TITLE PAGE

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)

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

Sponsor Name: Alexion Pharmaceuticals, Inc.

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Regulatory Agency Identifier Number(s)

IND: 153070
EudraCT: 2021-001198-22
EU CT: 2023-508571-37
NCT: NCT05019521

Release Date: 30 Oct 2023

Sponsor Signatory:

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

[redacted]

Date

Medical Monitor Name and Contact Information can be found in the Study Contact List.

INVESTIGATOR'S AGREEMENT

I have read this study protocol amendment and agree to conduct the study in accordance with this protocol amendment, all applicable government regulations, the principles of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Guideline for Good Clinical Practice, and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol amendment.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

A complete protocol amendment history is provided in Section 10.14.

Amendment 3.0 (Global); 30 Oct 2023

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the European Union Clinical Trial Regulation (EU CTR) 536/2014 Article 2, 2 (13).

Overall Rationale for the Amendment:

This amendment was initiated to:

- Update secondary and exploratory study endpoints based on emerging scientific data
- Provide new information on drug interactions based in IB Ed 13 dated 16 Oct 2023
- Update text in preparation for transition into EU CTR
- Add text to align with current Alexion protocol template, recently updated according to applicable regulations

Section # and Name	Description of Changes	Brief Rationale
Title page Section 1.1 Synopsis	• Updated document version and date. • Added regulatory agency identifier number (EU CT number).	• Administrative changes.
All throughout the document	• Made minor editorial and consistency changes. • Changed NIMP to AxMP	• For clarity, typographic consistency, style, and formatting edits. • Updated in accordance with EU CTR.
Section 1.1 Synopsis Section 3 Objectives and Endpoints	• Exploratory endpoints for macular ellipsoid zone (EZ), outer retinal integrity, and subretinal pigment epithelium (sub-RPE) compartment/drusen/RPE complex were upgraded to secondary endpoints • Exploratory endpoint on microperimetry revised: Previous endpoint: • ~~Change from Baseline in macular sensitivity as assessed by mesopic microperimetry in study eye, fellow eye, and both~~	• Emerging data show that EZ and sub-RPE/drusen/RPE complex analyses are highly important in GA studies, thus these exploratory endpoints are being upgraded to secondary endpoints. • The microperimetry endpoint has been revised to provide methodology details

Section # and Name	Description of Changes	Brief Rationale
	~~eyes combined to Week 52 and Week 104~~ New endpoint: • Incidence of patients with predefined change in any predefined grid pattern by mesopic microperimetry in the study eye, fellow eye, and both eyes combined.	
Section 1.3 Schedule of Activities	Updated Tables 1 to 3 to add medication error, drug abuse and misuse-	• To align with Section 8.4.5 and Section 10.7
Section 6.5.1 Allowed Medications Section 10.9 Allowed Medications	Updated sections and associated table to include new information on potential drug interactions: • Added text on the need for caution when co-administering danicopan with drugs known to be P-gp and/or BCRP substrates. • Updated Table 13: List of CYP3A4, P-gp, and UGT1A1/2B7 Sensitive Substrates and associated footnotes	• Updated with new information from drug-drug interaction study; in alignment with updated IB Ed 13
Section 8.2.2 Secondary Efficacy Assessments Section 8.2.2.1 Anatomical Measures	• Details on EZ and sub-RPE compartment/drusen/RPE complex moved up from Section 8.2.3 Exploratory Efficacy Assessments to Section 8.2.2. Secondary Efficacy Assessments, with updated subsections: -Section 8.2.2.1.1. Macular Ellipsoid Zone and Outer Retinal Integrity -Section 8.2.2.1.2. Sub-RPE Compartment/Drusen/RPE Complex • Added list of parameters from SD-OCT images	• To reflect change in endpoints (Synopsis; Section 3).
Section 8.2.3.2. Mesopic Microperimetry	• Added that “a difference of 7 decibels (dB) would represent a minimal clinically meaningful	• To provide additional information on microperimetry

Section # and Name	Description of Changes	Brief Rationale
	change on microperimetry" measures.	
Section 8.4.5 and Section 10.7 Medication Error, Drug Abuse, and Drug Misuse	• Updated text on data collection and reporting details.	• Updated in accordance with EU CTR.
Section 9.1.1. Primary Hypothesis	• Updated "mean change" to "mean rate of change" all throughout this section	• To provide clarity
Section 9.4.5.1 Analyses of Primary Efficacy Endpoint	• Updated estimand attributes	• To align with the Statistical Analysis Plan (SAP)
Section 9.4.5.2.1 Analyses of Secondary Efficacy Endpoints at Week 52 Section 9.4.5.2.2. Analyses for Secondary Efficacy Endpoints at Week 104'	• Updated list and description of endpoints • Update description of statistical models	• To reflect change in endpoints (Synopsis; Section 3). • For clarity
Section 10.1.1 Regulatory and Ethical Considerations	• Updated text on process for data protection and reporting data breaches.	• Updated in accordance with EU CTR and EU GDPR and the current Alexion protocol template.
Section 10.1.5 Data Protection	• Updated text on process for data protection and reporting data breaches.	• Updated in accordance with EU CTR and EU GDPR and the current Alexion protocol template.
Section 10.1.7 Data Quality Assurance	• Added text on duration for retention of records and documents pertaining to the conduct of the study.	• Updated in accordance with EU CTR.
Section 10.1.8 Source Documents	• Updated definitions and requirements of source documents	• Updated in accordance with GCP and current protocol template
Section 10.1.9 Study and Site Start and Closure	• Updated text on reasons for early study termination	• Updated in accordance with applicable regulations and current protocol template
Section 10.1.10 Publication Policy	• Added text on publication of results and authorship	• Updated to align with current Alexion/AstraZeneca publication policy
Section 10.5 Clinical Laboratory Test	• Updated frequency of creatine kinase sampling to every visit	• For safety monitoring

Section # and Name	Description of Changes	Brief Rationale
Section 10.10 Handling of Human Biological Samples	• Added new section on biological samples	• Updated to align with current Alexion/AstraZeneca policy

Abbreviations: AxMP = auxiliary medicinal product; Ed = edition; EU CTR = European Union Clinical Trial Regulation 536/2014; EU GDPR = European Union General Data Protection Regulation; GA = geographic atrophy; GCP = Good Clinical Practice; IB = Investigator's Brochure; NIMP = non-investigational medicinal product; SD-OCT = spectral domain optical coherence tomography

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1. PROTOCOL SUMMARY

1.1. Synopsis

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)

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

Regulatory Agency Identifier:

IND: 153070

EudraCT: 2021-001198-22

EU CT: 2023-508571-37

NCT: NCT05019521

Rationale: This proof of concept (POC) dose-finding study is designed to evaluate the efficacy, safety, and pharmacokinetics (PK) of danicopan in patients with geographic atrophy (GA) secondary to AMD.

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

Objectives	Endpoints
	• 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 Minnesota Low Vision Reading Test (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

Objectives	Endpoints
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 incomplete to complete retinal pigment epithelium and outer retinal atrophy (iRORA to cRORA) from Baseline to Week 52 and Week 104 in the study eye, fellow eye, either eye, and both eyes combined using spectral domain optical coherence tomography (SD-OCT) images • Incidence of patients with conversion from high-risk drusen 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 • Incidence of patients with conversion from intermediate AMD (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

Objectives	Endpoints
	• 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 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 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 predefined change in any predefined grid pattern by mesopic microperimetry in the study eye, fellow eye, and both eyes combined.

Objectives	Endpoints
• 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 subpopulation

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; 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

Overall Design:

This is a multicenter Phase 2, randomized, double-masked, placebo-controlled, dose-finding, parallel-group study to evaluate the efficacy, safety, and PK of danicopan compared to placebo in patients ≥ 60 years with GA secondary to AMD. Eligible patients will be randomized (1:1:1:1) with stratification to 1 of 4 treatment groups (3 active treatment groups and 1 placebo group). The primary efficacy analysis will be performed when all patients complete the Week 52 Visit or discontinued. Secondary efficacy and safety analyses, and exploratory analyses will be performed when all patients complete the Week 104 Visit or discontinue.

There are 2 potential interim analyses (IA) planned for this study. The first interim analysis (IA1) for futility may be conducted when approximately 50% patients have completed the Week 28 Visit. The second interim analysis (IA2) may be conducted when approximately 50% of patients complete Week 52 Visit. 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 of each dose compared to placebo will be conducted.

A dose with the optimal benefit-risk profile could be identified at the IA2 or primary analysis for Phase 3 development. Placebo patients will be re-randomized to one of the 3 active treatment groups at Week 52, or switched to the optimal dose, if already identified. If an optimal dose is identified, all patients who have at least 52 weeks of treatment on their originally assigned dose will be switched to the selected optimal dose for the remainder of the study. Masked treatment paradigm will be maintained throughout the study.

Disclosure Statement: This is a Phase 2, placebo-controlled, double-masked, parallel-treatment study.

Number of Patients: Approximately 332 patients aged ≥ 60 years will be enrolled, with 83 patients per dose group.

Intervention Groups and Duration:

This study has 4 treatments arms: 100 mg twice daily (bid) dose group, 200 mg bid dose group, 400 mg once daily (qd) dose group, and a placebo group. 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.

Data Monitoring Committee: Yes

Ethical Considerations and Benefit-Risk Assessment

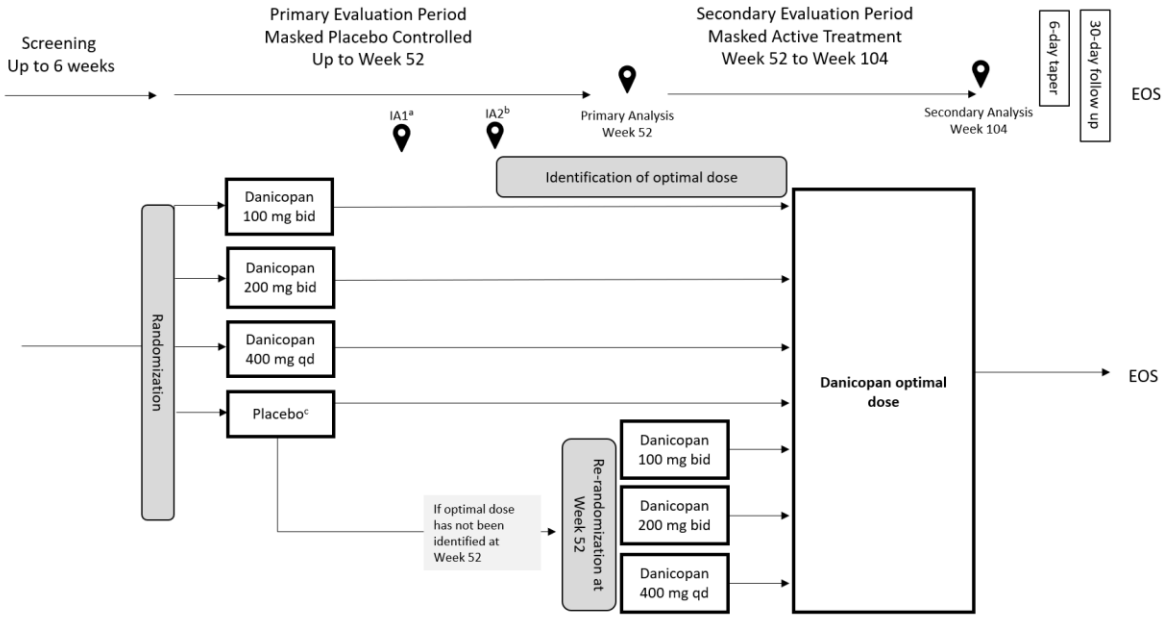
This study will be conducted as specified in this protocol and in accordance with the following:

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

A thorough benefit-risk assessment has been performed for danicopan. Measures will be taken to minimize risk to study participants. The potential risks identified in association with danicopan are justified by the anticipated benefits that may be afforded to participants with GA secondary to AMD.

1.2. Study Schema

Figure 1: Study Design and Schematic



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

1.3. Schedule of Activities

Table 1: Schedule of Activities for Screening and the Primary Evaluation Period (Up to Week 52)

Procedure	Screening	Primary Evaluation Period (Masked Treatment)								Notes
Visit	**Up to 6 weeks**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	X = in-clinic visit; HV = home visit by VHS; HV may be turned into in-clinic visit per agreement between patient and site but following the same HV assessments.
Weeks	**-6 to 0**		**2**	**4**	**8**	**16**	**28**	**40**	**52**	
Days and Window	**-42 to -1**	**1**	**15 ± 2**	**29 ± 4**	**57 ± 4**	**113 ± 4**	**197 ± 4**	**281 ± 4**	**365 ± 4**	
Visit Type	**X**	**X**	**HV**	**X**	**X**	**X**	**X**	**X**	**X**	
Informed consent	X									To be obtained before any study-related procedures are performed
Inclusion and exclusion criteria	X	X								Eligibility to be confirmed prior to randomization. See Section 5
Randomization		X								
Demography	X									
Full PE including height and weight	X	X			X				X	Height only required at Screening
Abbreviated PE				X		X	X	X		Abbreviated PE = a targeted PE that includes, at a minimum, body system relevant examination based on Investigator judgement and patient symptoms
Vital signs	X	X	X	X	X	X	X	X	X	
Medical history	X									
Prior and current medications	X	X								
FSH for females	X									
Screening tests for HIV, HBV, HCV	X									

Table 1: Schedule of Activities for Screening and the Primary Evaluation Period (Up to Week 52)

Procedure	Screening	Primary Evaluation Period (Masked Treatment)								Notes
Visit	**Up to 6 weeks**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	X = in-clinic visit; HV = home visit by VHS; HV may be turned into in-clinic visit per agreement between patient and site but following the same HV assessments.
Weeks	**-6 to 0**		**2**	**4**	**8**	**16**	**28**	**40**	**52**	
Days and Window	**-42 to -1**	**1**	**15 ± 2**	**29 ± 4**	**57 ± 4**	**113 ± 4**	**197 ± 4**	**281 ± 4**	**365 ± 4**	
Visit Type	**X**	**X**	**HV**	**X**	**X**	**X**	**X**	**X**	**X**	
Vaccination or confirmation of vaccination against *Neisseria meningitidis*	X	< ----------continuous monitoring ----------								See Section 6.5.1.1
Laboratory assessments (including chemistry, hematology, urinalysis, and LFTs)	X	X	X	X	X	X	X	X	X	VHS will collect blood samples at HV.
PK		X		X		X	X	X	X	PK samples will be collected predose, and 2 h postdose for all visits except for Week 4. For Week 4, PK samples should be collected on predose, 2 h, and 4 h post dose.
PD (Bb and AP activity)		X		X		X	X	X	X	AP activity samples will be collected at the same time points as PK samples; Bb samples will be collected at predose; at ET; Bb and AP activity samples will be collected once.
Biomarkers		X		X		X	X	X	X	Biomarkers will be collected predose and also once at ET
Genetic samples (optional)		X								
12-lead ECG		X							X	Single tracing
Drug dispensing		X		X	X	X	X	X	X	At each clinic visit, site should ensure patient has sufficient study drug till their next clinic visit

Table 1: Schedule of Activities for Screening and the Primary Evaluation Period (Up to Week 52)

Procedure	Screening	Primary Evaluation Period (Masked Treatment)								Notes
Visit	**Up to 6 weeks**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	X = in-clinic visit; HV = home visit by VHS; HV may be turned into in-clinic visit per agreement between patient and site but following the same HV assessments.
Weeks	**-6 to 0**		**2**	**4**	**8**	**16**	**28**	**40**	**52**	
Days and Window	**-42 to -1**	**1**	**15 ± 2**	**29 ± 4**	**57 ± 4**	**113 ± 4**	**197 ± 4**	**281 ± 4**	**365 ± 4**	
Visit Type	**X**	**X**	**HV**	**X**	**X**	**X**	**X**	**X**	**X**	
Drug accountability			X	X	X	X	X	X	X	Patients are instructed to bring their study drugs at each clinic visit
AE/SAE monitoring	< ---------- continuous monitoring ---------- >									Continuous monitoring of AE/SAEs (including pregnancy in female partners of male patients) starts at time of signing the ICF and continues until EOS
Medication error, drug abuse and misuse	< ---------- continuous monitoring ---------- >									See Section 8.4.5 and Section 10.7. Monitoring started with PA 2.0
Concomitant medications monitoring	< ---------- continuous monitoring ---------- >									Continuous monitoring (reporting of concomitant medications) starts at time of signing the ICF and continues until EOS
Review patient safety card	< ---------- continuous monitoring ---------- >									Patients to carry card at all times
PATIENT-REPORTED OUTCOMES										All PROs and QoL assessments should be completed as early as possible during visits, before ocular assessments
NEI VFQ-25		X			X		X	X	X	
EQ-5D-5L		X			X		X	X	X	
Lawton IADL		X			X		X	X	X	

Table 1: Schedule of Activities for Screening and the Primary Evaluation Period (Up to Week 52)

Procedure	Screening	Primary Evaluation Period (Masked Treatment)								Notes
Visit	**Up to 6 weeks**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	X = in-clinic visit; HV = home visit by VHS; HV may be turned into in-clinic visit per agreement between patient and site but following the same HV assessments.
Weeks	**-6 to 0**		**2**	**4**	**8**	**16**	**28**	**40**	**52**	
Days and Window	**-42 to -1**	**1**	**15 ± 2**	**29 ± 4**	**57 ± 4**	**113 ± 4**	**197 ± 4**	**281 ± 4**	**365 ± 4**	
Visit Type	**X**	**X**	**HV**	**X**	**X**	**X**	**X**	**X**	**X**	
OCULAR ASSESSMENTS										Ocular assessments are to be performed on both eyes (OU); tests that do not need pupil dilation should be done first
BCVA testing on ETDRS chart (starting at 4 m)	X	X			X	X	X	X	X	Non-dilated, to be administered first monocularly (right/left eye) and then binocularly (both eyes).
LL BCVA testing on ETDRS chart (starting at 4 m)		X					X		X	Non-dilated, to be administered first monocularly (right/left eye) and then binocularly (both eyes).
Reading Speed (MNRead or Radner Reading Charts)[a]		X					X		X	Non-dilated, to be administered first monocularly (right/left eye) and then binocularly (both eyes).
Mesopic microperimetry[b]	X[c]						X		X	Non-dilated, only in microperimetry subpopulation
Slit lamp examination	X	X			X	X	X	X	X	
Tonometry/IOP	X	X			X	X	X	X	X	Goldmann applanation tonometry must be used at Screening. Tono-pen or other calibrated tonometers can be used at other times. IOP measurement recommended prior to dilation. Goldmann applanation tonometry must also be used to verify the reading of ≥ 30 mmHg occurring at any time.

Table 1: Schedule of Activities for Screening and the Primary Evaluation Period (Up to Week 52)

Procedure	Screening	Primary Evaluation Period (Masked Treatment)								Notes
Visit	**Up to 6 weeks**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	X = in-clinic visit; HV = home visit by VHS; HV may be turned into in-clinic visit per agreement between patient and site but following the same HV assessments.
Weeks	**-6 to 0**		**2**	**4**	**8**	**16**	**28**	**40**	**52**	
Days and Window	**-42 to -1**	**1**	**15 ± 2**	**29 ± 4**	**57 ± 4**	**113 ± 4**	**197 ± 4**	**281 ± 4**	**365 ± 4**	
Visit Type	**X**	**X**	**HV**	**X**	**X**	**X**	**X**	**X**	**X**	
Dilated binocular indirect ophthalmoscopy	X	X			X	X	X	X	X	
FAF	X	X			X	X	X	X	X	Recommended order of imaging is FAF, NIR, SD-OCT, FA, CFP. Administration of artificial tears between acquisition of each eye for FAF/NIR and SD-OCT is recommended.
NIR	X	X			X	X	X	X	X	
SD-OCT	X	X			X	X	X	X	X	
Fluorescein angiography	X						X		X	
CFP	X						X		X	
Biometry (if available)[d]	X									

[a] Reading speeds will only be assessed if charts are available in the local language.
[b] Microperimetry should be performed prior to any imaging.
[c] Microperimetry should be carried out twice per eye during Screening.
[d] Biometry should be performed if the site has the equipment; otherwise, spherical equivalent refractive error should be determined.

Abbreviations: AE = adverse event; AP = alternative pathway; Bb = Bb fragment of complement factor B; BCVA = best-corrected visual acuity; CFP = color fundus photography; ECG = electrocardiogram; ETDRS = Early Treatment Diabetic Retinopathy Study; EOS = end of study; EQ-5D -5L = EuroQol 5-dimension 5-level questionnaire; ET = early termination; FA = fluorescein angiography; FAF = fundus autofluorescence; FSH = follicle stimulating hormone; h = hour; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HV = home visit; IADL = Instrumental Activities of Daily Living; ICF = informed consent form; IOP = intraocular pressure; LFT = liver function test; LL BCVA= low luminance best-corrected visual acuity; MNRead = Minnesota Low-Vision Reading Test; NEI VFQ-25 = National Eye Institute Visual Function Questionnaire, 25-item version; NIR = near infrared reflectance; OU = oculus uterque/both eyes; PA = protocol amendment; PD = pharmacodynamic; PE = physical examination; PK = pharmacokinetics; PRO = patient-reported outcome; QoL = quality of life; SAE = serious adverse event; SD-OCT = spectral domain optical coherence tomography; VHS = visiting health service

Table 2: Schedule of Activities for the Secondary Evaluation Period (Week 52 to Week 104) and Optimal Dose Transition

Procedure	Secondary Evaluation Period (Masked Treatment) Weeks 52 to 104							Optimal Dose Transition[a] After Week 52				Notes
Visit	**9**	**10**	**11**	**12**	**13**	**14**	**15**					X = in-clinic visit; HV = home visit by VHS HV may be turned into in-clinic visit per agreement between patient and site but following the same HV assessments.
Weeks	**54**	**56**	**60**	**68**	**80**	**92**	**104**	**Optimal Dose**	**+2**	**+4**	**+8**	
Days and Window	**379 ±2**	**393 ±4**	**421 ±4**	**477±4**	**561±4**	**645±4**	**729 ±4**		**±2**	**±4**	**±4**	
Visit Type	**HV**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**HV**	**X**	**X**	
Full PE including weight		X	X					X		X	X	
Abbreviated PE				X	X	X						Abbreviated PE = a targeted PE that includes, at a minimum, body system relevant examination based on Investigator judgement and patient symptoms.
Vital signs		X	X	X	X	X		X		X	X	
N meningitidis vaccination status assessment/ vaccination, if needed	< ----------continuous monitoring ---------- >							< -continuous monitoring- >				See Section 6.5.1.1
Laboratory assessments (including chemistry, hematology, urinalysis, and LFTs)	X	X	X	X	X	X	X	X	X	X	X	VHS will collect blood samples at HV.
12-lead ECG							X					
Drug dispensing		X	X	X	X	X	X					At each clinic visit, site should ensure patient has sufficient study drug till their next clinic visit
Drug accountability		X	X	X	X	X	X	X		X	X	Patients are instructed to bring their study drugs at each clinic visit

Table 2: Schedule of Activities for the Secondary Evaluation Period (Week 52 to Week 104) and Optimal Dose Transition

Procedure	Secondary Evaluation Period (Masked Treatment) Weeks 52 to 104							Optimal Dose Transition[a] After Week 52				Notes
Visit	**9**	**10**	**11**	**12**	**13**	**14**	**15**					X = in-clinic visit; HV = home visit by VHS HV may be turned into in-clinic visit per agreement between patient and site but following the same HV assessments.
Weeks	**54**	**56**	**60**	**68**	**80**	**92**	**104**	**Optimal Dose**	**+2**	**+4**	**+8**	
Days and Window	**379 ±2**	**393 ±4**	**421 ±4**	**477±4**	**561±4**	**645±4**	**729 ±4**		**±2**	**±4**	**±4**	
Visit Type	**HV**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**HV**	**X**	**X**	
AE/SAE monitoring	< ----------continuous monitoring ---------- >							< -continuous monitoring- >				
Concomitant medications monitoring	< ----------continuous monitoring ---------- >							< -continuous monitoring- >				
Medication error, drug abuse and misuse	< ----------continuous monitoring ---------- >							< -continuous monitoring- >				See Section 8.4.5 and Section 10.7; Monitoring started with PA 2.0
Review patient safety card	< ----------continuous monitoring ---------- >							< -continuous monitoring- >				Patients to carry card at all times
PATIENT REPORTED OUTCOMES												All PROs and QoL assessments should be completed as early as possible during visits, before ocular assessments
NEI VFQ-25			X		X		X					
EQ-5D-5L			X		X		X					
Lawton IADL			X		X		X					
OCULAR ASSESSMENTS												Ocular assessments are to be performed on both eyes (OU); tests that do not need pupil dilation should be done first
BCVA testing on ETDRS chart'(starting at 4 m)			X	X	X	X	X					Non-dilated, the test will be administered first monocularly (right/left eye) and then binocularly (both eyes).

Table 2: Schedule of Activities for the Secondary Evaluation Period (Week 52 to Week 104) and Optimal Dose Transition

Procedure	Secondary Evaluation Period (Masked Treatment) Weeks 52 to 104							Optimal Dose Transition[a] After Week 52				Notes
Visit	**9**	**10**	**11**	**12**	**13**	**14**	**15**					X = in-clinic visit; HV = home visit by VHS HV may be turned into in-clinic visit per agreement between patient and site but following the same HV assessments.
Weeks	**54**	**56**	**60**	**68**	**80**	**92**	**104**	**Optimal Dose**	**+2**	**+4**	**+8**	
Days and Window	**379 ±2**	**393 ±4**	**421 ±4**	**477±4**	**561±4**	**645±4**	**729 ±4**		**±2**	**±4**	**±4**	
Visit Type	**HV**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**HV**	**X**	**X**	
LL BCVA testing on ETDRS chart'(starting at 4 m)							X					Non-dilated, the test will be administered first monocularly (right/left eye) and then binocularly (both eyes).
Reading Speed (MNRead or Radner Reading Charts)[b]							X					Non-dilated, the test will be administered first monocularly (right/left eye) and then binocularly (both eyes).
Mesopic microperimetry[c]							X					Non-dilated, only in microperimetry subpopulation
Slit lamp examination			X	X	X	X	X					
Dilated binocular indirect ophthalmoscopy			X	X	X	X	X					
Tonometry/IOP			X	X	X	X	X					Tono-pen or other calibrated tonometers can be used. IOP measurement recommended prior to dilation. Goldmann applanation tonometry must also be used to verify the reading of ≥ 30 mmHg occurring at any time.
FAF			X	X	X	X	X					Recommended order of imaging is FAF, NIR, SD-OCT,
NIR			X	X	X	X	X					

Table 2: Schedule of Activities for the Secondary Evaluation Period (Week 52 to Week 104) and Optimal Dose Transition

Procedure	Secondary Evaluation Period (Masked Treatment) Weeks 52 to 104							Optimal Dose Transition[a] After Week 52				Notes
Visit	**9**	**10**	**11**	**12**	**13**	**14**	**15**					X = in-clinic visit; HV = home visit by VHS HV may be turned into in-clinic visit per agreement between patient and site but following the same HV assessments.
Weeks	**54**	**56**	**60**	**68**	**80**	**92**	**104**	**Optimal Dose**	**+2**	**+4**	**+8**	
Days and Window	**379 ±2**	**393 ±4**	**421 ±4**	**477±4**	**561±4**	**645±4**	**729 ±4**		**±2**	**±4**	**±4**	
Visit Type	**HV**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**HV**	**X**	**X**	
SD-OCT			X	X	X	X	X					fluorescein angiography, CFP. Administration of artificial tears between acquisition of each eye for FAF/NIR and SD-OCT is recommended.
Fluorescein angiography							X					
CFP							X					

[a] If optimal dose is identified, all patients who have completed Week 52 will start the transition to the optimal dose at the next scheduled visit. See Section 6.6.1.
[b] Reading speeds will only be assessed if charts are available in the local language.
[c] Microperimetry should be performed prior to any imaging.

Abbreviations: AE = adverse event; BCVA = best-corrected visual acuity; CFP = color fundus photography; ECG = electrocardiogram; ETDRS = Early Treatment Diabetic Retinopathy Study; EQ-5D-5L = EuroQol 5-dimension 5-level questionnaire; FAF = fundus autofluorescence; h = hours; HV = home visit; IADL= Instrumental Activities of Daily Living; IOP = intraocular pressure; LFT = liver function test; LL BCVA= low luminance best-corrected visual acuity; MNRead = Minnesota Low-Vision Reading Test; NEI VFQ-25 = National Eye Institute Visual Function Questionnaire, 25-item version; NIR = near infrared reflectance; PA = protocol amendment; PE = physical examination; OU = oculus uterque/both eyes; PRO = patient reported outcome; QoL = quality of life; SAE = serious adverse event; SD-OCT = spectral domain optical coherence tomography; VHS = visiting health service

Table 3: Schedule of Activities for Early Termination, Taper, and Follow-up

	Un-scheduled Visit[a]	Early Termination	Taper 6 days[b]		Follow-up (EOS) 30 days	Notes
Visit			**T1**	**T2**		X = in-clinic visit; HV = home visit by VHS; HV may be turned into in-clinic visit per agreement between patient and site but following the same HV assessments.
Weeks						
Days and Window			**D1 to D3**	**D4 to D6**	**30 +7 post last dose**	
Visit Type	**X**	**X**	**HV**	**HV**	**X**	
Full physical examination including weight	X	X			X	
Abbreviated PE						Abbreviated PE = a targeted PE that includes, at a minimum, body system relevant examination based on Investigator judgement and patient symptoms
Vital signs	X	X			X	
N meningitidis vaccination status assessment/ vaccination, if needed	X	X	X	X		See Section 6.5.1.1
Laboratory assessments (including chemistry, hematology, urinalysis, and LFTs)	X	X			X	VHS will collect blood samples at HV.
PD (Bb and AP activity)		X				ET samples for PD and biomarkers only applicable for the first 52 weeks. No samples after Week 52.
Biomarkers		X				
12-lead ECG		X			X	Single tracing.
Drug dispensing		X[b]				Patients are provided with sufficient study drug to last until their next clinic visit.
Drug accountability		X	X	X	X	Patients are instructed to bring their study drugs at each visit.
AE/SAE review	X	X	X	X	X	

Table 3: Schedule of Activities for Early Termination, Taper, and Follow-up

	Un-scheduled Visit[a]	Early Termination	Taper 6 days[b]		Follow-up (EOS) 30 days	Notes
Visit			**T1**	**T2**		X = in-clinic visit; HV = home visit by VHS; HV may be turned into in-clinic visit per agreement between patient and site but following the same HV assessments.
Weeks						
Days and Window			**D1 to D3**	**D4 to D6**	**30 +7 post last dose**	
Visit Type	**X**	**X**	**HV**	**HV**	**X**	
Medication error, drug abuse and misuse	X	X	X	X	X	See Section 8.4.5 and Section 10.7; Monitoring started with PA 2.0
Concomitant medications review	X	X	X	X	X	
Review patient safety card	X	X	X	X	X	Patients to carry card at all times.
PATIENT REPORTED OUTCOMES						All PROs and QoL assessments should be completed as early as possible during visits.
NEI VFQ-25		X				
EQ-5D-5L		X				
Lawton IADL		X				
OCULAR ASSESSMENTS						Ocular assessments are to be performed on both eyes (OU); tests that do not need pupil dilation should be done first.
BCVA testing on ETDRS chart (starting at 4 m)	X	X				Non-dilated, the test will be administered first monocularly (right/left eye) and then binocularly (both eyes).
LL BCVA testing on ETDRS chart (starting at 4 m)		X				Non-dilated, the test will be administered first monocularly (right/left eye) and then binocularly (both eyes).

Table 3: Schedule of Activities for Early Termination, Taper, and Follow-up

	Un-scheduled Visit[a]	Early Termination	Taper 6 days[b]		Follow-up (EOS) 30 days	Notes
Visit			**T1**	**T2**		X = in-clinic visit; HV = home visit by VHS; HV may be turned into in-clinic visit per agreement between patient and site but following the same HV assessments.
Weeks						
Days and Window			**D1 to D3**	**D4 to D6**	**30 +7 post last dose**	
Visit Type	**X**	**X**	**HV**	**HV**	**X**	
Reading Speed (MNRead or Radner Reading Charts)[c]		X				Non-dilated, the test will be administered first monocularly (right/left eye) and then binocularly (both eyes).
Mesopic microperimetry[d]		X				Non-dilated; only in microperimetry subpopulation.
Slit lamp examination	X	X				
Dilated binocular indirect ophthalmoscopy	X	X				
Tonometry/IOP	X	X				Tono-pen or other calibrated tonometers can be used. IOP measurement recommended prior to dilation. Goldmann applanation tonometry must also be used to verify the reading of ≥ 30 mmHg occurring at any time.
FAF	X	X				Recommended order of imaging is FAF, NIR, SD-OCT, fluorescein angiography, CFP. Administration of artificial tears between acquisition of each eye for FAF/NIR and SD-OCT is recommended.
NIR	X	X				
SD-OCT	X	X				
Fluorescein angiography		X				
CFP	X	X				

[a] Unscheduled visits for safety and worsening of vision; indicated and additional assessments may be performed if deemed necessary by the Investigator
[b] Tapering will be masked; masked blister packs will be provided to patients possibly at ET, Week 104, or unscheduled visit. See Table 9.
[c] Reading speeds will only be assessed if charts are available in the local language.
[d] Microperimetry should be performed prior to any imaging.

Table 3: Schedule of Activities for Early Termination, Taper, and Follow-up

Abbreviations: AE = adverse event; AP = alternative pathway; Bb = Bb fragment of complement factor B; BCVA = best-corrected visual acuity; CFP = color fundus photography; D = Day; ECG = electrocardiogram; ETDRS = Early Treatment Diabetic Retinopathy Study; EOS = end of study; EQ-5D-5L = EuroQol 5-dimension 5-level questionnaire; ET = early termination; FAF = fundus autofluorescence; IADL= Instrumental Activities of Daily Living; IOP = intraocular pressure; LFT = liver function test; LL BCVA= low luminance best-corrected visual acuity; MNRead = Minnesota Low-Vision Reading Test; NEI VFQ-25 = National Eye Institute Visual Function Questionnaire, 25-item version; NIR = near infrared reflectance; OU = oculus uterque/both eyes; PA = protocol amendment; PE = physical examination; QoL = quality of life; SAE = serious adverse event; SD-OCT = spectral domain optical coherence tomography; VHS = visiting health service

Table 4: Pharmacokinetic and Pharmacodynamic Blood Sampling During the Primary Evaluation Period (Up to Week 52)

	BL		Week 4			Week 16, 28, 40, 52		ET
Time After Dosing (Hour ± 10 min)	**Predose[a]**	**2h**	**Predose[a]**	**2h**	**4h**	**Predose[a]**	**2h**	
PK plasma samples[b]	X	X	X	X	X	X	X	
PD: AP activity[c]	X	X	X	X	X	X	X	X
PD: Bb concentration[c]	X		X			X		X
Plasma/serum samples for additional non-genetic biomarker testing[c]	X		X			X		X

[a] Predose samples: Patients should be instructed to take their dose onsite, with a snack or meal. The time when the previous 2 doses were taken (12 and 24 hours prior to blood draw) should be recorded.
[b] PK samples will be drawn predose and postdose.
[c] AP activity samples will be collected at the same time as the PK samples and once at ET. Bb and biomarkers will be collected predose and also once at ET.
Abbreviations: AP = alternative pathway; Bb = Bb fragment of complement factor B; bid = twice daily; BL = Baseline; ET = early termination; h = hour; min = minutes; PD = pharmacodynamic(s); PK = pharmacokinetic(s); qd = once daily.

2. INTRODUCTION

Age-related macular degeneration is a leading cause of blindness in the developed world by causing 2 advanced forms of disease: 1) neovascular age related macular degeneration (nAMD; wet form), and 2) GA (dry form). Both advanced forms of AMD are preceded by a decades-long process of retinal degeneration beginning at the boundary (Bruch's membrane) between the vascular-rich choroid and the photoreceptor-supporting retinal pigment epithelium (RPE). This results in the development of retinal and subretinal pigment epithelial deposits of protein /lipid /inflammatory products known as drusen. Some as yet undetermined trigger predisposes disease progression to either an initial nAMD path or a GA path, but neither are mutually exclusive, as it is possible for both to occur in 1 eye, or even for the drusen to resolve without sequelae (Danis, 2015). The development of nAMD results in structural alterations, exudation, hemorrhage, disciform scarring, and disruption of the photoreceptors leading to loss of vision. If untreated, this can result in legal blindness within 12 months (Guyer, 1986; Wong, 2008). The development of GA is heralded by the loss of RPE which progresses in an ever-expanding radius to eventually encompass the center of the macula (eg, the fovea), resulting in photoreceptor loss, central scotoma, legal blindness, and significant reduction of independence and quality of life (QoL) (Nielsen, 2020).

Approximately 8.7% of the world population between age 30 to 97 years old has some stage of AMD (Wong, 2014), with a projected increase of ~50% from 2020 to 2040, to affect up to 288 million people (Leng, 2023). Disease risk is multifactorial, with age, genetics, environment, behavior, diet, and lifestyle all implicated in development and progression of the disease. Epidemiology shows a substantial increase in AMD risk with advanced age. In the US, the prevalence of nAMD in individuals 65 to 69 years is 0.63% and increases to 8.18% in individuals 80 years and older. Estimated GA prevalence is 0.48% in the 65 to 69 age group, and 6.89% in those aged over 80 years (Friedman, 2004).

2.1. Study Rationale

This proof of concept (POC) dose-finding study is designed to evaluate the efficacy, safety, and PK of danicopan in the treatment of patients with GA secondary to AMD.

2.1.1. Unmet Medical Need

Multiple agents with different mechanism of actions, including neuroprotectors, immunomodulators, anti-inflammatory agents, and complement inhibitors have been investigated or are under clinical investigation for the treatment of GA (Nebbioso, 2019; Sastre-Ibáñez, 2018).

As of 17 Feb 2023, pegcetacoplan intravitreal injection has been approved in the US for treatment of GA secondary to AMD. Modest efficacy of pegcetacoplan observed in the OAKS and DERBY trials was accompanied with increased risk of conversion to neovascular AMD compared to sham injection (Singh, 2023). Frequent intravitreal injections come with high patient burden. There is a high unmet clinical need for treatments with less invasive and burdensome mode of administration.

2.1.2. Complement Dysregulation in AMD

The complement pathway of immune regulation consists of 3 parallel arms: the classical pathway (CP), the lectin pathway, and the alternative pathway (AP). Unlike the other two pathways, the AP is continuously activated to surveil for pathogens for prompt elimination. To prevent damage to the surrounding normal host tissues during activation, AP is tightly controlled by various complement regulatory proteins. Otherwise, the products formed during the activation, such as complement component 3 (C3) fragments, complement component 5a, and membrane attack complex, will cause host tissue damage by inducing phagocytosis, inflammation, and cell lysis. In fact, dysregulation of AP has been implicated in the pathogenesis of AMD. In 2005, multiple genetic studies showed that complement factor H (FH; a key regulator in AP) polymorphism has been associated with AMD (Edwards, 2005; Hageman, 2005; Haines, 2005; Klein, 2005). Later studies have confirmed the dysregulation of the complement system, particularly the AP, in the pathogenesis of AMD (Lynch, 2019; McHarg, 2015; Merle, 2015; Merle, 2015b; Scholl, 2008; Yates, 2007). Recently, another large AMD genetics study (Fritsche, 2013) using a meta-analysis of 17,000 AMD cases and more than 60,000 control identified multiple genetic risk loci, including complement factors H, B and I and C3 provided additional evidence of the role of dysregulation of AP in the development of AMD. Factor D (FD) is an essential molecule required for AP activation. By inhibiting FD, we hypothesize that the tissue damage precipitated by AP dysregulation can be prevented, positioning FD inhibition strategy as a potential therapeutic strategy for the treatment of GA secondary to AMD.

2.1.3. Danicopan

Danicopan (ALXN2040, formerly ACH-0144471) is an oral small molecule inhibitor of FD being developed for AP - mediated diseases. Danicopan was shown to be safe and efficacious as add-on treatment in patients with paroxysmal nocturnal hemoglobinuria (PNH) concurrently receiving background complement component 5 (C5) inhibitors.

Danicopan binds reversibly to FD with high affinity (K_D = 0.44 nM) and demonstrates potent inhibition of AP activity under both in vitro and in vivo conditions. Danicopan can also bind reversibly to melanin but with ~ 20,000-fold lower affinity (K_D = 8.56 µM, the mean value of K_D determined with synthetic melanin and melanin from *Sepia officinalis*), leading to the observation of selective retention and accumulation of danicopan in ocular melanin-containing tissues of rats and rabbits including RPE and choroid, 2 tissues of critical importance in the development of GA.

Additionally, based on data from rabbit studies, danicopan is able to pass the blood-retina barrier, distributing to the retinal tissue following oral dosing. This has 2 potential advantages: 1) oral administration results in selective retention of danicopan in ocular tissues containing melanin (eg, choroid and RPE) as well as delivery to the retina, 2) systemic administration effectively targets both eyes.

Danicopan inhibition of FD represents an opportunity to interrupt the complement cascade and, thus, prevent progression and vision loss.

A description of the properties, toxicology, pharmacology, efficacy, and safety of danicopan is provided in the Investigator's Brochure (IB) and Investigational Medicinal Product Dossier.

2.2. Benefit/Risk Assessment

2.2.1. Risk Assessment

Based on clinical trial experience and cumulative clinical trial safety data of danicopan at doses with similar systemic exposures, danicopan has been demonstrated to be well tolerated and safe. Treatment with danicopan in humans has not raised any unexpected safety concerns.

There are 2 risks closely monitored in clinical trials: liver enzyme elevations and *Neisseria meningitidis* infection.

Table 5: Potential and Identified Risks and Mitigation Strategies

Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Meningococcal infections (potential risk)	Patients receiving Factor D complement inhibitor therapy may have increased risk of infections, particularly *N meningitidis*.	Patients must be vaccinated or revaccinated against meningococcal infections as described in this protocol. Patients should be monitored for early signs of meningococcal infection and treated with appropriate antibiotics, if necessary. Patients must carry the Patient Safety Card at all time for quick disclosure of any potential signs or symptoms of infection. See Section 2.2.1.1 and Section 6.5.1.1 for more information on vaccinations.
Liver enzyme elevations (identified risk)	Hepatobiliary cholestasis was seen in dog toxicology studies and was characterized by icterus, elevated AST, ALT, ALP, GGT, and TBIL (primarily direct bilirubin), with histological findings. Dose limiting toxicity of transient and self-limiting liver enzyme elevation was observed in healthy volunteer study at doses of 500 mg bid and 800 mg bid. Based on the PNH program, elevations in liver enzymes are considered as an identified risk. The majority of these cases were transient and nonserious. All participants were asymptomatic without any significant clinical consequence.	Exclusion of patients with abnormal liver function tests as specified in the exclusion criteria in Section 5.2.2. Liver function tests are routinely performed to monitor for potential cases of drug-induced liver toxicity. Strict stopping criteria are included ensuring prompt discontinuation of any patient with evidence of liver enzyme elevation. See Section 2.2.1.2.

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; bid = twice daily; GGT = gamma-glutamyl transferase; PNH = paroxysmal nocturnal hemoglobinuria; TBIL = total bilirubin

2.2.1.1. Potential Risk of Meningococcal Infection

Since a primary function of the complement system is to fight infections, pharmacologic inhibition of the complement system could theoretically result in an increased rate or severity of infections. As suggested by individual case reports with complement system deficiencies, including FD, inhibition of the complement system may result in a lifetime increased risk of infection, notably with *N meningitidis* (Biesma, 2001; Granoff, 2019; Hiemstra, 1989; Sprong, 2006; van den Broek, 2019).

Patients receiving terminal complement inhibitor therapy such as C5 inhibitor, in general, have increased susceptibility to *N meningitidis* (Socié, 2019). FD inhibition does not affect the CP and does not completely inhibit the terminal portion of the complement system. FD inhibition appears to have little impact on bactericidal and opsonophagocytic activity in vaccinated individuals (Granoff, 2019; Konar, 2017; van den Broek, 2019).

To increase risk awareness and promote quick disclosure of any potential signs or symptoms of infection experienced by the patients during the course of the study, patients will be provided a Patient Safety Card as described in Section 8.3.6.

2.2.1.2. Identified Risk of Liver Enzyme Elevations

In dog toxicology studies, hepatobiliary cholestasis has been observed at systemic exposures higher than those intended for clinical use. This effect was reversible and could be monitored with hepatic safety biomarkers.

In human healthy volunteers, elevations in alanine aminotransferase (ALT) and aspartate amino transferase (AST) with no increase in bilirubin levels have been observed in 2 subjects in the multiple ascending dose study (MAD; ACH471-002) with the high doses of 500 mg bid and 800 mg bid for 14 days.

Based on results in the PNH program, elevations in liver enzymes are considered as an identified risk. The majority of cases were transient and nonserious. All participants were asymptomatic without any significant clinical consequence.

These elevations were not associated with signs or symptoms of hepatic failure, occurred several days after completion of dosing, and were self-limiting. A dose taper was instituted in subsequent studies as a risk mitigation measure. See Section 6.1.2 for details on dose tapering.

Exclusion of patients with abnormal liver function tests are clearly specified in Section 5.2.2. Rigorous stopping criteria are included ensuring prompt discontinuation of any patient with evidence of liver enzyme elevation (see Section 7).

A detailed description of the potential and identified risks of danicopan is provided in the IB.

2.2.1.3. Coronavirus Disease 2019

The coronavirus disease 2019 (COVID-19) pandemic is active in many countries at the time of this original protocol. Given this unique circumstance, specific consideration has been given to the risks and benefits of the study as they relate to COVID-19, and the global and local changes that exist as a result of the pandemic. This assessment is described in Section 10.11. Risk assessment for COVID-19 vaccination is described in Section 10.12.

2.2.2. Benefit Assessment

2.2.2.1. Unmet Need

Age-related macular degeneration is a leading cause of blindness in the developed world and GA as the late form of AMD has a significant impact on patient's QoL. In the early stages of GA without foveal involvement, patients typically show minimal changes in central visual acuity (VA). However, patients often still experience significant symptoms from visual dysfunction, such as dense parafoveal scotomas (eg, leading to difficulties with face recognition), difficulty driving, delayed dark adaptation, reduced contrast sensitivity, and decreased reading speed (Heier, 2020; Sunness, 1996; Sunness, 1999a; Sunness, 1995). In the later stages, as the GA lesion expands into the fovea, a profound decrease in central VA occurs with a decline in activities of daily living (Heier, 2020; Lindblad, 2005). GA is bilateral in most patients with advanced AMD (Lindblad, 2009; Sunness, 1999b).

Based on data from pegcetacoplan (a C3 inhibitor) and avacincaptad pegol (a C5 inhibitor) studies (Jaffe, 2020; Liao, 2020; Nebbioso, 2019), complement modulation strategies have demonstrated a signal for the ability to slow the growth of GA. Both treatments are administered as frequent intravitreal injections, presenting a significant patient burden. There exists a need for GA treatments that are less invasive and burdensome.

Danicopan has been shown to be an efficacious inhibitor of FD in studies on paroxysmal nocturnal hemoglobinuria. This efficacy, alongside the specific affinity for melanin-containing tissues and the ability to cross the blood retina barrier, makes danicopan a logical candidate for the treatment of GA. The potential benefit of danicopan for treatment of GA, if demonstrated to be efficacious, is slowing or halting the disease progression or conversion from early to late stage at which irreversible anatomical and functional loss happens.

2.2.2.2. Route of Administration

Danicopan as an oral FD inhibitor has potential benefits over intravitreal injections (eg, C3 and C5 inhibitors), including

- Potential improvement in treatment adherence, especially among patients with fear of injections
- Reduction of patient and caregiver burden for avoiding frequent clinic visit for treatments ie, intravitreal injection.
- Potential minimization of the risk of ocular injection-related adverse events (AEs).
- Oral administration of danicopan in patients with GA will result in systemic exposure and enable concurrent treatment of both eyes, which is a significant benefit for patients with GA since most patients have both eyes involved.
- Relative to the previous systemic administration of C5 inhibitors, danicopan offers the advantage of localization and retention at the target tissues.
- Oral administration of danicopan may have the potential benefit of allowing the opportunity of the intervention at the early stage of the disease in which patients may not have noticeable VA change, to potentially reduce the risk of disease progression to late

stage, whereas therapies using intravitreal injection may be difficult to be accepted by GA patients at the early stage with no visual symptoms.

2.2.3. Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to patients in this study, the risks identified in association with danicopan are justified by the anticipated benefits that may be afforded to patients with GA secondary to AMD.

More detailed information about danicopan may be found in the IB.

3. 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 Minnesota Low Vision Reading Test (MNRead) Acuity Charts or Radner Reading Charts

Objectives	Endpoints
• 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 incomplete to complete retinal pigment epithelium and outer retinal atrophy (iRORA to cRORA) from Baseline to Week 52 and Week 104 in the study eye, fellow eye, either eye, and both eyes combined using spectral domain optical coherence tomography (SD-OCT) images • Incidence of patients with conversion from high-risk drusen to late AMD from Baseline to Week 52 and Week 104 in the

Objectives	Endpoints
	study eye, fellow eye, either eye, and both eyes combined using SD-OCT images • Incidence of patients with conversion from intermediate AMD (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 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 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

Objectives	Endpoints
	• 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 predefined change in any predefined grid pattern 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 subpopulation

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; 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

4. STUDY DESIGN

4.1. Overall Design

Study ALXN2040-GA-201 is a multicenter, double-masked, randomized, placebo-controlled, parallel-group, dose-finding study to evaluate 3 dose levels of danicopan compared to placebo in patients with GA secondary to AMD.

Patients will be assigned (1:1:1:1) by stratified randomization (with 3 stratification factors described in Section 6.3.1) to 1of 4 dose groups:

- 100 mg bid
- 200 mg bid
- 400 mg qd
- Placebo

Approximately 332 patients aged ≥ 60 years will be enrolled, with 83 patients per dose group.

This study evaluates the efficacy, safety, and PK of danicopan compared to placebo in patients ≥ 60 years with GA secondary to AMD. Eligible patients will be randomized (1:1:1:1) with stratification to one of four treatment groups (3 active treatment groups and 1 placebo group). The primary efficacy analysis will be performed when all patients complete the Week 52 Visit or discontinue (Section 6.6.4). Secondary efficacy and safety analyses, and exploratory analyses will be performed when all patients complete the Week 104 Visit or discontinue.

There are 2 potential interim analyses (IA) planned for this study. The first interim analysis (IA1) for futility may be conducted when approximately 50% patients have completed the Week 28 Visit. The second interim analysis (IA2) may be conducted when approximately 50% of patients complete Week 52 Visit. 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 of each dose compared to placebo will be conducted. Placebo patients will be re-randomized to 1 of the 3 active treatment groups at Week 52, or switched to the optimal dose, if identified. A dose with the optimal benefit-risk profile (see Section 9.5.2) could be identified at the IA2 or primary analysis for Phase 3 development. If an optimal dose is identified, all patients who have at least 52 weeks of treatment on their originally assigned dose will be switched to the selected optimal dose for the remainder of the study. Masked treatment paradigm will be maintained all throughout the study.

4.2. Scientific Rationale for Study Design

Table 6: Study Design Rationale for ALXN2040-GA-201

Design Element	Rationale
This is a double-masked, randomized, placebo-controlled study.	○ A randomized, double-masked study design minimizes bias to treatment allocation. ○ The term "masked" (used in lieu of "blinded") is considered appropriate in the therapeutic area of ophthalmology. ○ Comparison with placebo will look at the intrinsic pharmacological action of danicopan.
Patients will be randomized across 4 dose groups in a 1:1:1:1 ratio using randomization with stratification	○ Stratification according to study eye characteristics ensures balanced distribution of patients across the different dose groups with respect to GA severity. See Section 6.3.1.
The study is conducted in patients with GA aged ≥ 60 years	○ This age group assures a balanced representation of the GA patient population, while focusing on patients who are more likely to suffer from an accelerated deterioration of their GA status. See Section 4.2.4.
The primary endpoint is change from Baseline at Week 52 in the sqrt of total GA lesion area in the study eye of an individual patient	○ To minimize variability, the eye that meets all eligibility criteria is designated as the study eye. In case both eyes are eligible, the right eye is designated as the study eye. ○ Square root of GA lesion area has been used as a US FDA approvable anatomical marker for disease progression in clinical studies. ○ See Section 4.2.1 and Section 4.2.3.
Duration of study	○ Based on current knowledge on GA lesion growth, a clinically meaningful effect is expected to be observed at 1 year, hence the Primary Treatment Period of 52 weeks was chosen. ○ Functional outcomes trail anatomical findings (typically seen at 12 months), making a 104-week outcome a more reliable indicator of stability and durability of visual functional outcomes. ○ See Section 4.2.2.
Secondary endpoints consist of anatomical and functional outcomes	○ A combined anatomical (with multimodal imaging techniques) and functional assessment strategy allows to capture changes

Table 6: Study Design Rationale for ALXN2040-GA-201

Design Element	Rationale
	in retinal function associated with progressive GA changes from AMD. ○ Oral administration of danicopan in patients with GA will result in systemic exposure and enable concurrent treatment of both eyes. ○ See Section 4.2.3.2.

Abbreviations: AMD = age-related macular degeneration; GA = geographic atrophy; sqrt = square root

4.2.1. Study Eye and Fellow Eye

Systemic treatment with danicopan affects both eyes. For standardization purposes, the primary and secondary efficacy analyses will be measured in the pre-specified study eye per individual patient. In this study, ocular assessments will be performed in both eyes at Screening. The eye that meets all eligibility criteria is designated as the study eye and the other eye will be used as the fellow eye. In case of bilateral GA wherein both eyes are eligible, the right eye is designated as the study eye.

Exploratory analyses may be performed on the study eye, the fellow eye, and both eyes combined.

4.2.2. Study Duration

The study consists of a Screening Period of up to 6 weeks and a 104-week Masked Treatment Period. Treatment is followed by a 6-day Taper and a 30-day Follow-up is scheduled after the last taper dose. The total study duration per patient is approximately 115 weeks.

The 52-week time point for primary efficacy analysis was selected based on current knowledge about the rate of GA lesion growth (Dugel, 2020; Liao, 2020), and the projected duration of observation required to detect a clinically meaningful effect of treatment (eg, prevention of photoreceptor death through inhibition of GA growth) on slowing lesion growth relative to placebo.

Functional outcomes trail anatomical findings typically seen at 1 year (52 weeks). An overall duration of 104 weeks of the randomized double-masked treatment period allows for a more reliable indicator of stability and durability of visual functional outcomes and for the assessment of prevention of disease progression.

The total study duration of approximately 115 weeks allows an evaluation period relevant to the course of disease progression.

4.2.3. Outcome Measures

4.2.3.1. Primary Outcomes: Square Root of GA Lesion Area

The primary efficacy outcome measure of this study is the change in the square root (sqrt) of total GA lesion area (in mm) from Baseline at Week 52 as assessed by fundus autofluorescence (FAF) in the study eye. Although the kinetics of GA progression are highly variable among

individual patients, a growing body of evidence suggests that specific characteristics of the lesions may be important in predicting disease progression and outcomes. Therefore, the quantitative measurement of total GA lesion area progression by FAF imaging has become an acceptable anatomic marker used as clinical endpoint for clinical studies (Holz, 2007; Holz, 2018; Liao, 2020; Sadda, 2016). The sqrt transformation of the GA lesion area measurements eliminates variability dependence on baseline lesion size (Feuer, 2013; Yehoshua, 2014).

4.2.3.2. Secondary Outcomes: Anatomical and Functional Outcomes

A combined anatomical (with multimodal imaging techniques) and corresponding functional assessment strategy that incorporates many different aspects of visual function is appropriate in capturing changes in visual function associated with progressive GA changes from AMD.

In this study, a combination of anatomical and functional tests to assess disease progression and visual deficits will be used as outcome measures.

Anatomical outcomes will be based on changes in GA lesion area using different imaging modalities.

Functional outcomes will be based on changes in best-corrected visual acuity (BCVA) scores, low luminance visual acuity (LLVA) scores, the low luminance deficit (LLD) calculated from these 2 scores (BCVA-LLVA), and reading speeds.

Patient-reported outcomes (PRO) will be assessed using the National Eye Institute Visual Function Questionnaire, 25-item version (NEI VFQ-25).

These tests are described in Section 10.3 and Section 10.4.

4.2.3.3. Exploratory Outcomes

Exploratory analyses will be performed based on anatomical and functional outcomes.

Disease progression of AMD will be followed by quantifying conversion from 1 disease stage to another based on disease classification described in Section 10.2.

Functional outcomes will be based on changes in BCVA scores, LLVA scores, the LLD calculated from these 2 scores in fellow eye and both eyes. Functional retinal response including number of scotomatous points and change in macular sensitivity will be assessed by mesopic microperimetry in the microperimetry eligible subpopulation.

Anatomical outcomes will be based on anatomical measures on the fellow eye and both eyes combined, including changes in the area and sqrt area of the total GA lesion, changes in drusen volume, and incidence of patients with conversion from incomplete retinal pigment epithelium and outer retinal atrophy (iRORA) to complete retinal pigment epithelium and outer retinal atrophy (cRORA), as measured by spectral-domain optical coherence tomography (SD-OCT). The ellipsoid zone (EZ) and subretinal pigment epithelium (sub-RPE) compartment/drusen/RPE complex analyses will also be included.

4.2.3.4. Patient Reported Outcomes

Both nAMD and GA can lead to the loss of vision that may be severe and irreversible, resulting in a significant loss of QoL and inability to perform activities of daily living. Collection of PROs using QoL instruments and visual functioning questionnaires in clinical trials has been

recommended by regulatory bodies (Csaky, 2017). Change in QoL and daily living functioning are measured as exploratory endpoints using validated instruments, as described in Section 10.4.

4.2.4. Patient Population

Epidemiology studies show a substantial increase in AMD risk with age. Prevalence is highest in age groups ≥ 75 years (Augood, 2006; Lambert, 2016).

The study population of ≥ 60 years of age supports a balanced representation of the GA patient population with a reported mean (± standard deviation [SD]) age of 79 ± 8 years (Yaspan, 2017). This also provides the opportunity to capture the photoreceptor degeneration and conversion events and rules out unilateral GA in younger patients that may be due to other diseases such as myopia, uveitis, post trauma, or radiation.

4.3. Justification for Dose

One of the key objectives for this study is to test potentially efficacious and safe doses and dose regimens of danicopan and to support the selection of an appropriate dose for subsequent clinical development.

The 100 mg bid, 200 mg bid, and 400 mg qd dose regimens proposed for Study ALXN2040-GA-201 are based on the simulation results. Plasma PK exposures for these proposed doses are predicted to remain below the identified exposures where tolerability limit was observed in the MAD study (ACH471-002, see IB for further details). These doses are predicted to achieve > 90% alternative pathway hemolysis (APH) inhibition for the entire dose interval in the potential eye tissue targets: the retina and the choroid-RPE retinal side (melanosomes), and partial-to-complete APH inhibition in the choroid-RPE capillary-bed side (peripheral). Based on data from the literature, retina, and choroid-RPE on the retinal side are more likely to be the target eye tissues. However, the choroid-RPE on the capillary-bed side cannot be completely ruled out as a potential target. The proposed doses allow for the assessment of two different dosing intervals, ie, bid vs qd. The 400 mg qd dose regimen, if shown to be safe and effective, would be more convenient for patients and encourage better compliance relative to bid dosing. An up to 2-fold uncertainty of model prediction on PK and APH inhibition in the target eye tissues is anticipated as the physiological eye parameters in humans were translated from Dutch-Belted rabbits.

4.4. Definitions of Study Periods and End of Study

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

The Secondary Evaluation Period starts from Week 52 and ends at Week 104 (Table 2).

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 Table 3. See details in Section 7.

Follow-up: A follow-up visit is scheduled 30 (+ 7) days after the last dose (including taper doses, Table 3) of study drug.

End of study (EOS; study level completion): The end of the study is defined as the date the last patient completes the last visit (including the Taper and Follow-up, Table 4).

Refer to the SoA in Section 1.3.

5. STUDY POPULATION

Each consented patient must meet all eligibility criteria at both the Screening Period and the Day 1 Visit. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

5.1.1. General Inclusion Criteria

1. Age ≥ 60 years, male or female.
2. All patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.
3. For female patients, confirmation of non-childbearing potential based on follicle-stimulating hormone (FSH) test at Screening only.
4. For nonsterile male patients, agreement to use a highly effective or acceptable method of contraception with their partner(s) of childbearing potential from the first day of dosing to 90 days after their last dose of study drug. Males who are surgically sterile do not need to employ additional contraception.
5. For male patients, agreement not to donate sperm while enrolled in this study and for 90 days after their last dose of study drug.
6. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.1.2. Ocular Inclusion Criteria

At Screening, the eye that meets all eligibility criteria is designated as the study eye and the other eye will be the fellow eye. In case of bilateral GA wherein both eyes are eligible, the right eye is designated as the study eye (see Section 4.2.1). In cases where both eyes are eligible, if eligibility status of the designated study eye changes during review of eligibility criteria on Day 1 prior to randomization, the other eye can be designated as the study eye if all eligibility criteria are met.

To be eligible, there should be a presentation of GA secondary to AMD in at least one eye, characterized by:

7. The study eye must have the specified VA (range of 84 to 24 letters; 20/20 to 20/320) using Early Treatment Diabetic Retinopathy Study (ETDRS) charts at starting distance of 4 meters.
8. Adequate clarity of ocular media, adequate pupillary dilation, and fixation assessed by slit lamp examination and indirect ophthalmoscopy to permit the collection of good quality images as determined by the Investigator.
9. Axial length ≤ 26.0 mm measured by biometry (if available) or spherical equivalent refractive error ≤ 6.0 diopter of myopia.

- For patients with history of refractive or cataract surgery in the study eye, axial length ≤ 26.0 mm measured by biometry (if available) OR preoperative spherical equivalent refractive error ≤ 6.0 diopter of myopia.

10. The entire GA lesion must be completely visualized on the macula centered field 2 of the FAF image, must be able to be imaged in its entirety, and must not be contiguous with any areas of peripapillary atrophy.
11. Total GA lesion area of 0.5 to 17.76 mm^2 (~0.2 to 7 disc area [DA]) per eye measured by FAF. If GA is multifocal, at least one focal lesion must be ≥ 0.5 mm^2 (~0.2 DA).
12. The entire GA lesion must be > 1 µm outside of the foveal center.

5.2. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

5.2.1. Ocular Exclusion Criteria

1. GA in the study eye due to cause other than AMD (pathological myopia, monogenetic macular dystrophies eg, Stargardt/cone-rod dystrophy) or toxic maculopathies (eg, chloroquine/ hydroxychloroquine maculopathy) per Investigator's judgement.
2. GA and concomitant nAMD in the study eye.
3. Have previously received intravitreal anti-vascular endothelial growth factor (VEGF) injections in study eye for intraocular vascular disease.
4. Have previously received any stem cell or gene therapy for any ophthalmological condition in either eye.
5. Use of any investigational medicinal product (ie, participation in interventional clinical studies for any ophthalmic indications) or use of any regulatory approved treatment for GA in the study eye regardless of route of administration within the last 3 months or 5 half-lives of the last dose of the investigational or commercial product (whichever is longer).
6. Previous laser photocoagulation for nAMD, diabetic macular edema, retinal vein occlusion and proliferative diabetic retinopathy in the study eye.
7. Previous photodynamic therapy (Visudyne) or transpupillary thermotherapy in the study eye.
8. Previous external beam radiation therapy and/or any other irradiation (eg, isotope, charged particle, photon, x-ray) to the study eye and respective orbit, head, and/or neck.
9. Previous intravitreal delivery of steroid or device implantation, with the exception of intraocular lens, in the study eye. A single intravitreal steroid injection for cystoid macular edema after cataract surgery ≥ 3 months prior to Screening is permitted in the study eye.
10. Presence of an active ocular disease in the study eye that in the opinion of the Investigator compromises or confounds visual function or interferes with study assessments, including but not limited to cataract, uveitis, keratitis, scleritis or

endophthalmitis, vitreous hemorrhage, other macular diseases (eg, clinically significant epiretinal membrane, full thickness macular hole, RPE tear in macula), central serous retinopathy, uncontrolled glaucoma, proliferative diabetic retinopathy.

11. History of any of the following in the study eye:
    a. retinal detachment or full thickness macular hole
    b. glaucoma-filtering surgery including microinvasive glaucoma surgery (MIGS)
    c. vitrectomy, submacular surgery, or any surgical intervention for AMD
    d. prophylactic subthreshold laser treatment for AMD
    e. intraocular surgery (including lens replacement surgery) within 3 months prior to Screening.
12. History of any of recurrent infectious or inflammatory eye disease in either eye.
13. If the following changes occur between Screening and Day 1 in the study eye, as determined by eligibility review before randomization at Day 1:
    a. the Snellen equivalent is no longer between 20/20 to 20/320 OR
    b. significant anatomical changes (ie, large subretinal hemorrhage, RPE rip, pigment epithelial detachment, or other conditions that meet the exclusion criteria per Investigator's discretion).

5.2.2. General Exclusion Criteria

14. Known or suspected complement deficiency
15. History of *N meningitidis* infection.
16. Active bacterial or viral infection, a body temperature > 38°C (100.4°F) on 2 consecutive daily measures, evidence of other infection, or history of any febrile illness within 14 days prior to first study drug administration.
17. History of malignant disease within the past 5 years or ongoing, including solid tumors and hematologic malignancies (with the exception of basal cell and squamous cell carcinomas of the skin that have been completely excised and are considered cured).
18. Abnormal liver function tests, defined as:
    a. ALT, AST, alkaline phosphatase (ALP) or direct bilirubin > 2 × upper limit of normal (ULN) at Screening
    b. Patients with Gilbert's Syndrome will not be excluded. If increased bilirubin is suggestive of Gilbert's syndrome, the patient has to provide documentation of the diagnosis or will be tested for this condition.
19. Evidence of hepatitis B infection (positive hepatitis B surface antigen [HBsAg] or positive core antibody (anti-HBc) with negative surface antibody [anti-HBs]) or hepatitis C viral infection (HCV antibody positive), except for patients with documented successful treatment and documented sustained virologic response (SVR) at Screening.
20. Evidence of human immunodeficiency virus (HIV antibody positive) infection at Screening.

21. Estimated glomerular filtration rate < 30 mL/min/1.73 m^2 and/or are on dialysis. eGFR will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.
22. Hypersensitivity to the investigational drug (danicopan) or any of its excipients, or to fluorescein sodium for injection (known fluorescein hypersensitivity previously successfully pre-medicated can be performed per Investigator discretion).
23. Participation in non-ophthalmologic clinical trials involving last dose administration of another investigational medicinal product within 5 half-lives (if known) or within 30 days for systemic non-biologics or 6 months for biologics, whichever is longer.
24. History or presence of any medical or psychological condition that, in the opinion of the Principal Investigator, would make the patient inappropriate for the study or unable to comply with study procedures or put the patient at undue risk or confound the results of the study.

5.3. Microperimetry Eligibility Criteria

A subset of patients will be included in a microperimetry subpopulation. The eligibility criteria for microperimetry are as follows:

- Meeting all the inclusion criteria in Section 5.1 and none of the exclusion criteria in Section 5.2.
- Eyes able to detect fixation target.
- Total elapsed time to complete a microperimetry test is ≤ 30 minutes in duration per test
- Fixation losses must be ≤ 20%.

5.4. Lifestyle Considerations

5.4.1. Meals and Dietary Restrictions

Danicopan is taken orally with food. See Section 6.1.1 for details of study drug administration.

5.5. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomly assigned to study drug. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (eg, failed eligibility criteria), and any AEs, including any serious adverse events (SAEs) and any related concomitant medication, occurring during the Screening Period.

Individuals who do not meet the criteria for participation in this study (screen failure) due to a reason that is expected to resolve or has resolved may be rescreened based on discussion and agreement between the Investigator and the Medical Monitor. Participants who are rescreened outside of the Screening window are required to sign a new ICF. During rescreening, the patient must repeat all required screening assessments as defined in Screening Visit in the SOA.

6. STUDY INTERVENTION

6.1. Study Intervention Administered

For this study, the intervention is the administration of study drugs shown in Table 7.

Table 7: Study Drugs

	Danicopan	**Placebo**
IMP and AxMP	IMP	IMP
Type	small molecule drug	placebo
Dose formulation	tablet	tablet
Unit dose strength	100 mg	N/A
Dose levels	100 mg bid, 200 mg bid, 400 mg qd	matching placebo
Route of administration	oral	oral
Use	experimental	placebo control
Sourcing	provided by Sponsor	provided by Sponsor
Packaging and labeling	tablets are provided in blister packs and bottles	tablets are provided in blister packs and bottles
Other names and aliases	ALXN2040, ACH-0144471	N/A

Abbreviations: bid= twice daily; IMP = investigational medicinal product; N/A = not applicable; AxMP = auxiliary medicinal product; qd = once daily

6.1.1. Study Drug Administration

The study drugs will be dispensed to the patients at the clinic visits, mostly to be taken at home at the specified dosing regimen. At each clinic visit, the site should ensure that the patient has sufficient drug supply until the next clinic visit. Patients will be instructed to bring back all unused tablets at each clinic visit for accountability.

At certain clinic visits (see SoA) that require PK sample collection, patients should be instructed to administer their study drugs at the clinic for predose blood sample collection (Table 4).

The study drugs (danicopan or matching placebo) will be provided as tablets which are identical in appearance. The composition of the masked study treatments is shown in Table 8.

At home, patients will take their tablets twice daily with food and water, one dose of 4 tablets in the morning, and a second dose of 2 tablets in the evening. The time interval between the 2 doses should be approximately 12 hours.

At certain clinic visits (see SoA Section 1.3), patients will be instructed to take their morning dose of 4 tablets at the clinic to enable predose blood collection.

Table 8: Masked Study Drug Administration Weeks 1 to 104

Timing	Dose Group[a]			
	100 mg bid	**200 mg bid**	**400 mg qd**	**Placebo**
Morning dose, with food and water	100 mg	100 mg	100 mg	placebo
	placebo	100 mg	100 mg	placebo
	placebo	placebo	100 mg	placebo
	placebo	placebo	100 mg	placebo
Approximately 12 hours				
Evening dose, with food and water	100 mg	100 mg	placebo	placebo
	placebo	100 mg	placebo	placebo

[a] Doses are given as tablets in 100 mg strengths
Abbreviations: bid = twice daily; qd = once daily

6.1.2. Dose Tapering

In the MAD Study ACH471-002, ALT elevations were observed at high doses in 2 subjects after dosing was ceased. The elevations were transient and not considered of clinical significance. However, this temporal relationship suggests that the sudden withdrawal of FD inhibition may be associated with liver enzyme elevations. A dose taper was instituted in subsequent studies as a risk mitigation measure.

If possible, tapering should be initiated during dose interruptions, study discontinuation, or study completion. The dose of danicopan or placebo will be tapered over a 6-day period according to the dose tapering regimen described in Table 9. In case of discontinuation, the patient will complete the ET Visit, if possible, prior to tapering and should take the study drug per protocol until the tapering period begins.

Taper doses will be taken only in the morning with food and water. Masking must be maintained during tapering as shown in Table 9.

Table 9: Study Drug Taper Schedule

	Dose group							
	100 mg bid		200 mg bid		400 mg qd		Placebo	
	Taper dose	Masked (tablets to be taken)	Taper dose	Masked (tablets to be taken)	Taper dose	Masked (tablets to be taken)	Taper dose	Masked (tablets to be taken)
Taper Period 1 (Taper Days 1 to 3), mornings[a]	**100 mg qd**	100 mg placebo	**200 mg qd**	100 mg 100 mg	**200 mg qd**	100 mg 100 mg	**placebo**	placebo placebo
Taper Period 2 (Taper Days 4 to 6), mornings[a]	**0 mg**	placebo	**100 mg qd**	100 mg	**100 mg qd**	100 mg	**placebo**	placebo

[a] During taper, patients will take tablets in the morning with food and water.
Abbreviations: bid = twice daily; D = day; qd = once daily; T = taper
T1 and T2 visits are done on Taper D1 to D3 and Taper D4 to D6, respectively, by visiting healthcare service.
T1 Visit should assess safety and give instructions to taper dosing. T2 Visit should assess safety and give instructions to terminate dosing.

In case the tapering is not tolerated, there should be a discussion between the Investigator and the Medical Monitor.

At the end of the Tapering Period, the patient will be scheduled for a Follow-up Visit 30 (+ 7) days after the last taper dose of the study drug.

Data collected at the time of study drug discontinuation, Taper, and Follow-up and for any further evaluations that need to be completed are provided in the SoA (Section 1.3).

6.1.3. Study Drug Packaging and Labeling

The study drugs will be labeled according to the country's regulatory requirements. At a minimum, the label should contain:

- The protocol number
- Lot number/expiry date
- Alexion name and address
- Instructions for use and storage

6.2. Preparation/Handling/Storage/Accountability

The study drugs will be formulated and packaged by the Sponsor or its designee; therefore, no specific preparation instructions are required.

At the pharmacy, the study drug must be stored at 15°C to 30°C (59°F to 86°F). Patients must be instructed to keep their study drugs in the original container at room temperature.

The Principal Investigator or designee (eg, pharmacist) is responsible for ensuring storage as per the label on the drug product at the site and adequate accountability of all used and unused study drugs.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drugs received and that any discrepancies are reported and resolved before use of the study drugs.

Only patients enrolled in the study may receive the study drugs and only authorized site staff may supply or administer the study drugs. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

This responsibility includes the reporting of any temperature excursions and product complaints to AlexionIMPTE@alexion.com and productcomplaints@alexion.com within 1 business day of awareness. A product complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, usability, safety, effectiveness, or performance of a product or clinical study material and/or its packaging components after it is has been released for distribution to an end customer that affects the performance of such product.

The Investigator or designee (eg, pharmacist) will maintain records of interventional product delivered to the study site, the inventory at the study site, the distribution to and use by each participant, the storage or disposal of materials at the study site or the return of materials to the sponsor. These records should include dates, quantities, batch/serial numbers, expiration dates, in-clinic temperature log, and unique code numbers assigned to the interventional product and study participants.

Investigational product will not be returned to the Sponsor or disposed of until accountability has been fully monitored.

Further guidance regarding preparation, handling, storage, and accountability and information for the final disposition of unused study drugs is provided in the IB or Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Masking

6.3.1. Randomization and Stratification

This is a double-masked, placebo-controlled study with randomization. After Screening, eligible patients will be assigned across the 4 dose groups in a 1:1:1:1 ratio using stratified randomization. Stratification will be performed according to the study eye characteristics listed below to ensure balanced distribution of patients 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 vs 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).

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

All patients will be centrally assigned to randomized study treatment using an interactive voice or web response system (IVRS/IWRS) or other automated tool.

At the start of the study, patients will be assigned a unique randomization number. The randomization number encodes the patient's assignment to one of the 4 treatment arms of the study, according to the randomization schedule generated prior to the study.

6.3.2. Masking

Masking of treatment allocation will be observed during the entire study. The masked drug administration is described in Section 6.1.1 and Table 8.

During this period, images will be read centrally by masked graders according to the Central Reading Manual.

The Investigator and the study staff must ensure keeping the treatment masked unless unmasking is absolutely necessary.

6.3.3. Unmasking

In rare cases, masking may need to be broken due to an AE or other medical emergency.

Unmasking (breaking randomization code) should only be performed/done in extraordinary/rare/exceptional circumstances when knowledge of the treatment assignment is important for patient safety.

In case of an emergency, the Investigator has the sole responsibility for determining if unmasking of a patients' treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination.

If a patient's treatment assignment is unmasked, Alexion must be notified within 24 hours after breaking the masking. The IVRS/IWRS will be programmed with mask-breaking instructions. In the event that emergency unmasking is necessary, the IVRS/IWRS will provide clear step-by-step instructions for the Investigator to follow.

If the Investigator decides that unmasking is warranted, the unmasking will be done for that specific patient only. In addition, the Investigator has to ensure that disclosure of treatment allocation for that specific patient will only be restricted to the relevant personnel and health authorities. The Investigator should not reveal the treatment allocation to the Medical Monitor or

any other individuals (eg, clinical study team, contract research organization [CRO] or investigational site), unless absolutely necessary.

Any patient who is unmasked before study completion will be discontinued from the study.

6.4. Study Intervention Compliance

Patients will continuously self-administer the study drug, unless instructed otherwise. Compliance with the study drug will be assessed by direct questioning and counting returned tablets during the site visits and recorded in the source documents. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

A record of the quantity of the number of tablets dispensed to and taken by each patient must be maintained and reconciled with the number of tablets and compliance records. Treatment start and stop dates, including dates for planned and unplanned dose delays and/or dose reductions will also be recorded in the eCRF.

See Section 6.6.2 and Section 6.6.3 for more information about missed doses and dose interruptions, respectively.

Patients should be advised on the importance of taking the study drug according to the protocol (Section 6.1.1). Patients who do not adhere to protocol specified visit schedule and procedures, and who do not adhere to study drug administration (eg, generally considered as having < 80% treatment compliance during the identified treatment period) may be regarded as non-compliant to the protocol. If poor compliance with the study protocol continues, discontinuation should be considered. See also information on missed doses and dose interruptions in Section 6.6.

6.5. Prior and Concomitant Therapies

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) other than protocol-specified procedural medications (eg, dilating drops, anesthetic drops, fluorescein dyes, vaccines) that the patient is receiving at the time of enrollment or receives during the study must be recorded in the electronic case report form (eCRF) along with:

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

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

Prior and concomitant medications, including background therapy, will be reviewed as specified in the SoA (Section 1.3).

Prior medications and/or vaccines (including vitamins, herbal preparations, and those discussed in the eligibility criteria [Section 5]) and procedures (eg, surgery, biopsy, physical therapy) that the patient receives or undergoes ≤ 30 days prior to Screening or during the Screening Period, as well as any meningococcal vaccine administered within the last 3 years, will be recorded in the patient's eCRF.

Concomitant medications (including any medication, vitamins, herbal preparation or supplements) and procedures are those received on or after the first study intervention date (Day 1), including those started before Day 1 and continued after Day 1.

Any concomitant medication deemed necessary for the patient's care during the study, or for the treatment of any AE, along with any other medications, other than those listed as disallowed medications in Section 6.5.2, may be given at the discretion of the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding all medications are recorded in full, in the patient's source documents and eCRF.

Vaccination and antibiotics administered for prophylaxis of meningococcal infection (if applicable) during the study will also be recorded.

6.5.1. Allowed Medications

At the discretion of the Investigator, patients may continue to receive medications and standard treatments administered for other conditions. Patients enrolled may have previously taken oral supplements of vitamins and minerals for treatment of dry AMD, and these may be continued during the study. Previous and ongoing regulatory approved intravitreal fellow eye treatment of GA and anti-VEGF treatment for exudative and/or non-exudative nAMD is permitted. If, during the study, the Investigator suspects development of neovascularization in the study eye or fellow eye, administration of an anti-VEGF agent according to product label is allowed.

For ease of reference, see Section 10.9 for a non-comprehensive list of medications allowed in this patient population.

Use of specific concomitant medications with a narrow therapeutic index (ie, P-glycoprotein [P-gp] or breast cancer resistance protein [BCRP] substrates) will be considered on a case-by-case basis with decisions made by the Principal Investigator in discussion with the Medical Monitor, based on available knowledge of danicopan as well as the characteristics of the potential concomitant medication. Concomitant administration of tacrolimus is permitted if therapeutic drug monitoring of tacrolimus exposure is conducted in accordance with recommendations in the product label.

Clinical drug-drug interaction studies indicate that danicopan is an inhibitor of P-gp and BCRP transporters. Caution may be needed when co-administering danicopan with drugs known to be P-gp and/or BCRP substrates (eg, some statins). Details are provided in the Investigator's Brochure.

6.5.1.1. Vaccines

To reduce the risk of meningococcal infection, all patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Vaccines against serotypes A, C, Y, W135, and B where available, are recommended to prevent common pathogenic meningococcal serotypes. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics from the first day of study drug treatment until 2 weeks after vaccination.

Patients must be vaccinated or revaccinated according to current national vaccination guidelines or local practice for vaccination use with complement inhibitors. Vaccination may not be

sufficient to prevent meningococcal infection. All patients should be monitored for early signs of meningococcal infection, evaluated immediately if infection is suspected, and treated with appropriate antibiotics, if necessary.

Patients should be vaccinated or revaccinated against other pathogens according to current national vaccination guidelines or local practice for vaccination use as part of standard of care of underlying disease and age group.

6.5.2. Disallowed Medications and Therapy

There are no disallowed medications or procedures during the study.

6.6. Dose Modification and Interruptions

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient.

Regardless of modifications or interruptions, masking of dose assignment should be maintained all throughout the study unless emergency unmasking (Section 6.3.2 and Section 6.3.3) is necessary.

6.6.1. Switching to Optimal Dose

If an optimal dose is identified, all patients with at least 52 weeks of treatment, as specified in the SoA (Section 1.3) will transition to the optimal dose at the next scheduled visit when drug supply is made available. Placebo patients will be rerandomized to one of the 3 active treatment groups at Week 52, or switched to the optimal dose, if already identified. Masking of dose assignment will be maintained till the end of the study.

The timing of transitioning to optimal dose will be programmed into the IVRS/IWRS to ensure that masking is maintained till then end of the study.

6.6.2. Missed Doses

The study drug (danicopan or placebo) should be taken as prescribed by the protocol and without interruption during the course of the study, whenever possible. In case of a dose missed (defined as dose at a single timepoint, morning or evening) inadvertently, the patient should continue with administration of a regularly scheduled next dose. Adding the missed dose at the next dosing time is not allowed. Information on missed doses should be recorded in the eCRF. See Section 6.6.3 for information about dose interruptions.

6.6.3. Dose Interruptions

If the study drug (danicopan or placebo) has to be stopped or interrupted for any reason, dose tapering should occur per Table 3 and Table 9, and assessment should be made if the stop is temporary and discussion about the reasons for interruption and plans for potential re-initiation should occur between the Investigator and the Medical Monitor. Re-initiation of treatment with the study drug should be done under careful clinical monitoring, including laboratory monitoring and after consultation with the Medical Monitor. If upon resumption of treatment, the patient has a recurrence of the event, permanent discontinuation should be considered as described in Section 7.

Any temporary preplanned treatment interruption should be discussed between the Investigator and the Medical Monitor and tapering should be considered (refer to Section 6.1.2).

The patient should continue participation until the end of the study and continue all scheduled assessments as per SoA (see Section 1.3) unless the pre-specified events for treatment discontinuation have been met. Any interruption of study drug and the reason for the interruption should be fully documented in the source documents and eCRF.

6.6.4. Permanent Dose Discontinuation

If the study drug (danicopan or placebo) is permanently discontinued for any reason (see Section 7), the dose of danicopan or placebo will be tapered over a 6-day period, and the patient will complete the ET Visit, if possible, prior to tapering as described in Section 6.1.2, (Table 9).

A patient who permanently discontinues the study drug is also permanently discontinued from the study.

7. DISCONTINUATION OF STUDY DRUG AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Drug

In rare instances, it may be necessary for a patient to permanently discontinue (definitive discontinuation) the study drug. If the study drug is definitively discontinued, the patient will be dose tapered as described in Section 6.1.2, and have a final follow-up 30 days after the last dose of the study drug.

A patient is free to withdraw from the study at any time without jeopardizing future medical care. In addition, the Principal Investigator (or designee) may decide, for reasons of medical prudence or patient noncompliance, to discontinue dosing of study drug for an individual patient. The Principal Investigator will discontinue the study drug in any patient who meets any reasons listed below, and should notify the Medical Monitor immediately, and if possible, before dosing is terminated. Anytime a patient has to discontinue the study drug, the dose tapering instructions and schedule (see Section 6.1.2, Table 9) should be followed unless the patient cannot tolerate tapering of study drug or the discontinuation is due to an SAE. In case tapering is not tolerated, there should be a discussion between the Investigator and the Medical Monitor.

Patients will discontinue the study drug if any of the following occur during the study:

- Illness that would, in the judgment of the Investigator, affect assessment of clinical status to a significant degree.
- Development of any of the following liver function test abnormalities:
  - ALT or AST > 8 × ULN
  - ALT or AST > 5 × ULN for more than 2 weeks
  - ALT or AST > 3 × ULN and total bilirubin > 2 × ULN or international normalized ratio > 1.5, in the absence of warfarin anticoagulation
  - ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
- Persistent Grade 3-4 toxicity (including a clinically significant laboratory abnormality) despite appropriate intervention necessitating discontinuation of study participation or that, in the judgment of the Investigator, compromises the ability to continue study-specific procedures, or it is considered not to be in the patient's best interest to continue the study.
- Development of rhegmatogenous retinal detachment or Stage 3 or 4 macular hole during the course of the study.
- Development of malignancy in eye, orbit, head, or neck that needs radiation therapy.
- Patient request to discontinue for any reason.
- Patient non-compliance with the protocol. In case of significant deviations from the protocol for any reason (eg, oversight, accident, inadvertent error, etc), the Investigator (or designee) and Sponsor Medical Monitor will discuss and reach a joint

decision about patient discontinuation from the study. This joint decision will be fully documented per study procedures.

- Discontinuation of the study at the request of the Sponsor, regulatory agency, or Ethics Committee or Institutional Review Board (IRB).
- Any other condition or circumstance that would jeopardize the welfare of the patient if s/he were to continue in the study.

Details on early termination/discontinuation are detailed in Section 7.2.

7.2. Patient Discontinuation/Withdrawal from the Study

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

A patient may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This activity is expected to be uncommon. At the time of discontinuing from the study, if possible, an ET Visit should be conducted as shown in the SoA (Section 1.3). The reason for patient discontinuation must be recorded in the source documents and eCRF at the ET Visit. The ET Visit marks the end of efficacy assessments. This will be followed by a 6-day tapering and a final Follow-up Visit (EOS Visit) scheduled 30 days after the last dose (including taper doses). Safety assessments will continue during the taper and the follow-up until study completion. The Follow-up Visit can be omitted if it falls within 5 days of the ET Visit.

Refer to the SoA for data to be collected at the time of study discontinuation/ET Visit, Taper period, and Follow-up, and for any further evaluations that need to be completed.

If the patient withdraws consent for disclosure of future information, Alexion may retain and continue to use any data collected before such a withdrawal of consent. If a patient withdraws from the study, the patient may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3. Lost to Follow-up

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

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

- The site must attempt to contact the patient to reschedule the missed visit as soon as possible, counsel the patient on the importance of maintaining the assigned visit schedule, and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient. An example of contact effort escalation/due diligence would include 3 telephone calls, followed by a certified letter to the patient's last known mailing address or local equivalent, if earlier attempts fail

to regain contact with patient. These contact attempts should be documented in the patient's medical record.

- Should the patient continue to be unreachable, s/he will be considered lost to Follow-up.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.9.

7.4. Intervention After the End of the Study

The study drug will not be provided to the patients after the last scheduled dosing. See SoA in Section 1.3. Upon completion of the last study visit (EOS), patients will return to the care of their treating physician.

See Section 4.4 for definition of EOS.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

There are two types of study visits: in-clinic visits and home visits by a visiting health service (in countries where available). All visits must be complied with according to the SoA (Section 1.3). Patients may opt to convert home visits to in-clinic visits per agreement with site personnel, but the home visit assessments will still be followed. Changes in visit type should be noted in source documentation.

Immediate safety concerns should be discussed with Alexion immediately upon occurrence or awareness to determine if the patient should continue or discontinue study drug.

Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.

Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3). See Section 10.5 for the list of clinical laboratory tests.

8.1. Screening

During Screening, there should be an ongoing discussion between the Investigator and the Medical Monitor regarding eligibility criteria.

The Principal Investigator or designee is responsible for administering and obtaining freely given informed consent before the patient enters the study and before any study related procedures are performed. Each patient will sign (written or electronic) an ICF (see Section 10.1.3). This may include additional consent forms for HIV testing or other procedures which may be performed prior to patients being accepted into the study.

All screening evaluations (SoA, Section 1.3, Table 1) must be completed during the Screening Period and then reviewed at Day 1 to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Individuals who do not meet the criteria for participation in this study (screen failure) due to a reason that is expected to resolve or has resolved may be rescreened based on discussion and agreement between the Investigator and the Medical Monitor. Participants who are rescreened outside of the Screening window are required to sign a new ICF. During rescreening, the patient must repeat all required screening assessments as defined in Screening Visit in the SoA.

8.1.1. General Screening

As part of the screening process, patients will be evaluated for vaccination requirements as detailed in Section 6.5.1.1. A Patient Safety Card will be issued at Screening.

A window of up to 6 weeks is permitted to allow screening and any required vaccinations. Screening procedures may be spread over more than 1 visit within the 6-week Screening Period. The screening clinic and laboratory procedures listed in Section 10.5 must be performed and

documented prior to dosing. This will include a review of the inclusion and exclusion criteria. The patient's medical history will be reviewed, and a complete physical examination will be conducted.

Female participants in this study are postmenopausal and therefore not of child-bearing potential. See definitions in Section 10.8.1. An FSH test will be performed at Screening for confirmation.

If screening laboratory assessments show elevated indirect bilirubin levels in conjunction with normal liver function tests (AST and ALT), or if the patient has a history of unexplained jaundice, unexplained high bilirubin levels, or a history otherwise suggestive of Gilbert's syndrome, the patient will be tested for this condition. If the patient has a history of Gilbert's syndrome it should be documented as the patient's medical history. Refer to the Laboratory Manual for testing procedure.

8.1.2. Ocular Screening

At Screening, all patients will undergo a monocular test on both eyes. The "study eye" is defined as the eye that meets all eligibility criteria at Screening. For patients with bilateral GA with both eyes meeting the eligibility criteria, the right eye will be taken as the study eye. The other eye will be used as the "fellow eye".

The following ocular assessments will be conducted for both eyes during Screening. It is recommended to follow the order of the procedures as listed below. Assessments that require non-dilation of the pupils must be performed first:

- BCVA assessed on ETDRS chart at a starting distance of 4 m (perform prior to dilating eyes). The test will be administered first monocularly (right/left eye) and then binocularly (both eyes)
- For the microperimetry subpopulation: mesopic microperimetry will be performed on both eyes without dilation. Two tests per eye will be performed and up to 3 attempts are allowed to meet the eligibility criteria during the Screening Visit
- Slit-lamp examination on both eyes
- Intraocular pressure (IOP) measurement of both eyes (recommended prior to dilating eyes; Goldmann applanation tonometry must be used at Screening)
- Dilated binocular indirect high-magnification ophthalmoscopy on both eyes
- Retinal imaging to be performed in the following recommended order: FAF, near infrared reflectance (NIR), SD-OCT, fluorescein angiography (FA), and color fundus photography (CFP) will be performed per Central Reading Manual and training materials. Administration of artificial tears between acquisition of each eye for FAF/NIR and SD-OCT is recommended. Before any study images and microperimetry are obtained, site personnel, test images, and systems and software (where applicable) will be certified/validated by the reading center as specified in the Central Reading Manual. During the eligibility assessment, if the FAF images were reviewed to be ungradable per Central Reading Center, the FAF images will be repeated as soon as feasible

- If available, biometry (preferred) on both eyes to measure axial length. If biometry is not available, spherical equivalent refractive error is to be used.

Details of these ocular assessments are provided in Section 10.3.

All ocular images at Screening will be read centrally by trained graders according to a Central Reading Manual. Eligibility assessment by the Central Reading Center based on reading of screening images should be considered by the Investigator when confirming that potential patients meet all eligibility criteria. Discrepancies in eligibility confirmation may be discussed between the Investigator, Medical Monitor, and Central Reading Center.

Prior to randomization at Day 1, the inclusion and exclusion criteria will be reviewed to confirm eligibility. If eligibility status of the designated study eye changes during review of eligibility criteria on Day 1 prior to randomization, the other eye can be designated as the study eye if all eligibility criteria are met.

8.2. Efficacy Assessments

Efficacy will be based on anatomical, functional and health-related QoL assessments at in-clinic visits. The assessments should be done in the sequence shown and detailed in the SoA (Section 1.3) and Section 10.3.

- Patient-reported outcomes
- BCVA testing (starting at 4 m)
- LL BCVA testing (starting at 4 m)
- Reading Speed (MNRead or Radner Reading Charts)
- Mesopic microperimetry for microperimetry subpopulation
- Slit lamp examination
- Tonometry/IOP, measurement of both eyes (recommended prior to dilating eyes).
- Dilated binocular indirect ophthalmoscopy
- Ocular imaging, recommended to be done in the following order: FAF, NIR, SD-OCT, FA, and CFP. Administration of artificial tears between acquisition of each eye for FAF/NIR and SD-OCT is recommended.

All ocular images at Screening will be read centrally by trained graders according to a Central Reading Manual.

8.2.1. Primary Efficacy Assessment

The primary objective of this study is to evaluate the effect of different dosage regimens of danicopan on the progression of GA secondary to AMD.

GA lesion area in mm^2 will be measured by FAF in the study eye at the time points indicated in Section 1.3. The total GA lesion area (mm^2) will be transformed into sqrt (mm).

FAF provides high-contrast retinal images particularly valuable for the detection of atrophic areas. FAF images will be taken according to the SoA (Section 1.3) and sent to reading center for

total GA lesion area measurement. Grading of FAF images for the primary efficacy assessment will be centrally performed by trained masked graders per the Central Reading Manual.

A detailed description of FAF is provided in Section 10.3.

8.2.2. Secondary Efficacy Assessments

Several anatomical and functional measures will be utilized to evaluate the effect of danicopan on GA progression in the study eye. In all cases, assessments that require non-dilated eyes should be performed first prior to dilation.

8.2.2.1. Anatomical Measures

GA lesion area in mm^2 will be measured by FAF for both eyes at the time points indicated in Section 1.3. The total lesion area will be transformed into sqrt.

A description of the FAF procedure is provided in Section 10.3.

8.2.2.1.1. Macular Ellipsoid Zone and Outer Retinal Integrity

Photoreceptor loss will be assessed by measuring the percent of macular EZ total attenuation using SD-OCT. The EZ is considered to be formed mainly by mitochondria within the ellipsoid layer of the outer portion of the inner segments of the photoreceptors. In SD-OCT, decreases in the integrity and intensity of the EZ have been correlated with the reduction in cone photoreceptors and retinal sensitivity in retinal degenerative diseases, including AMD and macular telangiectasia type 2 (Lara-Medina, 2019; Mukherjee, 2017; Pfau, 2020b; Tao, 2016).

The following parameters will be assessed from SD-OCT images:

- EZ-RPE mean central 1-mm subfield thickness
- EZ-RPE mean central macular 2 mm thickness
- Outer nuclear layer (ONL)-RPE mean central 1 mm subfield thickness
- ONL-RPE mean central macular 2 mm thickness
- EZ-RPE macular volume
- Percent macular EZ total attenuation
- Percent macular EZ partial attenuation
- 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
- Targeted EZ integrity based on other analysis targets (eg, correlation with microperimetry patterns)

8.2.2.1.2. Sub-RPE Compartment/Drusen/RPE Complex

Sub-RPE compartment measures reflect the disease burden between the RPE and Bruch's membrane. Generally, this measure should be close to zero in normal eyes. In this volumetric assessment and higher order optical coherence tomography (OCT) analysis, the following parameters will be assessed:

- Sub-RPE central 1 mm subfield mean thickness
- Sub-RPE central macular 2 mm subfield mean thickness
- Panmacular sub-RPE volume
- Percent macular Total RPE Attenuation (ie, surrogate for SD-OCT-based measure of GA area).
- Percent central 1 mm subfield Total RPE attenuation
- Percent central macular 2 mm subfield Total RPE attenuation

8.2.2.2. Functional Measures

Monocular BCVA scores, and LLVA scores, and LLD score (BCVA-LLVA) will be assessed by ETDRS chart at a starting distance of 4 meters at the time points indicated in Section 1.3. The test will be administered first monocularly (right/left eye) and then binocularly (both eyes). These measures must be performed prior to dilation of the eyes.

Reading speeds will be assessed by MNRead Acuity Charts or Radner Reading Charts at the time points indicated in the SoA in Section 1.3. The test will be administered first monocularly (right/left eye) and then binocularly (both eyes). Reading speed testing is only applicable if the charts are available in the local language.

For a description of the reading charts and other functional measures, refer to Section 10.3.

8.2.2.3. Patient Reported Outcomes

The NEI VFQ-25 scores will be assessed as a secondary endpoint. See details of PROs in Section 8.10 and Section 10.4.

8.2.3. Exploratory Efficacy Assessments

Other anatomical and functional outcomes will be measured and analyzed in an exploratory manner.

8.2.3.1. GA Lesion Area by SD-OCT

GA lesion area measured by SD-OCT will also be evaluated by masked graders per the Central Reading Manual. A description of the SD-OCT procedure is provided in Section 10.3.

8.2.3.2. Mesopic Microperimetry

Mesopic microperimetry using the grid customized for our study will be conducted in a subset of patients who meet the eligibility criteria for microperimetry (microperimetry subpopulation, Section 23). Microperimetry should be performed prior to eye dilation and any imaging

procedure. Two microperimetry tests per eye should be conducted during Screening Visit and once per eye in the follow-up visits.

A grid customized for this study will be utilized to measure the macular sensitivity by patterns of up to 61 testing points in the study eye and fellow eye.

Microperimetry will evaluate retinal sensitivity which has been shown to be well correlated with anatomical changes in intermediate age related macular degeneration (iAMD) and GA patients in multiple studies (Alibhai, 2020; Jones, 2016; Pfau, 2020a; Welker, 2018; Wu, 2015). A difference of 7 decibels (dB) would represent a minimal clinically meaningful change on microperimetry (Weinreb, 2009).

A scotoma is an area of reduced sensitivity in the visual field. Mesopic microperimetry evaluates macular functional response and macular sensitivity by quantifying scotomatous points (nonresponding points or "dense" scotomas) in the macula (Csaky, 2019). The number of scotomatous points and mean changes from Baseline in macular sensitivity within the grid customized for the study in the study and fellow eyes will be evaluated by the reading center. See Section 10.3.

8.2.3.3. Disease Conversion

SD-OCT along with other imaging techniques including FAF, FA, NIR (Section 10.3) will be used to evaluate the disease conversion in both eyes, according to classification of AMD (see Section 10.2). SD-OCT has become an essential imaging technology to evaluate the macula. SD-OCT affords us an opportunity to identify the early stages of the atrophic process before lesions are clinically visible or detected as atrophy by CFP or FAF. In addition, the depth resolved nature of SD-OCT imaging allows us to evaluate tissue layer by layer, which is important because the severity of cellular loss in atrophic disease may vary among layers. SD-OCT has been widely used in recent clinical studies for GA (Holz, 2017; Sadda, 2018).

Anatomical lesion features from iAMD including high risk drusen, iRORA, non-exudative nAMD will be identified from SD-OCT images by masked graders per the Central Reading Manual, the conversion to late AMD including complete retinal pigment epithelium and outer retinal atrophy (cRORA) and exudative nAMD will be tracked over time including:

- Conversion from iRORA to cRORA will be assessed at Week 52 and Week 104.
- Conversion from high risk drusen to late AMD at Week 52 and Week 104
- Conversion from iAMD to late AMD will be assessed at Week 52 and Week 104.

The assessment will be based on standard disease classification definitions provided in Section 10.2, Table 11.

8.2.3.4. Drusen Volume

Evidence from previous study demonstrated that patients with a drusen volume over 0.03 mm^3 had an increased risk for developing late AMD compared with those with lower drusen volumes (Abdelfattah, 2016; Folgar, 2016). Drusen volume in the fellow eye with early/iAMD will be measured using SD-OCT images by masked graders per the Central Reading Manual at the time points indicated in Section 1.3.

8.3. Safety Assessments

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

8.3.1. Physical Examinations

A complete physical examination will be performed as indicated in the SoA (Section 1.3). A complete physical examination will include, at a minimum, an assessment of general appearance and a review of systems. Height (at Screening only) and weight will also be measured and recorded. Measurements of height and weight should be taken with the patients in light clothing or underwear and without shoes.

An abbreviated physical examination will be conducted at all other in-clinic visits, as indicated in the SoA (Section 1.3). An abbreviated physical examination includes, at a minimum, body system relevant examination based on Investigator judgement and patient symptoms. Additional brief, complete, or symptom-driven physical examinations may be conducted at the discretion of the Investigator or designee and/or when patients present with AEs. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2. Vital Signs

Body temperature, pulse rate, respiratory rate, and systolic and diastolic blood pressure (mmHg) will be assessed.

Vital signs will be measured after 5 min rest and will include temperature, systolic and diastolic blood pressure, and pulse, and respiratory rate.

8.3.3. Electrocardiograms

A single 12-lead electrocardiogram (ECG) will be conducted as outlined in the SoA (Section 1.3) to obtain heart rate (HR), PR, QRS, QT, and QTcF intervals. All ECG recordings will be 12-lead and will be performed after the patient has rested quietly for at least 5 minutes in a supine position and before blood is drawn (whenever possible). The occurrence of depolarization or repolarization disorders, arrhythmic disorders or other abnormalities will be noted.

In some cases, it may be appropriate to repeat an abnormal ECG to rule out improper lead placement as contributing to the ECG abnormality. It is important that the leads are placed in approximately the same positions each time in order to achieve precise ECG recordings.

All ECGs will be reviewed by a central ECG reader. All ECG parameters and assessments must be recorded or stored in the patient's source documents. ECG reports will be reviewed by the Investigator or designee. Any clinically significant ECG finding must be reported as an AE.

8.3.4. Clinical Safety Laboratory Assessments

All protocol-required laboratory assessments, as defined in Section 10.5, Table 12, must be collected in accordance with the Laboratory Manual and the SoA (Section 1.3).

8.3.4.1. Blood Collection

Patients should refrain from heavy exercise 24 hours before blood collection. Walking and light exercise are acceptable. Patients will be in a seated or supine position during the blood

collection. Specific instructions for sample collection, processing, and shipping will be provided in a separate Laboratory Manual. If central laboratory tests results are not obtainable in a timely manner, samples may be collected at an unscheduled visit and analyzed locally. See the Laboratory Manual for additional information.

8.3.4.2. Abnormalities

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the final dose of study drug should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the Investigator or medical monitor.

- If such values do not return to normal/Baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and Alexion notified.
- Laboratory assessments performed at the institution's local laboratory that require a change in patient management or are considered clinically significant by the Investigator must be recorded in the AE or SAE eCRF. When possible, parameter value outside of the reference range should be entered in a free text field.

8.3.5. Pregnancy and Contraception

- Female participants in this study are postmenopausal and therefore not of child-bearing potential. This will be confirmed following FSH testing at Screening.
- Contraception guidance for male patients with partners of childbearing potential is provided in Section 10.8.
- Pregnancy data from female spouses/partners of male patients will be collected from the first dose of the study drug during safety monitoring. If a pregnancy is reported, the Investigator must immediately inform Alexion within 24 hours of awareness of the pregnancy and follow the procedures outlined in Section 10.8.4

8.3.6. Patient Safety Card

Before the first dose of the study drug, a Patient Safety Card will be provided to patients to carry with them at all times until 30 days after the final dose of the study drug. The card is provided to increase patient awareness of the risk of meningococcal infections and promote quick recognition and disclosure of any potential signs or symptoms of infection experienced during the course of the study and to inform patients on what actions must be taken if they are experiencing signs or symptoms of infection.

At each visit throughout the study, the study staff will ensure that the patient has the Patient Safety Card. Additional discussion and explanation of the potential risks, signs, and symptoms

will occur at specific time points as part of the review of the Patient Safety Card and throughout the study as described in the SoA in Section 1.3.

8.3.7. Monitoring for Neovascular AMD Development

During the study, the development of nAMD (non-exudative and exudative) will be monitored. Neovascularization is suspected if the patient has > 5 ETDRS letters of VA loss between the current visit and the immediate past visit. If possible, this diagnosis should be assessed by FAF, FA, SD-OCT, and CFP, and confirmed by the reading center prior to initiation of anti-VEGF treatment per product label. The development of nAMD will be captured as an AE and recorded. Following development of nAMD in either eye, study drug should be continued and patients are encouraged to continue all study procedures as per protocol.

8.4. Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Section 10.6.

All AEs will be reported to the Investigator or qualified designee by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study drug or study procedures, or that caused the patient to discontinue the study drug (see Section 8).

Procedures for recording, evaluating, follow-up, and reporting AEs and SAEs are outlined in Section 10.6.

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

All AEs and SAEs will be collected from the signing of the ICF until 30 days after final (including taper) dose of study drug is administered.

All SAEs will be recorded and reported to Alexion immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.6. The Investigator will submit any updated SAE data to Alexion within 24 hours of the date the investigational site became aware of the event.

Investigators are not obligated to actively seek AE or SAE data after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify Alexion.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.6.

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

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow-up on each patient at subsequent visits/contacts. All SAEs will be followed up until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.6.

8.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification of an SAE by the Investigator to Alexion is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study drug under clinical investigation are met.

Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. Alexion will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/Independent Ethics Committees (IECs), and Investigators.

Alexion is required to submit individual suspected unexpected serious adverse reaction reports (defined in Section 10.6.2 in the format of MedWatch 3500 or Council for International Organizations of Medical Sciences (CIOMS) I Form to health authorities and Investigators as required. Forms submitted to Investigators will be masked to treatment assignment. In limited circumstances, the masking may be broken in the case of urgent safety issues that could compromise patient safety.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from Alexion will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Under the EU CTR 536/2014, events other than SAEs (eg, unexpected events) that may impact the benefit-risk balance should be reported. See definitions in Section 10.6.5.

8.4.5. Medication Error, Drug Abuse, and Drug Misuse

Medication error, drug abuse, and drug misuse will be collected from signing of the applicable version of ICF through the last scheduled procedure shown in the SoA (Section 1.3).

8.4.5.1. Timelines

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

The full definitions and examples of medication error, drug abuse, and drug misuse can be found in Section 10.7.

8.4.5.2. Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an investigational medicinal product (IMP) or an auxiliary medicinal product (AxMP) that either causes harm to the participant or has the potential to cause harm to the participant.

8.4.5.3. Drug Abuse

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

8.4.5.4. Drug Misuse

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

8.5. Treatment of Overdose

For this study, any dose of the masked study drug greater than that specified in the protocol will be considered an overdose. Overdoses are medication errors that are not considered AEs unless there is an untoward medical occurrence resulting from the overdose.

The Sponsor does not recommend specific treatment for an overdose; general supportive measures are recommended below.

In the event of an overdose, the Investigator/Treating Physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the patient for any AE/SAE.
3. If necessary, based on consultation with the Medical Monitor, obtain a plasma sample for PK analysis or safety laboratory assessments.
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient.

8.6. Pharmacokinetics

- Biomatrix samples (eg, plasma, serum, whole blood, and urine) will be collected from all patients for measurement of concentrations of the study drug as specified in the SoA (Section 1.3, Table 4).
- Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and Alexion. The timing of sampling may be altered during the course of the study, based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Instructions for the collection and handling of biological samples will be provided in the Laboratory Manual. The actual date and time (24-hour clock time) of each sample will be recorded.

- Samples will be used to evaluate the PK of danicopan. Samples collected for analyses of drug concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Study drug concentration information that may unmask the study will not be reported to investigational sites or masked personnel until the study has been unmasked. Additional information on sample collection and shipping instructions will be provided in a separate Laboratory Manual.

8.7. Pharmacodynamics

- For all patients, blood samples for pharmacodynamic (PD) evaluations (serum AP activity and plasma Bb fragment of complement factor B (Bb) concentration) will be collected at scheduled time points as delineated in the SoA (Section 1.3). The allowable deviation window for postdose PD blood sample collection is detailed in Table 4.
- Instructions for blood sampling, collection, processing to serum and plasma, and sample shipment will be provided in the Laboratory Manual. The actual date and time (24hour clock time) of each sample will be recorded.
- Samples from all patients will be assayed even if the patients do not complete the study.
- PD assessments that may unmask the study will not be reported to investigative sites or masked personnel until the study has been unmasked.

8.8. Genetics

Subject to patient consent, a sample will be collected at Day 1 for potential genetic analysis. The genes encoding the following proteins, but not limited to, may be examined: complement factor D (FD), factor B (FB), factor H (FH), factor I (FI) and factor H related 1-5 (FHR1-5) proteins.

The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.

Alexion or designee will store the collected samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on danicopan continues but no longer than 5 years after the study ends or other period as per local requirements.

8.9. Exploratory Biomarkers

- Collection of samples for exploratory biomarker research is also part of this study.
- The following samples for biomarker research are required and will be collected from all patients in this study as specified in the SoA (Section 1.3, Table 4).
  - Biomarkers to be assessed include but are not limited to serum CP activity, serum C3 concentration, plasma FD concentration.

- Plasma samples will be stored and analysis may be performed on biomarkers including, but not limited to, FHR4 concentration (Cipriani, 2020), for their association with disease progression and clinical responses to danicopan.

The samples may be used to develop methods, assays for prognosis, diagnostics, and/or treatment monitoring related to the disease (early AMD to advanced AMD and complement inhibition).

The results of biomarker analyses may be reported in the CSR or in a separate study summary.

Alexion or designee will store the collected samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on danicopan continues but no longer than 5 years after the study ends or other period as per local requirements.

8.10. Health Related Quality of Life and Activities of Daily Living Assessments

Health-related QoL will be evaluated using the EuroQol 5-dimension 5-level (EQ-5D-5L) and NEI VFQ-25 questionnaires. Activity of daily living will be assessed using the Lawton Instrumental Activities of Daily Living (IADL) Scale.

Patient reported outcomes will be captured on paper. Validated local language versions of each of the tools will be provided, as needed. All measures should be administered by the Investigator or a qualified site staff, if possible, prior to other study procedures at visits specified in the SoAs.

8.10.1. National Eye Institute 25-item Visual Function Questionnaire

The NEI VFQ-25 scores will be analyzed as a secondary endpoint. The instrument (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. A composite score averages the vision related domains and ranges from 0 (worse) to 100 (best). The NEI VFQ-25 in patients with GA has been demonstrated to be a reliable and valid measure (Sivaprasad, 2018). If possible, the NEI VFQ-25 should be administered by the Investigator or a qualified site staff prior to other study procedures at visits specified in the SoAs.

8.10.2. EuroQol 5-Dimensions 5-Level

The EQ-5D-5L scores will be analyzed as an exploratory endpoint. This is a standardized instrument to measure health-related QoL and has been used in a wide range of health conditions. The EQ-5D-5L is defined by 5 dimensions: mobility, usual activities, self-care, pain/discomfort, and anxiety/depression. A 0 to 100 health state visual analog scale (VAS) accompanies the 5 dimensions, where 0 indicates worst health and 100 best health. A 0 to 1 index or utility score is calculated from the 5 dimensions using a preference-based value set, where 0 indicates a health state equivalent to death and 1 indicates perfect health. Negative values indicate health states considered worse than death. If possible, the EQ-5D-5L should be

administered by the Investigator or a qualified site staff prior to other study procedures at visits specified in the SoAs.

8.10.3. Lawton Instrumental Activities of Daily Living

The Lawton IADL (Lawton, 1969) scores will be analyzed as an exploratory endpoint. This is an assessment that evaluates the patient's ability for independent living. The IADL is used to capture the ability in functioning at the present time and in evaluating functioning improvements or deterioration over time. 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. The change from Baseline scores will be calculated at its prespecified time points as shown in the SoAs. If possible, the IADL should be administered by the Investigator or a qualified site staff prior to other study procedures at visits specified in the SoAs.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

9.1.1. Primary Hypothesis

The primary null hypothesis is that there is no dose-response effect for danicopan treatment in mean rate of change from Baseline in sqrt of total GA lesion area (mm) at 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 change from Baseline in sqrt of total GA lesion area (mm) at Week 52 in the study eye (the mean rate of change in at least one danicopan treatment arm is less than the mean rate of change in placebo).

9.2. Sample Size Determination

A total of approximately 332 patients will be randomized in 1:1:1:1 ratio to one of the four 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 of GA lesion 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 of GA lesion area at Week 52. The Multiple Comparison Procedure and Modeling (MCP-Mod) approach is used to establish the proof of concept (POC) with 4 candidate dose-response models at IA2 and Week 52. Further details will be provided in the statistical analysis plan (SAP). Based on simulations, this sample size will provide at least 90% power to detect the dose-response effect at Week 52 with 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.

9.3. Populations for Analyses

The analysis sets are defined as follows:

Table 10: Analysis Sets

Analysis Set	Description
Randomized Set	All randomized patients grouped by randomized treatment group (for reporting disposition, demographics, and baseline characteristics).
Full Analysis Set	All randomized patients who receive at least 1 dose (full or partial) of study drug grouped by randomized treatment group.

Table 10: Analysis Sets

Analysis Set	Description
Safety Set	All patients who receive at least 1 dose (full or partial) of study drug grouped by treatment actually received (for reporting exposure and safety data).
Per Protocol Set	All randomized patients who receive at least 1 dose (full or partial) of study drug and have no important protocol deviations that are likely to impact efficacy.
Pharmacokinetic (PK) Analysis Set	All patients who receive at least 1 dose (full or partial) of study drug and have at least 1 measurable concentration value
Pharmacodynamic (PD) Analysis Set	All patients who receive at least 1 dose (full or partial) of study drug and have at least 1 measurable PD value.

Abbreviations: PD = pharmacodynamic; PK = pharmacokinetic

9.4. Statistical Analyses

Statistical methods described in this section will be further elaborated in a separate SAP. Inference from efficacy analyses will be based on a 2-sided Type I error of 0.1 unless stated otherwise. The efficacy analysis population will be the full analysis set (FAS) unless stated otherwise. Summary statistics will be computed and displayed by treatment group and by visit, where applicable. Descriptive statistics for continuous variables will minimally include the number of patients, mean, SD, minimum, median, and maximum. For categorical variables, frequencies, and percentages will be presented. Graphical displays will be provided as appropriate.

9.4.1. Enrollment and Disposition

The number of patients screened, screen failures, and randomized patients will be presented. Enrollment information will be presented by randomization strata and treatment groups. The number of patients discontinued and reasons for discontinuation from the Primary Evaluation Period (Day 1 to Week 52), the Secondary Evaluation Period (Weeks 52 to 104), and the overall study will be summarized.

9.4.2. Demographics, Baseline Characteristics, Inclusion and Exclusion Criteria, and Protocol Deviations

All demographic information and baseline characteristics will be reported by the assigned treatment group and overall. The number and percentage of patients not meeting specific inclusion or exclusion criterion will be summarized. A similar summary will be provided for important protocol deviations based on prespecified categories.

9.4.3. Medical/Surgical History, Physical Examination

The medical and surgical history will be summarized by System Organ Class (SOC) and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1 or higher. Baseline physical examination information will also be summarized.

9.4.4. Prior and Concomitant Medications

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. All prior and concomitant medications will be summarized. Medications will be coded using the World Health Organization Drug Dictionary.

9.4.5. Efficacy Analyses

All efficacy analyses will be conducted on the FAS. Summary statistics will be computed and displayed by treatment group and visit for all efficacy endpoints.

9.4.5.1. Analyses of Primary Efficacy Endpoint

The attributes for the primary estimand are as follows:

- Treatment: Danicopan and placebo.
- Population: Patients with GA secondary to AMD as defined by the protocol inclusion/exclusion criteria.
- Variable: Change from Baseline to Week 52 in sqrt of 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.
- Summary measure: Treatment difference in mean rate of change from Baseline in sqrt of total GA lesion area at Week 52 between danicopan and placebo.

The objective of the primary analysis is to establish the proof of concept by detecting a dose response effect of danicopan treatment compared to placebo. The MCP-Mod approach (Bretz, 2005) will be used to establish the proof of concept with the pre-specified 4 candidate dose response models. Model-specific optimal contrast will be constructed based on the estimated mean change from Baseline at week 52 for each treatment group derived from the mixed-effect model for repeated measures (MMRM) approach as follows:

The model will include change from Baseline at postbaseline visits in the sqrt GA lesion area as the dependent variable and the following list of independent variables as fixed effects: time (years, continuous), the interaction between time (years, continuous) and treatment, baseline sqrt of GA lesion area, and the randomization strata.

In addition, the patient-specific random slope will be added to the model with an unstructured variance-covariance matrix to model the correlations among repeated measurements within each patient. Other covariance structures will be implemented if a convergence issue occurs. The Kenward-Rogers 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 missing at random. Further details will be provided in the SAP.

Given that the study may conduct an early proof of concept assessment at interim analysis 2 (see Section 9.5), adjusted Type I error boundaries will be derived using an alpha spending function (Hwang, Shih, and DeCani Gamma family) (Hwang, 1990) for IA2 and Week 52 analyses. Given the 1-sided nature of the dose-response hypothesis, the overall Type I error is considered for the primary analysis is 0.05. The multiplicity-adjusted p-values corresponding to the 4 optimal contrasts will be compared to the alpha boundary applicable for the Week 52 analysis. The POC will be established if at least one multiplicity-adjusted p-value is less than the alpha boundary.

If the POC is established, pairwise comparisons versus placebo will be performed to identify treatment arm(s) superior to placebo with statistical significance, with Hommel's multiplicity adjustment based on the estimated mean change derived from the MMRM approach described above. Same adjusted Type I error boundaries will be used as defined above.

The rate of change from Baseline (mm/year) for each treatment group will be estimated based on the coefficients for time and the interaction of time and treatment from the above mentioned MMRM model.

Sensitivity analyses using MMRM will be performed, the model will include change from Baseline in the sqrt GA lesion area as the dependent variable and the following list of independent variables as fixed effects: treatment, visit (categorical), the interaction between visit (categorical) and treatment, baseline sqrt of GA lesion area, and the randomization strata.

9.4.5.2. Analyses of Secondary Efficacy Endpoint(s)

9.4.5.2.1. 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 secondary efficacy endpoints at Week 52 include:

- 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 score
- Change from Baseline to Week 52 in macular 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 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) includes the following list of independent variables as fixed effects: time (years, continuous), the interaction between time (years, continuous) and treatment, baseline total GA lesion area, and the randomization strata. Treatment will include 4 groups: placebo, 100 mg bid, 200 mg bid, and 400 mg qd. The rate of change from Baseline (mm^2/year) for each treatment group will be estimated based on the coefficients for time and the interaction of time and treatment from the MMRM. In addition, the patient-specific random slope will be added to the model. The Kenward-Rogers 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 missing at random.

A sensitivity analysis using MMRM will be performed, the model will include change from Baseline in the total GA lesion area as the dependent variable and the following list of independent variables as fixed effects: treatment, visit (categorical), the interaction between visit (categorical) and treatment, baseline total GA lesion area, and the randomization strata.

The models for change from Baseline in BCVA, LLVA, LLD (BCVA-LLVA), monocular reading speed, NEI VFQ-25, macular EZ and sub-RPE compartment/drusen/RPE complex parameters include the following list of independent variables as fixed effects: treatment, visit (categorical), the interaction between visit (categorical) and treatment, corresponding baseline, and the randomization strata. Treatment group will include placebo, 100 mg bid, 200 mg bid, and 400 mg qd. In addition, the patient-specific random effect for visit will be added to the model with an unstructured variance-covariance matrix to model the correlations among repeated measurements within each patient. Other covariance structures will be implemented if a convergence issue occurs. Further details will be provided in the SAP. The Kenward-Rogers 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 missing at random.

9.4.5.2.2. Analyses for Secondary Efficacy Endpoints at Week 104

The objectives of the secondary analyses at are to evaluate the effect of danicopan on anatomical and functional outcomes of GA. Placebo patients 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 treatment groups are not different for the mean of the respective endpoints at Week 104; the alternative hypotheses are that at least two treatment groups are different for the mean of the respective endpoints at Week 104.

The secondary efficacy endpoints at Week 104 include:

- 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 score
- Change from Baseline to Week 104 in macular 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) include the following list of independent variables as fixed effects: time (years, continuous), the interaction between time (continuous) and treatment, corresponding baseline, and the 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. In addition, the patient-specific random slope will be added to the model. The Kenward-Rogers 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 missing at random.

The models for change from Baseline in BCVA, LLVA, LLD (BCVA-LLVA), monocular reading speeds, NEI VFQ-25, macular EZ, and sub-RPE compartment/drusen/RPE complex parameters include the following list of independent variables as fixed effects: treatment, visit (categorical), the interaction between visit (categorical) and treatment, corresponding baseline, and the 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. In addition, the patient-specific random effect for visit will be added to the model with an unstructured variance-covariance matrix to model the correlations among repeated measurements within each patient. Other covariance structures will be implemented if a convergence issue occurs. The Kenward-Rogers 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 missing at random.

9.4.5.3. Multiplicity Adjustment

Multiplicity adjustment will be conducted to control the family-wise error rate associated with multiple dose-response analyses and pairwise comparisons versus placebo at IA2 and Week 52. The Gamma spending function (Hwang, 1990) will be used for the alpha adjustment at IA2 and Week 52 analyses. If POC is established based on dose-response analysis, pairwise comparisons versus placebo will be performed with Hommel's step-up multiplicity adjustment. No

multiplicity adjustment will be done for secondary endpoint analyses. Further details will be provided in the SAP.

9.4.5.4. Analyses of Exploratory Endpoint(s)

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 patients in the FAS who were randomized to optimal danicopan dose and the placebo patients 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 nominal alpha level of 0.1. The treatment effects will be quantified by the estimated differences between the groups based on their original treatment arms (optimal dose vs. placebo) for both early-start and delayed-start periods. Additional details will be provided in the SAP.

Other analyses of exploratory endpoints, including the microperimetry subgroup analyses of the microperimetry endpoints will be described in the SAP. The MP subgroup includes all randomized patients who receive at least 1 dose of study drug and meet the eligibility criteria for microperimetry.

9.4.6. Safety Analyses

All safety analyses will be made on the Safety Set. The safety and tolerability of danicopan will be assessed based on AEs, clinical laboratory findings, vital sign findings, and ECG results.

Analysis and reporting for AEs will be based on ocular and non-ocular TEAEs, including treatment-emergent serious adverse events (TESAEs), defined as AEs with onset on or after the date of the first dose of study drug.

Treatment-emergent AEs and TESAEs will be summarized by MedDRA SOC and Preferred Term and by relationship to the study drug; TEAEs will also be summarized by severity. Patient-years adjusted event rates will be generated to characterize the long-term safety profile.

Laboratory measurements, including changes from Baseline at each visit and shifts from Baseline, if applicable, will be summarized descriptively. Weight, ECG, and vital signs will also be summarized using descriptive analyses.

9.4.7. 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 patients, mean/geometric mean, SD, median, minimum, and maximum) will be used to summarize the PK concentration data.

Descriptive statistics will be presented for all danicopan PD endpoints at each sampling time. The PD effects of danicopan will be evaluated by assessing the absolute 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.

9.5. Interim Analyses

9.5.1. Interim Analysis 1

The IA1 for futility may be conducted when approximately 50% of patients have completed the Week 28 Visit. 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 9.4.5 will be used for the conditional power calculation.

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

The Data Monitoring Committee (DMC) will capture the outcome of IA1 on the recommendation form in the charter. At IA1, additional assessment for macular EZ, outer retinal integrity, RPE compartment/drusen/RPE complex may be done by the unmasked Sponsor team (independent of the study team) for potential considerations of study futility and signal of anatomical response.

9.5.2. Interim Analysis 2

The IA2 may be conducted when approximately 50% of patients complete Week 52 Visit. There are two objectives of IA2.

- Futility assessment
- Early establishment of POC

A futility analysis that is similar to the IA1 will be conducted first. If the criterion for futility is not met, a dose-response analysis will be performed similarly as described in the Interim Analysis SAP and Section 9.4.5.1. The early dose-response effect at IA2 will be established if any multiplicity adjusted *p*-value from MCP-Mod is less than the alpha boundary from the Gamma spending function at IA2. All patients will continue in the study regardless of the establishment of early POC at IA2.

If early dose-response effect is established, pairwise comparison of each active treatment versus placebo will be performed with Hommel's step-up multiplicity adjustment method. The adjusted p-values will be compared to the same alpha boundary used for dose-response analysis at IA2.

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

The DMC will capture the outcome of IA2 on the recommendation form in the charter.

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

Upon receipt of the DMC recommendation, the final determination if the optimal dose can be identified, will be made by an unmasked Sponsor team (independent of the study 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 patients either complete the Week 52 Visit or discontinue, and will be based on the totality of data.

The detailed analysis strategies will be pre-specified in interim analysis plan (IAP).

9.6. 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 IA.

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

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, substantial protocol amendments (ie, modifications), ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator/Alexion and reviewed and approved by the IRB/IEC before the study is initiated.
  - If any of these documents require regulatory/health authority approval per local regulations, Alexion will also obtain such approval before the study is initiated.
- Any substantial amendments to the protocol will require IRB/IEC and regulatory/health authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- For studies to be approved by the Medicines and Healthcare products Regulatory Agency: The Investigator will notify the IRB/IEC of deviations from the study protocol or GCP as defined by UK legislation as a serious breach or as required by IRB/IEC procedures.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures per local regulations
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, EU Directive 2001/20/EC, EU CTR 536/2014 for clinical studies, and all other applicable local regulations
  - Promptly notifying Alexion of any (potential) serious breach of the protocol or regulations (including if a data breach compromises the integrity, confidentiality, or availability of the personal data of participants) so that legal and ethical obligations are met. A ‘serious breach’ means a breach likely to affect to a

significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.

- In certain regions/countries, Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - Alexion will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority (including data protection authorities and, if applicable, affected participants in case of a personal data breach), IRB/IEC, and Investigators. Under EU CTR 536/2014, Alexion is required to enter details of serious breaches into the European Medicines Agency (EMA) Clinical Trials Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The Investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the Investigator/institution are able to identify the occurrence of a (potential) serious breach, including personal data breaches.
  - A (potential) serious breach is promptly reported to Alexion or delegated party, through the contacts (email address or telephone number) provided by Alexion.
- Where applicable:
  - Alexion and the site have taken all necessary steps to avoid personal data breaches and have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining and keeping systems and information technology (IT) security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).
  - Both Alexion and the study site have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
  - In compliance with applicable laws, the data controller for the processing activity where the personal data breach occurred (Alexion or respectively the study site) will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
  - If participants need to be notified of a personal data breach, the notification to participants is done by the site for the data breaches that occur within the processing activities for which the site is the data controller. For data breaches that occur within the processing activities of Alexion as the data controller, the notification is done in collaboration with the site and is performed by the site and/or Investigator, acting on behalf of Alexion, so that Alexion has no access to the identifying personal information of the participants. The site and/or Investigator shall conduct the notification by contacting the participants using the information that they gave for communication purposes in clinical research.

  - If a personal data breach occurs in a processor's systems engaged by Alexion, the processor under contractual obligations with Alexion promptly and in due course after discovering the breach, notifies Alexion and provides full cooperation with the investigation. In these cases, to the extent Alexion is the data controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to participants. If the personal data breach needs to be notified to the participants, the notification is done in collaboration with the site and is performed by the site and/or Investigator, acting on behalf of Alexion, so that Alexion has no access to the identifying personal information of the participants.

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- It is the responsibility of the Investigator or designee to obtain signed (written or electronic signature) informed consent from all participants, or the participant's legally authorized representative, prior to performing any study-related procedures including screening assessments.
- The Investigator or designee will explain the nature of the study (including but not limited to the objectives, potential benefits and risks, inconveniences, and the participant's rights and responsibilities) to the participant or his/her legally authorized representative, defined according to local and country regulations where the study is taking place, and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent or a certified translation, if applicable, that meets the requirements of 21 CFR 50, local regulations, EU General Data Protection Regulation (GDPR), ICH GCP guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The participant's medical record must include a statement that signed (written or electronic) informed consent was obtained before any screening procedures were performed with a participant, and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF(s).
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study, as applicable.

- A copy of the signed (written or electronic) informed consent documentation (ie, a complete set of participant information sheets and fully executed signature pages) must be provided to the participant or the participant's legally authorized representative, as applicable. This document may require translation into the local language. Original signed (written or electronic) consent forms must remain in each participant's study file and must be available for verification at any time.

10.1.4. Recruitment Strategy

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

10.1.5. Data Protection

- Participants will be assigned a unique identifier by a Trusted Third Party contracted by Alexion. Any participant records or datasets that are transferred to Alexion will contain the identifier only; participant names, initials, or any information which would make the participant identifiable will not be transferred.
- Participants must be informed that their personal study-related and coded (pseudonymized) data, who will have access to their personal data, how and how long it will be used, and that it will be used by Alexion in accordance with local data protection law. In addition, multiple local laws require that participants must also be informed of any individuals rights they may have with regard to their personal data. Participants will be informed about how their personal study-related data will be disclosed, and are provided with the appropriate legal basis for which a controller processes their personal data. The level of disclosure, the security controls used to protect their data, and information regarding any transfer of their personal data outside of their country or region must also be explained to the participant.
- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Alexion, appropriate IRB/IEC members, any third parties acting on behalf of Alexion, and inspectors from regulatory authorities.
- Alexion and the site as a data controller have implemented privacy and security controls designed to help protect participant personal data, including information security controls, firewalls, incident detection, and secure transfer measures.
- The contract between Alexion and study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

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

10.1.6. Dissemination of Clinical Study Data

Study-related information and study results may be posted on publicly accessible clinical study databases (eg, the US website www.clinicaltrials.gov or the EU website www.clinicaltrialsregister.eu), as appropriate, and in accordance with national, regional, and local regulations.

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

- Study is still ongoing in other countries or regions

- Study is part of an ongoing review for approval by Health Authorities; study result data deferral request can be submitted.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to Alexion or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Alexion or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
  - Remote source data verification may be employed where permitted by local regulations.
  - The scope of the source data verification will be described in detail in the Clinical Monitoring Plan.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for at least 25 years after study completion or per local regulations or institutional policies. No records may be destroyed without the written approval of Alexion. No records may be transferred to another location or party without written notification to Alexion. Clinical study documents and records required as part of the trial master file (TMF) are archived and stored by Alexion for at least 30 years.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The Investigator or designee will prepare and maintain adequate and accurate source documents (eg, medical records,

ECGs, AE and concomitant medication reporting, raw data collection forms) designed to record all observations and other pertinent data for each participant.

- Data reported on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The eCRFs must be completed by the Investigator or designee as indicated in the site delegation log. Source documents are filed at the investigational site. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available to Alexion, Alexion delegates, and health authorities, as requested.
- Definition of what constitutes source data and its origin can be found in monitoring guidelines.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Alexion or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Per ICH E6 (R2) guidelines and good documentation practice requirements, source documents and study records in all media (eg, paper, electronic) must be Attributable, Legible, Contemporaneous, Original, Accurate, and Complete.

10.1.9. Study and Site Start and Closure

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

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

Study sites will be closed after the study is completed or following the decision to close or terminate the study. A study site is considered closed when all participants have completed the EOS or ET Visit, all data have been collected and entered into the electronic data capture (EDC) system, all required documents and study supplies have been collected and reconciled, and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by Alexion or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Alexion’s procedures, or ICH GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Total number of participants included earlier than expected
- Discontinuation of further study drug development

Alexion or health authority may terminate the study for reasonable cause. Conditions that may warrant stopping or discontinuing the study may include but are not limited to:

- The incidence or severity of AEs in this study indicate a potential health hazard to participants taking part in the trial.
- If any information leads to conclude that the benefit/risk ratio of the clinical trial is negative.
- Alexion decision to suspend or discontinue testing, evaluation, or development of the study intervention

If the study is prematurely terminated or suspended, Alexion shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate patient therapy and/or follow-up.

10.1.10. Publication Policy

- Alexion strives to publish results from all research studies regardless of whether the findings are positive, negative, or inconclusive, or whether the product is investigational, licensed, or has been discontinued or withdrawn from the market. The minimum commitment is to all Phase 2 and Phase 3 clinical studies. Alexion also commits to publish other studies of significant scientific or medical importance including, but not limited to Phase 1 clinical studies, discovery, research, epidemiology, and health economics and outcomes research.
- Where possible, primary manuscripts reporting results of the primary efficacy endpoint or the final results will be submitted for publication to peer-reviewed, indexed (eg, PubMed, Scopus, Embase) journals within 12 to 18 months of the primary evaluation date or EOS, whichever is earlier.
- Investigators who participate as authors in manuscripts derived from Alexion-sponsored studies will agree to the prerequisites as outlined in the Alexion Author Letter of Agreement prior to engaging in manuscript development.
- The Investigator agrees to submit proposals for new manuscripts (whether or not the proposed analyses are derived from protocol-specified endpoints) to Alexion for review and consideration. All manuscripts or abstracts emanating from approved proposals are to be submitted to Alexion for review before submission to the journal/society. This allows Alexion to protect proprietary information and provide comments.
  - The proprietary nature of some development work may preclude publication. In some cases, it may be necessary to delay a publication to allow Alexion to ensure protection of intellectual property.
- Primary publications, including congress and journal publications, containing the protocol-specified results of a study should occur prior to the publication of individual study site results or case reports. Alexion's policy prohibits duplicate

publication, whereby the same results must not be published in multiple peer-reviewed journal manuscripts.

  - Encore congress publications may be appropriate to allow communication of research findings to relevant audience and geographical regions.

- Alexion will comply with the requirements for publication of study results as defined by the Pharmaceutical Research and Manufacturers of America and the International Committee of Medical Journal Editors and per the Alexion Publication Policy. In accordance with standard editorial and ethical practice, Alexion will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship recommendations and per the Alexion Publication Policy.
  - Alexion will publish Plain Language Summaries and include patients and/or caregivers as reviewers for readability and understanding of lay person language.
- No compensation shall be provided to external Authors for authorship of publication, including drafting or revising a publication. Alexion may reimburse the presenting Author of an Alexion-supported publication for travel, lodging, and registration to present a poster or oral presentation at scientific meeting, consistent with the Alexion Global Procurement and Sourcing Procedure, the Alexion Antibribery Anticorruption Policy, and the Alexion Global Travel and Expense Policy.
- Authors must disclose financial or personal affiliations that could be considered a conflict of interest in the publication.
  - Investigators who participate as authors in manuscripts derived from Alexion sponsored studies will agree to the prerequisites as outlined in the Alexion Author Letter of Agreement prior to engaging in manuscript development.
- More details are provided in the Alexion/AstraZeneca Publication Policy

10.1.11. Good Clinical Practice Compliance

Alexion and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 R2, EU Directive 2001/20/EC, EU CTR 536/2014 as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of Alexion and/or the company organizing/managing the research on behalf of Alexion to inspect study data, participants' medical records, and eCRFs in accordance with current GCP and respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

Alexion ensures that local regulatory authority requirements are met before the start of the study. Alexion (or designee) is responsible for the preparation, submission, and confirmation of receipt

of any regulatory authority approvals required prior to release of the study drug for shipment to the site.

10.2. Disease Classification of Age-Related Macular Degeneration

The disease classification of AMD is presented in Table 11. The definitions to be used in analyses will be outlined by the Reading Center documentations.

Table 11: Clinical Classification of AMD

Classification of AMD	Subcategory	Definition
No apparent aging changes[a]	N/A	• No drusen AND • No AMD pigmentary abnormalities[b]
Normal aging changes[a]	N/A	• Only drupelets (small drusen ≤ 63 µm) AND • No AMD pigmentary abnormalities[b]
Early dry AMD[a]	N/A	• Medium drusen > 63 µm and ≤ 125 µm AND • No AMD pigmentary abnormalities[b]
Intermediate dry AMD[a] (iAMD)	High-risk drusen	Large soft drusen, drusen with hollow core, or subretinal drusenoid deposit observed in SD-OCT[c]
	Non-exudative neovascular AMD[d]	Evidence of macular neovascularization by SD-OCT, but no leakage on FA and no macular fluid by SD-OCT imaging
	iRORA[e]	• A region of signal hypertransmission into the choroid, AND • A corresponding zone of attenuation or disruption of the RPE, with or without persistence of basal laminar deposits, AND • Evidence of overlying photoreceptor degeneration, that is, subsidence of the INL and OPL, presence of a hyporeflective wedge in the HFL, thinning of the ONL, disruption of the ELM, or disintegrity of the EZ, AND • When these criteria do not meet the definition of cRORA

Table 11: Clinical Classification of AMD

Classification of AMD	Subcategory	Definition
Late wet (exudative neovascular) or dry (geographic atrophy) AMD[a]	cRORA[f]	• Region of hypertransmission of at least 250 µm in diameter in any lateral dimension, AND • Zone of attenuation or disruption of the RPE of at least 250 µm in diameter, AND • Evidence of overlying photoreceptor degeneration. Features of photoreceptor degeneration include all of the following: – loss of the IZ, EZ, and ELM and thinning of the ONL. • AND absence of scrolled RPE or other signs of an RPE tear.
	Exudative neovascular AMD[d]	• Evidence of macular neovascularization and macular fluid by SD-OCT, evidence of leakage on FA.

[a] Ferris (2013) Beckman Initiative for Macular Research Classification Committee
[b] AMD pigmentary abnormalities are any definite hyper- or hypopigmentary abnormalities associated with medium or large drusen but not associated with known disease entities
[c] Zweifel (2010)
[d] Laiginhas (2020)
[e] Guymer (2020) Classification of Atrophy Meeting Report 4
[f] Sadda (2018) Classification of Atrophy Meeting Report 3
Abbreviations: AMD = age-related macular degeneration; cRORA = complete RPE and outer retinal atrophy; ELM = external limiting membrane; EZ = ellipsoid zone; FA = fluorescein angiography; HFL = Henle fiber layer; iAMD = intermediate AMD; INL = inner nuclear layer; iRORA = incomplete RPE and outer retinal atrophy; IZ = interdigitation zone; N/A = not applicable; OCT = optical coherence tomography; ONL = outer nuclear layer; OPL = outer plexiform layer; RPE = retinal pigment epithelium; SD-OCT = spectral-domain optical coherence tomography

10.3. Ocular Assessments

It is recommended that ocular assessments should be performed according to the sequence described below. Assessments that do not require dilation must be performed before dilation is implemented.

All assessments must be performed by trained and certified personnel (eg, a licensed medical doctor of ophthalmology or ocular technician) according to the Central Reading Manual.

10.3.1. Best-Corrected Visual Acuity Testing

BCVA will be measured at following schedule specified in the SoA (Section 1.3) prior to dilation. Monocular BCVA for both eyes and binocular BCVA tests will be conducted.

- The following are needed to conduct the examination:
  a. Examination lane of adequate dimensions to allow testing at required starting distance of 4 meters
  b. Standard chair with a firm back
  c. Set of 3 visual acuity charts (Original Series ETDRS Charts R, 1, and 2, EU Wide ETDRS Charts 1, 2, 3, or PV Number Charts 2750, 2750A, and 2750B)
  d. Retro-illuminated fluorescent or LED lightbox
  e. Study frame
  f. Study lens set
- A VA specifications document, procedure manual, and training materials will be provided to the investigational sites.
- The VA examination room and equipment must be validated before any VA examinations are performed.

10.3.2. Low Luminance Best-Corrected Visual Acuity Testing

The same requirements as the BCVA described in Section 10.3.1 apply for LL BCVA. In addition, LLVA will be measured by placing a 2.0-log-unit neutral density filter (Kodak Wratten 2.0 Neutral Density Filter) over the best correction for that eye and having the patient read the normally illuminated ETDRS charts.

10.3.3. Reading Speed Testing

One of two reading speed instruments may be used. Reading speed testing is only applicable if the charts are available in the local language.

10.3.3.1. Minnesota Low-Vision Reading Test (MNRead)

The MNRead acuity cards can be used to measure the reading speed according to the schedule specified in the SoA (Section 1.3). Both monocular and binocular reading speed will be recorded. The MNRead acuity cards consist of single, simple sentences with equal numbers of characters. The print is a proportionally spaced font, similar to that found in many newspapers and books. The cards contain sentences with 19 different print sizes. The text is printed with high contrast (approximately 85%). Each sentence contains 60 characters (including space between each word and at the end of each line) printed as three lines with even left and right margins. The

vocabulary used in the sentences is selected from words appearing with high frequency in second- to third-grade reading materials (Calabrèse, 2016). The detailed information about equipment required, card illumination, viewing distance, test procedure and instruction to patients will be provided to the study sites prior to the start of the study. Examples of the MNReading Charts are found in https://www.precision-vision.com/products/visual-acuity-reading-charts/reading-charts/hand-held-reading-charts/mnread-chart-in-english-spanish/.

10.3.3.2. Radner Reading Cards

The Radner Reading Cards (Radner, 2017) can be used to measure the reading speed if MNRead card is not available. The assessment is to be conducted in each eye separately and then with both eyes open at the schedule specified in the SoA (Section 1.3). The test consists of 24 short sentences that are highly comparable in terms of number of words, word length, position of words, lexical difficulty, and syntactical complexity. The detailed information about equipment required, card illumination, viewing distance, test procedure and instruction to patients will be provided to the study sites prior to the start of the study. Examples of the Radner Reading Card are found in https://www.precision-vision.com/products/visual-acuity-reading-charts/reading-charts/hand-held-reading-charts/radner-reading-chart-in-multiple-languages/.

10.3.4. Mesopic Microperimetry at Selected Sites

Mesopic microperimetry will be performed in a subset of patients (microperimetry subpopulation).

Assessments with a validated microperimetry device will be performed at the schedule specified in the SoA (Section 1.3).

The test should be performed by certified personnel trained on the microperimetry device using grid customized for the study.

The microperimetry will be performed on patients who meet eligibility criteria as defined in the inclusion and exclusion criteria (Section 5). If the Investigator determines that both eyes of a patient meet the eligibility criteria for study eye, mesopic microperimetry will be performed on both eyes at Screening. Two tests per eye will be performed and up to 3 attempts are allowed to meet eligibility criteria during the Screening Visit.

The Central Reading Center will provide the study manual and training materials. Microperimetry operators, systems, and software will be certified prior to any evaluation of patients.

10.3.5. Slit-lamp Examination

Slit lamp biomicroscopy must be completed by a licensed medical doctor of ophthalmology or ocular technician.

It will be performed for both eyes at the schedule specified in the SoA (Section 1.3) to assess eyelids/conjunctiva, cornea, iris, pupil, lens, anterior chamber, and anterior vitreous.

10.3.6. Tonometry/Intraocular Pressure

Intraocular pressure will be conducted for both eyes after all VA assessments have been conducted.

- Measure IOP according to the Investigator's standard of care, recommended prior to dilating the eyes. Goldmann applanation tonometry must be used at Screening. Tono-pen or other calibrated tonometers can be used at other times. Goldmann applanation tonometry must also be used to verify the reading of ≥ 30 mmHg occurring at any time
- Within a single patient, utilize the same instrument type to measure IOP during each visit after screening.
- Record the measurement in mmHg.

10.3.7. Dilated Binocular Indirect High-Magnification Ophthalmoscopy

Dilated fundus examination for both eyes will be performed using indirect high magnification ophthalmoscopy by a licensed medical doctor of ophthalmology or ocular technician.

- Assess the vitreous, retina, macula, choroid, optic nerve, and cup/disc ratio.
- Document all clinical observations.

10.3.8. Ocular Imaging Assessments

- Ocular images will be taken after dilation.
- The Central Reading Center will provide sites with the Central Reading Manual and training materials for specified study ocular images and microperimetry (at selected sites). Before any study images and microperimetry are obtained, site personnel, test images, and systems and software (where applicable) will be certified/validated by the Central Reading Center as specified in the Central Reading Manual.
- All ocular images and microperimetry results will be obtained by trained site personnel at the study sites and forwarded to the Central Reading Center for independent analysis and/or storage.
- All images will be transferred to the Central Reading Center as digital files (ie, no printed images will be sent).
- For angiography, digital angiograms must be used while conducting angiographic evaluations. Film-based angiography is not acceptable.
- All images will be pseudonymized to protect patient privacy.
- Images will be assessed centrally by graders masked to the patient treatment allocation
- As much as possible, the same equipment and system will be used for the duration of the study.
- Refer to the Central Reading Manual
- The following imaging assessments will be performed for both eyes, recommended to be done in the following order:

1. FAF
2. NIR
3. SD-OCT

4. FA
5. CFP

- Administration of artificial tears between acquisition of each eye for FAF/NIR and SD-OCT is recommended.

10.3.9. Biometry

At Screening, if equipment is available, axial length will be measured for both eyes using biometry according to the Investigator's standard of care.

10.4. Patient-Reported Outcome Instruments

10.4.1. National Eye Institute 25-Item Visual Function Questionnaire

Detailed information about this questionnaire with the correct version and the validated language versions, if needed, will be provided to the study sites prior to the start of the study. More information about this questionnaire can be found in https://www.rand.org/health-care/surveys_tools/vfq.html (Mangione, 2001; Radner, 2017).

10.4.2. EuroQol 5-Dimension 5-Level

Detailed information about this questionnaire with the correct version and the validated language versions, if needed, will be provided to the study sites prior to the start of the study. More information about this instrument is found in https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/.

10.4.3. Lawton Instrumental Activities of Daily Living Scale

Detailed information about this questionnaire with the correct version and the validated language versions, if needed, will be provided to the study sites prior to the start of the study (Graf, 2008).

10.5. Clinical Laboratory Tests

- The tests detailed in Table 12 will be performed by the central laboratory as indicated.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be available in the patient's source documents.
- Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 12: Protocol-Required Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other Assessments[1]
Complete blood count (CBC), including: Red blood cell (RBC) count White blood cell (WBC) count **WBC differential (absolute and percent):** - neutrophils - lymphocytes - monocytes - eosinophils - basophils Hematocrit (Hct) Hemoglobin (Hgb) Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Mean platelet volume (MPV)	**Liver function tests:** -Alanine aminotransferase (ALT) -Alkaline phosphatase -Aspartate aminotransferase (AST) -Gamma-glutamyl transferase (GGT) Albumin Bicarbonate (HCO_3) Bilirubin (fractionated)[2] Blood urea nitrogen (BUN) Calcium Calculated eGFR[3] Chloride C-reactive protein (CRP) Creatine kinase[4] Creatinine Glucose[5] HbA1c (glycated hemoglobin)	**Analysis including:** Bilirubin Color Glucose Ketones Leukocytes Nitrite Occult blood pH Protein Specific gravity Urobilinogen Microscopic examination of sediment	**Biomarkers:** Alternative pathway activity Bb C3 Classical pathway activity Factor D **Serology:** -HCV antibody and HBV antigen -HIV-1 and HIV-2 antibodies UGT1A1 (Gilbert's)[6] Genetic biomarkers (optional) Drug concentrations for PK FSH for females

Table 12: Protocol-Required Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other Assessments[1]
Platelet count PT/PTT/INR Red cell distribution width (RDW) Reticulocyte count (absolute and percent)	Lactate dehydrogenase **Lipid profile including:** Cholesterol/HDL ratio High-density lipoprotein cholesterol (HDL-C) Low-density lipoprotein cholesterol (LDL-C) Non-HDL-C Total cholesterol Triglycerides Very low-density lipoprotein cholesterol (VLDLC) Potassium Sodium Total protein Uric acid		

1. Check the SoA for specific time points when these tests should be done.
2. Fractionate and obtain measurements of direct and indirect bilirubin for all patients. If indirect bilirubin levels are > ULN at Screening but ALT and AST are normal, test for Gilbert's syndrome.
3. Provide estimated glomerular filtration rate (eGFR) based on Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) creatinine equation (2009) for patients ≥ 19 years of age and based on the "bedside Schwartz" equation (2009) for patients < 19 years of age.
4. Perform at Baseline, and then subsequently at every visit, a lab sample is collected.
5. If glucose is > ULN, reflexively test HbA1c.
6. Test only if medical or family history suggestive of Gilbert's Syndrome.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unmask the study will not be reported to investigative sites or other masked personnel until the study has been unmasked. In case emergency unmasking is necessary, see Section 6.3.3.

10.6. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.6.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (ICH E2A). • **Note**: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease [new or exacerbated] temporally associated with the use of the study drug, whether or not considered related to the study drug.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events Not Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): The condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (eg, hospitalization for elective surgery if planned before the signing the ICF, admissions for social reasons or for convenience). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • A medication error (including intentional misuse, abuse, and overdose of the product) or use other than what is defined in the protocol is not considered an AE unless there is an untoward medical occurrence as a result of a medication error. • Cases of pregnancy that occur during maternal or paternal exposure to study drug are to be reported within 24 hours of Investigator/site awareness. Data on fetal outcome and breastfeeding will be collected for regulatory reporting and safety evaluation.

Events Not Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

10.6.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
1. Results in death
2. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it was more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.
4. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
5. Is a congenital anomaly/birth defect
6. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-

An SAE is defined as any untoward medical occurrence that, at any dose:

threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

An event that is assessed as serious by the Investigator and/or Alexion that is not listed in the appropriate Reference Safety Information (RSI) and has been assessed that there is at least a reasonable possibility that the event is related to the investigational medicinal product by the Investigator and/or Alexion.

Alexion has procedures that will be followed for the recording, medical assessment, and expedited reporting of SUSARs that are consistent with global regulations, legislation, and guidance documents.

Suspected unexpected serious adverse reactions will undergo expedited reporting to the national regulatory authorities, IRBs/IECs, and Investigators following local regulatory reporting requirements where applicable.

10.6.3. Recording and Follow-Up of AE and/or SAE

Recording of AE and/or SAE

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is not acceptable for the Investigator to send photocopies of the patient's medical records to Alexion in lieu of completion of the Alexion AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by Alexion. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to Alexion.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories from National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0, published 27 Nov 2017:

- Grade 1: Mild (awareness of sign or symptom, but easily tolerated)
- Grade 2: Moderate (discomfort sufficient to cause interference with normal activities)
- Grade 3: Severe (incapacitating, with inability to perform normal activities)
- Grade 4: Life-threatening
- Grade 5: Fatal

Recording of AE and/or SAE

An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between the study drug and each occurrence of each AE or SAE. An Investigator causality assessment must be provided for all AEs (both nonserious and serious). This assessment must be recorded in the eCRF and on any additional forms, as appropriate. The definitions for the causality assessments are as follows:
  - Not related: There is no reasonable possibility the study drug caused the AE.
    - The AE has a more likely alternative etiology; it may be due to underlying or concurrent illness, complications, concurrent treatments, or effects of another concurrent drug.
    - The event does not follow a reasonable temporal relationship to administration of the study drug.
  - Related: There is a reasonable possibility the study drug caused the AE.
    - The AE has a temporal relationship to the administration of the study drug.
    - The event does not have a likely alternative etiology.
    - The event corresponds with the known pharmaceutical profile of the study drug.
    - There is improvement on discontinuation and/or reappearance on rechallenge.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to Alexion. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Alexion.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Alexion to elucidate

Follow-up of AEs and SAEs
the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • New or updated information will be recorded in the originally completed eCRF. • The Investigator will submit any updated SAE data to Alexion within 24 hours of receipt of the information.

10.6.4. Reporting of SAEs

SAE Reporting to Alexion via an Electronic Data Collection Tool
• All SAEs will be recorded and reported to Alexion immediately and within 24 hours of awareness. • The primary mechanism for reporting an SAE to Alexion will be the EDC system. • If the electronic system is unavailable or site staff is unable to process the SAE via the EDC system at the time that the Investigator or site becomes aware of an SAE, the site will use the paper Contingency Form for SAE Reporting via facsimile or email. Facsimile transmission or email may also be used in the event of electronic submission failure. – Email: clinicalsae@alexion.com or Fax: + 1.203.439.9347 • The site will enter the SAE data into the EDC system as soon as it becomes available. • When further information becomes available, the EDC should be updated immediately with the new information and an updated SAE report should be submitted to Alexion Global Drug Safety (GDS) within 24 hours of Investigator/site awareness. • After the patient has completed the study, no new data or changes to existing data are expected to be entered in the EDC system. o If a site receives a report of a new SAE from a study patient which the Investigator considers to be related to the study drug, or the site receives updated data on a previously reported SAE after the EDC system has been taken offline, then the site can report this information on a paper Contingency Form for SAE Reporting via facsimile or email.

10.6.5. Unexpected Events

Apart from the reporting of SUSARs, there may be other events which are relevant in terms of benefit-risk balance and which should be reported in a timely manner according to regional and national requirements eg, EU CTR 536/2014 (48). It is important for patient safety that, in addition to SAEs and reactions, all unexpected events that might materially influence the benefit-risk assessment of the study intervention or that would lead to changes in the administration of the study intervention or in overall conduct of a clinical trial should be reported. Examples of such unexpected events include an increase in the rate of occurrence of expected serious adverse reactions which may be clinically important, a significant hazard to the patient population, such as lack of efficacy of a medicinal product, or a major safety finding from a newly completed animal study (such as, carcinogenicity).

Under the EU CTR 536/2014 (49), where unexpected events require an urgent modification of a clinical trial, it should be possible for Alexion and the Investigator to take urgent safety measures

without awaiting prior authorization. If such measures constitute a temporary halt of the clinical trial, Alexion should apply for a substantial modification before restarting the clinical trial.

10.7. Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or Alexion AxMP that either causes harm to the participant or has the potential to cause harm to the participant.

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

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

Medication error includes situations where an error:

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

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

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

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

- Errors related to or resulting from IRT/RTSM - including those which led to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose (refer to Section 8.5) for information on overdose])
- Participant failed to return unused medication or empty packaging

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

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or Alexion AxMP for a perceived reward or desired non-therapeutic effect.

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

Examples of drug abuse include but are not limited to:

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

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or Alexion AxMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or Alexion AxMPs, outside the intended use as specified in the protocol, including deliberate administration of the product by the wrong route.

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

Examples of drug misuse include but are not limited to:

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

10.8. Contraceptive Guidance and Collection of Pregnancy Information

10.8.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

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

Postmenopausal Female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause prior to the Day 1 Visit.

A high FSH level in the postmenopausal range will be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement may be required.

Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal, highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.8.2. Contraception Guidance for Female Patients

All female patients in this study are postmenopausal and of non-child-bearing potential as confirmed by FSH test at Screening. Contraception for female patients is not needed.

10.8.3. Contraception Guidance for Male Patients

Contraceptive use by male patients should be consistent with local regulations regarding the methods of contraception utilized for those participating in clinical studies. If teratogenic effects are suspected to be transferred to a fetus/embryo from a female spouse/partner of a male patient, pregnancy follow-up information will be obtained for the partner who becomes pregnant (refer to Section 10.8.4.1). In these cases, follow-up will be conducted on the pregnant partner in the same manner as a female patient who becomes pregnant during the study.

10.8.3.1. Guidance for Male Patients

Contraception is the responsibility of the heterosexually active male patients in the study, regardless of his female partner's method of contraception.

Male patients who have had a vasectomy > 6 months prior to the first dose of the study drug must use a condom with or without spermicide during heterosexual intercourse. Male patients who have had a vasectomy < 6 months prior to the first dose of the study drug and those who have not had a vasectomy must use a condom with or without spermicide during heterosexual intercourse for at least 90 days after their final dose of the study drug.

10.8.3.2. Sexual Abstinence for Male Patients

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. In this study, abstinence is only acceptable if consistent with the patient's preferred and usual lifestyle. Abstinent male patients who become heterosexually active must use a condom with or without spermicide during intercourse.

Periodic abstinence (eg, calendar, symptothermal, or post ovulation methods for a female partner) is not considered a highly effective method of contraception for male patients.

Male patients must not donate sperm from the Day 1 Visit until 90 days after their final dose of the study drug.

10.8.4. Collection of Pregnancy Information

Pregnancy data will be collected during this study for all female spouses/partners of male patients after the first dose of study drug.

Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of study drug via semen following paternal exposure. If a male patient's female spouse/partner becomes pregnant during the conduct of this study, the Investigator must submit the "Pregnancy/Breastfeeding Reporting and Outcome Form" to Alexion GDS via facsimile or email. When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion GDS. If additional follow-up is required, the Investigator will be requested to provide the information.

Pregnancy is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly). Elective abortions without complications should not be reported as AEs.

10.8.4.1. Male Patients with Partners Who Become Pregnant

- The Investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. This applies only to male patients who receive the study drug.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate "Pregnancy/Breastfeeding Reporting and Outcome Form" and submit it to Alexion within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Alexion. Generally, the follow-up will be no longer than 3 months following the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.9. Allowed Medications

Clinically significant drug-drug interaction between danicopan and medications that are substrates of cytochrome P450 subfamily 3A4 (CYP3A4), and/or uridine 5'-diphospho-glucuronosyltransferase (UGT) are not anticipated (see Investigator's Brochure).

Clinical drug-drug interaction studies indicate that danicopan is an inhibitor of P-gp and BCRP transporters. Caution may be needed when co-administering danicopan with drugs known to be P-gp and/or BCRP substrates (eg, some statins). For more details, refer to the Investigator's Brochure.

For ease of reference, a non-comprehensive list of medications that are sensitive substrates for CYP3A4, P-gp, and/or UGT1A1/2B7, which are allowed in this patient population, is provided in **Error! Reference source not found.** below.

Use of specific concomitant medications with a narrow therapeutic index (ie, P-gp or BCRP substrates) will be considered on a case-by-case basis with decisions made by the Principal Investigator in discussion with the Medical Monitor, based on available knowledge of danicopan as well as the characteristics of the potential concomitant medication.

Table 13: List of CYP3A4, P-gp, and UGT1A1/2B7 Sensitive Substrates

Classification	Medication
CYP3A4 substrate	alfentanil, aliskiren[b], ambrisentan[b], apixaban[b], atorvastatin[a], avanafil, azithromycin[b], budesonide, buprenorphine, buspirone, cannabidiol, cerivastatin[a,b], colchicine[b], conivaptan, cyclosporine[b], dabigatran etexilate[b], darifenacin, darunavir, dasatinib, domperidone[b], dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, fentanyl, ibrutinib, indinavir, irinotecan, lomitapide, loperamide[b], lovastatin[a], lurasidone, maraviroc, midazolam, naloxegol, nisoldipine, quetiapine, quinidine[b], ranolazine[b], rivaroxaban[b], saquinavir, sildenafil, simvastatin[a], sirolimus[b], tacrolimus[b], ticagrelor[b], tipranavir, tolvaptan, triazolam, upadacitinib[b], vardenafil, venetoclax[b]
P-gp substrate[c]	aliskiren, ambrisentan, apixaban, atorvastatin, azithromycin, berotralstat, cerivastatin, colchicine, cyclosporine, dabigatran etexilate, digoxin, domperidone, edoxaban, fexofenadine, loperamide, phenytoin, quinidine, ranolazine, rivaroxaban, sirolimus, tacrolimus, ticagrelor, upadacitinib, venetoclax
UGT1A1 substrate	buprenorphine, carvedilol, dabigatran etexilate, irinotecan, telmisartan
UGT2B7 substrate	acemetacin, ambrisentan, buprenorphine, cannabidiol, carvedilol, codeine, dabigatran etexilate, diclofenac, etodolac, flurbiprofen, ibuprofen, indomethacin, ketorolac, lorazepam, loxoprofen, naloxone, naproxen, oxazepam, suprofen, zaltoprofen

Abbreviations: CYP = cytochrome P450 subfamily 3A4; P-gp = P-glycoprotein;
UGT = uridine 5'-diphospho-glucuronosyltransferase

[a] These CYP3A substrates are also BCRP substrates; caution may be needed in co-administering with danicopan.

[b] These CYP3A substrates are also P-gp substrates; caution may be needed in co-administering with danicopan.

[c] Caution may be needed in co-administering with danicopan.

10.10. Handling of Human Biological Samples

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

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

10.10.1. Chain of Custody

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

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

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

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

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

All appropriately consented samples will be retained will be retained for a maximum of 25 years from study completion or as per applicable requirements.

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

10.10.2. Withdrawal of Informed Consent for Donated Biological Samples

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

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

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

The Investigator:

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

- Ensures that the participant and Alexion are informed about the sample disposal.

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

10.11. COVID-19 Risk Assessment

As such, the benefit a patient may receive from treatment with danicopan is potentially significant. Based on the mechanism of action of danicopan and clinical experience, there is no evidence to suggest patients will have a higher risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or a more severe course of disease than the general population. Risk factors for severe illness as those already observed in the general population remain for patients receiving danicopan. The site Investigator will therefore balance the risk/benefit considerations in the study patient taking these factors into account.

The potential operational risks identified, and mitigation measures put in place in light of the COVID-19 pandemic are provided in Table 14.

Table 14: Potential Risks and Mitigation Measures due to COVID-19

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
Potential risks		
Healthcare institution availability for non-COVID-19 related activities	COVID-19 pandemic may impact the workload of healthcare institutions globally and may reduce staff availability to perform non-urgent activities and non-COVID-19 related activities.	During the time that the COVID-19 pandemic is active, Alexion will not open study sites or enroll new patients at sites unless the sites have the resourcing and capabilities to implement the study per protocol.
Data quality and integrity	Lack of availability of site personnel to perform study assessments and capture study specific data in a timely manner and to maintain adequate quality standards. Lack of availability of site personnel to ensure adequate and continuous chain of custody, storage conditions, and monitoring for investigational product and biological samples. Inability of study monitors and quality personnel to conduct in-person visits to exercise adequate oversight of study execution at investigational sites. Missing data (COVID-19 pandemic may impact study visit schedules and increase missed visits and/or patient study discontinuations inadvertently resulting in	During the time that the COVID-19 pandemic is active, Alexion will only open study sites that report enough personnel capacity to sufficiently conduct clinical study-related activities. During this timeframe, patient eligibility as well as site capacity will be reviewed by the site Investigator and the study Medical Monitor prior to Screening. Each site is also evaluated for the capacity to perform remote monitoring visits and remote source data verification. During the time that the COVID-19 pandemic is active, it will be important to capture

Table 14: Potential Risks and Mitigation Measures due to COVID-19

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
	missing data [eg, for protocol-specified procedures]).	specific information in the eCRF that explains the reason the data is missing (eg, missed study visits or patient study discontinuations due to COVID-19).

Abbreviations: COVID-19 = coronavirus disease 2019; eCRF = electronic case report form

10.12. COVID-19 Vaccine Risk Assessment

There is currently no information available evaluating the safety and efficacy of COVID-19 vaccines in participants treated with ALXN2040. It is unlikely that the immune response to a COVID-19 vaccine (and therefore the efficacy of the vaccination) would be diminished by danicopan administration, based on danicopan's mechanism of action. It is also unlikely that COVID-19 vaccination would impact danicopan's mechanism of action.

Vaccination may further activate complement. As a result, patients with complement-mediated diseases may experience increased signs and symptoms of their underlying disease. Therefore, patients should be closely monitored for disease symptoms after recommended vaccination.

Because vaccines may activate complement, if possible, consider vaccination when the underlying complement-mediated disease is clinically controlled and subsequent complement blockade is relatively high, shortly after administration.

Local and national guidelines should be consulted for recommendations related to COVID-19 vaccination.

The potential risks identified and mitigation measures put in place in light of the COVID-19 vaccination rollout are provided in Table 15.

Table 15: Potential Risks and Mitigation Measures due to COVID-19 Vaccine

Risks category	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential risks		
Data quality and integrity	Missing data due to appointments for COVID-19 vaccination or side effects of COVID-19 vaccine may impact study visit schedules and increase missed visits and/or participant study discontinuations, inadvertently resulting in missing data (eg, for protocol-specified procedures).	Capture specific information in the eCRF that explains the reason the data are missing (eg, missed study visits due to appointments for COVID-19 vaccination or side effects of COVID-19 vaccine).

Abbreviation: COVID-19 = coronavirus disease 2019; eCRF = electronic case report form

10.13. Abbreviations

The following abbreviations and terms are used in this study protocol.

Table 16: Abbreviations and Specialist Terms

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMD	age-related macular degeneration
AP	alternative pathway
APH	alternative pathway hemolysis
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AxMP	auxiliary medicinal product
Bb	Bb fragment of complement factor B
BCRP	breast cancer resistance protein
BCVA	best-corrected visual acuity
bid	twice daily
C3	complement component 3
C5	complement component 5
CFP	color fundus photography
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum (peak) plasma concentration of the drug
COVID-19	coronavirus disease 2019
CP	classical pathway
CRO	contract research organization
cRORA	complete retinal pigment epithelium and outer retinal atrophy
CSR	clinical study report
C_{trough}	concentration at the end of the dosage interval
CTIS	Clinical Trials Information System
CYP3A4	cytochrome P450 subfamily 3A4
DA	disc area

Table 16: Abbreviations and Specialist Terms

Abbreviation	Definition
dB	decibel
DMC	Data Monitoring Committee
DPIA	data protection impact assessment
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
EQ-5D-5L	EuroQol 5-dimension 5-level questionnaire
ET	early termination
ETDRS	Early Treatment Diabetic Retinopathy Study
EU CTR	European Union Clinical Trial Regulation
EU GDPR	European Union General Data Protection Regulation
EZ	ellipsoid zone
FA	fluorescein angiography
FAF	fundus autofluorescence
FAS	full analysis set
FD	factor D
FH	factor H
FSH	follicle-stimulating hormone
GA	geographic atrophy
GCP	Good Clinical Practice
GDS	Global Drug Safety
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IA	interim analysis or interim analyses
IADL	Instrumental Activities of Daily Living
iAMD	intermediate age-related macular degeneration
IB	Investigator's Brochure
ICF	informed consent form

Table 16: Abbreviations and Specialist Terms

Abbreviation	Definition
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IOP	intraocular pressure
IRB	Institutional Review Board
iRORA	incomplete retinal pigment epithelium and outer retinal atrophy
IRT	Integrated Response Technology
IVRS	interactive voice response system
IWRS	interactive web response system
LL BCVA	low luminance best-corrected visual acuity
LLD	low luminance deficit
LLVA	low luminance visual acuity
MAD	multiple ascending dose
MCP-Mod	Multiple Comparison Procedure and Modeling
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model for repeated measures
MNRead	Minnesota Low-Vision Reading Test
nAMD	neovascular age-related macular degeneration
NEI VFQ-25	National Eye Institute Visual Function Questionnaire, 25-item version
NIR	near infrared reflectance
ONL	outer nuclear layer
PA	Protocol amendment
PD	pharmacodynamic(s)
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
POC	proof of concept
PRO	patient reported outcome
qd	once daily
QoL	quality of life

Table 16: Abbreviations and Specialist Terms

Abbreviation	Definition
QTL	quality tolerance limit
RPE	retinal pigment epithelium
RTSM	Randomization and Trial Supply Management
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SD-OCT	spectral-domain optical coherence tomography
SoA	schedule of activities
SOC	System Organ Class
sqrt	square root
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
VA	visual acuity
VEGF	vascular endothelial growth factor
WOCBP	woman of childbearing potential

10.14. Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the Table of Contents.

DOCUMENT HISTORY			
Document	**Type of Amendment (Global or Country-specific)**	**Date**	**Summary of Key Changes in the Amendment**
Protocol Amendment 2.0	Global	30 Mar 2023	To add exploratory anatomical endpoints To add text in preparation for transition into EU CTR To incorporate changes from Administrative Letter #1
Protocol Amendment 1.0	Global	10 May 2022	To streamline the study design and schedule of activities to reduce complexity and minimize burden to sites and patients. To update objectives and endpoints and statistical sections to reflect changes in study design and emerging data, streamline SoA to minimize complexity and patient burden, and incorporate. To provide clarification on several eligibility criteria based on feedback from sites. The changes had no impact on the eligibility of randomized patients. To update the statistical analysis sections to add details on the interim analyses and reflect changes in endpoints. To include changes implemented in country-specific amendments as requested by local health authorities.
Amendment 0.10	France	03 May 2022	To address feedback on PA 0.8 from the French health authorities
Amendment 0.9	Germany	03 Mar 2022	To address feedback on PA 0.6 from the German health authorities (BfArM) and to update inclusion criteria.
Amendment 0.8	France	15 Feb 2022	To address feedback from the Independent Ethics Committee in France.
Amendment 0.7	Italy	15 Feb 2022	To address feedback from health authorities in Italy (AIFA) and to add an inclusion criterion for extrafoveal GA lesions from PA 0.4.

DOCUMENT HISTORY			
Amendment 0.6	Germany	10 Feb 2022	To address questions from the German health authorities (BfArM).
Amendment 0.5	UK	07 Dec 2021	To add an inclusion criterion for extrafoveal GA lesions that was implemented in PA 0.4.
Amendment 0.4	Local, Multiple Countries	23 Nov 2021	To add an inclusion criterion for extrafoveal GA lesions.
Amendment 0.3	UK	22 Nov 2021	To address questions from MHRA
Amendment 0.2	Local, Multiple Countries	08 Nov 2021	To add the EudraCT and NCT numbers on the cover page of the protocol.
Amendment 0.1	Local, Multiple Countries	28 Jul 2021	To clarify eligibility criteria with respect to the use of biometry and for patients with history of cataract surgery or pathological myopia.
Original Protocol	Not applicable	24 Feb 2021	Not applicable.

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