TITLE PAGE

STATISTICAL ANALYSIS PLAN

Final Analysis of Study

Version Number:2.0

Protocol Title: A Phase 2, Double-Masked, Placebo-Controlled, Dose Range Finding Study of Danicopan (ALXN2040) in Patients with Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration (AMD)

Protocol Number: ALXN2040-GA-201

Amendment Number: 3.0 (Global) and 3.1 (US)

Compound: Danicopan (ALXN2040)

Study Phase: Phase 2

Short Title: Proof of concept and dose-finding study of danicopan in patients with geographic atrophy secondary to AMD

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Version History

This Statistical Analysis Plan (SAP) for study ALXN2040-GA-201 is based on the protocol amendment (PA) 3.0 (Global) dated 30 Oct 2023 and PA 3.1 (US) dated 23 May 2024.

SAP Version	Approval Date	Change	Rationale
1.0	15 Jun 2023	Not Applicable	Original version
2.0	07 Jun 2024	• Moved EZ/Sub-RPE endpoints and the analyses from exploratory endpoints/analyses sections to secondary endpoints/analyses sections as per protocol. • Updated microperimetry endpoint as per protocol and added the corresponding analysis. • Added placebo-based sensitivity analysis as recommended by FDA.	Updates as per protocol amendment PA 3.0 and PA 3.1, and FDA feedback for SAP V1.0.

APPROVAL SIGNATURES

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
AR(1)	Autoregressive (1)
ALT	alanine aminotransferase (SGPT)
AMD	age-related macular degeneration
AP	alternative pathway
AST	aspartate aminotransferase (SGOT)
AUC	area under the concentration-time curve
Bb	Bb fragment of complement factor B
BCVA	best-corrected visual acuity
bid	twice daily
BMI	body mass index
BP	blood pressure
CI	confidence interval
C3	complement component 3
C_{max}	maximum (peak) plasma concentration of the drug
COVID-19	coronavirus disease 2019
cRORA	complete retinal pigment epithelium and outer retinal atrophy
CS	compound symmetry
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	concentration at the end of the dosage interval
CV%	coefficient of variation
DA	disc area
DMC	Data Monitoring Committee
ECG	electrocardiogram
EOS	end of study
EQ-5D-5L	EuroQol 5-dimension 5-level questionnaire
ETDRS	Early Treatment Diabetic Retinopathy Study
EZ	ellipsoid zone
FAF	fundus autofluorescence

Abbreviation	Definition
FAS	Full Analysis Set
FD	factor D
GA	geographic atrophy
HR	heart rate
IA	interim analysis
IA1	Interim Analysis 1
IA2	Interim Analysis 2
IAP	Interim Analysis Plan
IADL	Instrumental Activities of Daily Living
iAMD	intermediate age-related macular degeneration
IOP	intraocular pressure
iRORA	incomplete retinal pigment epithelium and outer retinal atrophy
LLD	low luminance deficit
LLVA	low luminance visual acuity
LS	least square
MAR	missing-at-random
MCP-Mod	multiple comparison procedure and modeling
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MNAR	missing-not-at-random
MMRM	Mixed-effect Model for Repeated Measures
MNRead	Minnesota L Reading Test
MP	microperimetry
NEI VFQ-25	National Eye Institute Visual Function Questionnaire, 25-item version
ONL	outer nuclear layer
PA	protocol amendment
PD	pharmacodynamics
PEP	primary evaluation period
PK	pharmacokinetics
POC	proof-of-concept
PPS	Per Protocol Set
PT	Preferred Term

Abbreviation	Definition
PTAEs	pre-treatment adverse events
PY	patient-years
qd	once daily
QoL	quality of life
RPE	retinal pigment epithelium
RR	Respiration rate
SAE	serious adverse events
SAS®	Statistical Analysis Software®
SAP	Statistical Analysis Plan
SD	standard deviation
SD-OCT	spectral-domain optical coherence tomography
SE	standard error
SEP	Secondary evaluation period
SoA	Schedule of Activities
SOC	System Organ Class
sqrt	square root
SS	Safety Set
TEAEs	treatment-emergent adverse events
TESAE	treatment-emergent serious adverse event
TOEP	toeplitz structure
ULN	upper limit of normal
VA	visual acuity
VAS	visual analog scale
WHO-DRUG	World Health Organization Drug Dictionary

1. INTRODUCTION

This Statistical Analysis Plan describes the statistical methods for analyzing data of the Study ALXN2040-GA-201, "A Phase 2, Double-Masked, Placebo-Controlled, Dose Range Finding Study of Danicopan (ALXN2040) in Patients with Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration (AMD)".

The scope of this analysis plan includes all efficacy, safety, pharmacokinetics, and pharmacodynamics data collected during the study. The table, figure, and listing specifications will be provided in a separate Data Presentation Plan document.

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of different dosage regimens of danicopan on the progression of GA secondary to AMD compared to placebo	• Change from Baseline to Week 52 in the square root (sqrt) of total GA lesion area (mm) in the study eye* as measured by fundus autofluorescence (FAF) *All patients will undergo monocular test on both eyes. The study eye is the eye that meets eligibility criteria. If both eyes are eligible, the right eye is taken as the study eye.
Secondary	
• To evaluate the effect of danicopan on disease progression utilizing anatomical measures in the study eye	• Change from Baseline to Week 104 in the sqrt of the total GA lesion area (mm) in the study eye as measured by FAF • Change from Baseline to Week 52 and Week 104 in the total GA lesion area (mm^2) in the study eye as measured by FAF • Change from Baseline to Week 52 and Week 104 in macular ellipsoid zone (EZ) and outer retinal integrity in the study eye, the fellow eye, and both eyes combined as measured by SD-OCT • Change from Baseline to Week 52 and Week 104 in subretinal pigment epithelium (sub-RPE) compartment/drusen/RPE complex in the study eye, fellow eye and both eyes combined as measured by SD-OCT

• To evaluate the effect of danicopan on disease progression utilizing functional measures in the study eye	• Change from Baseline to Week 52 and Week 104 in monocular best-corrected visual acuity (BCVA) scores in the study eye as assessed by Early Treatment Diabetic Retinopathy Study (ETDRS) chart • Change from Baseline to Week 52 and Week 104 in monocular low luminance visual acuity (LLVA) scores in the study eye as assessed by ETDRS chart • Change from Baseline to Week 52 and Week 104 in low luminance deficit (BCVA-LLVA) in the study eye • Change from Baseline to Week 52 and Week 104 in monocular reading speeds in the study eye as assessed by MNRead Acuity Charts or Radner Reading Charts
• To evaluate the effect of danicopan on patient reported outcomes (PROs) in patients with GA secondary to AMD	• Change from Baseline to Week 52 and Week 104 in National Eye Institute Visual Function Questionnaire (NEI VFQ-25) scores
• To evaluate the PK and pharmacodynamics (PD) of danicopan in patients with GA secondary to AMD	• Plasma concentrations of danicopan over time • PD biomarkers, ex vivo serum AP activity, and plasma Bb concentration over time
• To evaluate the safety and tolerability of danicopan in patients with GA secondary to AMD	• Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and ocular TEAEs, SAEs, and clinical laboratory abnormalities, and events leading to discontinuation of study drug throughout the study
Exploratory	
• To evaluate the effect of danicopan on health-related quality of life and activities of daily living	• Change from Baseline to Week 52 and Week 104 in EQ-5D-5L • Change from Baseline to Week 52 and Week 104 in Lawton Instrumental Activities of Daily Living (IADL)
• To evaluate the effect of danicopan on disease progression utilizing exploratory anatomical measures	• Change from Baseline to Week 52 and Week 104 in the sqrt of the total GA lesion area (mm) in fellow eye and both eyes as measured by FAF • Change from Baseline to Week 52 and Week 104 in the total GA lesion area (mm^2) in fellow eye and both eyes as measured by FAF • Percent change from Baseline to Week 52 and Week 104 in the total GA lesion area (mm^2) in the study eye, fellow eye and both eyes combined as measured by FAF

	• Percent change from Baseline to Week 52 and Week 104 in the sqrt of the total GA lesion area (mm) in the study eye, fellow eye and both eyes combined as measured by FAF • Incidence of patients with conversion from iRORA to cRORA from Baseline to Week 52 and Week 104 in the study eye, fellow eye, either eye, and both eyes combined using SD-OCT images • Incidence of patients with conversion from high-risk drusen to late AMD from Baseline to Week 52 and Week 104 in in the study eye, fellow eye, either eye, and both eyes combined using SD-OCT images • Incidence of patients with conversion from iAMD to late AMD from Baseline to Week 52 and Week 104 in the study eye, fellow eye, either eye, and both eyes combined using SD-OCT images • Number of conversions from iAMD to late AMD from Baseline in the study eye, fellow eye, and both eyes combined to Week 52 and Week 104 • Change from Baseline to Week 52 and Week 104 in drusen volume (mm^3) in the fellow eye with early or iAMD as measured by SD-OCT • Change from Baseline to Week 52 and Week 104 in total GA lesion area (mm^2) and sqrt of the total GA lesion area (mm) in the study eye, the fellow eye, and both eyes combined as measured by SD-OCT • Percent change from Baseline to Week 52 and Week 104 in the total GA lesion area (mm^2) and sqrt of the total GA lesion area (mm) in study eye, fellow eye and both eyes combined as measured by SD-OCT
• To evaluate the effect of danicopan on disease progression utilizing exploratory functional measures	• Change from Baseline to Week 52 and Week 104 in best-corrected visual acuity (BCVA) scores in the fellow eye as assessed by Early Treatment Diabetic Retinopathy Study (ETDRS) chart • Change from Baseline to Week 52 and Week 104 in low luminance visual acuity (LLVA) scores in the fellow eye as assessed by ETDRS chart • Change from Baseline to Week 52 and Week 104 in low luminance deficit (BCVA-LLVA) in the fellow eye • Change from Baseline to Week 52 and Week 104 in binocular BCVA scores as assessed ETDRS chart

	• Change from Baseline to Week 52 and Week 104 in binocular LLVA scores as assessed by ETDRS chart • Change from Baseline to Week 52 and Week 104 in binocular low luminance deficit (BCVA-LLVA) • Change from Baseline to Week 52 and Week 104 in monocular reading speeds in fellow eye as assessed by MNRead Acuity Charts or Radner Reading Charts • Change from Baseline to Week 52 and Week 104 in binocular reading speeds as assessed by MNRead Acuity Charts or Radner Reading Charts • Number of scotomatous points assessed by mesopic microperimetry for the evaluation of the macular functional response in study eye, fellow eye, and both eyes combined at Week 52 and Week 104[a] • Incidence of patients with prespecified change from Baseline to Week 52 and Week 104 in retinal sensitivity in any predefined grid pattern containing at least 5 contiguous test points as assessed by mesopic microperimetry in the study eye, fellow eye, and both eyes combined
• To evaluate the effect of optimal danicopan dose on disease progression at the end of delayed-start period (Week 104) compared to the end of early-start period (Week 52) for the study eye	• Change from Baseline to Week 52 and Week 104 in the sqrt of the total GA lesion area (mm) in the study eye as measured by FAF
• To evaluate exploratory PD biomarkers	• Concentrations of exploratory biomarkers over time, including serum CP activity and serum (or plasma) C3 and FD concentrations

[a] Microperimetry endpoints will be assessed in the microperimetry subgroup.

Abbreviations: AMD = age-related macular degeneration; AP = alternative pathway; Bb = Bb fragment of complement factor B; BCVA = best-corrected visual acuity; C3 = complement component 3; CP = classical pathway; cRORA = complete retinal pigment epithelium and outer retinal atrophy; EQ-5D-5L = EuroQol 5-dimension 5-level questionnaire; ETDRS = Early Treatment Diabetic Retinopathy Study; EZ = ellipsoid zone; FAF = fundus autofluorescence; FD = factor D; GA = geographic atrophy; IADL = Instrumental Activities of Daily Living; iAMD = intermediate age-related macular degeneration; iRORA = incomplete retinal pigment epithelium and outer retinal atrophy; LLD = low luminance deficit; LLVA = low luminance visual acuity; MNRead = Minnesota Low Vision Reading Test; NEI VFQ-25 = National Eye Institute Visual Function Questionnaire, 25-item version; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PRO = patient reported outcome; RPE = retinal pigment epithelium; SAE = serious adverse event; sqrt = square root; SD-OCT = spectral-domain optical coherence tomography; TEAE = treatment-emergent adverse event

1.2. Study Design

Study ALXN2040-GA-201 is a multicenter Phase 2, randomized, double-masked, placebo-controlled, dose finding, parallel-group study to evaluate the efficacy, safety, and

pharmacokinetics of danicopan compared to placebo in participants ≥ 60 years with GA secondary to AMD. Eligible participants will be assigned (1:1:1:1) by stratified randomization to one of the 4 treatment groups (3 active treatment groups and 1 placebo group):

- 100 mg twice daily (bid)
- 200 mg bid
- 400 mg once daily (qd)
- Placebo

Stratification will be performed according to the study eye's characteristics listed below to ensure a balanced distribution of participants across the different dose groups with respect to GA severity. Three stratification factors will be used, namely:

- GA lesion size < 1 disc area (DA) versus ≥ 1 DA
- Subfoveal* versus extrafoveal GA lesion and microperimetry eligibility (Yes) versus extrafoveal GA lesion and microperimetry eligibility (No)**
- Unifocal versus multifocal GA lesion

Note:

*For this study, extrafoveal is defined as > 1 µm from the center of the fovea, and subfoveal is ≤ 1 µm from the center of the fovea (Heier, 2022).

**Participants who are unable to provide microperimetry data (eg, participants who do not undergo microperimetry eligibility screening or participants who do not meet microperimetry eligibility criteria) will be categorized as "microperimetry eligibility (No)."

There are a total of 12 randomization strata, as shown in Table 1.

Table 1: Randomization Strata

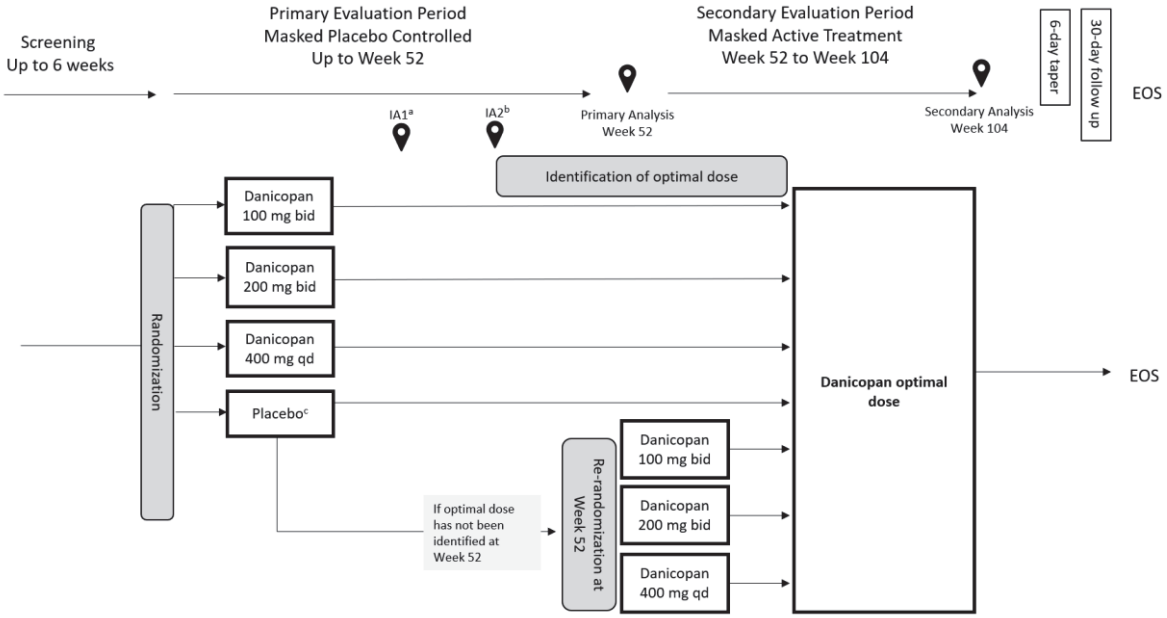
Strata	Strata Description
1	GA lesion size < 1 DA, Subfoveal, Unifocal
2	GA lesion size < 1 DA, Subfoveal, Multifocal
3	GA lesion size < 1 DA, Extrafoveal + MP Eligibility (Yes), Unifocal
4	GA lesion size < 1 DA, Extrafoveal + MP Eligibility (Yes), Multifocal
5	GA lesion size < 1 DA, Extrafoveal + MP Eligibility (No), Unifocal
6	GA lesion size < 1 DA, Extrafoveal + MP Eligibility (No), Multifocal
7	GA lesion size ≥ 1 DA, Subfoveal, Unifocal
8	GA lesion size ≥ 1 DA, Subfoveal, Multifocal
9	GA lesion size ≥ 1 DA, Extrafoveal + MP Eligibility (Yes), Unifocal
10	GA lesion size ≥ 1 DA, Extrafoveal + MP Eligibility (Yes), Multifocal
11	GA lesion size ≥ 1 DA, Extrafoveal + MP Eligibility (No), Unifocal
12	GA lesion size ≥ 1 DA, Extrafoveal + MP Eligibility (No), Multifocal

Abbreviations: DA = disc area; GA = geographic atrophy; MP = microperimetry

Approximately 332 participants aged ≥ 60 years will be enrolled, with 83 participants per treatment group.

1.2.1. Study Schema

Figure 1: Study Design and Schematic



Abbreviations: bid = twice daily; EOT = end of treatment; qd = once daily
[a] The futility analysis (interim analysis 1 [IA1]) may be conducted when approximately 50% participants complete Week 28 visit or discontinued.
[b] The futility and dose-response analyses (interim analysis 2 [IA2]) may be conducted when approximately 50% participants complete Week 52 visit or discontinued. If the dose-response is positive, pairwise comparisons will be performed at IA2.
[c] Placebo participants will be transitioned after 52 weeks to the optimal dose, or, if not identified, will be re-randomized at Week 52 to one of the active treatment groups until the optimal dose has been determined.

The study consists of a Screening Period of up to 6 weeks and a Masked Treatment Period (approximately 2 years). Treatment ends with a 6-day Taper, followed by a Follow-up Visit 30 days after the last taper dose. The potential total study duration per patient is approximately 115 weeks.

Analyses for the primary efficacy endpoint and other Primary Evaluation Period (PEP) endpoints will be performed when all participants complete the Week 52 visit or discontinued. Analyses for the Secondary Evaluation Period (SEP) endpoints will be performed when all participants complete the Week 104 visit or discontinued. All participants will be transitioned to the optimal active dose after Week 52, if identified.

There are 2 potential interim analyses (IA) planned for this study. The first interim analysis (IA1) for futility may be conducted when approximately 50% participants have completed the Week 28 visit or discontinued. The second interim analysis (IA2) may be conducted when approximately 50% of participants complete Week 52 visit or discontinued. At IA2, a futility analysis will be conducted first. If the study is not considered futile, dose response analysis will be performed. If the dose response analysis is positive, a pair-wise comparison will be conducted to identify the effect of the different doses against placebo. Placebo participants will be re-randomized to one of

the 3 active treatment groups at Week 52, or switched to the optimal dose, if identified. An optimal dose with the best benefit-risk profile could be identified at the IA2 or primary analysis for Phase 3 development. Masked treatment paradigm will be maintained throughout the study. If an optimal dose is identified, all participants who have completed at least Week 52 visit with their originally assigned dose will be switched to the selected optimal dose for the remainder of the study when supplies are available.

1.2.2. Definitions of Study Periods and End of Study

The Primary Evaluation Period is from Day 1 to Week 52.

The Secondary Evaluation Period starts from Week 52 and ends at Week 104.

Masked Treatment Period starts from Day 1 to Week 104.

Study completion (patient level): A patient is considered to have completed the study if they have completed all periods of the study, including the Taper, Follow-up, and the last scheduled procedure shown in the Schedule of Activities (SoA).

Early termination (ET) or discontinuation: A patient is considered to early terminate from the study if they discontinued from the study before completing the last visit as described in SoA.

Follow-up: A follow-up visit is scheduled 30 (+ 7) days after the last dose (including taper doses) of study drug.

End of study (EOS; study level): The end of the study is defined as the date the last patient completes the last visit (including the Taper and Follow-up).

2. STATISTICAL HYPOTHESES

The primary null hypothesis is that there is no dose-response effect for danicopan treatment in mean rate of change from Baseline in the sqrt of the total GA lesion area (mm) over Week 52 in the study eye (the mean rate of change in danicopan treatment arms are the same as the mean change in placebo).

The alternative hypothesis is that there is a dose-response effect for danicopan treatment compared to placebo in the mean rate of change from Baseline in the sqrt of the total GA lesion area (mm) over Week 52 in the study eye (the mean rate of change in at least one danicopan treatment arm is less than the mean change in placebo).

3. ANALYSIS SETS

Table 2: Analysis Sets

Analysis Set	Description
Randomized Set	All randomized participants grouped by randomized treatment group (for reporting disposition).
Full Analysis Set (FAS)	All randomized participants who receive at least 1 dose (full or partial) of study drug grouped by randomized treatment group.
Safety Set (SS)	All participants who receive at least 1 dose (full or partial) of study drug grouped by treatment actually received (for reporting exposure and safety data). For a patient to be analyzed according to the treatment they actually received, they would have to receive that treatment for the entire duration of the study treatment period.
Per Protocol Set (PPS)	All randomized participants who receive at least 1 dose (full or partial) of study drug and have no important protocol deviations that are likely to impact efficacy. Specifically, PPS will include all participants in FAS who meet all of the following criteria: • Took at least 80% of the required treatment doses in the Primary Evaluation Period • Met all ocular inclusion criteria and did not meet any ocular exclusion criteria in the study • Never received the wrong randomized treatment during the Primary Evaluation Period • Had no other important protocol deviations that may impact the assessment of the primary efficacy endpoint
Pharmacokinetic (PK) Analysis Set (PKAS)	All participants who receive at least 1 dose (full or partial) of study drug and have at least 1 measurable concentration value.
Pharmacodynamic (PD) Analysis Set (PDAS)	All participants who receive at least 1 dose (full or partial) of study drug and have at least 1 measurable PD value.

4. STATISTICAL ANALYSES

4.1. General Considerations

All data collected in this study will be presented using summary tables, figures, and data listings.

Statistical analyses will include tabulations of summary data, inferential analyses, by-patient listings, and figures. Summary statistics will be computed and displayed by treatment group and by visit, where applicable. Descriptive statistics for continuous variables will include but not be limited to the number of participants, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, frequencies and percentages will be presented. Graphical displays will be provided as appropriate.

Inference from efficacy analyses will be based on a 2-sided Type I error (α) = 0.1 and 90% confidence intervals (CIs) will be produced unless stated otherwise. The efficacy analysis population will be FAS unless stated otherwise.

The baseline value for analysis and reporting will be based on the last non-missing measurement on or prior to the first dose of the study drug unless stated otherwise.
Missing safety data will not be imputed.

Analyses will be performed using the Statistical Analysis Software® (SAS®) Version 9.4 or higher. Adverse events (AEs) will be coded using latest version of the standardized Medical Dictionary for Regulatory Activities (MedDRA). Prior and concomitant medications will be coded with the latest World Health Organization Drug Dictionary (WHO-DRUG) version.

4.2. Primary Estimand and Endpoint Analysis

The primary efficacy endpoint analysis will be performed on the FAS.

4.2.1. Definition of Estimand

The attributes for the primary estimand are as follows:

- Treatment: Danicopan (100 mg bid, 200 mg bid, and 400 mg qd) and placebo.
- Population: Participants with GA secondary to AMD as defined by the protocol inclusion/exclusion criteria.
- Variable: Change from Baseline to Week 52 in the sqrt of the total GA lesion area in the study eye as measured by FAF.
- Intercurrent events: Any treatment discontinuation. The treatment policy strategy will be used. For the primary analysis, all available data will be used for the analysis regardless of treatment discontinuation and no imputations for missing data will be performed, assuming the data are missing at random (MAR).
- Summary measure: Treatment difference in mean rate of change from Baseline in sqrt of total GA lesion area in the study eye at Week 52 between Danicopan and placebo.

4.2.2. Main Analytical Approach

The multiple comparison procedure and modeling (MCP-Mod) dose-response approach (Bretz, 2005) will be used to establish the proof of concept (POC) with 4 pre-specified candidate dose-response models and to test for statistical significance in the difference between the dose groups and placebo. Details on the implementation of the MCP-Mod including the candidate dose-response models, optimal contrasts, the estimation of statistical information are described in the Interim Analysis Plan (IAP).

The MCP-Mod analysis will use the estimated mean change from baseline to week 52 to test for a dose-response and if statistically significant to test between the dose groups and placebo. The mean change from Baseline at week 52 will be estimated using a mixed-effect model for repeated measures (MMRM).

The MMRM will include change from Baseline in the sqrt GA lesion area at postbaseline visits as the dependent variable. The model will include fixed effects of time (years), treatment-by-time interaction, covariates of baseline sqrt of GA lesion area, and the categorical effect of randomization strata. Time will be calculated as: $\frac{(\text{FAF GA lesion assessment date} - \text{date of first dose of study drug} + 1)}{365.25}$. If the number of participants in a randomization stratum is less than 4, the stratum will be combined with the corresponding stratum which has the same lesion size group and focality group. A random slope effect will be added to model the within-patient correlation. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Significance tests will be based on least-squares means. If IA2 is conducted, the significance levels at IA2 and at the end of the primary analysis period will be based on a Hwang-Shih-DeCani Gamma family (gamma = -10) alpha spending function (Hwang, 1990). The primary treatment comparison will be on the mean change from Baseline to week 52 which is equivalent to the annual rate of change estimated from the model. 90% confidence intervals will be generated. The model described is often referred to as a linear mixed effects model.

No imputation for missing data will be performed. In the context of the MMRM described above, this assumes that data are MAR.

Hypothesis testing will proceed as described in the IAP.

With a 2-sided Type I error of 0.1 and the 1-sided nature of the dose-response hypothesis, the overall Type I error for the primary analysis is 0.05 (1-sided). Example alpha boundaries are included in Table 3. The multiplicity-adjusted p-values corresponding to the 4 optimal contrasts will be compared to the alpha boundary applicable for the IA2 and Week 52 analyses. POC will be established if at least one multiplicity-adjusted p-value is less than the alpha boundary at IA2 (early POC) or at Week 52.

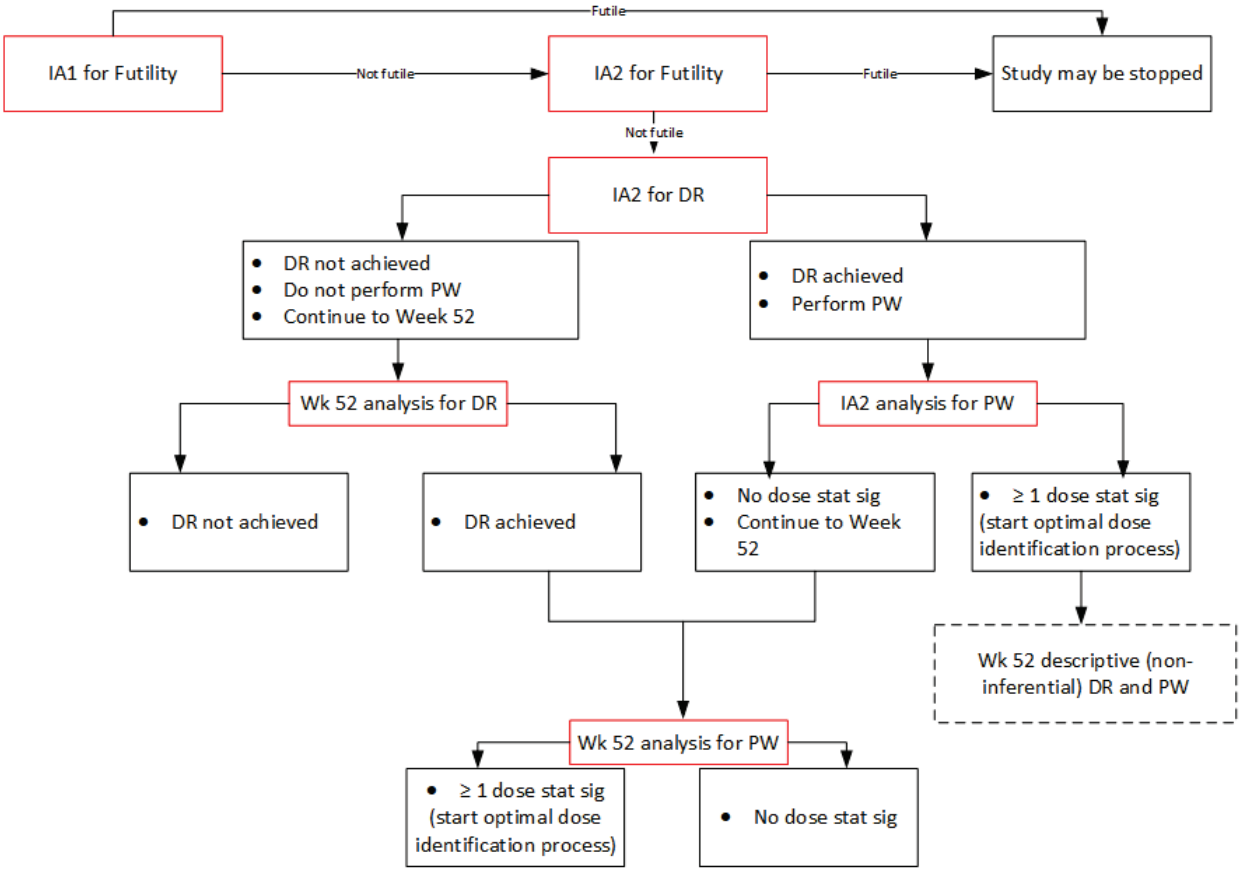
Table 3: Examples of alpha Boundaries for Hwang, Shih, and DeCani gamma-family α- spending function (with gamma=–10, overall 1-sided α=0.05)

Information Fraction	Interim Analysis 2 (α_1)	Week 52 Analysis (α_2)
80%	0.0068	0.0497
85%	0.0112	0.0495

If the POC is established, pairwise comparisons versus placebo will be used to test for the difference in the mean change from baseline to week 52 between the treatment arms and placebo. Hommel's multiplicity adjustment will be used with the Type I error boundaries defined above.

The decision tree for IA2 and Week 52 is presented in Figure 2 below.

Figure 2: Decision Tree for Interim and Week 52 Analyses



Abbreviations:
DR: dose-response
PW: pairwise comparison against placebo
Stat sig: Statistically significant

Note:
Alpha penalty is paid for IA2 and Week 52 analyses
Multiplicity adjustments are done for pairwise comparison

In addition to the analyses described above, the observed sqrt of total GA lesion area and the change from Baseline value at each visit will be summarized by treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum).

4.2.3. Sensitivity MMRM Analyses

Three sensitivity analyses will be conducted. These analyses will use a model different from the model used for the primary analysis. This model can be used to assess the robustness of the primary analysis results to deviations from the assumption of linearity and to the MAR assumption. The MMRM will include change from Baseline in the sqrt GA lesion area at postbaseline visits as the dependent variable. The model will include categorical effects of treatment, visit, treatment-by-visit interaction, the fixed covariates of baseline sqrt of GA lesion area, and the categorical effect of randomization strata. If the number of participants in a randomization stratum is less than 4, the stratum will be combined with the corresponding stratum which has the same lesion size group and focality group. The postbaseline visits will include Week 8, 16, 28,40 and 52.

An unstructured variance-covariance matrix will be used to model the correlations among repeated measurements within each patient. The following covariance structures will be implemented if a convergence issue occurs in the specified order: Toeplitz structure (TOEP), autoregressive (1) (AR(1)), and compound symmetry (CS). The Kenward-Roger method will be used to estimate the denominator degrees of freedom. The LS-means, the associated SEs, the p-values and the 90% CIs of the mean change from Baseline at Week 52 for each treatment arm and the difference between the danicopan arm and placebo will be calculated and plotted.

Sensitivity Analysis 1: This analysis will assess the robustness of the primary efficacy analysis to deviations from the linearity assumption. No missing data will be imputed under the assumption of MAR.

Sensitivity Analysis 2: A tipping point sensitivity analysis will be performed to assess the robustness of the primary efficacy analysis to deviations from the MAR assumption. This approach uses delta-adjustment to impute missing data under the missing not at random assumption (MNAR). This approach assumes that participants who discontinue from danicopan treatment experience worsening, defined by a prespecified adjustment (delta) in the primary endpoint compared with the observed values from participants that continue the study to next visit (Ratitch, 2014; Ratitch, 2013). Since an increase in the sqrt of total GA lesion area indicates worsening, a fixed set of positive delta values (from less conservative to more conservative) will be used to shift the change in the sqrt of total GA lesion area associated with missing values for the active treatment group, and the tipping point multiple imputation analysis as described by Ratitch et al will be applied (Ratitch, 2013). For each delta value, imputed values for missing sqrt of total GA lesion area at each time point will be obtained by first sampling from an MAR-based multiple imputation (MI) model including the variables of treatment, baseline values, and values observed at all scheduled visits during the 52-week Primary Evaluation Period and then adding the value of delta to all imputed values in the danicopan arm. The mean change from Baseline in the sqrt of total GA lesion area will then be analyzed using the same MMRM model specified above using the complete dataset of observed values and delta-adjusted, imputed values. The results from 100 imputed datasets will be combined using SAS MIANALYZE procedure to obtain an overall test statistic for the specified shift parameter value of delta.

The treatment effect will be estimated, and the value of delta for which the estimated treatment effect is no longer statistically significant will be considered as the "tipping point" in the sense that the positive conclusion drawn from the primary MMRM analysis is reversed when participants who drop out are assumed to experience this fixed worsening after the discontinuation visit. After such a tipping point is determined, clinical judgment will be applied as to the plausibility of the assumptions underlying this tipping point. This methodology is expected to inform what it would take to overturn study conclusions based on varying assumptions about missing data. A zero value of delta will be considered equivalent to the corresponding standard MAR-based MI. For this analysis, a series of delta values for the sqrt of total GA lesion area increasing in increments of 0.01mm will be applied (i.e., 0, 0.01, 0.02,…). Refer to Section 6.4.1 for further details and SAS sample code for the tipping point analysis.

Sensitivity Analysis 3: A placebo-based imputation will be performed to assess the robustness of the primary efficacy analysis to deviation from the MAR assumption. For participants who discontinued treatment, responses after treatment discontinuation, for all groups, will be imputed with multiple imputation methodology based on the response for placebo treated participants. Multiple imputation will be performed at each visit sequentially, using a regression method obtained only from placebo treated participants. After obtaining complete data sets for each visit, these complete data sets will be analyzed using MMRM analysis, and inferences from each complete data set will be combined to obtain an overall test statistic for treatment effect. Refer to Section 6.4.2 for further details and SAS sample code for the placebo-based imputation and analysis.

4.2.4. Supplementary Analyses

If more than 5% of participants are be excluded for PPS, the analyses mentioned in previous Section 4.2.2 and Section 4.2.3 will be performed based on the PPS. The PPS will be determined prior to database lock. The impact of randomization stratification errors will be assessed using the observed strata in the analyses mentioned in previous Section 4.2.2 and Section 4.2.3, if there are more than 5% of participants with randomization stratification errors.

4.3. Secondary Efficacy Endpoints Analyses

All secondary efficacy endpoint analyses will be made on the FAS. No multiplicity adjustment will be done for secondary efficacy endpoints analyses.

4.3.1. Analyses for Secondary Efficacy Endpoints at Week 52

The objectives of the secondary analyses are to evaluate the effect of danicopan on anatomical and functional outcomes of GA. The null hypotheses associated with the secondary objectives are that there are no difference between danicopan treatment arms and placebo for the mean of the respective endpoints at Week 52; the alternative hypotheses are that at least one danicopan treatment arm is different than placebo for the mean of the respective endpoints at Week 52.

The following secondary efficacy endpoints at Week 52 will be analyzed and summarized:

- Change from Baseline to Week 52 in the total GA lesion area (mm^2) in the study eye
- Change from Baseline to Week 52 in monocular BCVA score in the study eye

- Change from Baseline to Week 52 in monocular LLVA score in the study eye
- Change from Baseline to Week 52 in low luminance deficit LLD score (BCVA-LLVA) in the study eye
- Change from Baseline to Week 52 in monocular reading speeds in the study eye
- Change from Baseline to Week 52 in NEI VFQ-25 scores
- Change from Baseline to Week 52 in EZ and outer retinal integrity in the study eye, the fellow eye, and both eyes combined as measured by SD-OCT
- Change from Baseline to Week 52 in sub-RPE compartment/drusen/RPE complex in the study eye, fellow eye and both eyes combined as measured by SD OCT

The macular EZ and sub-RPE related parameters extracted from SD-OCT images include the following:

- Percent macular EZ total attenuation (i.e, EZ-RPE thickness = 0 micron (μm))
- Percent macular EZ partial attenuation (i.e, EZ-RPE thickness ≤ 20μm)
- Percent central 1 mm subfield EZ total attenuation
- Percent central macular 2 mm subfield EZ total attenuation
- Percent central 1 mm subfield EZ partial attenuation
- Percent central macular 2 mm subfield EZ partial attenuation
- Outer nuclear layer (ONL)-RPE mean central 1 mm subfield thickness (μm)
- ONL-RPE mean central macular 2 mm thickness (μm)
- EZ-RPE Macular Volume (mm^3)
- EZ-RPE mean central 1-mm subfield thickness (μm)
- EZ-RPE mean central macular 2 mm thickness (μm)
- Sub-RPE central 1 mm subfield mean thickness (i.e., RPE-Bruchs membrane thickness, μm)
- Sub-RPE central macular 2 mm subfield mean thickness (μm)
- Panmacular Sub-RPE Volume (i.e., RPE-Bruchs membrane volume, mm^3)
- Percent macular Total RPE Attenuation
- Percent central 1 mm subfield total RPE attenuation
- Percent central macular 2 mm subfield total RPE attenuation

The treatment effect at Week 52 for secondary efficacy endpoints described above will be estimated based on MMRM approach using all available longitudinal data up to and including Week 52.

The model for change from Baseline in the total GA lesion area (mm^2) will include fixed effects of time (years), treatment-by-time interaction, covariates of baseline GA lesion area, and the categorical effect of randomization strata. Treatment will include 4 groups: placebo, 100 mg bid, 200 mg bid, and 400 mg qd. In addition, the patient-specific random slope will be added to the model. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Treatment comparison will be on the mean change from Baseline to week 52 which is equivalent to the annual rate of change estimated from the model. 90% confidence intervals will be generated.

No imputation for missing data will be performed after discontinuation from the study, assuming the data are MAR.

A sensitivity analysis using MMRM will be performed, the model for change from Baseline in the total GA lesion area will include categorical effects of treatment, visit, treatment-by-visit interaction, the fixed covariates of the corresponding baseline, and the categorical effect of randomization strata.

The models for change from Baseline in BCVA, LLVA, LLD (BCVA-LLVA), monocular reading speed, NEI VFQ-25 (composite score and subscale scores), macular EZ and sub-RPE compartment/drusen/RPE complex parameters will include categorical effects of treatment, visit, treatment-by-visit interaction, the fixed covariates of the corresponding baseline, and the categorical effect of randomization strata. Treatment group will include placebo, 100 mg bid, 200 mg bid, and 400 mg qd. An unstructured variance-covariance matrix will be used to model the correlations among repeated measurements within each patient. Other covariance structures will be implemented if a convergence issue occurs. The Kenward-Roger method will be used to estimate the denominator degrees of freedom.

No imputation for missing data will be performed after discontinuation from the study, assuming the data are MAR.

The LS-means, the associated SEs, p-values and the two-sided 90% CIs of the secondary efficacy endpoints at Week 52 for each treatment arm and the difference between the danicopan arm and placebo will be summarized and plotted.

In addition to the analyses described above, the observed total GA lesion area (mm^2), BCVA, LLVA, LLD (BCVA-LLVA), monocular reading speed, NEI VFQ-25, macular EZ and sub-RPE compartment/drusen/RPE complex parameters, and the change from Baseline values for these parameters at each visit will be summarized by treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum).

4.3.2. Analyses for Secondary Efficacy Endpoints at Week 104

The objectives of the secondary analyses at Week 104 are to evaluate the effect of danicopan on anatomical and functional outcomes of GA during the Secondary Evaluation Period. Placebo participants will be re-randomized to one of the 3 active treatment groups at Week 52. The new treatment groups without placebo for Week 104 analyses are: placebo→100 mg bid, placebo→200 mg bid, placebo→400 mg qd, 100 mg bid, 200 mg bid, and 400 mg qd.

The null hypotheses associated with the secondary objectives are that the means of the respective endpoints for the new treatment groups are not different at Week 104; the alternative hypotheses are that the means of the respective endpoints for the new treatment groups are different at Week 104.

The following secondary efficacy endpoints at Week 104 will be analyzed and summarized:

- Change from Baseline to Week 104 in the sqrt of the total GA lesion area (mm) in the study eye
- Change from Baseline to Week 104 in the total GA lesion area (mm^2) in the study eye
- Change from Baseline to Week 104 in monocular BCVA score in the study eye
- Change from Baseline to Week 104 in monocular LLVA score in the study eye
- Change from Baseline to Week 104 in low luminance deficit LLD score (BCVA-LLVA) in the study eye
- Change from Baseline to Week 104 in monocular reading speed
- Change from Baseline to Week 104 in NEI VFQ-25 scores
- Change from Baseline to Week 104 in EZ and outer retinal integrity in the study eye, the fellow eye, and both eyes combined as measured by SD-OCT
- Change from Baseline to Week 104 in sub-RPE compartment/drusen/RPE complex in the study eye, fellow eye and both eyes combined as measured by SD OCT

The treatment effect at Week 104 for secondary efficacy endpoints described above will be estimated based on MMRM approach using all available longitudinal data up to and including Week 104 and prior to optimal dose switch.

The models for change from Baseline in the sqrt of GA lesion area (mm) and the total GA lesion area (mm^2) will include fixed effects of time (years), treatment-by-time interaction, covariates of the corresponding baseline, and the categorical effect of randomization strata. Treatment will include 6 groups: placebo→100mg bid, placebo→200 mg bid, placebo→400 mg qd, 100 mg bid, 200 mg bid, and 400 mg qd. In addition, the patient-specific random slope will be added to the model with an unstructured variance-covariance matrix. Other covariance structures will be implemented if a convergence issue occurs. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. No imputation for missing data will be performed after discontinuation from the study, assuming the data are MAR.

The models for change from Baseline in BCVA, LLVA, LLD (BCVA-LLVA), monocular reading speeds, NEI VFQ-25 (composite score and subscale scores), macular EZ and sub-RPE compartment/drusen/RPE complex parameters will include categorical effects of treatment, visit, treatment-by-visit interaction, the fixed covariates of the corresponding baseline, and the categorical effect of randomization strata. Treatment will include 6 groups: placebo→100mg bid, placebo→200mg bid, placebo→400 mg qd, 100 mg bid, 200 mg bid, and 400 mg qd. An unstructured variance-covariance matrix will be used to model the correlations among repeated measurements within each patient. Other covariance structures will be implemented if a convergence issue occurs. The Kenward-Roger method will be used to estimate the denominator

degrees of freedom. No imputation for missing data will be performed after discontinuation from the study, assuming the data are MAR.

The LS-means, the associated SEs, the p-values and the two-sided 90% CIs of the secondary efficacy endpoints at Week 104 for each new treatment group and the difference between new treatment groups will be summarized and plotted.

In addition to the analyses described above, the observed total GA lesion area (mm^2), BCVA, LLVA, LLD (BCVA-LLVA), monocular reading speed, NEI VFQ-25, macular EZ and sub-RPE compartment/drusen/RPE complex parameters, and the change from Baseline values for these parameters at each visit will be summarized by new treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum). Additional exploratory correlation analyses will be performed between EZ parameters and functional endpoints.

If the optimal dose is identified, the secondary efficacy endpoints at Week 104 will be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum) by visit and treatment group for participants switched to optimal dose and randomized to danicopan treatments at baseline. The treatment will include 2 of the following groups: 100 mg bid → optimal dose, 200 mg bid →optimal dose, and 400 mg qd→ optimal dose.

The scoring algorithm for VFQ-25 can be found in Section 6.3.1.

4.4. Exploratory Endpoints Analyses

All exploratory efficacy endpoint analyses will be made on the FAS unless otherwise specified. The analysis results will be reported by treatment groups. No multiplicity adjustment will be done for the exploratory endpoints analyses.

4.4.1. Quality of Life

The treatment effect at Week 52 for the change from Baseline in EQ-5D-5L index score, EQ-5D-5L VAS, and IADL will be estimated based on MMRM approach using all available longitudinal data up to and including Week 52. The models for change from Baseline in EQ-5D-5L index score, EQ-5D-5L VAS, and IADL will include categorical effects of treatment, visit, treatment-by-visit interaction, the fixed covariates of the corresponding baseline, and the categorical effect of randomization strata. Treatment group will include placebo, 100 mg bid, 200 mg bid, and 400 mg qd.

The treatment effect at Week 104 for the change from Baseline in EQ-5D-5L index score, EQ-5D-5L VAS, and IADL will be estimated based on MMRM approach using all available longitudinal data up to and including Week 104 and prior to optimal dose switch. The models for change from Baseline in EQ-5D-5L index score, EQ-5D-5L VAS, and IADL will include categorical effects of treatment, visit, treatment-by-visit interaction, the fixed covariates of the corresponding baseline, and the categorical effect of randomization strata. Treatment will include 6 groups: placebo→100 mg bid, placebo→200 mg bid, placebo→400 mg qd, 100 mg bid, 200 mg bid, and 400 mg qd.

An unstructured variance-covariance matrix will be used to model the correlations among repeated measurements within each patient. Other covariance structures will be implemented if a

convergence issue occurs. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. No imputation for missing data will be performed after discontinuation from the study, assuming the data are MAR.

The LS-means, the associated SEs, the p-values and the two-sided 90% CIs of the change from Baseline in EQ-5D-5L index score, EQ-5D-5L VAS, and IADL at Week 52 and Week 104 for each treatment group and the difference between treatment groups will be summarized.

The observed and changes from baseline scores in EQ-5D-5L index score, EQ-5D-5L VAS, and IADL scores will be summarized by treatment group and visit using descriptive statistics (n, mean, SD, median, minimum, and maximum).

More detail about the calculation of EQ-5D-5L index score can be found in Section 6.3.2.

4.4.2. Anatomical Endpoints

4.4.2.1. Total GA Lesion Area and Sqrt of Total GA Lesion Area

The anatomical exploratory endpoints include:

- Change from Baseline to Week 52 and Week 104 in the sqrt of the total GA lesion area (mm) in fellow eye and both eyes as measured by FAF
- Change from Baseline to Week 52 and Week 104 in the total GA lesion area (mm^2) in fellow eye and both eyes as measured by FAF
- Percent change from Baseline to Week 52 and Week 104 in the total GA lesion area (mm^2) in the study eye, fellow eye and both eyes combined as measured by FAF
- Percent change from Baseline to Week 52 and Week 104 in the sqrt of the total GA lesion area (mm) in the study eye, fellow eye and both eyes combined as measured by FAF
- Change from Baseline to Week 52 and Week 104 in total GA lesion area (mm^2) and sqrt of the total GA lesion area (mm) in the study eye, the fellow eye, and both eyes combined as measured by SD-OCT
- Percent change from Baseline to Week 52 and Week 104 in the total GA lesion area (mm^2) and sqrt of the total GA lesion area (mm) in study eye, fellow eye and both eyes combined as measured by SD-OCT

The change and percent change from Baseline at Week 52 and Week 104 in the sqrt of the total GA lesion area (mm) and total GA lesion area (mm^2) measured by FAF in the fellow eye and both eyes combined, measured by SD-OCT in the study eye, fellow eye, and both eyes combined will be estimated using the same MMRM models proposed for the primary endpoint. For analyses at Week 52, all available longitudinal data up to and including Week 52 will be used. For analyses at Week 104, all available longitudinal data up to and including Week 104 and prior to optimal dose switch.

The observed, change from Baseline and percent change from Baseline for the sqrt of total GA lesion area and the total GA lesion area at each visit will be summarized by treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum).

4.4.2.2. Delayed-start Analysis for Sqrt of the Total GA Lesion Area

If optimal danicopan dose is established, to assess the effect of danicopan on disease progression in the sqrt of the total GA lesion area, a delayed-start analysis will be conducted by incorporating all data from the first 52 weeks (referred as early-start period) and second 52 weeks (referred as delayed-start period). The analysis population will include a subset of participants in the FAS who were randomized to the optimal danicopan dose and the placebo participants re-randomized to the optimal dose. The delayed-start analysis will be performed if the treatment effect at the end of early-start period for the population is statistically significant at 2-sided alpha level of 0.1. The treatment effects will be quantified by the estimated differences between the groups based on their original randomization treatment arms (optimal dose versus placebo) for both early-start and delayed-start periods from MMRM as follows:

The piece-wise linear mixed-effect model will include change from Baseline (including at Week 52 and at Week 104) in the sqrt of total GA lesion area as the dependent variable and the following list of independent variables as random effects: time (years, continuous), the first early-start interaction between time (years, continuous) and treatment (1 for optimal dose, 0 for placebo) for the early-start period, the second delayed-start interaction between new time (= time-1 year if time≥1) and new treatment indicator (0 for optimal dose, 1 for placebo switched to optimal dose).

4.4.2.3. Conversions From iRORA to cRORA, From High-risk Drusen to Late AMD, and from iAMD to Late AMD

The following conversion endpoints will be analyzed and summarized:

- Incidence of patients with conversion from iRORA to cRORA from Baseline to Week 52 and Week 104 in the study eye, fellow eye, either eye, and both eyes combined using SD-OCT images
- Incidence of patients with conversion from high-risk drusen to late AMD from Baseline to Week 52 and Week 104 in in the study eye, fellow eye, either eye, and both eyes combined using SD-OCT images
- Incidence of patients with conversion from iAMD to late AMD from Baseline to Week 52 and Week 104 in the study eye, fellow eye, either eye, and both eyes combined using SD-OCT images
- Number of conversions from iAMD to late AMD from Baseline in the study eye, fellow eye, and both eyes combined to Week 52 and Week 104

If a patient has at least one lesion converted from iRORA to cRORA from Baseline to Week 52 in the study eye, the patient will be counted as conversion (Yes) from Baseline to Week 52 in study eye. If a patient has at least one lesion converted from iRORA to cRORA from Baseline to Week 52 in the fellow eye, the patient will be counted as conversion (Yes) iRORA to cRORA from Baseline to Week 52 in the fellow eye. If a patient has at least one lesion converted from iRORA to cRORA from Baseline to Week 52 in either the study eye or in the fellow eye, the patient will be counted as conversion (Yes) from iRORA to cRORA from Baseline to Week 52 in either eye. If a patient has at least one lesion converted from iRORA to cRORA from Baseline to Week 52 in both the study eye and the fellow eye, the patient will be counted as conversion from iRORA to

cRORA from Baseline to Week 52 in both eyes combined. Other conversion endpoints will be defined similarly.

Patients with conversions from iRORA to cRORA from Baseline to Week 52 and Week 104 in study eye, fellow eye, either eye and both eyes combined will be summarized by frequencies and percentages. Only patients with iRORA at baseline will be included in the percentage calculations.

Patients with conversions from high-risk drusen to late AMD, where late AMD includes cRORA (GA) and exudative nAMD (Intraretinal fluid or Subretinal fluid) at Week 52 or Week 104 in study eye, fellow eye, either eye and both eyes combined will be summarized by frequencies and percentages. Only patients with high-risk drusen at baseline will be included in the corresponding percentage calculations.

Any conversion from iRORA to cRORA, or from high risk drusen to late AMD, or from non-exudative nAMD to late AMD is considered as a conversion from iAMD to late AMD. Patients with conversions from iAMD to late AMD at Week 52 or Week 104 in study eye, fellow eye, either eye and both eyes combined will be summarized by frequencies and percentages. Only patients with iAMD at baseline will be included in the corresponding percentage calculations.

The Pearson Chi-square test or Fisher's exact test (if any cell count is less than 5) will be performed to compare the conversion rates between danicaopan arm (100 mg bid, 200 mg bid or 400 mg qd) and placebo at Week 52 or between any pair of danicaopan doses (100 mg bid, 200 mg bid or 400 mg qd, placebo→100 mg bid, placebo→200 mg bid, or placebo→400 mg qd) at Week 104. The p-value, the estimated difference in the corresponding to conversion rate, and the 2-sided 90% CI of the difference will be summarized.

Number of conversions from iAMD to late AMD at each visit for both eye combined is the sum of the number of conversions from iAMD to late AMD at that visit for the study eye and for the fellow eye. The number of conversions from iAMD to late AMD will be summarized by treatment group and visit using descriptive statistics (n, mean, SD, median, minimum, and maximum).

Number and percentage of patients who developed nAMD in the study eye at postbaseline visit, and within this patient group the number and percentage of patients with baseline nAMD in the fellow eye will be summarized by visit and treatment group.

4.4.2.4. Drusen Volume

The treatment effect on the change in drusen volume (mm^3) for the fellow eye with early or iAMD as measured by SD-OCT will be evaluated using MMRM with the change from Baseline in drusen volume as the dependent variable. The independent variables will consist of treatment group, visit (categorical), the interaction between visit and treatment, the randomization strata, and baseline drusen volume.

The LS-means, the associated SEs, the p-values and the two-sided 90% CIs of the change from Baseline in drusen volume at Week 52 and Week 104 for each treatment group and the difference between treatment groups will be summarized.

The observed and changes from Baseline in drusen volume will be summarized by treatment group and visit using descriptive statistics (n, mean, SD, median, minimum, and maximum).

4.4.3. Exploratory Analyses for Functional Endpoints

4.4.3.1. Monocular and Binocular BCVA, LLVA, LLD, Monocular and Binocular Reading Speed

The following exploratory functional endpoints will be analyzed and summarized:

- Change from Baseline to Week 52 and Week 104 in BCVA scores in the fellow eye as assessed by ETDRS chart
- Change from Baseline to Week 52 and Week 104 in LLVA scores in the fellow eye as assessed by ETDRS chart
- Change from Baseline to Week 52 and Week 104 in low luminance deficit (BCVA-LLVA) in the fellow eye
- Change from Baseline to Week 52 and Week 104 in binocular BCVA scores as assessed ETDRS chart
- Change from Baseline to Week 52 and Week 104 in binocular LLVA scores as assessed by ETDRS chart
- Change from Baseline to Week 52 and Week 104 in binocular LLD (BCVA-LLVA)
- Change from Baseline to Week 52 and Week 104 in monocular reading speeds in fellow eye as assessed by MNRead Acuity Charts or Radner Reading Charts
- Change from Baseline to Week 52 and Week 104 in binocular reading speeds as assessed by MNRead Acuity Charts or Radner Reading Charts

The treatment effect on the change from Baseline in monocular and binocular BCVA, LLVA, and LLD endpoints above will be evaluated using the same MMRM models as proposed for the change from Baseline in monocular BCVA, LLVA, and LLD in the study eye in Section Data collected via the two reading charts will be pooled for analysis regardless of chart type. The change from Baseline mentioned above will be estimated using a similar MMRM model. The modified model replaces the baseline BCVA with the corresponding baseline endpoints and will include additional covariate for reading chart type (MNRead or Radner). Additional subgroup analyses will be performed to assess the consistency of findings across the two reading charts. More detail about the calculation of reading speed can be found in Section 6.3.4.

The observed and changes from Baseline values will be summarized by treatment group and visit using descriptive statistics (n, mean, SD, median, minimum, and maximum). The least-square mean, the associated standard error, the corresponding p-value and a two-sided 90% confidence interval of the mean change from Baseline for each treatment group and for the treatment difference between danicopan dose groups and placebo will be reported by treatment group and visit. The test for treatment difference will be conducted at two-sided 0.1 significance level.

Additional exploratory correlation analyses will be performed between EZ parameters and functional endpoints BCVA and LLVA scores.

4.4.3.2. Outcomes Assessed by Microperimetry

The microperimetry subgroup analyses will be performed for the following endpoints:

- Number of scotomatous points assessed by mesopic microperimetry for the evaluation of the macular functional response in study eye and fellow eye to Week 52 and Week 104in study eye and fellow eye to Week 52 and Week 104
- Incidence of patients with prespecified change from Baseline to Week 52 and Week 104 in retinal sensitivity in any predefined grid pattern containing at least 5 contiguous test points as assessed by mesopic microperimetry in the study eye, fellow eye, and both eyes combined

The MP subgroup includes all randomized patients who receive at least 1 dose of study drug and meet the eligibility criteria for microperimetry.

The observed and change from Baseline in the number of scotomatous points will be summarized by treatment group and visit using descriptive statistics (n, mean, SD, median, minimum, and maximum) in the study eye, fellow eye and both eyes combined.

For macular sensitivity as assessed by mesopic microperimetry, a grid customized for this study will be utilized to analyze the macular sensitivity by patterns with at least 5 and up to 61 testing points in the study eye, fellow eye, and both eyes combined (refer the testing pattern table in Section 6.3.5 in the appendix for details). The macular sensitivity for each pattern will be calculated as the average of the testing points within the pattern. The incidence of patients with at least 7 dB decrease from Baseline in MP sensitivity in any predefined grid pattern will be summarized by treatment group and visit using frequency and percentage in the study eye, fellow eye, and both eyes combined. Similarly, the incidence of patients with at least 7 dB increase from Baseline in MP sensitivity in any predefined grid pattern will be summarized.

4.5. Safety Analyses

All safety analyses will be made on the SS. AEs will be coded in using the latest version of MedDRA and presented by MedDRA SOC and preferred term. No formal hypothesis testing is planned. Unless otherwise specified, baseline is defined as the last available assessment prior to the first dose of study drug.

4.5.1. Study Duration, Exposure, and Treatment Compliance

The descriptive statistical analysis for study duration, drug exposure and treatment compliance will be performed for SS.

Study participation duration in number of days is calculated as the time in days from the signing of informed consent until the date of completion/discontinuation (or death) for study or period (i.e., study or period duration=date of completion/discontinuation (or death) for study or period - date of informed consent + 1).

Treatment exposure duration in number of days for a specific period is calculated as days from the first dose until the date of the last dose from the specific period (i.e., treatment exposure duration = date of last dose for the period – date of first dose for the period + 1). Treatment exposure

duration will be summarized by treatment group with descriptive statistics for Primary Evaluation Period, Secondary Evaluation Period, and Masked Treatment Period.

Treatment compliance for a patient is defined as: $\frac{\text{total number of tablets taken}}{\text{total tablets expected to receive}} \times 100$, where the total number of tablets taken is calculated as total number of tablets dispensed – total number of tablets returned for a specific period (excluding taper period and follow-up period) from study drug accountability assessment, and the total number of tablets expected to be received for a patient while on-study during a specific period = 6 tablets per day × period duration in number of days. Treatment compliance percentage will be summarized by treatment group with descriptive statistics for Primary Evaluation Period, Secondary Evaluation Period, and Masked Treatment Period. The number and proportion of participants who had treatment compliance percentage in range by decrements of 10% from 100% to 0% (ie, ≥ 90% to ≤100%, ≥80% to < 90%, ≥70% to <80%, ≥60% to < 70%, ≥50% to < 60%, ≥40% to <50%, ≥30% to <40%, ≥20% to <30%, ≥10% to <20%, ≥0% to <10%) will also be summarized. In addition, the study drug accountability assessment information will be summarized by treatment group for each period.

By-patient listings will be produced for study treatment duration and treatment compliance.

4.5.2. Adverse Events

AEs will be classified by SOC and PT using the latest available version of MedDRA and will be reported by treatment group including the pooled danicopan group for Primary Evaluation Period, Secondary Evaluation Period, and Masked Treatment Period.

Adverse events determined to have occurred before the first dose of the study drug will be classified as pretreatment adverse events. Adverse events that occur on or after the first dose of study drug or placebo will be considered TEAE. Analyses of Pre-Treatment Adverse Events (PTAEs) and TEAEs will be tabulated and presented separately. Participants having multiple AEs within a category (eg, overall, SOC, PT) will be counted once in that category. For severity/relationship tables, the patient's highest grade/most related event within a category will be counted. Percentages will be based on the number of treated participants in the SS within each treatment group. Event rate per 100 patient-years (PY) is defined as the number of events occurred within 100 PY. Specifically,

$$\text{Event rate} = \text{Total number of events}/\ \text{Total PY} \times 100$$

Where total PY is defined as the sum of the study duration (days)/365.25 for all participants in a treatment group. Tables will be sorted by Ocular/Non-ocular, by alphabetical order of SOC and by descending frequency of PT within SOC. PTs with same frequency will be sorted in alphabetical order. Listings will be provided for all TEAEs and PTAEs for the SS. Any TEAEs that lasted across treatment periods will be only counted once in the treatment period where the event started.

AEs will include the displays described in the following sub-sections.

4.5.2.1. Overall Summary of Adverse Events

An overall summary table of TEAEs will be presented. The number of TEAEs (n), number and percent of participants with TEAEs (n, %), and the event rate of TEAEs per 100 patient-years will be displayed for the following events categories:

- TEAEs
- Ocular TEAEs/Non-ocular TEAEs
- Drug related TEAEs/Not drug related TEAEs
- Drug related ocular TEAEs/Not drug related ocular TEAEs
- TEAEs by toxicity grades (Grade 1 to Grade 5)
- Ocular TEAEs by toxicity grades (Grade 1 to Grade 5)
- TEAEs leading to study treatment discontinuation
- Ocular TEAEs leading to study treatment discontinuation
- TEAEs leading to study discontinuation
- Ocular TEAEs leading to study discontinuation
- TEAEs leading to death
- Ocular TEAEs leading to death

The overall summary described above will also be produced separately for treatment-emergent serious adverse events (SAEs) with exception of TEAE toxicity grade.

4.5.2.2. TEAEs and SAEs by System Organ Class (SOC) and Preferred Term (PT)

The number of TEAEs, the number and percentage of participants with TEAEs, and the event rate of TEAEs per 100 patient-years will be presented by Ocular/Non-ocular, SOC and PT. Participants are counted once in each Ocular/Non-ocular, SOC and PT. SAEs will be summarized similarly. A summary by Ocular/Non-ocular and PT will also be produced for events occurring in ≥ 5% of participants for any treatment group. The ocular TEAEs or SAEs will be reported in a similar manner. Listings will be provided for all TEAEs and SAEs.

In addition, the summary of the number of TEAEs and the number and percentage of participants with events will also be produced for non-serious TEAEs for clinicaltrials.gov results posting purpose.

4.5.2.3. TEAEs and SAEs by SOC, PT, and Relationship

The number of TEAEs, the number and percentage of participants with TEAEs, and the event rate of TEAEs per 100 patient-years will be presented by Ocular/Non-ocular, SOC and PT as described above by relationship to study treatment (related, not related). If a patient has more than one occurrence of an AE, the strongest relationship to study treatment will be used in the summary table. SAEs will be summarized similarly. The ocular related TEAEs or SAEs will be reported by relationship to study treatment in a similar manner.

4.5.2.4. TEAEs by SOC, PT, and Toxicity Grade

The number of TEAEs, the number and percentage of participants with TEAEs, and the event rate of TEAEs per 100 patient-years will be presented by Ocular/Non-ocular, SOC and PT as described above by toxicity grade (Grade 1, Grade 2, Grade 3, Grade 4, Grade 5). If a patient has more than one occurrence of an AE, the highest grade will be used in the summary table. The ocular related TEAEs will be reported by toxicity grade in a similar manner.

4.5.2.5. Deaths, Other SAEs, and Other Significant Adverse Events

For TEAEs leading to study treatment discontinuation, study discontinuation, or death, the number of events, the number and percentage of participants with events, and the event rate of TEAEs per 100 patient-years will be presented by Ocular/Non-ocular, SOC and PT. The ocular TEAEs leading to study treatment discontinuation, study discontinuation, or death will be reported in a similar manner. Listings of TEAEs leading to treatment discontinuation, study discontinuation, or death will be produced as well.

Events of interest in this study include TEAEs of meningococcal infections and liver enzyme elevations. These events of interest will be summarized by treatment group.

4.5.3. Additional Safety Assessments

Other safety parameters will be summarized by treatment group for all participants in the SS for Primary Evaluation Period, Secondary Evaluation Period, and Masked Treatment Period population with data available. Listings and summaries may be provided for as appropriate.

4.5.3.1. Analyses for Laboratory Tests

Actual laboratory values, baseline values, and changes from Baseline in numeric central laboratory parameters will be summarized descriptively at each visit, by treatment group. Baseline is defined as the last non-missing assessment value prior to the first dose of study drug. The last record will be used if there are multiple records of laboratory measurements at postbaseline visits. All laboratory values will be classified as normal, below normal, or above normal based on normal ranges supplied by the central laboratory. Shift tables over time will be presented for all central laboratory values, where applicable, using normal, low, or high based on normal range values. For purposes of analyses, laboratory results based upon standardized units will be used.

Incidence of clinical laboratory abnormalities Grade 3 and above (based on version 5.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE]) will be summarized. For laboratory tests with CTCAE toxicity grades available, laboratory abnormalities will be summarized by worst treatment emergent grade.

For liver enzyme elevation, number and percentage of participants who had postbaseline laboratory values meeting any of the following criteria will be summarized by visit and treatment group:

- Alanine aminotransferase (ALT) >3 ×Upper Limit of Normal (ULN), 5 × ULN, 8 × ULN
- Aspartate aminotransferase (AST) >3 × ULN, 5 × ULN, 8 × ULN
- ALT >3 × ULN and total bilirubin >2 × ULN
- ALT >3 × ULN and total bilirubin >2 × ULN and alkaline phosphatase (ALP) < 2 × ULN

All central and local laboratory data will be presented in by-patient listings.

4.5.3.2. Vital Signs

The analysis of the following vital signs will be summarized descriptively: systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse rate (beats/min), respiratory rate (breaths/min), weight (kg), and temperature (°C).

Actual vital sign measurements, baseline values, and changes from Baseline in vital signs (blood pressure, pulse rate, respiratory rate, and systolic and diastolic blood pressure) at each visit will be summarized descriptively by treatment group. Baseline is defined as the last non-missing assessment value prior to the first dose of study drug. If there are multiple records of vital sign measurements at postbaseline visits, the last record will be used.

A listing of vital signs will be presented.

4.5.3.3. Physical Examinations

Number (%) of participants with abnormal physical examinations will be summarized by treatment group at each visit. Listings will also be produced.

4.5.3.4. Electrocardiograms (ECG)

Descriptive statistics by visit and treatment group will be presented for ECG parameters: heart rate (HR, beata/min), PR interval (msec), QRS duration ((msec), QT interval (msec), and corrected QT interval by Fridericia (QTcF; msec) values and for change from Baseline values.

Number and percentage of participants who had postbaseline abnormal ECG values meeting any of the following criteria will be summarized:

- QT, QTcF interval >450 msec
- QT, QTcF interval >480 msec
- QT, QTcF interval >500 msec
- QT, QTcF interval increases from baseline >30 msec
- QT, QTcF interval increases from baseline > 60 msec

A by-patient listing of ECG results will be presented.

4.6. PK/PD Analyses

PK exposure parameters such as AUC, C_{max}, and C_{trough} are going to be derived using the population PK modeling approach and will be reported in a separate population PK report.

Descriptive statistics (number of non-missing observation, mean, SD, coefficient of variation [CV], median, minimum, maximum, geometric mean, and geometric %CV) will be calculated and summarized for PK concentration data by visit and treatment group for all participants in PKAS, as appropriate. For concentration descriptive statistics, concentrations that are below the limit of quantification (BLQ) will be set to 0. Individual graphs of concentration-time profiles for individual patient may also be provided.

PD analyses will be performed for all participants in PDAS. Descriptive statistics (number of non-missing observation, mean, SD, coefficient of variation [CV], median, minimum, maximum, geometric mean, and geometric %CV) will be presented for all danicopan PD biomarkers (AP activity, Bb, FD, C3 and CP activity) by visit and treatment group, as appropriate. The PD effects of danicopan will be evaluated by assessing the actual values and changes and percentage changes from Baseline in serum or plasma concentrations over time, as appropriate.

Assessments of danicopan PK/PD relationships may be explored using data from this study or in combination with data from other studies.

In addition, the exposure response (PD biomarkers, clinical endpoints) relationship may be explored.

4.7. Other Analyses

4.7.1. COVID-19 Related Analysis

The following COVID-19 related data will be collected in this study:

- Missed study visits or assessments (and COVID-19 related reasons)
- Screen failure and patient disposition (impacted by COVID-19)
- COVID-19 exposure
- TEAEs related to COVID-19
- Protocol deviations related to COVID-19

The number of participants with missed study visits or assessments and the reasons (COVID related or other) will be summarized by treatment groups and overall.

The number of participants with screen failure and disposition status impacted by COVID-19 will be summarized by treatment groups and overall.

COVID-19 known exposure will be summarized by treatment groups and overall.

An overall summary table of TEAEs related to COVID-19 will be presented. The number of TEAEs related to COVID-19, the number and percentage of participants with TEAEs related to COVID-19, and the event rate per 100 patient-years will be presented by Ocular/Non-ocular, SOC and PT.

Protocol deviations related to COVID-19 will be summarized as the overall PDs.

4.7.2. Subgroup Analyses

Descriptive summaries for change from Baseline to Week 52 in the square root (sqrt) of total GA lesion area (mm) by FAF, total GA lesion area (mm^2) by FAF, BCVA, LLVA and LLD in the study eye will be produced for the following subgroups:

- Baseline GA lesion size: < 1 DA, ≥ 1 DA
- Foveal involvement: Subfoveal, Extrafoveal GA lesion
- Focality: Unifocal, Multifocal GA lesion
- Distance from foveal center group: The 4 quartile groups for the distance from foveal center at Baseline include minimum to $<25^{th}$ percentile (Q1), Q1 to < median, median to $<75^{th}$ percentile (Q3), Q3 to maximum
- Age category: 60 to <65 years, 65 to <70 years, 70 to <75 years, 75 to <80 years, 80 to < 85 years, and $\geq$ 85 years

- Sex: Male, Female

The TEAEs will be summarized for the same subgroups (no p-value will be produced for these subgroup analyses.

If there are more than 5% participants using approved GA intravitreal injections in the fellow eye, descriptive summaries for change from Baseline to Week 52 in the square root (sqrt) of total GA lesion area (mm) by FAF, total GA lesion area (mm^2) by FAF, BCVA, LLVA, LLD in the study eye and fellow eye, and TEAEs will be produced for this subgroup of participants.

4.8. Interim Analyses

Two unmasked interim analyses will be conducted by the data monitoring committee (DMC). The DMC will consist of a biostatistician and 4 physicians. The DMC will capture the outcome of IA1 and IA2 on the recommendation forms in the charter. See the DMC charter for more details.

The IA1 for futility may be conducted when approximately 50% of participants have completed the Week 28 visit or discontinued. The conditional power rule (probability of statistical significance at Week 52 based on the trend observed at the interim analysis) will be used for the futility analysis at IA1. The estimated treatment effect and variance at IA1 from MMRM as in Section 4.2.2. will be used for the conditional power calculation.

- If conditional power is <10% for each active e treatment compared with placebo, the study can be considered futile

At IA1, additional assessments for macular EZ and outer retinal integrity, and sub-RPE compartment/drusen/RPE complex may be done by unmasked Sponsor team (independent of the study team) for potential considerations of study futility and signal of POC.

The IA2 may be conducted when approximately 50% of participants complete Week 52 visit or discontinued. There are two objectives of IA2.

- Futility assessment
- Early establishment of POC

At IA2, additional assessments for macular EZ and outer retinal integrity, and sub-RPE compartment/drusen/RPE complex may be done by unmasked Sponsor team for potential considerations of study futility and signal of POC.

See the separate Interim Analysis Plan (IAP) for detailed analysis strategies for IA1 and IA2.

Provided deemed safe, a statistically significant danicopan treatment will constitute a set of potential danicopan regimens for optimal dose selection at IA2.

Upon receipt of the DMC recommendation, the final determination of the optimal dose will be made by an unmasked Sponsor team based on the totality of the data.

If the optimal dose is not identified at IA2, optimal dose selection will be performed again at the primary analysis when all participants complete the Week 52 Visit or discontinued and will be based on the totality of data.

4.9. Data Monitoring Committee

An independent DMC will be appointed by Alexion and is composed of experts in relevant fields with no direct relationship to the study. In this study, the independent DMC will be responsible for the review of efficacy and safety data, including data from the IAs.

The structure and the specific roles and responsibilities of the DMC and a schedule of meetings will be described in the DMC Charter.

4.10. Changes to Protocol-planned Analyses

Not applicable

5. SAMPLE SIZE DETERMINATION

Approximately a total of 332 participants will be randomized in 1:1:1:1 ratio to one of the 4 treatment arms within each stratum, assuming a 15% discontinuation rate within the first 52 weeks. According to assumptions made based on published data (Jaffe, 2020; Steinle, 2021) the mean annual increase in sqrt GA area of a single eye for the placebo group is estimated to be 0.41 mm. The common SD for all treatment groups is assumed to be 0.25 mm (Holz, 2018; Liao, 2020). Furthermore, the expected mean annual increase in at least one danicopan dose is assumed to be 0.3034 mm, which is equivalent to approximately 26% relative reduction compared to placebo or an absolute treatment difference of 0.1066 mm between placebo and danicopan treatment in the mean change from Baseline in sqrt GA area at Week 52. The MCP-Mod approach is used to establish the POC with 4 candidate dose-response models at IA2 and Week 52. Based on simulations, this sample size will provide at least 90% power to detect the dose-response effect at Week 52 with a 1-sided type I error rate of 0.05 after adjusting for multiplicity. If the POC is established, this sample size will also provide at least 90% power to detect a statistically significant difference between at least one danicopan treatment arm and placebo at Week 52 after appropriate multiplicity adjustment for pairwise comparison.

6. SUPPORTING DOCUMENTATION

6.1. Study and Participant Characteristics

6.1.1. Participant Disposition

A table summarizing the number of screened patients, number and percentage of screen failures, number and percentage of randomized participants among all screened participants and number of participants treated will be provided. By-patient listing of the reasons for screen failure will also be produced.

A summary of study disposition for all randomized participants will be provided, which will include the number and percentage of participants who have completed each evaluation period, number and percentage of participants who have prematurely withdrawn from the study, as well as the primary reasons for withdrawal for Primary Evaluation Period, Secondary Evaluation Period, and Masked Treatment Period (the entire study period). A by-patient data listing with disposition information will be provided.

The number and percentage of participants in each analysis set and a by-patient listed will be tabulated. The number and percentage of participants not meeting specific inclusion or exclusion criterion will be summarized and listed. The by-patient data listings of randomization information and consent status will also be provided.

6.1.2. Demographics, Baseline and Disease Characteristics, and Medical History

All demographic and baseline characteristics information will be summarized using the FAS and SS populations by treatment group and overall. No statistical test will be performed for homogeneity among treatment groups. Summary statistics will be presented by treatment group and overall. By-patient listings will be produced for all randomized participants.

6.1.2.1. Demographics

The following demographic variables will be summarized by descriptive statistics (n, mean, SD, median, minimum, and maximum) or by numbers and percent of participants in each category:

- Age (years) at randomization: descriptive statistics
- Age category (60 to <65 years, 65 to <70 years, 70 to <75 years, 75 to <80 years, 80 to < 85 years, and ≥ 85 years) – n (%)
- Sex (Male, Female) – n (%)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific islander, White, Not Reported, Unknown, and Other) – n (%)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, and Not Reported) – n (%)
- Study site region (Europe, Japan, North America, and Rest of Asia Pacific)
- Baseline weight (kg): descriptive statistics
- Baseline height (cm): descriptive statistics

- Baseline Body Mass Index (BMI) (kg/m^2): descriptive statistics
- BMI category (<18.5, ≥ 18.5 to < 25, ≥ 25 to < 30, and ≥ 30) – n (%)

Age, weight, and BMI will be reported based on the most recent data on or before Day 1 (the first dose of study drug).

6.1.2.2. Disease Characteristics

The following disease characteristics will be summarized by descriptive statistics (n, mean, SD, median, minimum, and maximum) or by numbers and percentage of participants in each category:

- BCVA, LL-BCVA, LLD for study eye, fellow eye, and both eyes
- Percent of participants with bilateral GA vs unilateral GA
- Percent of participants with baseline exudative AMD in the fellow eye
- Mesopic MP (Number of scotomatous points, macular sensitivity) for MP subpopulation
- Overall and sqrt total GA area at screening and frequency of participants in the following categories: GA lesion size < 1 DA versus ≥ 1 DA
- Foveal location of GA lesion (subfoveal versus extrafoveal)
- Distance from foveal center for extrafoveal group
- Focality of GA lesion (unifocal versus multifocal)

6.1.2.3. Medical and Surgical History and Baseline Physical Examination

Medical and surgical history will be classified by SOC and PT using the latest available version of MedDRA. Number and percent of participants for each category will be reported by treatment group and overall, for the FAS and SS.

Baseline physical examination information will also be summarized. By-patient listings will be created for medical history and physical examinations.

6.1.3. Prior and Concomitant Medications/Therapies

6.1.3.1. Prior and Concomitant Medications

Prior and concomitant medications/therapies will be summarized separately using the SS.

For analysis and reporting purposes, any medication started prior to first dose of study drug will be considered as prior medication and any medication taken by a patient that overlaps with the intake of the study drug will be considered as concomitant medication. Medications will be coded using the World Health Organization Drug Dictionary (WHO-DRUG) version in use at the time of the analysis. Medications summaries by treatment group and overall using number and percent of participants will be presented by WHO-DRUG Anatomical Therapeutic Chemical (ATC) Level 3 Class code and by WHO-DRUG generic name.

By-patient listings will be created for medical prior and concomitant medications. All meningococcal vaccinations administered within 3 years of dosing with study drug for participants will be listed separately as well.

6.1.3.2. Prior and Concomitant Non-Drug Therapies and Procedures

Prior non-drug therapies and procedures are defined as therapies and procedures taken or conducted prior to the first study treatment. Concomitant non-drug therapies and procedures are defined as therapies and procedures started on/after the date of the first dose of the study drug.

Prior and concomitant non-drug therapies and procedures will be coded using the MedDRA version in use at the time of the analysis. The number and percentage of participants with non-drug therapies and procedures coded to each MedDRA SOC and PT will be summarized by treatment group and overall using the SS.

By-patient listings of prior and concomitant non-drug therapies and procedures will be produced.

6.1.4. Protocol Deviations

All protocol deviations will be listed for all randomized participants. The number and percentage of participants with important protocol deviations for the categories provided in Table 4 will be summarized by the treatment group and overall.

Table 4: Protocol Deviation Categories

1. Eligibility and entry criteria 2. Investigational product 3. Concomitant medication 4. Informed consent 5. Laboratory assessment	6. Visit schedule 7. Study procedure/tests 8. Randomization 9. Safety reporting 10. Source document 11. Other

The following protocol deviations will be determined programmatically from the database:

1. Participants who did not take at least 80% of the required treatment doses in the Primary Evaluation Period
2. Participants who were stratified to a wrong stratification group
3. Participants who received wrong randomized treatment during in the Primary Evaluation Period

6.2. Technical Specifications for Derived Variables

The following derived data will be calculated prior to analysis.

6.2.1. Definition of Baseline Values

In general, Baseline is defined as the last non-missing assessment value prior to first dose of study drug unless otherwise specified. For the analysis of numeric changes from Baseline in laboratory parameters, only values from the central laboratory will be considered for baseline definition.

6.2.2. Change From Baseline

Change in values from Baseline will be calculated as

Change from Baseline = (subsequent value – baseline value), given that both the baseline value and subsequent value are non-missing.

6.2.3. Percent Change From Baseline

Percent change in values from Baseline will be calculated as

$$\% \text{ Change from Baseline} = \frac{\text{subsequent value} - \text{baseline value}}{\text{baseline value}} \times 100$$

given that the baseline value is non-missing and non-zero and the subsequent value is non-missing.

6.2.4. Analysis Visits

Since the actual study visits for a patient may not exactly coincide with their targeted visit date, the actual visit date will be mapped to the analysis visits as described below.

The analysis visits will be derived using pre-specified windows around the number of days during the study since the first dose of the study drug (called Day 1). The lower and the upper limits of the analysis windows are described in Table 5.

Table 5: Analysis Windows

Analysis Visit	Target Day	Low	High
Week 2	15	2	22
Week 4	29	23	43
Week 8	57	44	85
Week 16	113	86	155
Week 28	197	156	239
Week 40	281	240	323
Week 52	365	324	372
Week 54	379	373	386

Table 5: Analysis Windows

Analysis Visit	Target Day	Low	High
Week 56	393	387	407
Week 60	421	408	449
Week 68	477	450	519
Week 80	561	520	603
Week 92	645	604	687
Week 104	729	688	-

6.2.5. Adverse Events

The analysis of Adverse Events is described in detail in Section 4.5.2 .

TEAEs are events with start dates and start times on or after the date and time of the first study drug dose. If the start date of an AE is partially or completely missing and the end (stop) date and time of the AE does not indicate that it occurred prior to first dose, then the determination of treatment-emergent status will be based on the following:

If both start and end dates of AEs are completely missing, no imputation will be performed, and those AEs will be considered treatment-emergent.

<u>If the start date is partial:</u>

1. If only the day is missing:
   1.1. If the month/year of the start date is the same as those of the first study drug administration date, then the missing day will be imputed as the smaller non-missing value of (day of first study drug administration, day of the AE end date).
   1.2. Otherwise, impute the missing day as ‘01’.
2. If both day and month are missing:
   2.1. If the year of the AE start date coincides with the year of the first study drug administration date, the partial start date will be set as the first study drug date. If this leads to a date after the AE end date, then the missing day and month of the AE start date will be imputed as the day and month of the AE end date.
   2.2. If the year of the AE start date is different from the year of the first study drug administration date, the missing day and month of the AE start date will be imputed as the ‘01’ and ‘01’.

<u>If the stop date is partial:</u>

1. If only the day is missing:
   1.1. the missing day will be imputed as the last of the month adjusting for the leap-year.

2. If both day and month are missing:

    2.1. If the year of the AE end date coincides with the maximum of (the year of first study drug administration date or the year of the last study drug administration), then the missing month will be imputed as the month of the corresponding study drug administration date (first or last) and the missing day will be imputed as the last of the month adjusting for the leap-year.

    2.2. Otherwise, the missing day and month of the AE stop date will be imputed as the '31' and '12'.

6.2.6. Concomitant Medications/Therapies

If the start date of a medication/therapy is partially or completely missing and the end (stop) date of the medication/therapy does not indicate that it ended prior to first study drug, then the determination of the concomitant status will be based on the following:

If both start and end dates of medications are completely missing, no imputation will be performed, and those medications will be considered both prior and concomitant medications.

<u>If the end date is partial:</u>

1. If only the day is missing

    1.1. If the year and month coincide with those of the last study drug administration date, the end of medication will be set to the last study drug administration date.
    1.2. If the year and month do not coincide with those of the last study drug administration date, then the missing day will be imputed as the last day of the month considering leap year and month in consideration.

2. If both day and month are missing

    2.1. If the year coincides with that of the last study drug administration date, then missing month and day will be imputed as the month and day of the last study drug administration.
    2.2. If the year does not coincide with that of the last study drug administration date, then the missing month and day will be imputed as '12' and '31', respectively.

<u>If the start date is partial:</u>

1. If only the day is missing

    1.1. If the year coincides with that of the first study drug administration date, then do the following:
    1.2. If the month does not coincide with that of the first study drug administration date, then impute the missing day as '1'.
    1.3. If the month coincides with that of the first study drug administration date
        1.3.1. If the end date is greater than the first study drug administration date, then impute the missing day as the day of the first study drug administration date
        1.3.2. If the end date is less than or equal to the first study drug administration date, then impute the missing day as the day of the end date of medication.

1.4. Otherwise, if the year and the month do not coincide with those of the first dose date, then impute the missing day as '1'.

2. If both day and month are missing

2.1. If the year does not coincide with that of the first study drug administration date, then impute missing month as '1' and missing day as '1'.
2.2. If the year coincides with that of the first study drug administration date
2.2.1. If the end date is greater than the first study drug administration date, then impute the missing day and month as those of the first study drug administration
2.2.2. If the end date is less or equal to the first study drug administration date, then impute the missing day and the month as those of the end date of the medication.
2.3. If the start date is completely missing, the missing start date will be set as the earlier of the first study drug administration date and end of the medication date.

All other medications/therapies are considered Prior Medications/Therapies.

6.2.7. Medication Dates

For medication start dates, if day is missing, the first day of the month will be used. If month is missing, January will be used. For medication end dates, if day is missing, the last day of the month will be used. If month is missing, December will be used. If year is missing for start or end date, the analysis date will be considered missing.

6.3. Instrument Scoring Details

6.3.1. National Eye Institute 25-item Visual Function Questionnaire

The NEI VFQ 25 scores (Sivaprasad, 2018; Mangione, 2001) measures dimensions of self-reported vision-targeted health status of individuals with chronic eye conditions. The NEI VFQ 25 consists of 11 vision related domains: global vision rating, difficulty with near vision activities, difficulty with distance vision activities, limitations in social function related to vision, role limitations, dependency on others due to vision, mental health symptoms due to vision, driving difficulties, limitations with peripheral- and color-vision, and ocular pain.

The NEI VFQ 25 also includes a single item measuring general health, which is treated as a stand-alone item. A composite score averages the vision related domains and ranges from 0 (worse) to 100 (best). It is an unweighted average of the responses to all items except for the general health rating question. The NEI VFQ-25 subscale scores are an average of the items in the subscale transformed to a 0 (worse) to 100 (best) scale.

The scoring of NEI VFQ-25 is a two-step process. In step 1, the original numeric values from the survey are re-coded following the scoring rules outlined in Table 6:. Each item is then converted to a 0 to 100 scale. In step 2, items within each subscale are averaged together to create the 12 subscale scores. More detail can be found in Table 7. Items that are left blank (missing) are not considered when calculating the scale scores. Subscales with at least one item answered can be used to generate the average for all items in the subscale.

Table 6: Scoring Key: Recoding of Items

Item Numbers	Response Category	Recoded Value
1,3,4,15$c^{(a)}$	1	100
	2	75
	3	50
	4	25
	5	0
2	1	100
	2	80
	3	60
	4	40
	5	20
	6	0
5,6,7,8,9,10,11,12,13,14,16,16a, A3, A4, A5, A6, A7, A8, $A9^{(b)}$	1	100
	2	75
	3	50
	4	52
	5	0
	6	Missing
17,18,19,20,21,22,23,24,25, A11a, A11b, A12, A13	1	0
	2	25
	3	50
	4	75
	5	100
A1, A2	0 to 10	0 to 100

a. Item 15c has 4- response levels but is expanded to 5-levels using item 15b. If 15b = 1, then 15c should be recoded to '0'. If 15b = 2 or 3, then 15c should be recoded to missing.

b. "A" before the item number indicates that this item is an optional item from the appendix. It is encouraged to use all items including the optional item for a given subscale.

Table 7: Averaging of Items to Generate NEI VFQ-25 Subscale Scores

Scale	Number of Items	Items to be averaged
General Health	1	1
General Vision	1	2
Ocular Pain	2	4,19
Near Activities	3	5,6,7
Distance Activities	3	8,9,14
Vision Specific:		
Social Functioning	2	11,13
Mental Health	4	3,21,22,25
Role Difficulties	2	17,18
Dependency	3	20,23,24
Driving	3	15c, 16, 16a
Color Vision	1	12
Peripheral Vision	1	10

6.3.2. EQ-5D-5L Health State Index Calculations

The Euro Quality of Life-5L (EQ-5D-5L) is a self-assessed, health related QoL questionnaire. It is a measure of health status consisting of 2 parts. The first part assesses health in 5 dimensions including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each level is rated on a scale that describes the degree of problems in that area (i.e., I have no problems walking about, slight problems, moderate problems, severe problems, or unable to walk). The second part of the questionnaire consists of a visual analogue scale (VAS) on which the patient rates their perceived health from 0 (the worst imaginable health) to 100 (the best imaginable health).

The responses to the 5 EQ-5D dimensions can be converted into a single number called an index value. The index can be calculated by subtracting the appropriate weights listed in Table 8 for each dimension level of health state from 1. The weight for this study is provided by the US composite time trade-off (cTTO) method based on the Tobit model (Pickard, 2019). The calculation is illustrated below:

Table 8: EQ-5D-5L US Composite Time Trade-off (cTTO) Value Set

US cTTO		**Example: the value for health state 21354**
Full health (11111)		Full Health=1
Mobility level 2	-0.096	-0.096
Mobility level 3	-0.122	
Mobility level 4	-0.237	
Mobility level 5	-0.322	
Self-Care level 2	-0.089	0
Self-Care level 3	-0.107	
Self-Care level 4	-0.220	
Self-Care level 5	-0.261	
Usual Activity level 2	-0.068	
Usual Activity level 3	-0.101	-0.101
Usual Activity level 4	-0.255	
Usual Activity level 5	-0.255	
Pain/Discomfort level 2	-0.06	
Pain/Discomfort level 3	-0.098	
Pain/Discomfort level 4	-0.318	
Pain/Discomfort level 5	-0.414	-0.414
Anxiety/Depression level 2	-0.057	
Anxiety/Depression level 3	-0.123	
Anxiety/Depression level 4	-0.299	-0.299
Anxiety/Depression level 5	-0.321	
Health State Index Score		=1-0.096+0-0.101-0.414-0.299=0.090

6.3.3. Lawton Instrumental Activities of Daily Living (IADL)

The Lawton IADL (Lawton, 1969) scores is an assessment that evaluates the patient's ability for independent living. The Lawton IADL scale consists of 8 domains of functioning (food preparation, housekeeping, laundry, ability to use the telephone, mode of transportation, shopping, financial, and medication management). The instrument includes 8 dichotomous questions and its total score can range from 0 to 8. Low scores depict low function and dependence, whereas high scores high function and independence.

6.3.4. Reading Speed

Reading speed in words per minute will be calculated per the MNRead or Radner user's manuals, with no adjustment for reading inaccuracy.
For the MNRead chart, the reading speed is calculated as follows:

$$60 \times \frac{(10 - \text{errors})}{\text{reading time in seconds}}$$

Where errors are the number of words missed or read incorrectly.

For the Radner chart, the reading speed is calculated as:

$$60 \times \frac{14}{\text{reading time in seconds}}$$

The maximum reading speed for each patient will be used for the reading speed summaries.

6.3.5. Microperimetry Grid Patterns

The customized grid patterns for MP sensitivity are defined in Table 9 below for both right and left eyes:

Table 9 MP Grid Patterns

Pattern Number	Number of Loci	Pattern Number	Number of Loci
1	1-61 (Box C, Box N, and Box T)	**21**	32-41
2	1-21, 42-61 (Box C, Box T)	**22**	47-51
3	1-41 (Box C, Box N)	**23**	42-46
4	22-61 (Box N, Box T)	**24**	52-56
5	42-61 (Box T)	**25**	57-61
6	1-21 (Box C)	**26**	7-11
7	22-41 (Box N)	**27**	2-6
8	1-11, 22-31, 42-51	**28**	12-16
9	1, 12-21, 32-41, 52-61	**29**	17-21
10	47-51, 57-61	**30**	27-31
11	42-51	**31**	22-26
12	42-46, 52-56	**32**	32-36
13	52-61	**33**	37-41
14	7-11,17-21	**34**	1,7,9,17,19
15	2-11	**35**	1,2,4,7,9
16	2-6,12-16	**36**	1,2,4,12,14
17	12-21	**37**	1,12,14,17,19
18	27-31,37-41	**38**	1,7,9,12,14
19	22-31	**39**	1,2,4,17,19
20	22-26, 32-36	**40**	1,2,4,7,9,12,14,17,19

6.4. Additional Details on Statistical Methods

6.4.1. SAS Code for Tipping Point Sensitivity Analysis

The following illustrates the tipping point sensitivity analysis for the primary endpoint of change from Baseline to Week 52 in the sqrt of the total GA lesion area where a search is conducted for a tipping point that reverses the study conclusion from being favorable to active danicopan to being unfavorable. For the tipping point sensitivity analysis, the missing data mechanism for the missing change from Baseline values at Week 52 will be MNAR.

Markov Chain Monte Carlo imputation method will first be used to fill in the intermittent missing values under the assumption of MAR and generate a monotone missing data pattern (eg, 100 datasets will be generated). Below is example SAS code:

```
PROC MI DATA=<data set name> OUT=mono SEED=123654 NIMPUTE=100;
BY  trt;
MCMC IMPUTE=MONOTONE;
VAR base change16 – change52;
RUN;
```

Where trt is the randomized treatment group for the Primary Evaluation Period, base is the sqrt of total the GA lesion area value at Baseline, and change16 − change52 are the changes from Baseline in the sqrt of the total GA lesion area at the scheduled postbaseline visits from Week 8 to Week 52.

Subsequently, for a specific shift parameter value of delta, imputations are performed for missing change observations at all visits sequentially for all participants by sampling from an MAR-based MI model including the variables of randomized treatment group, baseline value, and values observed at all scheduled visits during the Primary Evaluation Period, then applying delta adjustments at each visit for participants treated in the danicopan arm. The following is example SAS code for the MI analysis for a specified shift parameter value of delta at Weeks X and Y:

```
PROC MI DATA = mono OUT = outmi SEED = 456987 NIMPUTE = 1;
BY _IMPUTATION;
CLASS  trt;
MONOTONE METHOD= REG;
VAR trt base change16 – change52;
MNAR ADJUST  (changeX / SHIFT = delta ADJUSTOBS = (trt = 'danicopan'));
MNAR ADJUST  (changeY / SHIFT = delta ADJUSTOBS = (trt = 'danicopan'));
RUN;
```

Once completed datasets are generated, each of the 100 imputed datasets will then be analyzed separately using the MMRM model specified in Section 4.2.3, and inferences from each completed dataset will be combined via PROC MIANALYZE procedure to obtain an overall test statistic for the specified shift parameter value of delta.

PROC MIANALYZE DATA= <MMRM lsmeans output>;
BY <visit>;
MODELEFFECTS <estimate>;
STDERR;
RUN;

Multiple shift parameter values will be tested until the inference concludes that statistical significance disappears. In the tipping point analysis for the primary endpoint, a series of delta values for the sqrt of the total GA lesion area increasing in increments of 0.01 mm will be applied (ie, 0.01, 0.02, …).

6.4.2. SAS Code for Placebo-based Sensitivity Analysis

The following illustrates the placebo-based sensitivity analysis for the primary endpoint of change from Baseline to Week 52 in the sqrt of the total GA lesion area. For participants who discontinued treatment, responses after treatment discontinuation, for all groups, will be imputed with multiple imputation methodology based on the response for placebo treated participants.

Similar to tipping point sensitivity analysis, MCMC imputation method will be used to fill in the intermittent missing values under the assumption of MAR and generate a monotone pattern (100 imputations will be generated).

Subsequently, multiple imputation will be performed at each visit sequentially, using a regression method obtained only from placebo treated participants with terms for baseline sqrt of GA lesion area, and values observed at all scheduled visits during the 52 weeks Primary Evaluation Period. Below is some sample code for the placebo-based pattern imputation at Week X:

```
proc mi data=monotone out=outmi seed=123 nimpute=1;
by imputation_;
class trt;
var base change16 – change52;
monotone reg(/details);
mnar model (changeX/modelobs=(trt=”placebo”))
run;
```

After obtaining complete data sets for each visit, these complete data sets will be analyzed using MMRM analysis, and inferences from each complete data set will be combined to obtain an overall test statistic for treatment effect.

7. REFERENCES

Bretz,F, Pinheiro JC, and Branson M. Combining multiple comparisons and modeling techniques in dose-response studies. Biometrics. 2005;61:738–48.

Heier J, Singh R, Wykoff C, et al. Efficacy of intravitreal pegcetacoplan in geographic atrophy: 24 month results from the phase 3 OAKS and DERBY trials. Retina Society. Pasadena, California;2022.

Holz FG, Sadda SR, Busbee B, et al. Efficacy and safety of lampalizumab for geographic atrophy due to age-related macular degeneration: CHROMA and SPECTRI phase 3 randomized clinical trials. JAMA Ophthalmol. 2018;136(6):666-677.

Hwang IK, Shih WJ, De Cani JS. Group sequential designs using a family of type I error probability spending functions. Stat Med. 1990; 9(12):1439-1445.

Jaffe GJ, Westby K, Csaky KG, et al. C5 inhibitor avacincaptad pegol for geographic atrophy due to age-related macular degeneration: A randomized pivotal phase 2/3 trial. Ophthalmology. 2020.

Lawton, M, Brody, E. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969; 9, 179-186.

Liao DS, Grossi FV, El Mehdi D, et al. Complement C3 inhibitor pegcetacoplan for geographic atrophy secondary to age-related macular degeneration: a randomized phase 2 trial. Ophthalmology. 2020;127(2):186-195.

Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD. Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol. 2001;119(7):1050-1058.

Pickard AS, Law EH, Jiang R, et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. Value Health.2019;22(8):931-941.

Ratitch B, O'Kelly M, Tosiello R. Missing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models. Pharm Stat. 2013;12(6):337-47. doi: 10.1002/pst.1549.

Ratitch B, O'Kelly M. Clinical Trials with Missing Data: A Guide for Practitioners: Wiley & Sons; 2014. p. i-xxix.

Sivaprasad S, Tschosik E, Kapre A, et al. Reliability and construct validity of the NEI VFQ-25 in a subset of patients with geographic atrophy from the phase 2 Mahalo study, Am J Ophthalmol. 2018;190:1-8.

Steinle NC, Pearce I, Monés J, et al. Impact of Baseline Characteristics on Geographic Atrophy Progression in the FILLY Trial Evaluating the Complement C3 Inhibitor Pegcetacoplan. Am J Ophthalmol. 2021;227:116-124.

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