

ANNEXON

biosciences

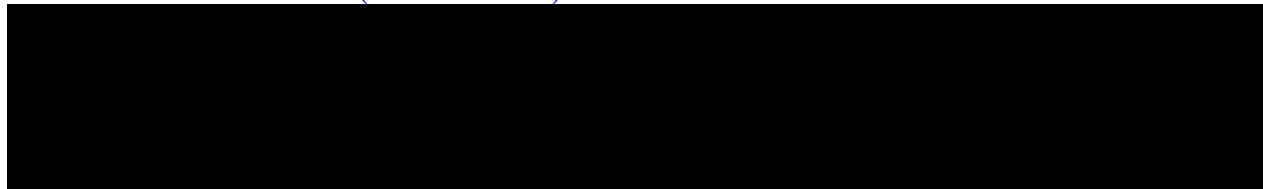
Statistical Analysis Plan

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)
Protocol Number:	ANX007-GA-01
Compound:	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
Sponsor Name:	Annexon Biosciences, Inc.
Legal Registered Address:	1400 Sierra Point Pkwy, Building C, 2nd Floor Brisbane, CA 94005
Regulatory Agency Identifier Number(s):	IND 130381, NCT04656561
Version Date:	Version 2.0: 01 May 2023

TABLE OF CONTENTS

Table of Contents	2
Version History	4
List of Abbreviations and Acronyms	5
1. Introduction.....	7
1.1 Objectives and Endpoints	7
1.2 Study Design.....	8
1.3 Sample Size Determination	9
2. Statistical Hypotheses	11
2.1 Multiplicity Adjustment.....	11
3. Analysis Sets	12
4. Statistical Analyses	14
4.1 General Considerations.....	14
4.2 Primary Endpoint Analysis.....	15
4.2.1 Definition of Endpoint(s).....	15
4.2.2 Main Analytical Approach.....	15
4.2.3 Sensitivity Analyses.....	16
4.2.4 Supplementary Analyses.....	17
4.3 Secondary Endpoint Analysis.....	17
4.3.1 Change from Baseline in GA Lesion Area at Month 12.....	17
4.3.2 Best Corrected Visual Acuity (BCVA).....	19
4.3.3 Loss of Photoreceptor	20
4.4 Exploratory Analyses.....	20
4.5 Safety Analyses.....	20
4.5.1 Extent of Exposure.....	21
4.5.2 Adverse Events	21
4.5.3 Intraocular Pressure (IOP)	23
4.5.4 Slit-Lamp Biomicroscopy and Indirect Ophthalmoscopy	24
4.5.5 Ocular Imaging	25
4.5.6 Physical Examination.....	25
4.5.7 Vital Signs.....	25
4.5.8 Clinical Laboratory Assessments.....	25
4.6 Other Analyses.....	26
4.6.1 Patient Disposition.....	26
4.6.2 Demographic and Baseline Characteristics	27
4.6.3 Medical History	28
4.6.4 Concomitant Medications	28
4.6.5 Concomitant Procedures	28
4.6.6 Subgroup Analyses	29
4.7 Interim Analysis.....	29
4.8 Changes to Protocol-planned Analyses	29
5. References.....	31

6. Supporting Documentation	32
Appendix 1. Schedule of Assessments as per Protocol, ANX007-GA-01, Version 5.0 (Amendment 4) dated 28 October 2022	33



VERSION HISTORY

This statistical analysis plan (SAP) for Study ANX007-GA-01 is based on the protocol v5.0.

SAP Version	Date	Change	Rationale
1.0	26 October 2022	Not applicable	Original version
2.0	01 May 2023		Final Version before the Data Base Lock scheduled for 08 May 2023 for the primary analyses

LIST OF ABBREVIATIONS AND ACRONYMS

ADA	Antidrug antibodies
AE	Adverse event
AESI	AE of special interest
AMD	Age-related macular degeneration
ANA	Antinuclear antibodies
BCVA	Best corrected visual acuity
CI	Confidence interval
CNV	Choroidal neovascularization
DSMC	Data Safety Monitoring Committee
EDC	Electronic data capture
EM	Every month
EOM	Every other month
ET	Early termination
ETDRS	Early Treatment Diabetic Retinopathy Study
FAF	Fundus autofluorescence
GA	Geographic atrophy
ICF	Informed consent form
IOP	Intraocular pressure
ITT	Intent-to-treat
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
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
mITT	Modified intent-to-treat
MMRM	Mixed-effect model for repeated measures
Near IR	Near infrared fundus reflectance
OCT	Optical coherence tomography
OCT-A	Optical coherence tomography angiography
PD	Pharmacodynamic or pharmacodynamics
PK	Pharmacokinetic or pharmacokinetics
PP	Per protocol
RPE	Retinal pigment epithelium
SAE	Serious adverse event

SD	Standard deviation
SD-OCT	Spectral domain optical coherence tomography
SE	Standard error
SOC	System Organ Class
TEAEs	Treatment-emergent AEs
VEGF	Vascular endothelial growth factor

1. INTRODUCTION

The purpose of this document is to provide details of the planned analyses for the ARCHER study (Protocol No: ANX001-GA-01). This Statistical Analysis Plan (SAP) supersedes the protocol in all specifications associated with data analyses and statistical methodologies. Any amendments to the SAP that are related to the primary and secondary endpoints will be made prior to study unmasking for the primary analysis at 12 months. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the clinical study report (CSR).

ARCHER study has a 12-month treatment period with an additional 6-month follow-up period. The primary analysis for the study will occur when all patients complete the Month 12 visit or have withdrawn earlier from the study and the data have been collected and cleaned. All post-Month 12 follow-up data collected prior to the database snapshot for the primary analysis may be presented on key safety outcomes. When all patients complete the study (i.e., the final follow-up visit at Month 18) or have withdrawn earlier from the study, and all data are collected and cleaned, the final database lock will occur. For key endpoints, the summary will include data for the overall study period (treatment + follow-up).

Specifications for data tables, listings and figures are detailed in a separate document, which will be finalized prior to unmasking for the primary analysis.

Unless specified otherwise, ocular outcome measures refer to assessments in the study eye hereafter.

1.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
To compare the geographic atrophy (GA) lesion growth rate from once monthly and once every other month intravitreal (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 (TEAEs)
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

Objectives	Endpoints
	- 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

The estimand for each of the above endpoints will be the difference between the pooled ANX007-treated arms (Every Monthly [EM] and Every-Other-Month [EOM]) and the pooled Sham-Control.

A larger growth rate is expected in GA lesions not involving the fovea center (non-subfoveal) at baseline. Rate of change (slope) in GA lesion area from baseline to Month 12 and mean change from baseline at 12 months in GA lesion area among eyes with non-subfoveal GA lesions in the study eye at baseline will be compared between the pooled ANX007-treated arms and the pooled Sham-control.

1.2 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 GA secondary to age-related macular degeneration (AMD). 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 all patients with non-subfoveal at baseline in the intent-to-treat [ITT] population). Only one eye per patient will be selected as the study eye. If both eyes are eligible, the study eye will be determined by the evaluating physician in consultation with the patient.

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 choroidal neovascularization (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. 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.

Schedule of Assessments for ARCHER study can be found in [Appendix 1](#).

Masking: All patients, study site personnel (except for those performing/assisting the IVT injections), the evaluating physician, the Sponsor and Sponsor representatives (e.g., 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.

An independent Data Safety Monitoring Committee (DSMC) has been 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.

1.3 Sample Size Determination

The sample size calculation designed in the original protocol is as following: approximately 270 patients were 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. [REDACTED]

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 (i.e., 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 (i.e., 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 Pooled 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). Since non-subfoveal subjects are accounting for about 49% of the total enrolled patients, $n=38$ per arm at Month 12 (i.e. a total 114 evaluable non-subfoveal patients) will yield a power of 80% to detect a difference between the pooled ANX007 arm and the pooled Sham control at a 2-sided α level of 0.1 for a common SD of 1.4 mm² (assuming that annual growth rate in GA lesion area for the pooled Sham control is 2.55 mm² and the treatment effect has 29.2% improvement).

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

In this SAP, the primary analysis is defined as the comparison between the pooled ANX007 treated arm versus the pooled Sham control based on all patients with non-subfoveal at baseline in the ITT set.

2. STATISTICAL HYPOTHESES

The null and alternative hypotheses for this study are:

$$H_0: \mu_{\text{sham pooled}} = \mu_{\text{ANX007 pooled}} \quad \text{vs} \quad H_A: \mu_{\text{sham pooled}} \neq \mu_{\text{ANX007 pooled}}$$

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

Similar hypotheses will be constructed for each of the endpoints with μ representing the corresponding mean for each of ANX007 arms, either pooled-ANX007, AM or AEOM, versus the pooled Sham control arm.

Unless specified otherwise, all comparisons will be two-sided.

2.1 Multiplicity Adjustment

The multiplicity adjustment procedure for the study will use a hierarchical approach to control the overall Type-I error (i.e., α). A total of 3 DSMC meetings to review safety data have been conducted prior to the study unmasking for the primary analysis. Adjusting for an alpha level of 0.001 for each DSMC review of data, the overall alpha level for the primary analysis of the study will be set at 0.097. Three key comparisons between the pooled ANX007 and the pooled Sham control arms in assessing the growth of GA lesion from baseline to Month 12 among eyes with non-subfoveal lesions at baseline and based on the ITT population will be ordered as follows:

Step	Endpoint	Comparison [Population]	Procedure and Significance (against $\alpha=0.097$)
1	Rate of change (slope) in GA lesion area from baseline to Month 12	ANX007 vs Sham control – with Monthly and Every Other Month cohorts pooled [ITT: non-subfoveal at baseline]	Based on a linear mixed-effect model (LME); Go to Step 2 if significant, otherwise STOP and comparisons in step 2 is considered as non-significant
2	Change in GA lesion area from baseline to Month 12	ANX007 vs Sham control – with Monthly and Every Other Month cohorts pooled [ITT: non-subfoveal at baseline]	Based on a mixed –effect model for repeated measures (MMRM). Go to Step 3 if significant, otherwise STOP and comparisons in Step 3 is considered as non-significant
3	Rate of change (slope) in GA lesion area from baseline to Month 12	ANX007 vs Sham control- – with Monthly and Every Other Month cohorts [ITT]	Based on LME.

Prior to unmasking for analysis, data will be reviewed by cohort (EM vs EOM) to assess any imbalance in evaluable rate for GA lesion area and untoward events.

Due to a change in the clinical development strategy to focus on the non-subfoveal subpopulation, the two ANX007 treated arms will be pooled to allow an adequate sample size for the comparisons against the pooled Sham control in this subpopulation.

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. The analysis will group patients based on the treatment arm they are assigned to.
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. The analysis will group patients based on the treatment arm they are assigned to. 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 (e.g., excluding data post an incidence of eMNV) 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 receive. <i>With the study drug administered monthly or every other month, for simplicity, patients will be grouped based on whether they receive any active ANX007 intravitreal injection on or before Month 3. See later in this Section for grouping rule.</i>

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.

Treatment group labels for data summaries will be:

- ANX007 Pooled
- ANX007 EM
- ANX007 EOM
- Sham Pooled
- Sham EM
- Sham EOM

Summary tables on patient disposition, demographics, baseline characteristics, safety data and descriptive efficacy summaries will include the summary for “All Patients” in addition to each of the first four (4) groups above (in the order of ANX007 EM, ANX007 EOM, ANX007 Pooled and Sham Pooled). Tables summarizing results from some statistical models on efficacy endpoints will include only those groups used in the model, e.g., ANX007 Pooled and Sham Pooled for the 2-arm models and ANX007 EM, ANX007 EOM and Sham Pooled for the 3-arm models.

With the study drug administered monthly or every other month, for simplicity, grouping patients for safety analysis will incorporate whether the “error” in receiving the dose not as assigned (active vs sham) occurred prior to Month 3. That is, patients will be grouped for the Safety Analysis Set as follows:

Randomization Assignment	ANX007 prior to Month 12	ANX007 prior to Month 3	Group for Safety Analysis
ANX007 EM	Yes	Yes	ANX007 EM
	Yes	No	ANX007 EM
	No	No	Sham EM (and Sham Pooled when applicable) *
ANX007 EOM	Yes	Yes	ANX007 EOM
	Yes	No	ANX007 EOM
	No	No	Sham EOM (and Sham Pooled when applicable) *
Sham EM	Yes	Yes	ANX007 EM
	Yes	No	Sham EM (and Sham Pooled when applicable) Data after the first active ANX007 will be excluded from the summary.
	No	No	Sham EM (and Sham Pooled when applicable) *
Sham EOM	Yes	Yes	ANX007 EOM
	Yes	No	Sham EOM (and Sham Pooled when applicable) Data after the first active ANX007 will be excluded from the summary.
	No	No	Sham EOM (and Sham Pooled when applicable) *

*Patients who did not receive any study treatment (ANX007 or Sham) will be excluded from the Safety Analysis set.

Data listings will be provided for patients receiving any doses (Active/Sham) not as assigned at randomization.

4. STATISTICAL ANALYSES

4.1 General Considerations

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/Early Termination (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.

[Note: When applicable, analyses specified for the primary 12-month data will be repeated for the 18-month data with relevant modifications on the models. The potential off-treatment impact on both safety and efficacy will be assessed.]

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

For each visit/assessment date, a corresponding Study Days will be derived from a reference date, which is the date of the first study treatment (ANX007/Sham) or the date of randomization for patients receiving no study treatment. Actual weeks, months, or years (for the analysis purpose) will be calculated by dividing the (Study Days – 1) with 7, 30.4375 and 365.25, respectively. The calculations are as follows:

$$\text{Study Days} = \text{Date of Visit/Assessment} - \text{Reference Date} + 1$$

$$\text{Weeks} = (\text{Study Days} - 1)/7$$

$$\text{Months} = (\text{Study Days} - 1)/30.4375$$

$$\text{Years} = (\text{Study Days} - 1)/365.25$$

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 on the ITT set 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 lesion focality (unifocal or multifocal). The stratification factor defined by history of or presence of CNV in the fellow eye (yes/no) is expected to have a negligible association with efficacy outcomes, and will not be adjusted in statistical models for efficacy endpoints. For analyses performed on the subgroup of the ITT set, the model will exclude the

relevant factor used to define the subgroup, e.g., excluding “lesion location” for the analyses on the non-subfoveal subgroup. In case of discrepancies in these stratification factors between the actual value at baseline and what has been entered into IWRS for randomization, unless specified otherwise, the actual value at baseline will be used to define subgroups and for the adjusted factors included in the statistical models. In the statistical models adjusting for baseline GA lesion area as a covariate, the lesion size stratification factor will not be included to avoid multicollinearity concerns.

Unless specifically noted, comparisons between ANX007 Pooled and Sham Pooled will be based on models with a 2-level “arm” factor, and pairwise comparisons between each ANX007 arm (EM or EOM) and the Sham control will be based on statistics derived from the statistical models with the 3-level (AEM, AEOM, and Sham Pooled) “arm” factor.

Unless specified otherwise, endpoints based on ocular assessments refer to data for the Study eye. Available data on the Fellow eye will be summarized descriptively.

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

4.2 Primary Endpoint Analysis

4.2.1 Definition of Endpoint(s)

The primary efficacy endpoint is the rate of change (slope) from baseline to Month 12 in GA lesion area in the Study eye as assessed by fundus autofluorescence (FAF) imaging. The FAF images will be collected at Screening, Baseline and every 3 months post baseline for both eyes and assessed by an independent Central Reading Center for GA lesion area at each visit for each eye.

The main analysis will use the GA lesion area (mm²) as reported (i.e., not transformed) for the Study Eye. The analysis using the rank transformed, and square root transformed measure will also be performed. Other transformed measures (e.g., logarithm) may also be considered.

4.2.2 Main Analytical Approach

The primary analysis is the comparison of the rate of change (slope) from baseline to Month 12 GA lesion area (mm²) between the pooled ANX007 arm and the pooled Sham control arm based on all patients with non-subfoveal at baseline in the ITT set, including all data as observed with no imputation.

A linear mixed-effect (LME) model 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 area, lesion focality, and baseline GA-by-time interaction, as well as the random effects across eyes of intercept and slope over timepoint. An example of SAS codes for the model is provided in [Appendix 2](#). The baseline GA-by-time interaction, assessing the impact of baseline value on the growth rate, will 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).

The mean slope, standard error (SE), and CI will be derived for the pooled ANX007 arm and the pooled Sham control from the model. The difference in mean slopes between the pooled ANX007 arm and the pooled Sham control, and the SE and 95% CI of this difference will also be provided.

To mitigate potential model assumptions violations and potential outlier issues, a nonparametric method of rank analysis of covariance (ANCOVA) will be conducted as supportive analyses. The rank ANCOVA includes rank (the rate of change (slope) from baseline to Month 12 GA lesion area derived from a linear regression) ~ rank (baseline GA lesion area) + treatment + lesion focality. An example of SAS codes for the model is provided in [Appendix 3](#). If the model assumptions and outliers have a large impact, the rank ANCOVA will be used to replace the prespecified primary analysis.

The above analyses of LME and rank ANCOVA will be repeated with the model including the 3-level treatment arm variable for the pairwise comparison of each of the ANX007 arms (AM or AEOM) vs. the pooled Sham control.

The analyses (LME and/or rank ANCOVA) on the whole ITT set with the extra lesion-location factor added to the model will also be performed. In addition, the analyses for the pooled ANX007 arm as well as each ANX007 arm vs. the pooled Sham control based on all patients with non-subfoveal at baseline and the ITT set will be performed on different time periods including but not limited to 0--6 months and 6-12 months, and comparisons of the treatment effect between these two time periods will be conducted.

4.2.3 Sensitivity Analyses

Prior to unmasking for analysis, data will be reviewed by cohort (EM vs EOM) to check the non-evaluable rates and the validity of the linearity assumption for the main LME model. The trend over time will be reviewed again by treatment group (after unmasking) to assess whether any transformation of the measures (e.g., square-root or logarithm) provides a better fit to the data or whether additional term(s) such as those to account breaking points in slope, should be included in the model.

The trend over the least-square means at each timepoint estimated from the mixed-effect model for repeated measures (MMRM) specified in a later section for secondary endpoints to analyze the change from baseline in GA lesion area may be viewed as one of sensitivity analyses of the primary endpoint.

The main model for the primary analysis using data (as observed) from all patients with non-subfoveal at baseline in the ITT set assumes missing at random (MAR). To evaluate the robustness of the primary analysis, sensitivity analyses based on difference analysis sets (e.g., PP set) and/or different approaches in handling missing data will be performed. In addition, sensitivity analysis excluding outliers will be performed. An outlier will be identified by the standard quantile-range approach. A patient with any GA grading in a study eye meeting the following criteria will be identified as an outlier: an individual slope in GA lesion size (raw slope) that is $>Q3 + 1.5IQR$ calculated in its corresponding subgroup of the ITT set classified by GA lesion location and GA lesion size for a total of 4 subgroups: non-subfoveal with lesion size $<7.5 \text{ mm}^2$, non-subfoveal with lesion size $\geq 7.5 \text{ mm}^2$, subfoveal with lesion size $<7.5 \text{ mm}^2$ and subfoveal with lesion size $\geq 7.5 \text{ mm}^2$.

If the non-evaluable rate for GA lesion area at 12 months (± 30 days) is more than 15% in any arm or if the difference in non-evaluable rate is 5% or more between any two arms, missing data will be handled by a multiple imputation (MI) with pattern-mixture model approach which incorporate the missing not at random (MNAR) assumption under some missing patterns. The detailed procedure is described in [Appendix 4](#).

The analyses described above will be repeated for the comparison of each ANX007 arm versus the pooled Sham control based on the ITT set. The analyses described above will also be repeated for the comparison of each ANX007 arm versus the pooled Sham control.

4.2.4 Supplementary Analyses

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. For example, a model similar to the final LME model used as the main analysis for the primary endpoint with a 4-level treatment arm variable (ANX007-SE, ANX007-FE, Sham-SE and Sham-FE with SE and FE stand for Study and Fellow eye respectively) or a 6-level variable (AEM-SE, AEM-FE, AEOM-SE, AEOM-FE, Sham-SE and Sham-FE), and a random effects over eyes within patient (subject) may be utilized to compare the difference in the rate of change (slope) between eyes within each treatment arm.

Impact of other baseline characteristics on the GA lesion growth rate such as presence of reticular pseudo drusen, GA lesion types (e.g., diffuse trickling), drusen characteristics (type, size, and volume), LL-BCVA (or LL-VD) and distance of GA lesion from fovea (if available) may be explored by adding the characteristics of interest to the existing LME model.

The main LME model for the primary endpoint will be applied to analyze the complete 18-month dataset including the observations in the 6-month follow up to assess the potential off-treatment impact on the rate of change in GA lesion area. Models with additional terms to account for the potential breaking point(s) in the slope will be explored, e.g., adding to the model a new timepoint variable, taking the value of 0 for assessments up to Month 12 and the value of the original timepoint variable (in year) subtracting by 1.0 for assessments after Month 12.

4.3 Secondary Endpoint Analysis

4.3.1 Change from Baseline in GA Lesion Area at Month 12

4.3.1.1 Definition of Endpoint(s)

As stated in Section [4.2.1](#), FAF imaging will be reviewed by the Central Reading Center to assess GA lesion area. Change from baseline in GA lesion will be calculated at each visit.

A square-root transformed version of the endpoints will be derived and change from baseline in square-root GA lesion will be calculated.

4.3.1.2 Main Analytical Approach

A MMRM including fixed effects of treatment, visit, treatment-by-visit interaction, baseline GA lesion area (as a covariate), baseline-by-visit interaction, and lesion focality will be used to analyze change from baseline in GA lesion area at Months 3, 6, 9, and 12 for all patients with non-subfoveal lesions at baseline in the ITT set. 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. An example of SAS codes for the model can be found in [Appendix 2](#). The baseline GA-by-visit interaction term will be removed from the final model if the interaction term has a >0.1 marginal p-value and removing the term improves the model's goodness of fit (as assessed by the fit statistics AICC).

The LS mean change from baseline at each visit will be estimated from the model for each arm. Standard errors (SE) and CIs of the LS means will be provided. The difference in LS means between the pooled ANX007 arm and the pooled Sham control, and the SE and CIs of the difference will also be computed at each visit.

The main model is applied to post-baseline data as observed in the ITT set (which is the same as using the mITT set which excluding eyes with no post-baseline GA lesion data) and the model includes the timepoint variable in the form of nominal visits. To utilize assessments observed at off-schedule timepoints, those observed within a window of ± 45 days the target study day for any nominal visit are mapped to the visit for analysis (see [Appendix 4](#)).

The analyses described above will be repeated by a 3-arm model for the comparison of each ANX007 arm versus the pooled Sham control based on all patients with non-subfoveal at baseline in the ITT set. The analyses described above will also be repeated for the comparison of the pooled as well as each ANX007 arm versus the pooled Sham control based on the ITT set (the analysis model will be identical to the main analysis except including the lesion location factor).

4.3.1.3 Sensitivity Analysis

To evaluate the robustness of the main analysis for the endpoint, sensitivity analyses based on difference analysis sets (e.g., PP set) and/or difference approaches (e.g., MI with pattern mixture models) in handling missing data will be performed. In addition, sensitivity analysis excluding outliers will be performed.

4.3.1.4 Supplementary Analyses

As stated in Section [4.3.1.2](#), LS mean change from baseline for each arm and between-arm differences in LS means will be provided for each visit. The results will be reviewed and treatment effect at these timepoints prior to Month 12 will be assessed. The same model will be performed on the square-root transformed version of the endpoint. Impact of other baseline characteristics on the GA lesion growth rate such as presence of reticular pseudo drusen, GA lesion types (e.g., diffuse trickling), drusen characteristics (type, size, and volume), baseline LL-BCVA (or LL-VD) and distance of GA lesion from fovea (if available) may be explored by adding the characteristics of interest to the existing LME model.

Changes from baseline in GA lesion area for both eyes of the patients with bilateral GA will be analyzed using a MMRM similar to the main model used for the corresponding Study-eye-only endpoint. The model will use a 4-level (or 6-level) treatment group variable as defined in Section [4.2.4](#) and with the repeated measures over eyes within patient (subject).

The analysis for the endpoint, change from baseline in GA lesion, will be repeated on the complete 18-month dataset including the observations in the 6-month follow up to assess the potential off-treatment impact on the change in GA lesion area.

4.3.2 Best Corrected Visual Acuity (BCVA)

BCVA of the study eye is assessed using ETDRS charts at a starting distance of 4 meters at Screening, Baseline and the monthly visits up to 12 months as well as Month-15 and Month-18 visits. On visits where both BCVA and LL-BCVA are assessed (Baseline Months 6, 12, 15 and 18), LL-VD will be derived by subtracting LL-BCVA from BCVA. Assessments observed at the Early Termination visit will be mapped to one of the scheduled visits with missing observations if the Early Termination visit occurred within ± 14 days of the visit (dated per the nominal study days derived by 30 days/month from the date of the first study treatment [or randomization date for patients receiving no study drug]). For example, map the assessment to Month 3 visit if the study day of the Early Termination visit is between 77 and 105 (inclusive). Change from baseline to in each of the three outcome measures (BCVA, LL-BCVA, and LL-VD) will be calculated for each post-baseline visit with available data. Both BCVA and LL-BCVA scores range from 0 to 100 letters with a higher score indicating a better vision. Negative numbers in the change from baseline in LL-VD indicate improving visual acuity deficit if BCVA is relatively unchanged. Interpretation on the treatment effect for change in LL-VD needs to be in companion with the effect on BCVA and LL-BCVA since an increase (worsening) in LL-VD could be due to a worsening in LL-BCVA or an improvement in BCVA.

A MMRM model similar to the one used for change from baseline in GA lesion area excluding the baseline-by-visit interaction term will be used to analyze each of the three change-from-baseline visual acuity endpoints (BCVA, LL-BCVA, or LL-VD) on the ITT set including data as observed at all post-baseline monthly visits up to 12 months. The model will have a fixed effect of treatment arm, visit, arm-by-visit interaction, the corresponding visual acuity assessment at baseline (as a covariate), lesion location, and lesion focality. (See [Appendix 2](#) for an example of SAS codes for the model.) LS mean change from baseline at each visit will be estimated from the model for each arm. Standard errors (SE) and CIs of the LS means will be provided. The difference in LS means between the pooled ANX007 arm and the pooled Sham control, and the SE and CIs of the difference will also be computed at each visit.

In addition to analyzing these visual acuity measurements and their changes from baseline as continuous variables with descriptive summaries and/or MMRM models, frequency distributions will be provided for the following ordinal variables by defining their categories based on certain cut points:

Continuous variable*	Categories (in letters) for the corresponding ordinal variable
BCVA (or LL-BCVA)	< 34, 34-68, 69-83, and > 83
Change from Baseline in BCVA (or LL-BCVA)	lost ≥ 30 , lost 15-29, lost 10-14, lost 5-9, changed -4 to 4, gained 5-9, gained 10-14, gained 15-29, gained ≥ 30 .
LL-VD	≥ 15 letters worse, 10-14 letters worse, 5-9 letters worse, 1-4 letters worse, no change (0 letters), 1-4 letters better, 5-9 letters better, 10-14 letters better, ≥ 15 letters better (i.e., BCVA is better/worse than LL-BCVA)
Change from Baseline in LL-VD	lost ≥ 15 , lost 10-14, lost 5-9, changed -4 to 4, gained 5-9, gained 10-14, gained ≥ 15

* Categories listed for the table above are meant to provide the specifications on cut points. These categories may be displayed using different labels in data listings and summary tables.

If there are some potential signals in the study eye reaching a certain clinical meaningful status (e.g., gained/lost at least 5, 10 or 15 letters in LL-VD, BCVA or LL-BCVA), Fisher's Exact tests and Cochran-Mantel-Haenszel tests stratified by strata defined by baseline GA lesion size, lesion location (if applicable) and lesion focality will be employed to compare the proportion of having such a status between the pooled ANX007 arm and the pooled Sham control. Logistic regression models adjusting for continuous covariates (e.g., baseline visual acuity assessment) in addition to stratification factors stated above will also be considered. In addition, time to achieving such a clinical meaningful status potentially differentiating the treated arms from the Sham control will also be illustrated by Kaplan-Meier curves along with median time to event and its 95% CI. A log-rank test stratified by categories defined by the baseline visual acuity scores (e.g., BCVA <55 vs ≥55 letters) be performed. Cox models adjusting for other factors will also be explored.

The analyses described above will be repeated for the comparison of each ANX007 arm versus the pooled Sham control based on all patients with non-subfoveal at baseline in the ITT set (excluding the lesion-location factor from the model). The analyses will also be repeated for the comparison of each ANX007 arm versus the pooled Sham control.

The analysis for these visual acuity endpoints will be performed in other specified subgroups as appropriate (see Section 4.6.6) and repeated on the complete 18-month dataset including the observations in the 6-month follow up to assess the potential off-treatment impact on the change in visual acuity.

4.3.3 Loss of Photoreceptor

Depending on data availability, changes in ellipsoid zone measurements by OCT will be summarized to assess the effect of ANX007 in the photoreceptor preservation.

4.4 Exploratory Analyses

The following exploratory variables will assess the systemic pharmacokinetic (PK) exposure and pharmacodynamic (PD) of ANX007 and evaluate the immunogenicity of ANX007:

- Serum ANX007 and C1q concentrations
- Number and percentage of patients with anti-ANX007 ADA in serum

Analyses on these variables will use the Safety set (and likely limited to those receiving any active dose of ANX007) and will mainly be summarized descriptively (with an addition of inter-quartile range and/or geometric mean as appropriate) as data allow for the main study report.

More comprehensive PK/PD analyses may be performed, and the analysis plan will be described in a separate document.

4.5 Safety Analyses

Safety will be assessed through the summary of ocular and non-ocular adverse events, serious adverse events, ocular assessments, deaths, laboratory test results, vital signs, and antibodies to ANX007 (ADA). Safety summaries for the 12-month treatment period will include all data from the screening period up to the Month 12 visit or the early termination visit for patients discontinued early from the study prior to Month 12. For patients who remain in the study for the 6-month follow-up period but miss the Month 12 visit, all data with onset (or examination or assessment) date between screening and 370 days following initial study drug administration will

be included in the 12-month summaries. Safety summaries for the complete 18-month data will include all data for both periods (12-month treatment + 6-month follow-up). By period summaries will be provided for some key variables as needed.

Safety data will be summarized descriptively using the Safety set for each treatment arm (ANX007 EM, ANX007 EOM, ANX007 Pooled, and Sham Pooled) as well as for All Patients, and by visit when applicable.

4.5.1 Extent of Exposure

The number of injections, number of missed injections and duration of treatment will be summarized by treatment arm using frequency counts and percentages for the mITT and Safety sets. The number of patients receiving injections at each visit (Day 1 and Months 1-11) will also be summarized by visit. For the summary using the mITT set, the number of patients receiving the treatment (ANX007 vs Sham) not as assigned at randomization at each visit will also be provided. As treatment is administered in the clinic by a trained unmasked injecting physician there is no need to assess compliance.

Duration of treatment will be calculated in days as follows:

Duration of treatment (days) = date of last injection – date of first injection +1,
and simply dividing the duration in days by 30.4375 to derive the duration of treatment in months.

The number of missed injections is defined as the scheduled injections missed up to discontinuation of study treatment.

4.5.2 Adverse Events

Verbatim descriptions of adverse events (AEs) will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms (Version 23.1). Treatment emergent AEs (TEAEs) are defined as those AEs that develop (i.e., emerge during and after treatment, having been absent pretreatment) or worsen on or after the date of first dose.

In general, TEAEs will be tabulated by the MedDRA coding terms: system organ class (SOC), and preferred term (PT). Unless specified otherwise, separate summaries will be prepared for non-ocular and ocular adverse events, with events in the study eye and fellow eye summarized separately. Summaries of adverse events by severity will be also provided.

An overview summary of TEAEs will be presented that includes the number of events and the number and percentage of patients who experienced at least one TEAE, by treatment arm and over all patients for TEAEs under each of categories listed in the following table, then by sub-categories defined by the intensity/severity for selected categories.

Category of TEAEs	Include summary by Severity?	By-SOC-PT summary?	By-SOC-PT summary for Severe AEs?
Any TEAEs	Yes	No	No
Ocular TEAEs (either eye)	No	No	No
Ocular TEAEs (Study eye)	Yes	Yes	Yes
Ocular TEAEs (Fellow eye)	Yes	Yes	No

Category of TEAEs	Include summary by Severity?	By-SOC-PT summary?	By-SOC-PT summary for Severe AEs?
Non-ocular TEAEs	Yes	Yes	Yes
Any SAEs	No	No	No
Ocular SAEs (Study eye)	Yes	Yes	No
Ocular SAEs (Fellow eye)	Yes	Yes	No
Non-ocular SAEs	Yes	Yes	No
TEAEs leading to death	No	A data listing instead	
AEs of Special Interest (AESI)*	Yes	Yes	Yes
TEAEs (Study eye) related to study medications or injection procedure	No	No	No
TEAEs (Study eye) related to study medications	Yes	Yes	Yes
TEAEs (Study eye) related to injection procedure	Yes	Yes	Yes
TEAEs (Fellow eye) related to study medications or injection procedure	No	No	No
TEAEs (Fellow eye) related to study medications	Yes	Yes	No
TEAEs (Fellow eye) related to injection procedure	Yes	Yes	No
Non-ocular TEAEs related to study medications or injection procedure	No	No	No
Non-ocular TEAEs related to study medications	Yes	Yes	No
Non-ocular TEAEs related to injection procedure	Yes	Yes	No
TEAEs (Study eye) leading to early treatment discontinuation	Yes	Yes	No
TEAEs (Fellow eye) leading to early treatment discontinuation	Yes	Yes	No
Non-ocular TEAEs leading to early treatment discontinuation	Yes	Yes	No
COVID related TEAEs	Yes	Yes	No

*AESI includes the following categories: choroidal neovascularization, endophthalmitis, retinal vasculitis retinal vascular occlusion, AEs resulting from medication error, and sight-threatening AEs.

For the patient level summary (i.e., number and percentage of patients experiencing at least an event), patients with multiple TEAEs under the same category being summarized will counted only once.

For selected TEAEs categories (see the third column of the above table), a tabulation summarizing the number and percentage of patients with TEAEs by SOC and PT for each treatment arm will be provided. For those selected categories indicated by the fourth column of the table, a tabulation summarizing the number and percentage of patients with severe TEAEs by

SOC and PT for each treatment arm will be generated. Instead of by SOC and PT, the AESIs will be summarized by the AESI-category, then by PT.

For tabulations summarizing TEAEs by SOC and PT, the SOC's will be ordered alphabetically, and PTs within a SOC will be displayed in descending order of frequency on All Patients (then sequentially on the ANX007 EM, ANX007 EOM, Sham Pooled arms).

Adverse events with missing onset date will be considered as treatment emergent. Adverse events with partial onset date will also be included as treatment emergent when the month (if it exists) and the year occur on or later than the month and year of the initial study drug administration date. TEAEs with a missing severity will be counted as severe in the summaries. Missing causality will be counted as related.

4.5.3 Intraocular Pressure (IOP)

Pre-IVT IOPs

Intraocular pressure (IOP) in the study eye will be measured prior to the IVT injection at every visit except Visit 2 (Week 2) and the type of tonometer used will be noted as either Tonopen, Air, Goldmann, or Other with other specified. A single measurement will be taken and will be recorded in mmHg for whole numbers only. The fellow eye will be measured at Screening, Visit 14 (Month 12/ET), and Visit 16 (Month 18) only.

The IOP values and change from baseline for the study eye will be summarized descriptively by visit for each treatment arm. Count and percentages will be provided at each visit by treatment arm for the following IOP categories defined by the IOP values and the change from baseline values:

IOP: < 10 mmHg, 10 to 21 mmHg, 22 to 30 mmHg, ≥ 30 mmHg

Change from baseline: ≥ 5 mmHg decrease, < 5 mmHg change, ≥ 5 mmHg increase

The number and percentage of study eyes with an incidence of pre-IVT IOP ≥ 30 mmHg at any time during the 12-month treatment period will be provided for each treatment arm.

When analyzing the complete 18-month data, the by-visit summaries will extend to include Month 15 and Month 18 visits. The number and percentage of study eyes with an incidence of pre-IVT IOP ≥ 30 mmHg at any time during the 12-month treatment period, and (separately) during the 6-month follow-up period will be provided for each treatment arm.

Post-IVT IOPs

At dosing visits, starting 30 min post-dose the patient's IOP will be measured until the post-IVT IOP is < 25 mmHg. IOP will be repeated as needed every 15 min until the patient's IOP is below 25 mmHg. The time to the last IOP measurement taken after the IVT, which can be interpreted as time-to-resolution of the IOP spike post-IVT.

Descriptive summary by treatment arm and the dosing visit will be provided for the time-to-resolution variable. The number and percentage of study eyes requiring >30 min for the IOP spike to resolve will also be provided.

If these descriptive statistics yield some signals of concern, the repeated time-to-resolution assessments will be analyzed using a MMRM with fixed effects of cohort (EM vs EOM),

treatment (ANX007 vs Sham), visit (Day 1, Months 2, 4, 6, 8, and 10), and all interaction terms defined by the 3 factors. Unstructured variance-covariance matrix will be used, unless the model does not converge, in which case a compound symmetry assumption will be utilized. LS means and difference in LS means estimated from the model could be used to compare any two groups of interest (e.g., EM vs EOM for eyes received ANX007, ANX007 vs Sham within each cohort, etc.). An alternative approach in using logistics regression model for repeated measures to analyze the repeated dichotomized outcomes (requiring >30 min to resolve) will also be explored.

4.5.4 Slit-Lamp Biomicroscopy and Indirect Ophthalmoscopy

The general ocular health is examined by Slit lamp biomicroscopy (pre- and post-dilation) and dilated funduscopy (indirect ophthalmoscopy) on all scheduled visits except Week 2. Abnormality findings of either clinically significant (CS) or not clinically significant (NCS) on the following fields will be reported:

Pre-dilation: Eyelid, Cornea (with fluorescein staining), Conjunctiva, Anterior Chamber, Iris, and Lens

Post-dilation: Vitreous, Retina, Macula, Choroid, Optic nerve, Peripheral vitreous, and Peripheral retina

For the abnormality in the anterior chamber (AC) or vitreous, AC cells, AC flare and vitreous haze will be assessed with quantitative grades/scores reported using the Standardization of Uveitis Nomenclature (SUN) ([Jabs et al 2005](#)), schemes adapted from [Hogan et al \(1959\)](#) and [Nussenblatt et al \(1985\)](#), respectively. The grade/score ranges from 0 to 4+ (or 5 for vitreous haze) with a higher grade indicating more intense in the severity of abnormality. In addition, the cup-disc ratio is also assessed.

Frequency distributions of AC cells, AC flare, and vitreous haze in the study eye at each visit will be provided for each treatment arm. Frequency distributions of the maximal grade/score (i.e., the worse outcome) for each of the three variables across all post-baseline assessments (including unscheduled visits) in the Study eye up to 12 months will also be provided for each treatment arm.

Descriptive summaries will be provided for cup-disc ratio of the Study eye by visit for each treatment arm.

A shift in status from Baseline to the worst outcome post-baseline up to 12 months in each of the fields assessed for the ocular health of Study eye will be qualified and summarized by treatment arm. “Abnormal (CS)” is considered as a worse outcome than “Abnormal (NCS)”. Derivation of the worst outcome post-baseline will omit the “Not Done” except for the cases where there are no post-baseline observations or all post-baseline observations are “Not Done”, in which the worst outcome post-baseline will be “Not Done”. That is, the shift in status from baseline to worst outcome post-baseline will have 16 possible combinations with 4 status (Normal, Abnormal (NCS), Abnormal (CS), and Not Done) each pre and post.

When analyzing the complete 18-month data, the by-visit summaries will be extended to cover Month 15 and Month 18. The summaries evaluating the 12-month treatment period as a whole will be repeated to evaluating the 6-month follow-period as a whole.

4.5.5 Ocular Imaging

SD-OCT, color fundus photos, FAF, near infrared fundus reflectance (Near IR), Intravenous fluorescein angiography (IVFA) and OCT A (at select sites) imaging will be graded by the Central Reading Center. Grading results on these multiple modalities of imaging that are associated with efficacy, safety and image quality will be mapped to SDTM and ADaM.

The GA lesion area is the primary efficacy outcome measure and will be analyzed as stated in earlier sections. Other assessments associated with GA in the Study eye (and Fellow eye if data is available) such as lesion location involving subfoveal or not, focality, presence of peripapillary atrophy confluent with GA, and presence of reticular pseudo drusen at baseline will be summarized with counts and percentages by treatment arm at baseline using the ITT set. The first three assessments will also be summarized for each of the post-baseline visits.

Evidence of prior or active CNV has been assessed as one of eligibility criteria for enrollment at Screening imaging. The number and percentage of Fellow eyes with prior or active CNV will be calculated for each treatment arm for the ITT set. Potential risk of CNV for the Study eye on post-baseline visits is assessed and the cases with definite evidence of macular CNV will be reported as an AE. Data from AE reporting and the imaging grading results will be cross-checked for any discrepancy on CNV reporting. Summaries for the incidence of CNV will be based on AE reporting.

The following key grading results from SD-OCT will be summarized descriptively: central subfield thickness (CST), incidence of subretinal fluid (SRF), intraretinal fluid (IRF), vitreomacular traction (VMT), subretinal hyper reflective material (SHRM), and Pigment Epithelial Detachment (PED). Whether the retinal anomaly, SRF, IRF, SHRM, and VMT, is within center 1mm or at the fovea center will also be summarized.

4.5.6 Physical Examination

A physical examination will be conducted at Screening and at Visit 14 (Month 12). Height (cm), weight (kg) and the following body systems will be measured: HEENT (head, eyes, ears, neck and throat), Dermatologic, Cardiovascular, Respiratory, Gastrointestinal, Neurological, Musculoskeletal, and Other. Results for each body system will be graded as normal, abnormal (NCS) and abnormal (CS). Results will be summarized for all body systems (except Other) by treatment group and for all actively treated patients using counts and percentages at each visit. Change from baseline will also be summarized for height and weight.

4.5.7 Vital Signs

Vital signs including temperature (C), systolic and diastolic blood pressure (mmHg), pulse rate (bpm), and respiration rate (breaths/min), will be summarized with continuous descriptive statistics by visit and treatment group for all actively treated patients. Change from baseline will also be summarized to each post-baseline visit.

4.5.8 Clinical Laboratory Assessments

Clinical laboratory assessments including serum chemistry, hematology, coagulation, and urinalysis are collected at specified visits. The quantitative variables will be summarized by treatment group with continuous descriptive statistics. The qualitative variables (counts and

percentages) will be summarized by treatment group and for all actively treated patients at each visit and time point (where appropriate). Change from baseline will also be summarized by treatment group and for all actively treated patients.

4.6 Other Analyses

4.6.1 Patient Disposition

Patient disposition will be summarized primarily for all randomized patients except that the number of screened patients, the number of re-screened patients, and the numbers and percentages of patients who were screen failures will be presented in the “All Patients” column. At maximum, one screen failure per patient will be counted. The number of patients (and percentage of the randomized patients) will be provided for those satisfying the following:

- Included in each of the Analysis sets (ITT, mITT, PP, and Safety)
- Completed/discontinued from treatment
- Completed/discontinued from the study.

Treatment completers will be those patients who have all scheduled injections or sham procedures through the 12-month treatment period. Patients who are not discontinued from the study will be considered study completers at Visit 16 (Month 18). Dispositions will be summarized by treatment arm and for all patients. For the primary analysis of 12-month data, patients discontinued from the study post the Month 12 visit will not be counted in the disposition table but will be included in the data listing.

The reasons for premature study and treatment discontinuation will be summarized by treatment arm for all discontinued patients. Percentages will be calculated using discontinued patients as the denominator (treatment or study). The reasons for study or treatment discontinuation include AE, Lost to Follow-up, Physician Decision, Protocol Violation, Screen Failure (for Study Discontinuation only), Study Terminated by Sponsor, Withdrawal by Subject, Pregnancy, Other, and Death. The disposition table will include a COVID-19 related section to summarize the COVID-19 related reason for treatment or study discontinuation.

The reasons for screen failure with the percentages calculated using total number of screen failures as the denominator will be tabulated.

Protocol deviations will be summarized for the following three main categories: All Protocol Deviations; COVID-19 Related Protocol Deviations; Not COVID-19 Related Protocol Deviations. For each of the three categories, the number and percentage of patients with any deviation, major deviation, and minor deviation will be summarized by treatment arm for all randomized patients. The protocol deviations that will be summarized include the following sub-categories:

- Informed Consent
- Inclusion/Exclusion and Randomization
- Test Article/Study Drug Administration and Assignment at Site
- Improper Protocol Procedures at Site (missed, repeated, not per protocol)
- Site’s Failure to Report SAE / AE

- Visit out of Window (missed, early, late)
- Subject's use of Prohibited Concomitant Medication, and Other.

A patient listing will be provided that includes the date of the deviation, the deviation category, the deviation description, the action taken, whether the deviation was COVID-19 related, and the classification of whether the deviation was judged to be major or minor in a masked review prior to the data snapshot for the 12-month analysis.

In addition, patient listings will be provided that include informed consent date, inclusion and exclusion criteria violations, and exclusions from the PP set. Details of the study randomization, including randomization date and time, randomized treatment and actual treatment, and the patient's stratification will also be included within a patient listing.

4.6.2 Demographic and Baseline Characteristics

Demographics

The demographic variables collected in this study include age, sex, females of childbearing potential with reason if not of childbearing potential, race, ethnicity, and country. Demographic variables will be summarized for the ITT set by treatment arm and for "All Patients".

Patients who record more than one race will be grouped into a single category denoted as Multiple Race.

Age will be reported in years and calculated using the following formula:

$$\text{Age} = (\text{Informed Consent Date} - \text{Date of Birth}) / 365.25, \text{ truncated as an integer}$$

The number and percentage of patients will also be provided for each of the Age groups categorized as follows: < 65 (years), ≥ 65 to < 75 (years), ≥ 75 to < 85 (years), and ≥ 85 (years).

Baseline Characteristics

The following baseline characteristics will be tabulated by treatment arm and for "All Patients" in the ITT set:

- Study Eye (OD/OS)
- Fellow Eye GA Presence
- Prior/active CNV in Fellow Eye
- Study eye and Fellow Eye separately:
 - Lesion location (subfoveal or non-subfoveal)
 - GA lesion size (as a continuous variable and dichotomized to $< 7.5 \text{ mm}^2$ or $\geq 7.5 \text{ mm}^2$)
 - Square-root transformed GA lesion size
 - Multifocal GA lesion
 - BCVA, LL-BCVA, and LL-VD in ETDRS letter score
 - IOP

Key demographics and baseline characteristics will be reported on the Randomization Schedule listing and on the individual assessments' listings when generated.

Any discrepancies on stratification factors between the values used at randomization and the actual values at baseline will be summarized by treatment arm.

4.6.3 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1. Table summaries of medical histories will be shown by treatment group and for All Patients in the ITT set. System Organ Classes (SOCs) and Preferred Terms (PTs) within a SOC will be ordered in descending frequency based on All Patients.

Non-ocular medical history will be summarized using discrete summary statistics and presented by treatment group at the patient level by SOC and PT using the Safety set. Ocular medical history will be similarly summarized separately at the patient level. If a patient reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a patient reports multiple conditions within the same SOC, that SOC will only be reported once.

4.6.4 Concomitant Medications

Concomitant medications will be coded using World Health Organization Drug Dictionary (WHODrug) Global, B3, September 2020 (or later version) and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and preferred name. If the ATC 4 classification is not provided, then the next lowest classification that is provided in the coding dictionary will be used. The preferred name will be defined as the active ingredient; if the active ingredient is not provided or includes more than two ingredients (e.g., multivitamins), then the drug name will be summarized as the preferred name. Any uncoded terms will be summarized under the ATC classification and preferred name of "Uncoded."

Prior medications are defined as those medications started and stopped prior to study drug administration. Concomitant medications are defined as those medications listed as having been taken (1) prior to initiation of study drug administration and continuing for any period of time following the first administration of study drug or (2) at any time following the first administration of study drug. Prior or concomitant categorization for medications with missing start/stop dates will use the conservative approach (such as categorizing them as on/post study drug initiation and ongoing). Detailed rule(s) will be incorporated onto the data derivation document or as an appendix for this SAP as needed.

Concomitant medications will be summarized using the Safety set by ATC class and preferred name. Medications will be tabulated for ocular and non-ocular separately with each treatment arm using frequencies and percentages. Patients may have more than one medication per ATC text. At each level of patient summarization, a patient will be counted once if he/she reports one or more medications.

The tabulations for concomitant medications will display ATC classes and preferred names within an ATC class in the order of descending frequency on All Patients (then sequentially on ANX007 EM, ANX007 EOM and Sham Pooled arms).

4.6.5 Concomitant Procedures

Concomitant procedures will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1. Data listings will be generated for all concomitant procedures including the verbatim, SOC and PT terms, and other relevant information such as date and reason(s) of the procedure, etc. No table summaries will be created.

4.6.6 Subgroup Analyses

Descriptive summaries on GA lesion area and its change from baseline value will be provided for each of the subgroups of the ITT set defined by the following key demographics variables and baseline characteristics:

- Age group: <75 vs ≥ 75 years
- Sex: female vs male
- Baseline GA lesion size: <7.5 mm² vs ≥ 7.5 mm²
- GA lesion location: subfoveal vs non-subfoveal
- GA lesion focality: multifocal vs unifocal (only when at least 10% in either group)

The growth rate (slope) and growth at Month 12 in GA lesion area will be analyzed for the above defined subgroups with the main LME, MMRM and rank ANCOVA models used for the corresponding primary endpoint performed on the patients with non-subfoveal at baseline. Influential statistics will be derived from the models.

Eyes with the diffused trickling characteristics potentially have a faster progression rate in GA lesion. Depending on data availability, analyses exploring the effect of diffused trickling characteristics at baseline will be performed.

The incidence of CNV in the Study eye will be summarized by the presence of prior/active CNV in the Fellow eye at baseline. Appropriate statistical method(s) will be utilized to assess whether having CNV in the Fellow eye increases the risk of CNV in the Study eye.

4.7 Interim Analysis

No formal interim analysis of efficacy outcomes, before unmasking for the primary analysis, is planned for the study. Ongoing safety data will be reviewed by an independent DSMC to ensure patient safety. The study will not be stopped for futility or early evidence of treatment effect. However, to account for efficacy data potentially being reviewed by the DSMC for the purpose of properly assessing the risk-benefit for any safety concerns, an alpha level of 0.001 will be allocated for each interim data review by the DSMC. A total of three (3) DSMC meetings reviewing the study data have been conducted before unmasking for the primary analysis. Subtracting these alpha penalty 3×0.001 from the overall alpha level of 0.1 leaves $\alpha = 0.097$ for the primary analysis.

4.8 Changes to Protocol-planned Analyses

Changes to protocol-planned analyses include the following:

- Alpha penalty of 0.001 for each DSMC review of interim data prior to unmasking for the primary analysis is incorporated.
- Allowed the Baseline*Visit interaction term in the MMRM model for change from baseline in GA lesion to be removed from the final model under some conditions (see Section 4.3.1.2 for details).
- Added another factor, the focality of GA lesion, to the statistical models for the primary and secondary efficacy endpoints. In addition, the stratification factor defined by history of or presence of CNV in the fellow eye is removed from these statistical models.

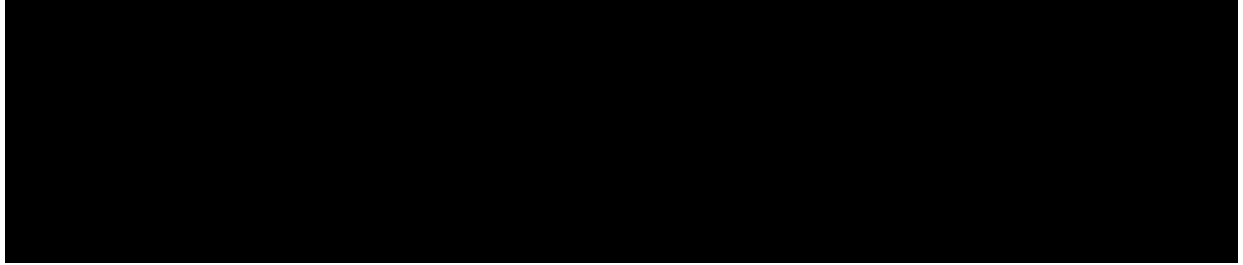
- Change the primary estimand to be based on the comparison between ANX007 Pooled and Sham Pooled among ITT patients with non-subfoveal lesion at baseline.

5. REFERENCES

- Hogan MJ, Kimura SJ, Thygeson P. Signs and symptoms of uveitis. I. Anterior uveitis. *Am J Ophthalmol.* 1959;47(5 Pt 2):155-170.
- Holekamp N, Wykoff CC, Schmitz-Valckenberg S, Monés J, Souied EH, Lin H, et al. Natural history of geographic atrophy secondary to age-related macular degeneration: results from the prospective Proxima A and B clinical trials. *Ophthalmol.* 2020;127(6):769-783.
- Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol.* 2005;140(3):509-516.
- Liao DS, Grossi FV, El Mehdi D, Gerber MR, Brown DM, Heier JS, et al. Complement C3 inhibitor pegcetacoplan for geographic atrophy secondary to age-related macular degeneration. *Ophthalmol.* 2020;127(2):186-195.
- Nussenblatt RB, Palestine AG, Chan C-C, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. *Ophthalmol.* 1985;92:467-471.

6. SUPPORTING DOCUMENTATION

Appendix 1: Schedule of Assessments



Appendix 1. Schedule of Assessments as per Protocol, ANX007-GA-01, Version 5.0 (Amendment 4) dated 28 October 2022

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**
Near IR	X**	X**				X**			X**			X**			X**	X**	X**

Assessment	Screening Day -30 to -1	12-Month Treatment Period ^a													Off Treatment		
		(±5-day visit window)													(±5-day visit window)		
		Day 1	(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
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

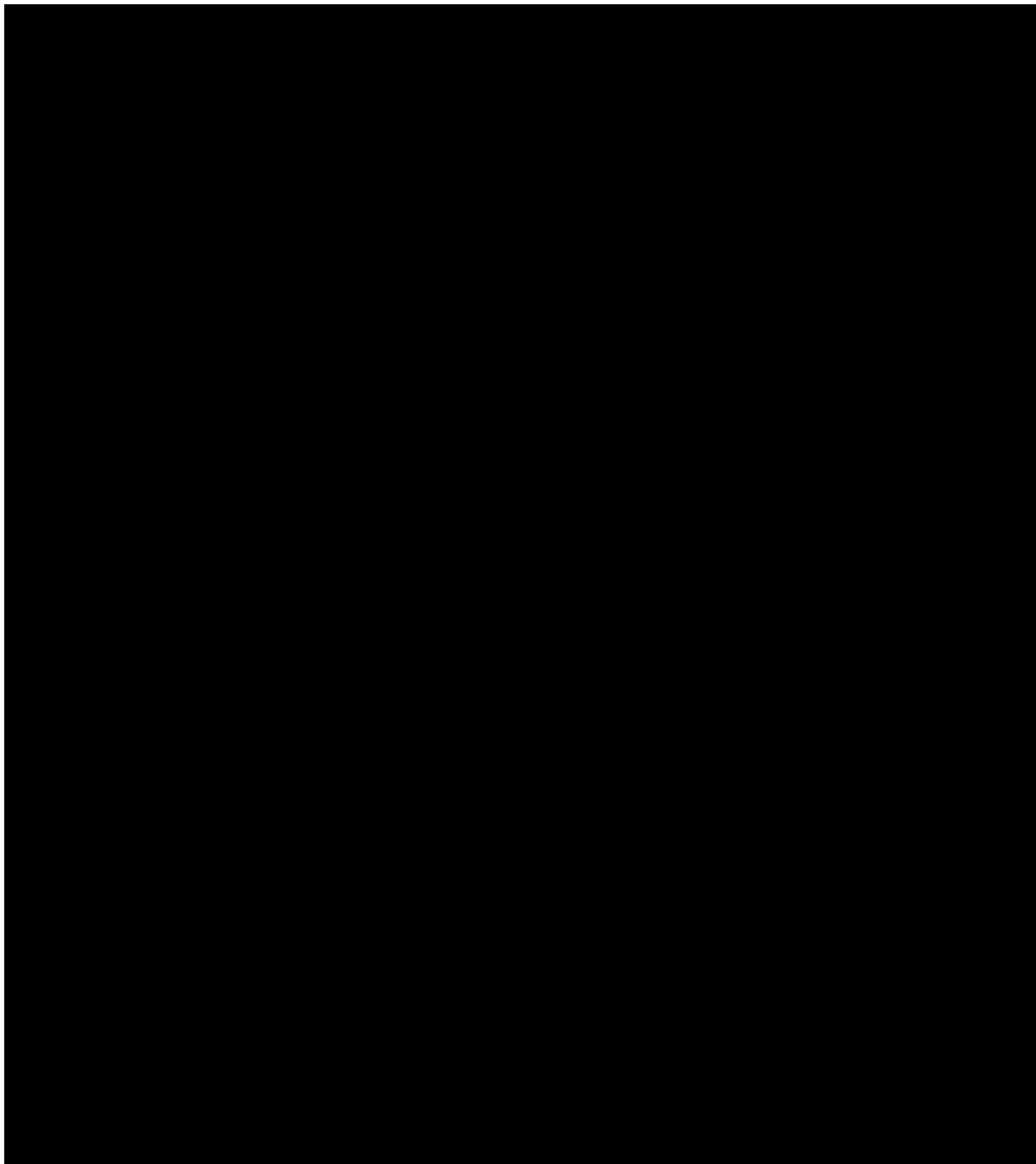
** Indicates procedure should be performed and recorded for both the study eye and the fellow eye.

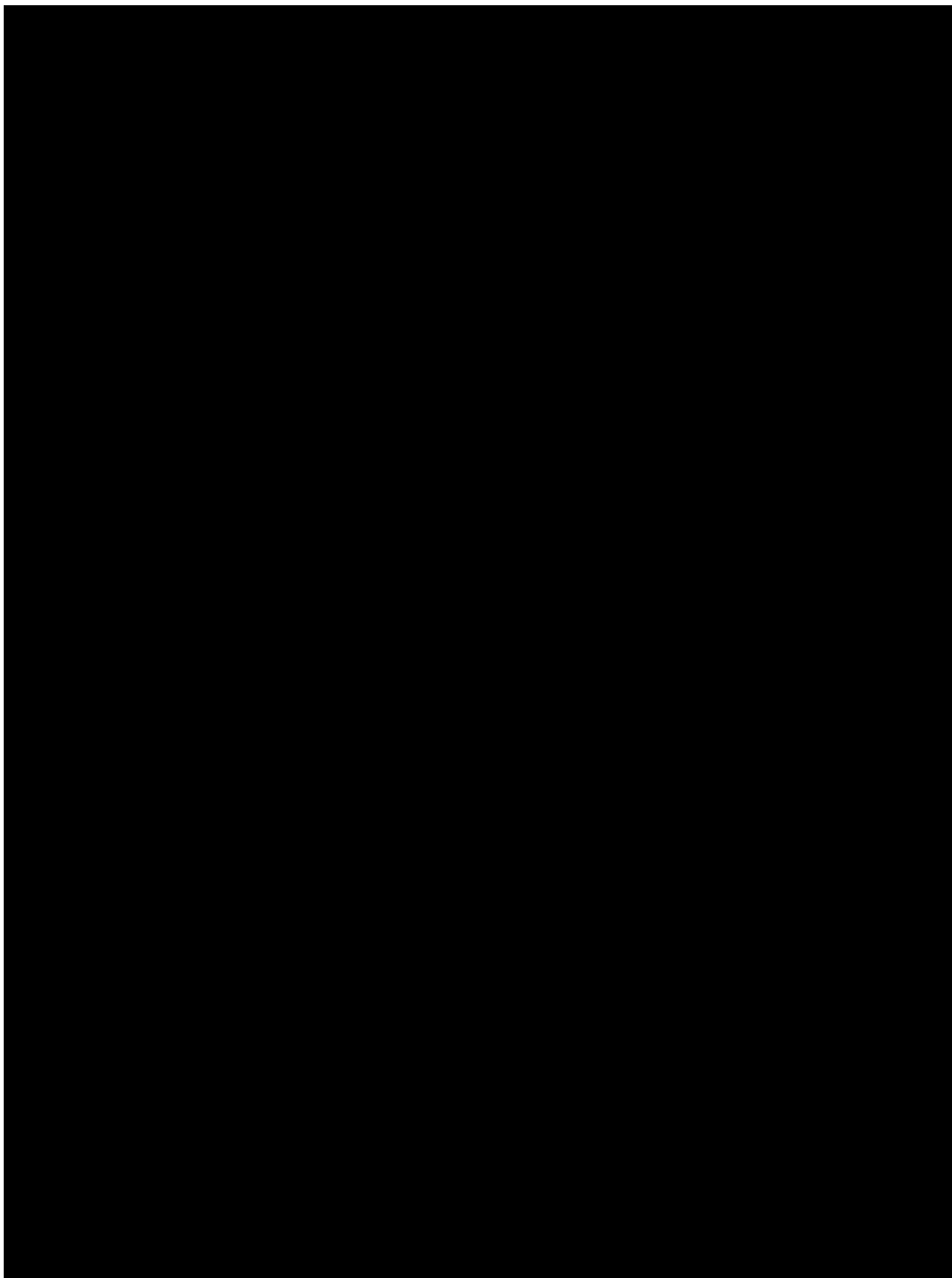
Note: Unscheduled visits may occur as described in Section 8.5.6.

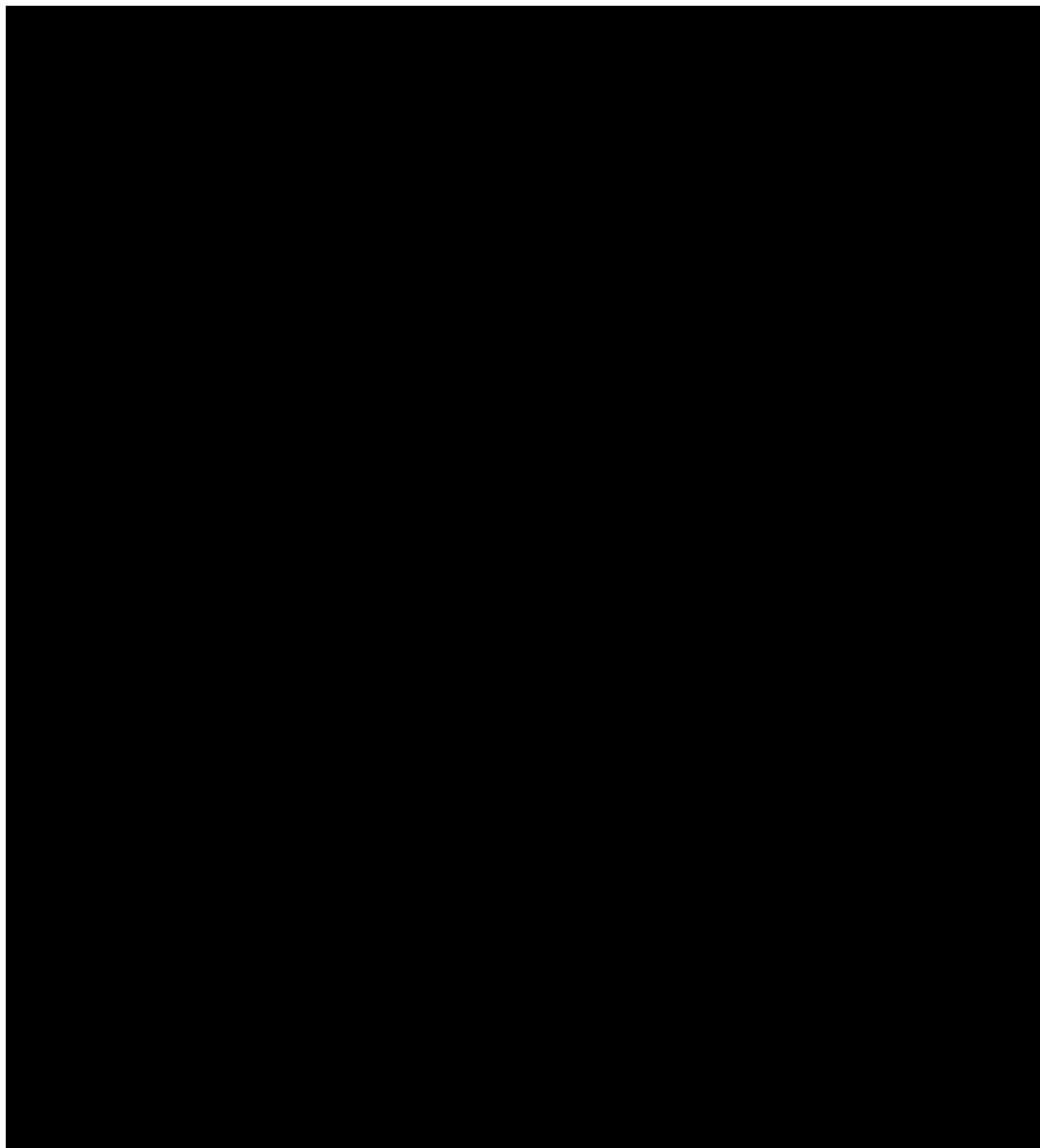
- ^a Assessments should be conducted prior to IVT/sham administration, unless otherwise specified. Visits should be scheduled on approximately the same calendar day each month ±5 days. Dosing should be separated by at least 14 days.
- ^b Lesion eligibility will be confirmed by the Central Reading Center 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 (e.g., 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.

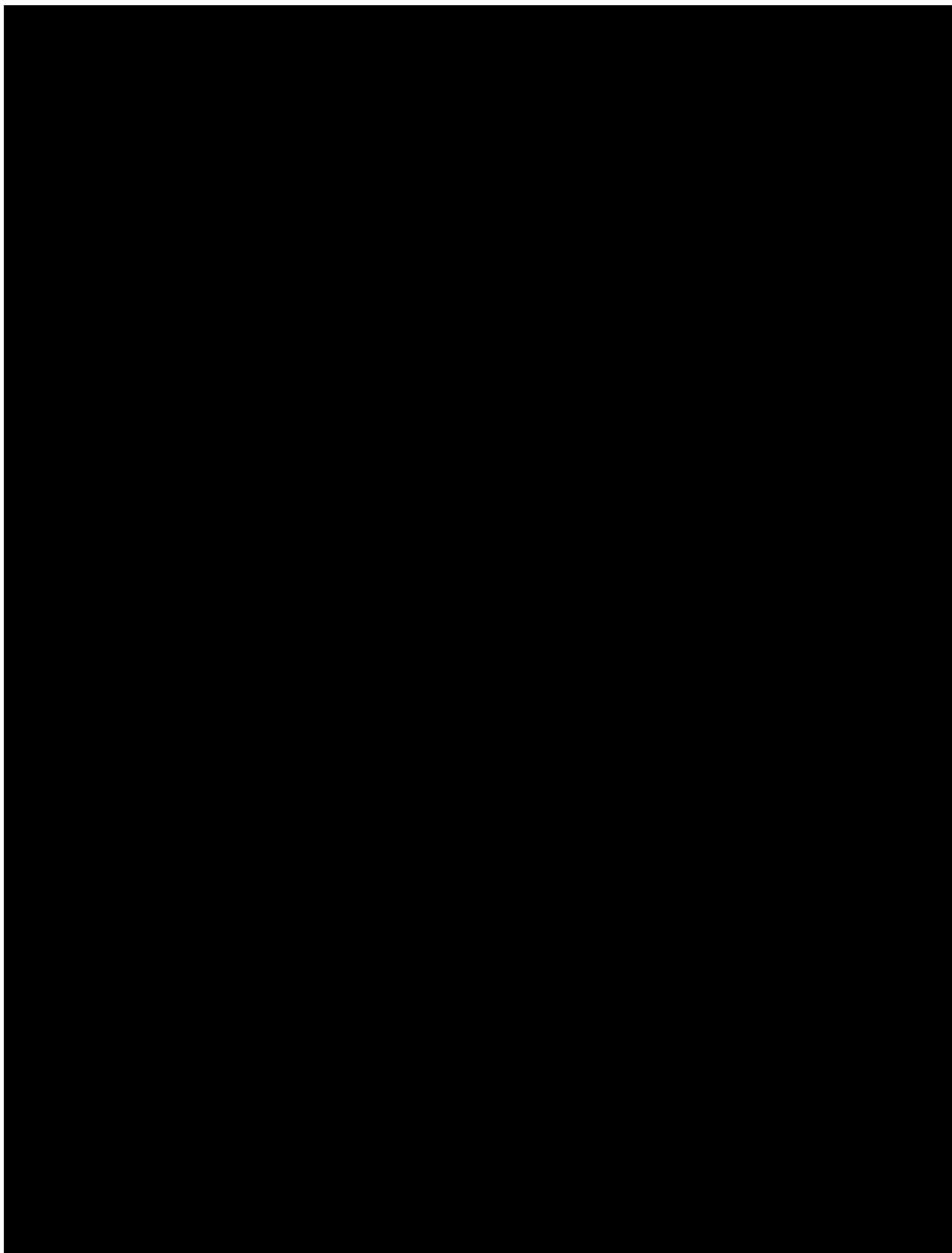
Abbreviations: ADA = antidrug (anti-ANX007) antibodies; ANA = antinuclear antibodies; BCVA = Best Corrected Visual Acuity; Clin Labs = clinical laboratory tests; EM = every month; EOM = every other month; ET = early termination; ETDRS = Early Treatment Diabetic Retinopathy Study; FAF = fundus autofluorescence; 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

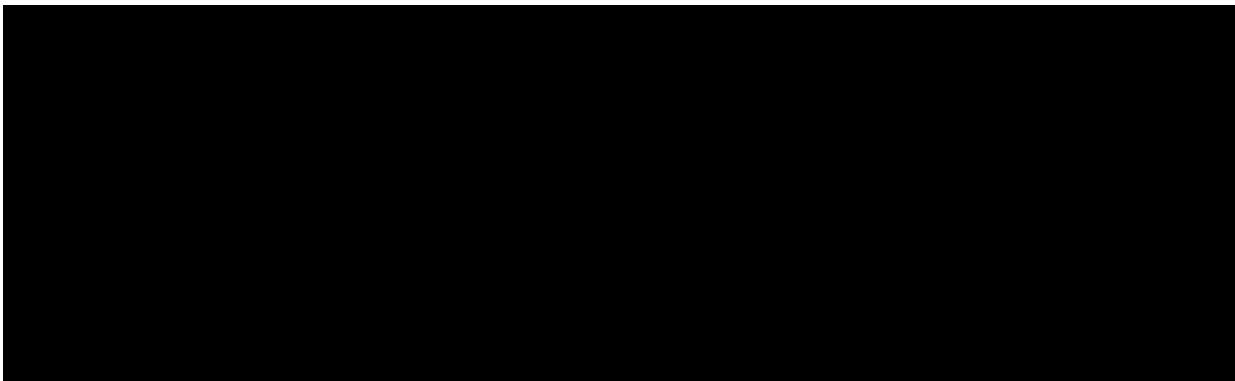






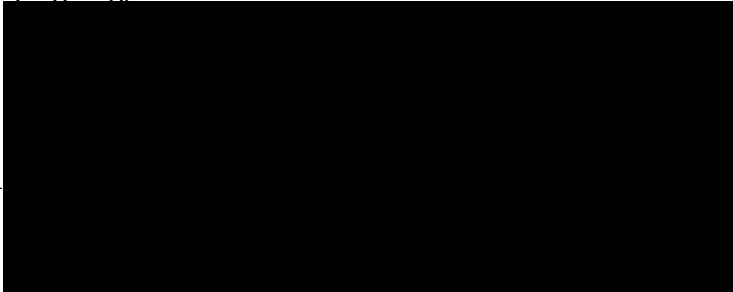






Signature Page

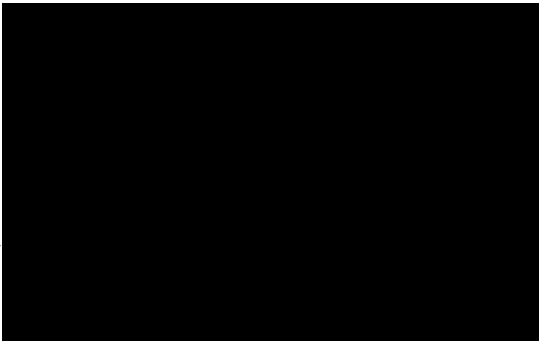
By signing, I attest I have reviewed this document and that it meets my approval.



May 02, 2023

Date

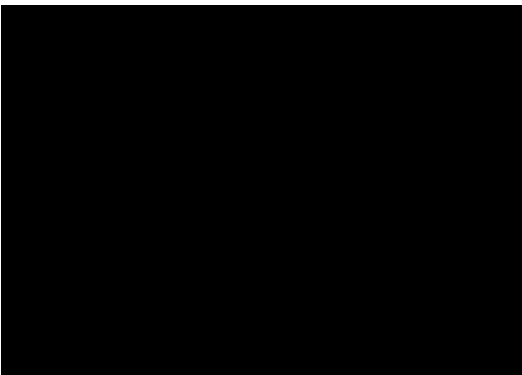
Annexon Biosciences



May 02, 2023

Date

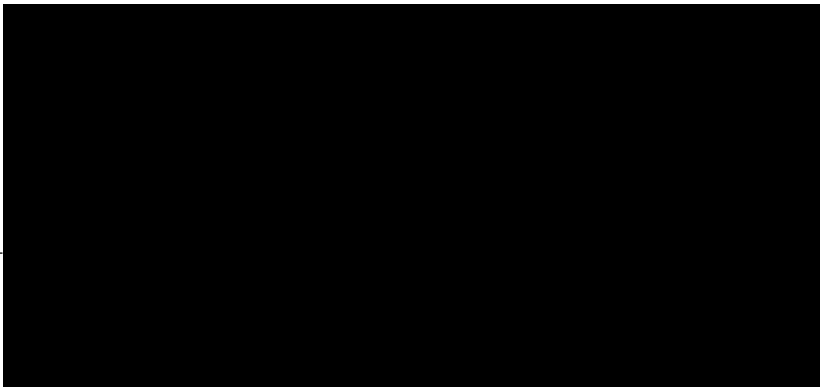
Annexon Biosciences



May 02, 2023

Date

Annexon Biosciences



May 02, 2023

Date

Annexon Biosciences