dose must be set to 0.05 mL.

Administration

The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide should be given prior to the injection. Prior to and 30 minutes following the intravitreal injection, patients should be monitored for elevation in intraocular pressure using tonometry. Monitoring may also consist of a check for perfusion of the optic nerve head immediately after the injection.

Patients should also be monitored for and instructed to report any symptoms suggestive of endophthalmitis without delay following the injection. Each prefilled syringe should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new prefilled syringe should be used and the sterile field, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before LUCENTIS is administered to the other eye.

After administration of LUCENTIS (ranibizumab injection):

1. Obtain IOP measurement at 30 minutes post-injection and then every 15 minutes until IOP < 21 mmHg. Intraocular pressure in excess of 30 mmHg for more than 15 minutes should be treated at the physician's discretion.
2. Proceed with injection of ANX007 as in [Appendix D](#). Patients may receive SoC and ANX007 intravitreal injections at the same visit or the injections may be scheduled on separate days.

Procedure for EYLEA (aflibercept): Please see EYLEA (aflibercept) label for diagrams and additional information.

Preparation for Administration (from the EYLEA (aflibercept) label):

The EYLEA prefilled glass syringe is sterile and for single use only. It should be inspected visually prior to administration. Do not use if particulates, cloudiness, or discoloration are visible, or if the package is open or damaged.

The intravitreal injection should be performed with a 30-gauge × ½-inch injection needle (not provided).

Administration:

The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include surgical hand disinfection and the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a topical broad-spectrum microbicide should be given prior to the injection.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (eg, eye pain, redness of the eye, photophobia, blurring of vision) without delay.

Each prefilled syringe should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new prefilled syringe should be used and the sterile field, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before EYLEA is administered to the other eye.

After administration of EYLEA (aflibercept):

1. Obtain IOP measurement at 30 minutes post-injection and then every 15 minutes until IOP < 21 mmHg. Intraocular pressure in excess of 30 mmHg for more than 15 minutes should be treated at the physician's discretion.
2. Proceed with injection of ANX007 as in [Appendix D](#). Patients may receive SoC and ANX007 intravitreal injections at the same visit or the injections may be scheduled on separate days.

APPENDIX F CONTRACEPTIVE AND BARRIER GUIDANCE

A. DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

1. Following menarche
 2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)
- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
 - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
 - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
 - 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.

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

B. CONTRACEPTION GUIDANCE

CONTRACEPTIVES^a ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods^b That Have Low User Dependency <i>Failure rate of < 1% per year when used consistently and correctly.</i>
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation^c • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS)^c • Bilateral tubal occlusion • Azoospermic partner (vasectomized or due to a medical cause) <i>Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.</i> Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods^b That Are User Dependent <i>Failure rate of < 1% per year when used consistently and correctly.</i>
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation ^c – oral – intravaginal – transdermal – injectable
Progestogen-only hormone contraception associated with inhibition of ovulation ^c – oral – injectable
Sexual abstinence <i>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 intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.</i>

^a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

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

^c If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

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

APPENDIX G GENETICS

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact intervention absorption, distribution, metabolism, and excretion; mechanism of action of the intervention; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples may be used for research related to ANX007 or GA and related diseases. They may also be used to develop tests/assays including diagnostic tests related to treatment of GA. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to ANX007 or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on ANX007 or study interventions of this class or indication continues but no longer than 5 years or other period as per local requirements.