A Phase 2, Randomized, Double-Masked, Placebo-Controlled Clinical Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Subcutaneous Injections of Elamipretide in Subjects with Age-Related Macular Degeneration with Geographic Atrophy (ReCLAIM-2)

NCT03891875

29-March-2022

STATISTICAL ANALYSIS PLAN

Trial Sponsor:	Stealth BioTherapeutics Inc.
Protocol Number:	SPIAM-202
IND Number:	114,234
Investigational Drug:	Elamipretide (MTP-131)
Indication:	Macular Degeneration
Dosage Form/Strength:	Elamipretide (MTP-131) 40 mg once daily for subcutaneous injection

Protocol Title: A Phase 2, Randomized, Double-Masked, Placebo-Controlled Clinical Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Subcutaneous Injections of Elamipretide in Subjects with Age-Related Macular Degeneration with Geographic Atrophy (ReCLAIM-2)

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GLOSSARY OF ABBREVIATIONS

Abbreviation	Term
ADE	Adverse device effect
AE	Adverse Event
AMD	Age-related macular degeneration
AUC_{0-24h}	Area under the plasma concentration time-curve from 0 to 24 hours
BCVA	Best-corrected visual acuity
COVID-19	Coronavirus Disease 2019
C_{max}	Maximum plasma concentration
CRF	Case Report Form
EDC	Electronic Data Capture
EZ	Ellipsoid Zone
FA	Fluorescein angiography
FAF	Fundus autofluorescence
GA	Geographic atrophy
IMP	Investigational Medicinal Product
ISR	Injection Site Reaction
LL	Low-luminance
LLQ	Low-Luminance Questionnaire
MMRM	Mixed Model for Repeated Measures
MedDRA	Medical Dictionary for Regulatory Activities
MTP-131	Elamipretide, SS-31, SBT-031,
OCT	Optical coherence tomography
OD	Oculus Dexter
OS	Oculus Sinister

OU	Oculus Uterque
PK	Pharmacokinetics
PopPK	Population Pharmacokinetics
PT	Preferred term

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GLOSSARY OF ABBREVIATIONS

QA	Quality Assurance
QC	Quality Control
RA	Reading acuity
RBC	Red blood cells
RDI	Relative Dose Intensity
SADE	Serious adverse device effect
SAE	Serious adverse event
SC	Subcutaneous
SD-OCT	Spectral domain-optical coherence tomography
SOC	System organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
TEADE	Treatment-emergent adverse device effect
TESADE	Treatment-emergent serious adverse devise effect
UADE	Unanticipated Adverse Device Effect
VFQ-39	Visual Function Questionnaire-39
WBC	White blood cells
WHO-DD	World Health Organization Drug Dictionary

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1. INTRODUCTION

This Statistical Analysis Plan (SAP) outlines the statistical methods for the display, summary and analysis of data collected within the scope of Stealth BioTherapeutics Inc (SBT). protocol SPIAM202 version 4.0, dated 06 Jan 2022. Protocol SPIAM-202 is a Phase 2, randomized, placebocontrolled, double-masked, multi-center, safety, efficacy, and pharmacokinetic (PK) trial to be conducted in the U.S. Approximately 180 subjects who have at least 1 eye with Age-related macular degeneration (AMD) with non-central Geographic atrophy (GA) is to be included (See Protocol Section 6.1 for details).

This SAP details the analysis of the data collected in the study and the presentation of the results of the analyses. The table, listing, and figure (TLF) shells are displayed in a companion document which provides information on the layout of the data displays. Analysis dataset specifications will be developed to detail the programming specifications and mapping rules needed to create the analysis datasets and the TLFs. All statistical analyses will be performed using SAS® version 9.4. Adverse events (AEs) will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA version 24.1 or newer).

As with any SAP, the proposed methods and approaches to the data analysis should be deemed as flexible. The analysis of the data should allow changes in the plan to the extent that deviations from the original plan would provide a more reliable and valid analysis of the data. As such, the statistical analysis to a certain degree is iterative since much of the planning is based on assumptions that require verification. The purpose of this plan is to provide general guidelines from which the analysis will proceed. Nevertheless, deviations from these guidelines must be substantiated by a sound statistical rationale.

The SAP should be read in conjunction with the study protocol and the Case Report Forms (CRFs). This version of the SAP has been developed using the final version of the protocol mentioned above and the final version of the annotated CRFs (v7.0) dated 4 February 2021.

1.1 COVID-19 Impact

The study is ongoing since the time of Coronavirus Disease 2019 (COVID-19) pandemic start. A memo/guidance from SBT was distributed to each site & IRB on 18 Mar 2020 describing that sites should follow their most current institutional guidelines on conducting clinical trial visits and assessments. If it is deemed safe by the Principal Investigator (PI) regarding potential subject exposure to COVID-19, study sites should continue clinic visits as outlined in the protocol. To minimize the risk for exposure, at the discretion of the PI, sites may reduce the number of assessments performed at each visit, prioritizing those related to safety, with the exception of the Baseline and End of Treatment visits, where all assessments should be performed. A detailed rationale should be documented in the patient source records and Electronic Data Capture (EDC) system if a reduced number of assessments are to be collected during a scheduled visit.

Because the schedule of assessments was not changed, there was no protocol amendment because of the

COVID-19. However, CRFs were modified (version 5.0 and 6.0) to collect the information and

accommodate for the impact of COVID-19 on the study conduct. These information include: study treatment discontinuations or study discontinuations related to COVID-19, protocol deviation related to COVID-19, phone visit (instead of physical visit) due to COVID-19, study drug assignment date is different than visit date, etc.

The impacts of COVID-19 on the study endpoints, as well as the analysis plan dealing with the potential missing data related to COVID-19 is discussed in more details in Section 7 Statistical Analysis.

2. STUDY OBJECTIVES

2.1 Primary Objective

- To evaluate the safety and tolerability of subcutaneous (SC) injections of elamipretide administered with the elamipretide delivery system in subjects with AMD with non-central GA.

2.2 Secondary Objectives

- To evaluate the efficacy of SC injections of elamipretide administered with the elamipretide delivery system in subjects with AMD with non-central GA.
- To study the PK profile of elamipretide and its metabolites.

3. STUDY DESIGN

3.1 Study Design

This Phase 2, randomized, placebo-controlled, double-masked, multi-center, safety, efficacy, and PK trial projected will enroll approximately 180 subjects who have at least 1 eye with AMD with non-central (i.e., extra-foveal) GA.

Subjects will be randomized in a 2:1 ratio (approximately 120 subjects in the treatment arm and 60 subjects in the placebo arm) to receive either 0.5 mL (40 mg) elamipretide or placebo administered with the elamipretide delivery system as a single daily SC injection. The following treatment groups are defined for this study:

Group	Treatment Period (48 Weeks)
A	Placebo
B	Elamipretide 40 mg

Safety, tolerability, and efficacy to be evaluated according to the protocol. Plasma samples for PK evaluations to be collected at Visit 3 (Week 4) and Visit 4 (Week 8). Ocular imaging is to be read by an independent reading center.

After completion of the 48-week Treatment Period (Visit 2 to Visit 8), subjects to be monitored for safety during the 4-week Follow-Up Period. The Follow-Up Period is an IMP administration-free period. A Follow-Up Visit to be scheduled at Week 52 (Visit 9) which signifies the end of the study.

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3.2 Randomization and Unmasking

Randomization to be used in this study to avoid bias in the assignment of subjects to study treatment groups, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are balanced across treatment groups, and to enhance the possible validity of statistical comparisons. Masked treatment to be used to reduce potential bias during data collection and evaluation of endpoints.

Eligible subjects to be randomized in a 2:1 ratio to treatment with either elamipretide or placebo with the use of an interactive response system within 14 days after the first screening visit. If a subject receives the treatment opposite of what was assigned during randomization, they will be analyzed according to the treatment they were supposed to receive in the efficacy analyses, but will be analyzed according to the treatment they actually received in the safety analyses.

Independent Biostatisticians from Statistics & Data Corporation (SDC) prepared the randomization codes for the subject and drug kit IDs. Both randomization codes will be released to the study biostatistician at Everest Clinical research after the final database lock.

3.3 Hypothesis Testing

For the analysis of primary efficacy endpoints, the following two-sided hypotheses will be carried out to evaluate the treatment effect of elamipretide group against placebo group in the LL BCVA endpoint:

$$H_0: \mu_{LL\,BCVA}^{MTP} = \mu_{LL\,BCVA}^{PLB} \; vs. \; H_a: \mu_{LL\,BCVA}^{MTP} \neq \mu_{LL\,BCVA}^{PLB}$$

*O· µLLBCVA - lluBCVA vs. a-/lLt,BCVA * llLLBCVA*

where $\mu_{LL\,BCVA}^{PLB}$ is the mean change in LL BVCA at the end of the treatment period (Week 48) for the placebo treatment group, and $\mu_{LL\,BCVA}^{MTP}$ is the mean change in LL BVCA at the end of the treatment period (Week 48) for the elamipretide treatment group.

Similar two-sided hypotheses will be carried out to evaluate the treatment effect of elamipretide group against placebo group in the co-primary endpoint, GA area (as measured by OCT):

$$HH_0: \mu\mu_{GGGGMMMMMM} = \mu\mu_{GGGGMMPPPP} \; vvvv. \; HH_{aa}: \mu\mu_{GGGGMMMMMM} \neq \mu\mu_{GGGGMMPPPP}$$

where $\mu\mu_{GGGG}{}^{MMPPPP}$is the mean change in GA area as measured by OCT (in mm, based on the square root transformed GA area measured in mm^2) at the end of the treatment period (Week 48) for the placebo treatment group, and $\mu\mu_{GGGG}{}^{MMMMMM}$ is the mean change in in GA area as measured by OCT at the end of the treatment period (Week 48) for the elamipretide treatment group.

A family-wise alpha level of 0.1 will be maintained for the primary endpoint family, using Hochberg's procedure at the primary time point of 48 weeks. If both primary endpoints are significantly different from placebo at the 0.1 (two-sided) level of significance (in favor of treatment), then both will be considered statistically significant. Otherwise, the endpoint with the smaller p-value of the two will be considered statistically significant, if the smaller p-value is less than 0.05 (two-sided).

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3.4 Interim Analysis

No comparative interim analyses to be conducted for this study.

3.5 Sample Size

A sample size of 180 subjects provides ≥ 80% power to detect a 5 letter (1 line) change from baseline mean difference in LL BCVA between drug and placebo, assuming a standard deviation of 11 letters, at a two-sided alpha-level of 0.1, and provides approximately 80% power to detect a 30% difference in the change from baseline in square root transformed total GA area by OCT between drug and placebo, assuming a standard deviation of 0.2 mm/year, and an average change of 0.33 mm/year, at a two-sided alpha-level of 0.1.

3.6 Study Procedures and Schedule of Assessments

Study procedures and their timing are summarized in the Schedule of Assessments (**Table 1)** and Study Schematic (**Figure 1**).

Table 1: Schedule of Assessments

Days/Weeks	Screening Period[a]	Treatment Period							Follow Up Period	Early Termination
Days/Weeks	Screening (Day -14 to Day -1)	Day 1[b] BL	Wk 4 ±3d	Wks 8 ±3d	Wk 12 ±3d	Wk 24 ±3d	Wk 36 ±3d	Wk 48 ±3d EOT	Weeks 52 (±3d) Follow Up EOS	Early Termination Visit
Visit	1	2	3	4	5	6	7	8	9	
Informed consent	X									
Demographics	X									
Medical/ocular history	X	X								
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Low-Luminance Questionnaire		X			X	X	X	X		X
Visual Function Questionnaire-39		X			X	X	X	X		X
EQ-5D-5L Questionnaire		X						X		X
Vital signs[c]	X	X	X	X	X	X	X	X		X
Physical examination[d]	X	X				X		X	X	X
Blood for safety[e]	X	X	X	X	X	X	X	X		X
Urinalysis	X	X	X	X	X	X	X	X		X
Exploratory plasma and urine samples[f]	X					X		X		
Pregnancy testing (serum)	X								X	X
Pregnancy testing (urine)		X	X	X	X	X	X	X		
Refraction	X	X	X	X	X	X	X	X		X
BCVA	X	X	X	X	X	X	X	X		X
Low-luminance BCVA	X	X	X	X	X	X	X	X		X

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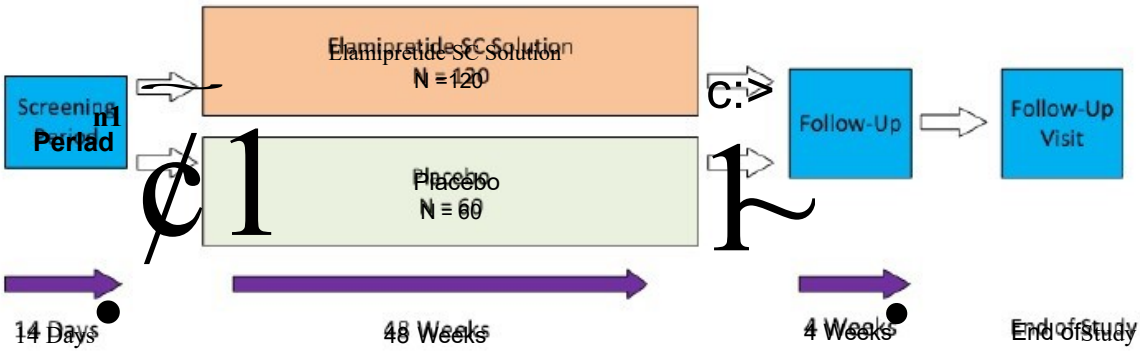
Days/Weeks	Screening Period[a]	Treatment Period							Follow Up	Early Termination
	Screening (Day -14 to Day -1)	Day 1[b] BL	Wk 4 ±3d	Wk 8 ±3d	Wk 12 ±3d	Wk 24 ±3d	Wk 36 ±3d	Wk 48 ±3d EOT	Week 52 (±3d) Follow Up EOS	Early Termination Visit
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Reading acuity at standard and low luminance	X	X	X		X		X	X		X
Slit lamp exam	X	X	X	X	X	X	X	X		X
IOP	X	X				X	X	X		X
Dilated fundus exam	X	X	X	X	X	X	X	X		X
SD-OCT	X	X			X	X	X	X		X
OCT angiography[g] (optional)	X	X			X	X	X	X		X
Fundus photography[h]	X	X			X	X	X	X		X
Fundus autofluorescence	X	X			X	X	X	X		X
Fluorescein angiography[i]	X									
Eligibility	X	X								
Randomization		X								
Dispense IMP and subject diary		X	X	X	X	X	X			
IMP accountability			X	X	X	X	X	X		X
IMP training[j]		X								
PK sampling[k]			X	X						X
AEs/ ADEs	X	X	X	X	X	X	X	X	X	X

Abbreviations: BCVA = best-corrected visual acuity; BL = baseline; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; OCT = optical coherence tomography; PK = pharmacokinetics; RPE = Retinal pigment epithelium; SD-OCT = Spectral domain-optical coherence tomography; VA = visual acuity.

Note: All ophthalmic testing is conducted on both eyes at each time point.

a. Screening procedures may be completed on more than one day, as long as all procedures are completed during the Screening Period. Re-screening of subjects may be allowed, depending on the reason for screen-failure, after consultation with the Sponsor.
b. The first day of treatment is defined as study Day 1.
c. Vital sign measurements include temperature, respiratory rate, sitting blood pressure after resting for 5 minutes, pulse and weight.
d. Physical examination will include assessment of head, eyes, ears, nose, and throat, general appearance, skin, chest, heart, abdomen, extremities, and nervous system. Height will only be recorded at the Screening Visit.
e. Blood for safety will consist of hematology panel and clinical chemistry.
f. Exploratory plasma and urine samples will be withdrawn and stored for future analysis. Analysis may include genetic and/or metabolomic testing (optional).
g. OCT angiography is optional. It is recommended for trial sites that has the OCT angiography capabilities.
h. Fundus examination will be utilized for safety assessment of the RPE, choroid, neuro-retina structure, retinal vessels, optic nerve, and vitreous
i. FA completed for reasons of standard of care and within 30 days prior to first dose can be used for screening purposes if official documentation is provided.
j. The IMP training checklist will be completed for the subject or caregiver at Day 1, prior to the first dose of IMP. Any new caregiver should complete IMP training at any trial site visit before administering IMP to a subject.
k. For the Week 8 visit, the subject will administer IMP at home, approximately 4 hours ± 1 hour before arriving at the trial site. Random PK sample to be taken at Early Termination Visit (one sample at any time during visit).

Figure 1: Study Schematic



4. DATA AND ANALYTICAL QUALITY ASSURANCE

The overall quality assurance procedures for the study data, statistical programming and analyses are described in Everest's Standard Operating Procedures. Detailed data management procedures are documented in the Data Management Plan, Data Validation Check Specifications, and Data Review Plan. Detailed statistical and programming quality control and quality assurance procedures are documented in the Statistical Analysis and Programming QC/QA Plan.

The study endpoints and analytic approaches are both prospectively defined and documented in the protocol and in this SAP. The SAP will be finalized, and protocol violations will be identified and decisions for inclusion and exclusion of subjects from the per-protocol analysis population will be made prior to the database lock and data analysis.

5. ANALYSIS POPULATIONS

5.1 Safety Population

The Safety Population includes all study subjects who receive at least 1 dose of IMP and analyzed according to treatment received. Safety data analysis will be conducted on all subjects in the Safety Population.

5.2 Intent-to-Treat (ITT) Population

The Intent-to-Treat Population includes all randomized subjects. Subjects will be analyzed in the treatment group to which they were randomized.

5.3 Modified Intent-to-Treat (mITT) Population

The Modified Intent-to-Treat Population includes all ITT subjects who receive at least one dose of IMP and have baseline and at least 1 post-baseline value for LL BCVA or GA area on OCT. Subjects will be

analyzed in the treatment group to which they were randomized. mITT population is the primary population for all efficacy analysis.

5.4 Per Protocol (PP) Population

The Per Protocol Population includes all mITT subjects that completed the study without major protocol violations/deviations likely to affect the primary efficacy outcome of the study as judged by a masked evaluation prior to the unmasking of the study treatment. Subjects will be analyzed according to the actual treatment they received.

Major protocol violations/deviations included but not limited to:

- Did not meet all Inclusion and Exclusion Criteria deemed to potentially impact efficacy finding
- Had <70% IMP dosing compliance
- Any identified at the blinded data review meeting where they are deemed to potentially impact efficacy findings

5.5 Pharmacokinetic (PK) Population

The Pharmacokinetic Population includes all trial subjects who have at least one evaluable PK sample taken during their participation.

6. SPECIFICATION OF ENDPOINTS AND VARIABLES

6.1 Demographic and Baseline Characteristics

Only assessments from Screening prior to the first administration of any study drug (Elamipretide or Placebo) will be summarized in the Baseline Characteristics listing.

Demographic data will be collected at the Screening visit and consists of the following:

1. Age in years (continuous) derived as the integer value of (Informed consent date – date of birth + 1) / 365.25.
2. Sex
3. Race
4. Ethnicity
5. Iris color

Baseline characteristics consist of the following:

1. Weight (kg) 2.
Height (cm)

3. Body Mass Index, BMI (kg/m²): is derived as weight in kg divided by height (in m)² at baseline visit
4. Vital signs (heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, and temperature)
5. Study Eye (OD or OS)
6. Baseline LL BCVA score (Letters)

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7. Baseline square root transformed GA area (in mm) by OCT
8. Baseline GA area (in mm^2) by OCT
9. Baseline LL RA LogMar Score
10. Baseline BCVA score (Letters)
11. Baseline square root transformed GA area (in mm) by FAF
12. Baseline GA area (in mm^2) by FAF
13. LL Deficit (in letters): define as the difference between BCVA and LL BCVA)
14. Baseline GA distance to fovea (in µm) by OCT
15. Baseline GA distance to fovea (in µm) by FAF

Ocular baseline characteristics are all for the study eye only.

6.2 Efficacy

Efficacy is the secondary objective of this study. All efficacy analyses will treat missing values as missing at random, with no imputation, unless otherwise specified. The primary population for all efficacy endpoints is mITT and the primary time point is week 48.

For efficacy endpoints, the unit of analysis will be the study eye as defined by the following:

- Study Eye: Eyes are eligible for analysis if they meet all of the inclusion criteria and none of the exclusion criteria. In the case that both eyes are eligible for analysis, the study eye will be the eye with worse LL BCVA at baseline. If the eyes have equal LL BCVA, then the right eye (OD) will be the study eye.

6.2.1 Study Day and Visit Window Definitions

Data obtained during unscheduled and early termination visits will be allocated to the scheduled visit corresponding to the visit window they fall in as specified in **Table 2**. If the actual visit is missing, the target time point will be used in determine the visit window. Phone visits will be considered as valid study visits in determining the visit window. Data will be analyzed based on the nominal visits and nominal time points. If the data from the nominal visit or time point is missing, data from unscheduled visits for the same nominal visit or time point will be used. If multiple unscheduled assessments fall in the same visit window or time point, the non-missing assessment closest to target time point will be selected for analysis. If

multiple values are the same number of days away from the target study day, then the latter value will be used.

First date on which subject received the study drug will be used as the Study Day 1. Study days for other visits will be calculated as follows:

Before Study Day 1 visit: Study Day = date of assessment – date of Study Day 1.

On or after Study Day 1 visit: Study Day = date of assessment – date of Study Day 1 + 1.

Last study date is the last visit date of any scheduled, unscheduled or early discontinuation visits. Last Study Day is calculated as:

Last Study Day = last study date – date of Study Day 1 + 1.

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The target study days of Study Site Visits are summarized in **Table 2** below.

Table 2 Time Windows for Efficacy Assessments

Scheduled Visit Number	Visit (label)	Visit Window (day)	Target Time Point (Study day)
1	Screening	-14 to -1	-14 to -1
2	Visit 2 (Baseline)	1	1
3	Visit 3 (Week 4)	2 to 43	29
4	Visit 4 (Week 8)	44 to 71	57
5	Visit 5 (Week 12)	72 to 127	85
6	Visit 6 (Week 24)	128 to 211	169
7	Visit 7 (Week 36)	212 to 295	253
8	Visit 8 (End of Treatment)	≥ 295	337

6.2.2 Primary Efficacy Variable

The primary efficacy variables are low luminance best-corrected visual acuity (LL BCVA) score and geographic atrophy (GA) area as measured by Optical coherence tomography (OCT), with primary time point at week 48.

- Primary Variable #1: Change in LL BCVA score from baseline at the end of treatment (Week 48) assessment measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale.
- Primary Variable #2: Change in square root transformed GA area from baseline at the end of treatment (Week 48) as measured by Optical coherence tomography (OCT).

6.2.3 Secondary Efficacy Variables

The secondary efficacy variables and endpoints include:

- Low-luminance reading acuity (LL RA): change in LL RA score from baseline at the end of treatment (Week 48)
- Best-corrected visual acuity (BCVA): change in BCVA score from baseline at the end of treatment (Week 48)
- GA area as measured by Fundus autofluorescence (FAF): change in GA area from baseline at the end of treatment (Week 48)

6.2.4 Exploratory Efficacy Variables

Exploratory efficacy variables include:

1. Volumetric OCT and ellipsoid zone (EZ) mapping as defined as:
   - Macular Percentage of EZ Total Attenuation

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   - Macular Percentage of EZ Partial Attenuation ○ Central 1-mm mean EZ-RPE thickness ○ Central 2-mm mean EZ-RPE thickness
2. National Eye Institute Visual Function Questionnaire-39 (VFQ-39) score
3. Reading acuity (RA) at standard light
4. Visual function by the Low-luminance Questionnaire (LLQ)
5. EQ-5D-5L score
6. Conversion to choroidal neovascularization (CNV)
7. BCVA and LL BCVA in non-study eyes
8. GA area as measured by OCT in non-study eyes with GA (the existence of GA for non-study eye is determined at the baseline from OCT).

6.3 Pharmacokinetic Measures

Characterization of the PK parameters of elamipretide and its metabolites in plasma, including apparent clearance, maximum plasma concentration (Cmax), and area under the plasma concentration time-curve from 0 to 24 hours (AUC0-24), will be performed via population PK (PopPK) modeling. PK sampling will be conducted at the time points and windows defined below.

Table 3 Time Windows for PK Samples			
Scheduled Visit Number	**Sample time**	**Analysis Window**	**Target Time Point (day)**
3	Pre-dose	-30 to 0 minutes	29
3	0.5 hour post-dose	± 5 minutes	29
3	1 hour post-dose	± 15 minutes	29
3	2 hour post-dose	± 15 minutes	29
4	4 hour post-dose	± 1 hour	57
4	8 hour post-dose	± 2 hour	57
Early Termination Visit	Random Sample		

6.4 Safety

The primary objective of this study is safety and tolerability. These are described by the following endpoints:

1. Incidence and Severity of Adverse events (AEs)/Adverse Device Effects (ADEs)
2. Changes from baseline in vital sign measurements
3. Changes from baseline in clinical evaluations (ocular and non-ocular) which include physical exam, slit lamp exam, applanation tonometry for intraocular pressure (IOP) assessment and dilated fundus exam

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4. Changes from baseline in clinical laboratory evaluations

6.4.1 Extent of Exposure to Study Medication and Treatment Compliance

Subjects to receive either 40 mg elamipretide or placebo administered with the elamipretide delivery system as a single daily SC injection. Study medication administration date and time is collected for dosing in the overall study drug administration log.

Treatment duration (days) defined as: (Last dose date+1) – (First dose date).

Study drug administration is captured on the subject diary. Number of doses expected and number of doses taken since last visit are collected at the scheduled visits on the CRF for subject diary. They will be used to compute the period % compliance between the scheduled visits, the overall % compliance .and relative dose intensity for the study. The calculation will be detailed in Section 7.3.2.

6.4.2 Adverse Events/Adverse Device Effects

The AE/ADE reporting period begins when the subject signs the informed consent and continues through the post-treatment follow-up period (Week 52), defined as 28 days after last administration of IMP. All subjects who receive at least 1 dose of elamipretide, whether they complete the treatment period or not, should enter the 28-day period as defined above.

ADE is an AE related to the use of an investigational medical device. AEs/ADEs will be collected in Adverse Event/Adverse Device Effect CRF page and coded using the latest version of the MedDRA. They will be summarized by system organ classification (SOC) and preferred term (PT).

6.4.2.1 Treatment-Emergent Adverse Events (TEAE)/ Treatment-Emergent Adverse Device Effects (TEADE)

An AE is considered treatment-emergent if the date of onset is after the first dose of study medication in the study, or if the AE worsened after the first dose of study medication (based on severity or seriousness).

6.4.2.2 Serious Adverse Events (SAE)/Serious Adverse Device Effects (SADE)

Adverse events/adverse device effects will be categorized as serious or non-serious using the definition specified in Section 10.8 of the study protocol.

6.4.3 Adverse Events/Adverse Device Effects Counting Rules

1. A subject with more than one different AE/ADE in a particular SOC will be counted only once in the total of subjects experiencing AEs/ADEs in that particular SOC within a given treatment group.

2. A subject having experienced the same event (AE/ADE preferred term) more than once during the study will be counted only once in the number of subjects with that event.

3. A subject having experienced the same event (AE/ADE preferred term) more than once with a different severity or seriousness will be counted only once with the worst grade and seriousness respectively.

4. A subject having experienced the same event (AE/ADE preferred term) more than once with a different causal relationship to the study drug or elamipretide delivery system will be counted only

once by considering the most-related documented degree of relationship associated with the particular treatment.

6.4.3.1 Adverse Events (AE)/Adverse Device Effects (ADE) Severity

The severity of AEs/ADEs will be evaluated as "Mild", "Moderate", and "Severe" using the criteria specified in Section 10.10.1 of the study protocol. If the severity is missing, then the severity will be set to "Severe" in the summaries of AEs/ADEs.

6.4.3.2 Relationship to the Investigational Medicinal Product

An AE/ADE will be qualified as either related (probable or possible related) or unrelated (unlikely related or unrelated) to IMP using the criteria specified in Section 10.10.2 of the study protocol. If the relationship to IMP is missing, then the relationship will be set to "probable" in the summaries of AEs/ADEs.

6.4.3.3 Adverse Events/Adverse Device Effects with Irregular Start/Stop Dates

Partial dates may be imputed when appropriate. Imputed dates will be used to determine Study Day. If a partial date is reported for the start of an adverse event, a complete date will be imputed by the following algorithm:

1. Only the year is reported: If the subject started receiving study drug in the previous year associated with the treatment period, then January 1 will be used as the starting date of the event. If the subject started receiving study drug in the year reported within the treatment period, then the date of the first dose of study drug will be used as the start of the event.

2. The month and year is reported: If the subject started receiving study drug prior to the month and year reported associated with the treatment period, then the first day of the month will be used as the starting date of the event. If the subject started receiving study drug during the month and year reported within the treatment period, then the date of the first dose of study drug will be used as the start of the event.

If a partial date is reported for the end of an adverse event and the adverse event is not continuing, a complete date will be imputed by the following algorithm:

1. Only the year is reported: If the subject started receiving study drug in the previous year associated with the treatment period, then the date of final study contact with the subject will be used as the end of the adverse event. If the subject started receiving study drug in the year reported within the treatment period, then the earlier of December 31 or the date of final study contact with the subject will be used as the end of the adverse event.

2. The month and year reported: The earlier of the last date of the month or the date of final contact with the subject within the same treatment period will be used as the end of the adverse event.

The above rules are subject to logical sense, for example, imputed start date should be on or prior to imputed end date.

6.4.4 Vital Signs

Vital signs measurements to include temperature (ºC), heart rate (beats/min), respiration rate (breaths/min) and blood pressure (mmHg), recorded in the sitting position after at least 5 minutes rest.

Baseline values for vital sign parameters are those measured at last evaluation prior to the first dose of study drug. Change from baseline to a time point t, denoted by $Change_t$, will be calculated as:

$$Change_t = Value_t - Value_{Baseline}.$$

6.4.5 Laboratory Data

The following clinical laboratory assessments will be performed and change from baseline will be calculated as described above.

Table 4 Clinical Laboratory Tests	
Chemistry	Alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, blood urea nitrogen, creatinine, creatine phosphokinase, glucose (nonfasting), lactate dehydrogenase, sodium, potassium, albumin, total protein, calcium, chloride, and bicarbonate
Hematology	Hemoglobin, hematocrit, erythrocyte (red blood cell [RBC]) count, leukocytes (white blood cells [WBC]) count, and differential (neutrophils, segmented; lymphocytes; monocytes; eosinophils; basophils), platelets, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration
Urinalysis	pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen, and leukocyte esterase; if the dipstick is abnormal for protein, blood, nitrite, or leukocyte esterase, include RBCs, WBCs, bacteria, and casts

Conversion to the International System of Units

All laboratory data will be stored in the database with the units in which they are originally reported. Laboratory data in summary tables and subject data listings will be presented in the International System of Units (SI units; Système International d'Unités). Laboratory data not reported in SI units will be converted to SI units before further processing or data analysis.

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Abnormal Values

Based upon laboratory normal ranges, laboratory test results will be categorized according to the normal range as low, normal, and high. Subjects with laboratory data outside the normal range will be listed with abnormal values flagged and clinical significance.

6.4.6 Slit Lamp Examination

The anterior segment of the eye is to be analyzed by slit lamp biomicroscopy. Magnification, slit beam, and examination procedure will be consistent with Investigator's standard practice. Findings which are deemed clinically significant by the Investigator will be documented on each subject's source document and corresponding CRF.

6.4.7 IOP (Applanation Tonometry)

IOP is to be assessed using Goldmann tonometry or Tonopen. The observed and change from baseline scores will be summarized descriptively for each visit

6.4.8 Dilated Fundus examination

Dilated indirect ophthalmoscopy is to be performed to examine the vitreous, retina, macula, choroid, optic nerve, and blood vessels. Findings that are deemed clinically significant by the Investigator will be documented on each subject's source document and corresponding CRF.

6.4.9 Physical Examination

The physical examination is to include assessment of head, eyes, ears, nose, and throat, general appearance, skin, chest, heart, abdomen, extremities, and the nervous system. Height will be measured at the Screening Visit only. Measurement of weight should be performed with the subject dressed in indoor clothing, shoes removed, and bladder empty. The results of physical examination with any clinical significant abnormalities to be reported on the CRF.

6.4.10 Concomitant Medications/Treatments

Prior and concomitant medications is to be recorded at Screening and during the study. Prior medication is defined as any medication taken before the first dose of the IMP. Concomitant medication is defined as any medication taken during the study between the date of the first dose of IMP and the last study date of the

subject. Any medications started after the last study date of the subject will not be considered concomitant medications.

All relevant information, including reason for use, dose, frequency and route, will be recorded for any medication administered or received prior and during the study.

Summaries of all concomitant medications taken during the course of the study will be presented in tabular form using Anatomical Therapeutic Chemical 4 classification codes and preferred drug name via the World Health Organization Drug Dictionary (WHO-DD) with latest version to be specified in the Clinical Study Report. For the summary tables, if a subject has taken a concomitant medication more than once, the subject will be counted only once for the medication.

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For medications with incomplete dates, imputation will be used to convert to a complete date. Imputed dates will be used to determine Study Day.

Partial medication start dates will be imputed as follows:

1. Only the year is reported: If the subject started receiving study drug in the year reported, then the date of the first dose of study drug will be used as the starting date of the medication. Otherwise, January 1 will be used as the start of the medication.

2. The month and year is reported: If the subject started receiving study drug during the month and year reported, then the date of first dose of study drug will be used as the starting date of the medication. Otherwise, the first day of the month will be used as the start of the medication.

Partial medication end dates will be imputed for non-ongoing medications as follows:

1. Only the year is reported: If the subject stopped receiving study drug in the year reported, then the date of the last dose of study drug will be used as the end date of the medication. Otherwise, December 31 will be used as the end of the medication.

2. The month and year is reported: If the subject stopped receiving study drug during the month and year reported, then the date of last dose of study drug will be used as the end date of the medication. Otherwise, the last day of the month will be used as the end of the medication.

The above rules are subject to logical sense, for example, imputed start date should be on or prior to imputed end date.

7. STATISTICAL ANALYSIS

7.1 General Data Handling Rules and Definitions

All data collected on case report forms will be provided in listings, except data collected only for confirmation of study entry criteria and for study administrative purposes. If any randomized patient is found to not have valid documented informed consent, that patient's data will be excluded from the report, except as necessary to document the error.

All analyses will be conducted using SAS version 9.4 or later.

Except where specified, all continuous variables will be summarized with descriptive statistics (the number of non-missing values, mean, standard deviation, median, lower and upper quartiles, minimum and maximum) and all categorical variables will be summarized with frequency counts and percentages, by treatment group. Unless otherwise specified, the mean and median will be displayed to 1 more decimal place than the original data, and standard deviation and standard error of the mean (if presented) should also be displayed to 2 more decimal place than the original data. All percentages for frequencies will be rounded to 1 decimal place. For eye-specific assessments, the analysis of the study eye is considered primary.

7.2 Missing Data and Imputation

Missing data will be maintained as missing in the analysis datasets, unless specified otherwise. For variables where missing data are imputed, the analysis dataset will contain a new variable with the imputed value and the original variable value will be maintained as missing.

The summary of missing study visit related to COVID-19, phone visits in replacement of site visits, missing assessments for the primary and key secondary endpoints because of the missing site visits related to COVID-19 will be summarized and listed.

The rate and pattern of missing data for the primary endpoint will be explored and summarized and depending on the extent of missing data and presumed missingness mechanisms, additional analyses may be conducted.

7.3 Subject Disposition

A disposition table for all subjects will be provided.

This tabulation will include the number of subjects: screened, randomized, received study treatment, discontinued study treatment, and discontinued study prematurely or completed the study. The tabulation will also include the number of subjects included in the Safety, ITT, mITT, PP, and PK populations. The number and percentage of randomized subjects who are included in the study populations will also be tabulated.

Reasons for early discontinuation will be summarized for all randomized subjects. The number and percentage of subjects excluded from the study treatment or study populations and the reasons of exclusions will be tabulated by treatment group. The number and percentage of subjects discontinued from the study treatment or study populations due to COVID19 will be tabulated by treatment group. Corresponding listings will also be provided.

7.3.1 Prior and Concomitant Medications

The number and percentage of subjects who have reported concomitant therapies from date of informed consent to the last study visit will be tabulated by using Anatomical Therapeutic Chemical 4 classification codes and preferred drug name via the World Health Organization Drug Dictionary (WHO-DD) in latest version, with version to be specified in the Clinical Study Report. This includes medications that were started before the study and are ongoing during the study. All medications will be summarized by treatment group and sorted alphabetically by ATC class level 2 and preferred drug name. For the summary tables, if a subject has taken a concomitant medication more than once, the subject will be counted only once for the medication, within a treatment group.

All prior and concomitant medication data will be presented in individual subject data listings.

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7.3.2 Extent of Exposure and Treatment Compliance

Subjects will receive either 40 mg elamipretide or placebo administered with the elamipretide delivery system as a single daily SC injection. Study medication administration date and time is collected for dosing in the study drug administration log.
Extent of exposure will be defined as the total number of days a subject is exposed to any study treatment.

Treatment duration (days) defined as: (Last dose date+1) – (First dose date).

For subjects who are lost to follow-up, extent of exposure will be calculated based on the last study visit attended. Duration of exposure will be tabulated and summarized by descriptive statistics by treatment group.

Study drug administration is captured on the subject diary. Number of doses expected and number of doses taken since last visit are collected at the scheduled visits on the CRF for subject diary. The overall compliance will be calculated as:

Overall Compliance (%) = A / B x 100
A = The sum of all doses taken
B = The sum of all doses expected

The relative dose intensity (RDI) will be calculated as:

RDI (%) = Actual Total Dose / Planned Total Dose in 48 weeks x 100

The planned total dose for 48 weeks dosing is calculated as 48 x 7 = 336. The actual total dose will be the summation of all dose take from the subject diary.

The overall compliance and relative dose intensity will be summarized in the trial and by treatment group for the mITT and PP populations. The number and percent of subjects falling into the following categories will be presented: <70%, 70-100% and >100%.

The data for overall compliance, as well as relative dose intensity will be presented in a listing.

7.3.3 Pregnancy Test

Pregnancy status findings will be listed.

7.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics which are listed in Section 6.1 will be summarized by treatment group. Descriptive demographic data will be provided in the tabulation as follows:

- Age: mean, standard deviation, median, minimum and maximum

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- Gender: male, female
- Race
- Ethnicity
- Iris color: number and percentage of subjects who have dark brown, blue, brown, hazel, green, gray, other colored iris.
- Study eye: OD or OS
- Baseline LL BCVA score (Letters)
- Baseline square root transformed GA area (in mm) by OCT
- Baseline GA area (in mm2) by OCT
- Baseline LL RA LogMar Score
- Baseline BCVA score (Letters)
- Baseline square root transformed GA area (in mm) by FAF
- Baseline GA area (in mm2) by FAF
- LL Deficit (in letters): define as the difference between BCVA and LL BCVA)
- Baseline GA distance to fovea (in µm) by OCT
- Baseline GA distance to fovea (in µm) by FAF

Continuous variables for baseline characteristics as provided in Section 6.1 (e.g. weight, height, vital signs etc.) will be summarized by descriptive statistics (n, mean, standard deviation, median, Q1 and Q3, minimum and maximum).

7.5 Efficacy Analyses

A family-wise alpha level of 0.1 will be maintained for the primary endpoint family, using Hochberg's procedure at the primary time point of 48 weeks. If both primary endpoints are significantly different from

placebo at the 0.1 (two-sided) level of significance (in favor of treatment), then both will be considered statistically significant. Otherwise, the endpoint with the smaller p-value of the two will be considered statistically significant, if statistically significant at the 0.05 (two-sided) level of significance.

No adjustments will be made to alpha levels to account for secondary or exploratory efficacy measures. Statistical tests (where performed) will be 2-sided.

Majority of efficacy analysis will be based on a mixed model for repeated measures (MMRM). In general, arithmetic mean and least square (LS) mean from MMRM for the change from baseline values will be plotted.

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7.5.1 Primary Efficacy Analysis

7.5.1.1 Primary Endpoint #1: LL BCVA

The actual LL BCVA score and the change in LL BCVA score from baseline (number of letters) will be summarized descriptively for each visit. Arithmetic mean difference, 95% Wald CI and nominal p-values by t-test will be presented for each post-baseline visit.

A mixed model for repeated measures (MMRM) will be used to explore the treatment effect of LL BCVA in the study eye. For the model, change from baseline LL BCVA scores are considered as dependent variables. The analysis model will include fixed effects for treatment arm, study visit, the treatment arm-byvisit interaction and baseline-by-visit interaction, baseline as a covariate, and a random effect for subject. The model will use the unstructured within-subject variance-covariance matrix. In the event an unstructured variance-covariance matrix does not converge, a Toeplitz structure will be used. The estimated least square (LS) means and their standard errors as well as the estimated treatment effect (differences between treatments) and p-values will be summarized at each visit. Refer to SAS code in Appendix 3.

Week 48 is the primary analysis time point and the corresponding p-value testing the treatment differences will be used in the primary comparison.

In addition, the following analysis examining individual responses will be reported for each treatment, at each time point in the study eye:

- The proportion of subjects with an improvement or loss of ≥ 1 line (5 letters)
- The proportion of subjects with an improvement or loss of ≥ 2 lines (10 letters)
- The proportion of subjects with an improvement or loss of ≥ 3 lines (15 letters)

A Generalized Estimating Equations (GEE) logistic regression will be performed for each category at each post-baseline visit. The model would include effects treatment, visit, treatment-by-visit interaction and laterality. Similar variance-covariance structure selection process will be used as in the primary analysis.

To assess the robustness of the primary results based on the mITT population, the analyses of the primary endpoint will be repeated for the PP population.

7.5.1.2 Primary Endpoint #2: GA area as measured OCT

GA area in mm^2 will be measured by optical coherence tomography (OCT) at all study visits including at the Early Termination visit (for subjects who withdraw early) except at the Week 4 and Week 8 visit. Based on recent meta-analysis for growth rate of geographic atrophy[5] , square root transformed total GA area (in mm) will be used in the primary analysis. The raw value of GA area in mm^2 will be analyzed as sensitivity analysis in similar manner.

A similar mixed model for repeated measures (MMRM) as in Section 7.5.1.1 will be used to explore the treatment effect of GA area as measured OCT in the study eye. Week 48 is the primary analysis time point and the corresponding p-value testing the treatment differences will be used as the primary comparison. (Page 26 of 35)

Arithmetic mean difference, 95% Wald CI and nominal p-values by t-test will be presented for each postbaseline visit.

The listing will show both the raw and square root transformed value for each eye and each visit.

7.5.2 Secondary Efficacy Analysis

Continuous secondary efficacy measures will be analyzed similarly to the primary endpoints using MMRM, with additional summaries as noted. Arithmetic mean difference, 95% Wald CI and nominal p-values by ttest will be presented for each post-baseline visit

7.5.2.1 LL RA

A reading acuity test was administered under standard lighting and LL conditions (using a 2.0-log neutral density filter) at all study visits including at the Early Termination visit (for subjects who withdraw early) except Week 8 visit.

7.5.2.2 BCVA

BCVA testing using the ETDRS chart will be conducted at every study visit. The change in BCVA score from baseline (number of letters) will be categorized using the following response criteria and presented for each treatment, at each visit in the study eye:

- The proportion of subjects with an improvement or loss of ≥ 1 line (5 letters)
- The proportion of subjects with an improvement or loss of ≥ 2 lines (10 letters)
- The proportion of subjects with an improvement or loss of ≥ 3 lines (15 letters)

7.5.2.3 GA area as measured by FAF

Similar as OCT, FAF will be used to determine areas of GA at all study visits including at the Early

Termination visit (for subjects who withdraw early) except at the Week 4 and Week 8 visit. The change from baseline on the square root transformed GA area (in mm) as assessed by FAF in the study eye will be analyzed. The raw value of GA area in mm^2 will be analyzed as sensitivity analysis in similar manner.

The listing will show both the raw and square root transformed value for each eye and each visit.

7.5.3 Exploratory Efficacy

Continuous exploratory efficacy measures will be analyzed using MMRM similarly to the primary endpoints.

7.5.3.1 Volumetric OCT and ellipsoid zone (EZ) mapping

Volumetric OCT and ellipsoid zone (EZ) mapping are defined as:

- Macular Percentage of EZ Total Attenuation
- Macular Percentage of EZ Partial Attenuation
- Central 1-mm mean EZ-RPE thickness
- Central 2-mm mean EZ-RPE thickness

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7.5.3.2 National Eye Institute VFQ-39

The VFQ-39 is designed to assess health-related quality of life of subjects with visual impairment and includes 11 domains: general vision, ocular pain, near activities, distance activities, vision-specific social functioning, vision-specific mental health, vision-specific role difficulties, vision-specific dependency, driving, color vision, and peripheral vision. Subjects will be asked to complete questionnaire at Baseline/Day 1, Week 12, Week 24, Week 36, Week 48 and at the Early Termination visit (for subjects who withdraw early from the study).

7.5.3.3 RA at standard light

The actual LL RA score and change from baseline in reading acuity measured as critical print size (logMAR) will be summarized at each visit and will be presented in a listing.

7.5.3.4 LLQ

The LLQ is a vision-related quality of life scale assessing mainly mesopic and scotopic functioning. Subjects will be asked 36 questions about problems that involve his/her vision under different lighting conditions. Subjects will be asked to complete this questionnaire at Baseline/Day 1, Week 12, Week 24, Week 36, Week 48 and at the Early Termination visit (for subjects who withdraw early from the study).

The LLQ is divided into 8 domains: Control questions, General dim light vision, Dim light reading, Driving or riding in car, Other Activities of Daily Living (ADLs), Mobility, Light transitions and glare and Peripheral vision.

7.5.3.5 EQ-5D-5L

The EQ-5D-5L is a questionnaire administered at Baseline/Day 1, Week 48 and at the Early Termination visit (for subjects who withdraw early from the study). It is designed to assess the subject's health at the time of the clinic site visit focusing on categories of mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and on how good/bad their heath is today. There are 2 sections: the descriptive system and visual analog scale (VAS).

The descriptive system is comprised of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each having 5 levels (no problems, slight problems, moderate problems, severe problems, and extreme problems). An index score comprised of the descriptive system will be derived using UK value set (van Reenan 2015).

The VAS records the subject's self-rated health on a 20-cm vertical line with endpoints labelled 'the best health you can imagine' and 'the worst healthy you can imagine'. The scale is numbered from 0 to 100, with 100 meaning the best health you can imagine, and 0 meaning the worst health you can imagine.

Index score of the5 dimensions and the VAS score will be analyzed separately based on analysis of covariance with baseline score as the covariate. See Appendix 3 for the sample SAS codes.

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7.5.3.6 Conversion to CNV

The study eye will be evaluated for conversion to CNV in an ongoing fashion. On the end of the study CRF page, a response of "yes", "no" or "unknown" will be provided to the question "Has the study eye converted to Wet AMD/CNV since baseline?" If a response of yes is provided, the subject is deemed to have converted to CNV. Conversion to CNV will be summarized with frequency counts and percentages by treatment group for the mITT and PP population and tested via Chi-square test or Fisher's Exact Test, for both study eye and non-study eye.

7.5.3.7 BCVA and LL BCVA in non-study eye

BCVA and LL BCVA testing using the ETDRS chart will be conducted at every study visit for each eye. The actual BCVA and LL BCVA score and the change in BCVA and LL BCVA score from baseline (number of letters) for the non-study eye will be analyzed similarly to the primary analysis.

7.5.3.8 GA area as measured by OCT in non-study eyes with GA

GA area as measured by OCT in non-study eyes with GA will be analyzed in a similar manner as for the study eye.

7.5.3.9 Correlation between EZ thickness and BCVA/LL BCVA and GA Progression

Pairwise Pearson correlation coefficients and p-values of the change from baseline will be reported for the following variables:

- Central 1-mm mean EZ-RPE thickness • Central 2-mm mean EZ-RPE thickness with
- BCVA
- LL BCVA
- square root transformed GA Area by OCT

7.5.4 Subgroup Analysis

Subgroup analysis will be performed both primary endpoints in mITT population for patients with:

- baseline lesion size >= or < 2.5mm^2
- baseline GA location ○ Extrafoveal GA (>= 150 um from foveal center) at Baseline ○ Foveal GA (< 150 um from foveal center) at Baseline

7.6 Pharmacokinetic/Pharmacodynamic/Pharmacogenomic

All data analyses related to PK data will be detailed in a separate PK Analysis Plan prior to database lock. A listing of PK sample collections will be provided in the individual subject data listings.

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7.7 Safety Analyses

7.7.1 Adverse Events/Adverse Device Effects

All AEs/ADEs will be coded to SOC and PT using the latest MedDRA. All reported AEs/ADEs will be listed, but only treatment-emergent adverse events (TEAEs)/treatment-emergent adverse device effects (TEADEs) will be summarized. In addition, TEAE excluding TEADE will also be summarized.

The incidence of all TEAEs/TEADEs/TEAE (Excluding TEADE), drug relationship with TEAEs/TEADEs/TEAE (Excluding TEADE), and severity of TEAEs/TEADEs/TEAE (Excluding TEADE) will be summarized by treatment group. If severity is missing, subjects will be included as severe (for severity). If drug relationship is missing, subjects will be included in related tables (i.e., considered related). Summary tables will be organized by SOC, then PT.

The following summaries will be presented for TEAEs/TEADEs/TEAE (Excluding TEADE) by treatment groups:

- Overall Summary of Treatment-Emergent Adverse Events/Treatment-Emergent Adverse Device Effects/TEAE(Excluding TEADE)
- Incidence of Treatment-Emergent Adverse Events/Treatment-Emergent Adverse Device Effects//TEAE(Excluding TEADE) by SOC and PT
- Incidence of Treatment-Emergent Ocular Adverse Events/Treatment-Emergent Adverse Device Effects/TEAE(Excluding TEADE) by SOC and PT
- Incidence of Treatment-Emergent Systemic Adverse Events/Treatment-Emergent Adverse Device Effects/TEAE(Excluding TEADE) by SOC and PT
- Incidence of Treatment-Emergent Serious Adverse Events/Treatment-Emergent Serious Adverse Device Effects/TEAE(Excluding TEADE) by SOC and PT
- Incidence of Treatment-Emergent Ocular Serious Adverse Events/Treatment-Emergent Serious Adverse Device Effects/TEAE(Excluding TEADE) by SOC and PT
- Incidence of Treatment-Emergent Systemic Serious Adverse Events/Treatment-Emergent Serious Adverse Device Effects/TEAE(Excluding TEADE) by SOC and PT
- Incidence of Injection Site Treatment-Emergent Adverse Events/ Treatment-Emergent Adverse Device Effects/TEAE(Excluding TEADE) by SOC and PT
- Incidence of Treatment-Emergent Adverse Events/Treatment-Emergent Adverse Device Effects/TEAE(Excluding TEADE) Leading to Discontinuation of Study Drug by System Organ Class and Preferred Term
- Incidence of Treatment-Emergent Adverse Events/Treatment-Emergent Adverse Device Effects/TEAE(Excluding TEADE) by SOC, PT and Relationship to Study Drug
- Incidence of Treatment-Emergent Ocular Adverse Events/Treatment-Emergent Adverse Device Effects/TEAE(Excluding TEADE) by SOC, PT and Relationship to Study Drug
- Incidence of Treatment-Emergent Systemic Adverse Events/Treatment-Emergent Adverse Device Effects/TEAE(Excluding TEADE) by SOC, PT and Relationship to Study Drug

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- Incidence of Study Drug Related Treatment-Emergent Adverse Events/Treatment-Emergent Adverse Device Effects/TEAE(Excluding TEADE) by System Organ Class and Preferred Term and Severity
- Incidence of Study Drug Related Ocular Treatment-Emergent Adverse Events/Treatment-Emergent Adverse Device Effects/TEAE(Excluding TEADE) by System Organ Class and Preferred Term and Severity
- Incidence of Study Drug Related Systemic Treatment-Emergent Adverse Events/TreatmentEmergent Adverse Device Effects/TEAE(Excluding TEADE) by System Organ Class and Preferred Term and Severity

All AE and SAE will be listed. TEAE leading to discontinuation and TEAE leading to death will be listed separately as applicable.

7.7.1.1 Deaths

Deaths will be provided as a listing, displaying treatment group, date of death and reason for death, and date of first and last study drug.

7.7.2 Clinical Laboratory Results

Laboratory parameters, SI results, SI reference ranges are provided by the central laboratory vendor (ICON Laboratory Services) and will be used. The normal/abnormal and normal/low/high flags will be derived based on the SI results, SI reference ranges when possible.

Summary tables for laboratory parameters (including hematology, chemistry, and urinalysis) will include descriptive statistics of change relative to baseline where appropriate.

Subjects with laboratory data outside the normal range will be listed with abnormal values flagged.

Shift tables (e.g., tables that show the number of subjects who are low, normal, or high at baseline versus each post-baseline scheduled assessment) will be produced.

The number and percentage of subjects with urinalysis results outside the normal range will be presented by endpoint and visit for each treatment group. Shift tables for urinalysis will show the number of subjects who are normal/abnormal at baseline and normal/abnormal at the end of the treatment period.

7.7.3 Vital Signs

Vital signs data will be summarized by changes from baseline values at each visit, for each treatment group using descriptive statistics.

Listing of vital signs data will be provided for all subjects in the safety population.

7.7.4 Physical Examination

Physical examinations results will be presented in subject data listings.

7.7.5 Ocular Safety Analysis

7.7.5.1 Slit Lamp Examination

Slit lamp examinations results will be presented in subject data listings. Shift tables reporting the number and percentage of subjects experiencing clinically significant abnormalities in slit lamp examination will be provided by visit for the mITT and PP population.

7.7.5.2 IOP (Applanation Tonometry)

IOP will be assessed using Goldmann tonometry or Tonopen. IOP data will be presented in subject data listings. The observed and change from baseline scores will be summarized descriptively by treatment group for each visit in shift tables.

7.7.5.3 Dilated Fundus Examination

Dilated fundus examinations results will be presented in subject data listings. The number and percentage of subjects experiencing clinically significant abnormalities in dilated fundus examination will be tabulated by treatment group in shift tables.

8. ANALYSES PERFORMED BEFORE DATABASE CLOSURE

No analysis is planned before database closure.

9. CHANGES FROM METHODS PLANNED IN THE PROTOCOL

Not Applicable.

10. STATISTICAL SOFTWARE

The statistical software to be used for generation of the tables, listings, and figures is SAS® version 9.4.

11. REFERENCES

1. Carol M. Mangione, MD. NEI VFQ-25 Scoring Algorithm – August 2000.
2. EQ-5D-5L User Guide. Basic information on how to use the EQ-5D-5L instrument. Version 2.1, April 2015.
3. FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency. FDA-2020-D-1106-0002, March 2020.van Reenan M, Janssen B. EuroQol Group
4. EQ-5D-5L User Guide: Basic information on how to use the EQ-5D-5L instrument. https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf (April 2015). 5. Wang J, Ying GS. Growth Rate of Geographic Atrophy Secondary to Age-Related Macular Degeneration: A Meta-Analysis of Natural History Studies and Implications for Designing Future Trials. Ophthalmic Res. 2021;64(2):205-215. doi: 10.1159/000510507. Epub 2020 Jul 28. PMID: 32721951.

APPENDIX 1 DATA HANDLING RULES

Category	Description	Data Handling Rules
Demographics	Age at informed consent	Age = integer ((date of informed consent signed – date of birth+1) / 365.25) For date of birth, if only day is missing, it is imputed by 15th of the month of birth. If both day and month are missing, it is imputed by July 1st of the year of birth.
Baseline	Baseline assessment for efficacy data	Baseline assessment is defined as last assessment prior to the first dose of study drug.
Timing	Study Day 1	First day subject is administered the study drug. Generally, the first dose date come from CRF "Study Drug Administration" page at the baseline visit. However, if a randomized subject was not administered with the study drug on-site, the first dose date (Study Day 1) would be assumed to be the next day at home (date of baseline visit + 1). This rule applied to the SDTM variables RFSTDTC/RFXSTDTC in DM domain.
Timing	Study Day	Study day = date of assessment – date of Study Day 1 + 1
Timing	Time from administered study drug	Time from dosing start = time of assessment – time of administration of study drug
Vital Signs/Lab	Change from baseline	$Change_t = Value_t – Value_{Baseline.}$. Baseline value is defined as the last evaluation performed prior to administration of study drug.
Drug Administration	Treatment duration (days)	Sum of treatment duration in each period: (Last dose date+1) – (First dose date).

APPENDIX 2 ANALYSIS DATASET SPECIFICATIONS

Analysis datasets (ADaM) will be built to gain efficiency and ensure consistency in data analyses and presentation for this trial. The specifications for the analysis data sets will be prepared in a separate document.

APPENDIX 3 SAS CODE FOR STATISTICAL ANALYSES

This section will be completed after examining the existing data and prior to the final signoff of this SAP.

Test	Table/Figure	SAS Codes for Modeling
Mixed model repeated measures (MMRM)	Efficacy endpoints with multiple postbaseline time points	PROC MIXED; WHERE PARAMCD='xxx'; CLASS SUBJECT TRT VISIT; MODEL CFB = TRT VISIT TRT*VISIT BASELINE BASELINE*VISIT; REPEATED VISIT/ TYPE = UN DDFM=KR SUB=SUBJECT; LSMEANS TRT*VISIT/CL DIFF ALPHA=0.05; LSMEANS TRT/CL DIFF ALPHA=0.05; RUN; **TYPE=TOEP will be used when TYPE=UN does not work;
Analysis of Covariance (ANCOVA)	Efficacy endpoints with a single postbaseline time point	PROC GLM; CLASS TRT; MODEL AVAL = TRT BASELINE / solution; LSMEANS TRT / STDERR PDIFF COV; RUN;

APPENDIX 4 MOCKUP TABLES, LISTINGS, AND GRAPHS (TLGS)

Mockup tables, listings, and graphs are presented in a separate document.