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STATISTICAL ANALYSIS PLAN

COAST

A Phase 3, Multicentre, Double-masked, Randomised Study to Evaluate the Efficacy and Safety of Intravitreal OPT-302 in Combination with Aflibercept, Compared with Aflibercept Alone, in Participants with Neovascular Age-related Macular Degeneration (nAMD)

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1 GLOSSSRY OF ABBREVIATIONS

Abbreviation	Description
ADA	Anti-OPT-302 Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
AMD	Age-related Macular Degeneration
APTC	Anti-Platelet Trialists' Collaboration
ATC	Anatomical Therapeutic Chemical
BCVA	Best-corrected Visual Acuity
BMI	Body Mass index
CD	Can't Determine
CI	Confidence Interval
CRF	Case Report Form
MH	Mantel-Haenszel
CNV	Choroidal Neovascularisation
CRT	Central Retinal Thickness
CST	Central Subfield Thickness
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EQ-5D	EuroQoL-5D
EQ-5D-5L	EuroQol-5D-5L
EQ-5D-V	EuroQol-5D with Vision bolt-on
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein Angiography
FCS	Fully Conditional Specification
IOP	Intraocular Pressure
IR	Intra-retinal
IRC	Independent Reading Centre
IRF	Intra-retinal Fluid
IVT	Intravitreal
IXRS	Interactive Randomization System
MAR	Missing at Random
Max	Maximum
MCH	Mean Corpuscular Haemoglobin
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum

Abbreviation	Description
mITT	Modified Intent to Treat (analysis population)
MMRM	Mixed Model for Repeated Measures
MNAR	Missing Not At Random
N/A	Not Applicable
NEI VFQ-25	National Eye Institute 25-item Visual Function Questionnaire
OCT	Optical Coherence Tomography
OCT-A	Optical Coherence Tomography Angiography
OD	Oculus Dextrus/Dexter (right eye)
OS	Oculus Sinister (left eye)
OU	Oculus Uterque (both eyes)
PCV	Polypoidal Choroidal Vasculopathy
PED	Pigment Epithelial Detachment
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PROs	Participant Reported Outcomes
PT	Preferred Term
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SE	Standard Error
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
SRF	Sub-retinal Fluid
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization
W52	Week 52

2 INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analyses planed in the protocol, and provides detailed statistical methods, rules and conventions to be used in the presentation and analysis of efficacy and safety data in the Clinical Study Reports (CSR) for study OPT-302-1005. Two CSRs are planned for this study:

A CSR reporting analyses at Week 52 (W52), which is the primary efficacy time point. The analyses include all efficacy and safety data during the efficacy phase up to Week 52 after all the randomized participants have completed the Week 52 visit or discontinued from the study prior to Week 52.

A CSR reporting final analyses on all the data from both the efficacy phase and the safety phase from the final data base lock (DBL) after all participants randomized into the study have completed the end of study visit at Week 100 or discontinued from the study.

The SAP will be finalized before the DBL for the analyses at Week 52. Any changes to the SAP after approval will be documented. This SAP is based on protocol version 2.0 (Amendment 1) dated 19 Dec 2023.

3 STUDY OBJECTIVES

All the objectives will be evaluated in the following two populations:

- Biomarker positive stratum: defined as the subset of participants with minimally classic or occult lesion classifications at Baseline based on the Independent Reading Center (IRC) reading at Baseline.
- Overall population: including all participants regardless of the lesion classifications.

In addition, primary and secondary endpoints will be summarized in biomarker negative population.

- Biomarker negative stratum: defined as participants with a predominantly classic lesion classification at Baseline based on the IRC reading at Baseline

3.1 Primary Objective

The primary objective is to determine the efficacy of intravitreal 2.0 mg OPT-302 when administered in combination with intravitreal 2.0 mg aflibercept, in participants with neovascular age-related macular degeneration (AMD).

3.2 Secondary Objectives

The secondary objectives are to determine the effects of intravitreal 2.0 mg OPT-302 when administered in combination with intravitreal 2.0 mg aflibercept from Baseline to (and at) Week 52 as determined by:

Efficacy:

- Changes in Early Treatment Diabetic Retinopathy Study (ETDRS) Best-corrected Visual Acuity (BCVA) letter score
- Changes in anatomical parameters (choroidal neovascularisation (CNV) area, sub-retinal fluid (SRF) and intra-retinal (IR) cysts)

Safety:

- Incidence of adverse events (AEs)
- Deterioration in ETDRS BCVA letter score
- Incidence of anti-OPT-302 antibody (ADA) formation.

Pharmacokinetic:

- Pharmacokinetic (PK) parameters of OPT-302.

3.3 Exploratory Objectives

The exploratory objectives of the study are to characterize the effects of intravitreal 2.0 mg OPT-302 when administered in combination with intravitreal 2.0 mg aflibercept in terms of changes in (and absolute):

- ETDRS BCVA letter scores from Baseline to (or at) Week 52
- Anatomical parameters (IR cysts, SRF, intra-retinal fluid [IRF], central retinal thickness [CRT], pigment epithelial detachment (PED) thickness, total lesion area, geographic atrophy area) from Baseline to (or at) Week 52
- ETDRS BCVA letter score from Baseline to (or at) Week 100
- Anatomical parameters (CNV area, CST, SRF and IR cysts, SRF, IRF, CRT, PED thickness, total lesion area, geographic atrophy area) from Baseline to Week 100
- Changes in National Eye Institute 25-item Vision Function Questionnaire (NEI-VFQ-25) and in EuroQol-5D-5L Questionnaire.

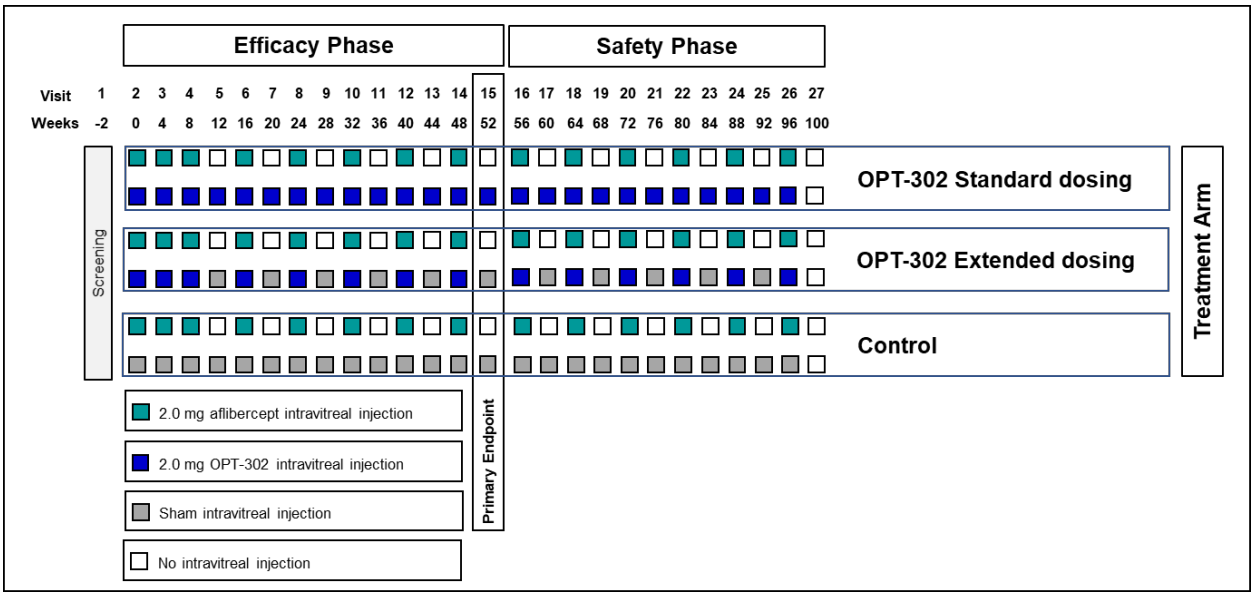
4 STUDY DESIGN

4.1 General Description

This study is a Phase 3, multicentre, randomized, parallel-group, sham-controlled, double-masked, study of approximately 102 weeks duration. Eligible study participants will be randomized at Baseline to one of three treatment arms in a 1:1:1 ratio:

- intravitreal 2.0 mg aflibercept followed by Standard Dosing 2.0 mg OPT- 302, referred as **OPT-302 standard dosing** arm in the following sections of the document
- intravitreal 2.0 mg aflibercept followed by Extended Dosing 2.0 mg OPT-302, referred as **OPT-302 extended dosing arm** in the following sections of the document
- intravitreal 2.0 mg aflibercept followed by a sham injection, referred as **Control arm** in the following sections of the document

Randomization is stratified by geographical region of the site (North America, South America, Europe / West Asia, Asia and Pacific), visual acuity at Baseline (> 54 letters vs. ≤ 54 letters), and lesion type (predominantly classic, minimally classic, or occult). The dosing regimen for each of the three treatment arms are demonstrated in the following graph.



The study has two phases, the Efficacy Phase (Baseline to Week 52 [Visit 15]) and the Safety Phase (Week 52 to Week 100 [Visit 15 to Visit 27]). Although efficacy and safety will be assessed during both study phases, the efficacy of OPT-302 is intended to be characterised during the Efficacy Phase (*via* the primary and secondary efficacy endpoints), and the safety of OPT-302 with long term (2-year) administration is intended to be characterised during the 2-year Efficacy Phase and Safety Phase.

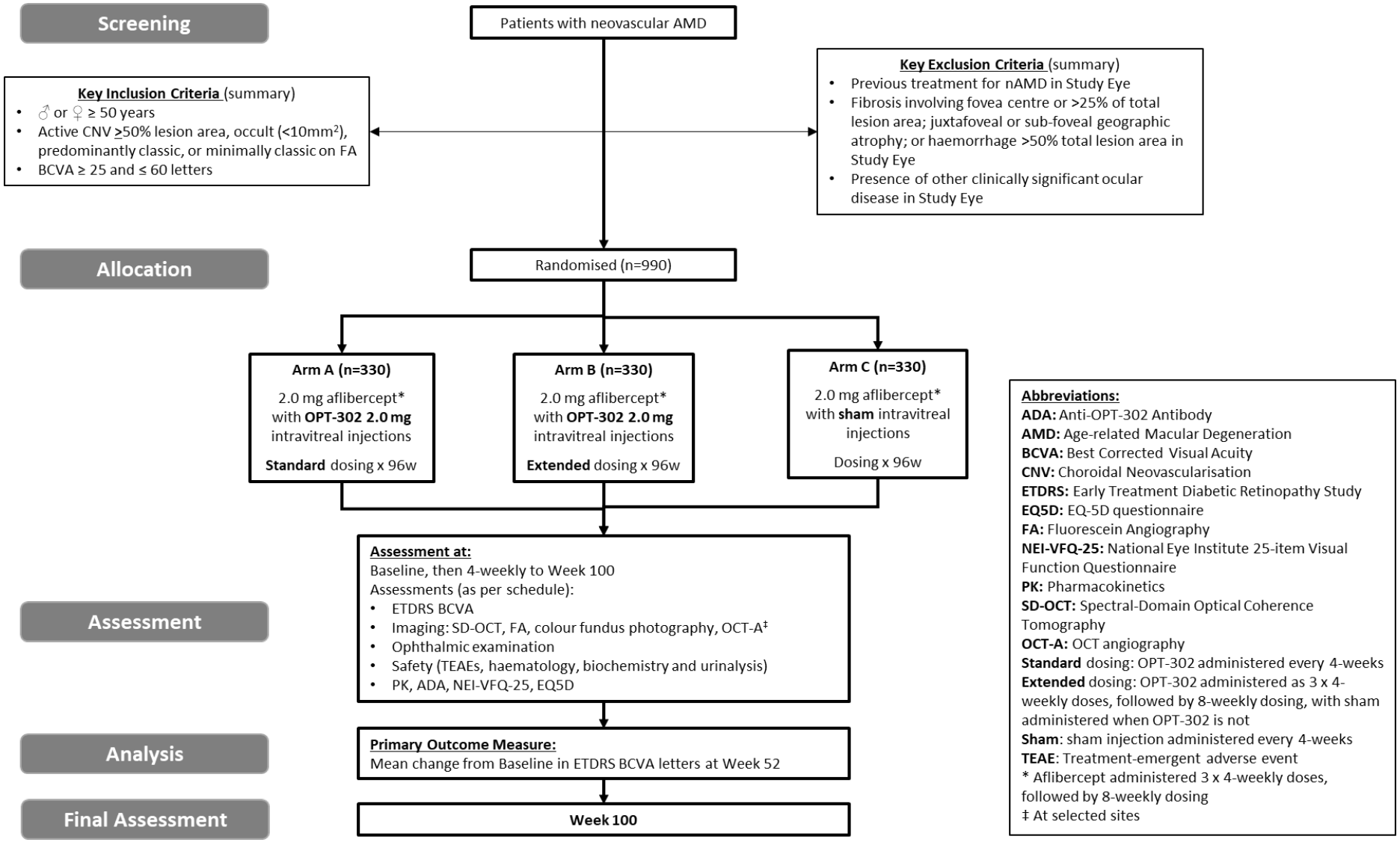
During the Efficacy Phase (Baseline to Week 52), study medication will be administered according to the randomization schedule, commencing at the Baseline visit through to Week 48. The primary endpoint will be determined at Week 52 (Visit 15). Once all study assessments have been completed at Week 52, the participant will enter the Safety Phase of the study (Week 52 to Week 100). Each participant will continue to receive the study medication and dosing regimen allocated at Baseline. A final follow-up visit will be conducted at Week 100 (Visit 27), approximately 4 weeks after the planned last administration of study medication at Week 96 (Visit 26).

During study visits, the following assessments will be performed according to the study schedule laid out in Table 1-1 of the study protocol: Ophthalmic examination including refraction and BCVA testing according to the standardized ETDRS protocol, slit lamp examination including indirect ophthalmoscopy, and intraocular pressure; fundus examination; fluorescein angiography (FA); color fundus photography (CFP); and SD-OCT, with OCT angiography (OCT-A) performed at selected sites. Safety will be assessed *via* collection of AEs, vital signs, urinalysis, and blood samples for determination of biochemistry and haematology parameters (and pregnancy test for women of childbearing potential only). Blood samples will also be taken periodically throughout the study for analysis of anti-OPT-302 antibody formation and pharmacokinetics (PK), and PROs will be assessed *via* the NEI VFQ-25 and EQ-5D-V questionnaires.

In order to maintain the study masking, all ocular imaging will be assessed by an independent reading centre (IRC), study assessments at site (including ETDRS BCVA and imaging) will be conducted by Assessing Investigators and technicians who are masked to study product, aflibercept and OPT-302/sham will be administered by an unmasked Treating Investigator, who is qualified to perform the intravitreal injection procedure, and independent from the masked study team.

Figure 1 provides an outline of the overall study design.

Figure 1 Study Design Schema



4.2 Schedule of Events

Schedule of events can be found in Table 1-1 of the study protocol.

4.3 Sample Size

It is intended to enroll approximately 990 participants into the study, approximately 330 participants in each of the three treatment groups. It is estimated that a sample size of 280 participants per treatment group, 840 in total, will be in the biomarker positive stratum (*i.e.* participants with minimally classic and occult lesions). This will provide approximately 90% power to detect a difference of 4.7 letters in this stratum, when using a two-sided false positive error rate of 0.02403, and when assuming a 10% rate of missingness and a standard deviation of 15 letters. Statistical significance would be achieved with an estimated improvement of 3.0 letters in the OPT-302 combination treatment arm relative to aflibercept alone in mean change in BCVA from Baseline to Week 52.

Note that an adjustment is made consistent with the use of a monitoring boundary of approximately 2-sided 0.001 at each of the 6 DMC meetings planned before the Week 52 analyses. To be precise, implementing a Fleming-Harrington-O'Brien (Fleming, 1984) boundary (see Table 1) the 2-sided boundary at each of the 6 DMC meetings will be 0.00100, 0.00116, 0.00136, 0.00159, 0.00182, and 0.00205. Therefore, the analysis at Week 52 will be conducted at two-sided 0.04806.

Table 1 Values of $\{\alpha_1, \alpha_2, \ldots, \alpha_K\}$ for K=7, α=0.05

Monte Carlo Simulation Results							
K =7							
α	α_1	α_2	α_3	α_4	α_5	α_6	α_7
0.05	0.00100	0.00116	0.00136	0.00159	0.00182	0.00205	0.04806

K= number of analyses; α = overall alpha; α_1 through α_6 = monitoring boundaries at each of five DMC meetings; α_7= alpha for analyses at W52.

It is expected that approximately 50 participants per treatment group, 150 in total, will have been randomized in the biomarker negative stratum at the time 840 participants have been randomized in the biomarker positive stratum. Hence, for a given comparison of an OPT-302 combination treatment arm against the aflibercept plus sham control arm, there will be approximately 330 participants per treatment group (of whom 50 participants would be in the biomarker negative stratum). Continuing to assume a 10% rate of missingness and a standard deviation of 15 letters, then the estimate required to achieve statistical significance for each pairwise comparison of an OPT-302 dosing regimen vs the sham control, in an analysis of the mITT analysis set in this pooled stratum, would be an improvement of 2.8 letters in mean change in BCVA from Baseline to Week 52; in turn, by the Rothmann criteria (Rothmann, 2012), an estimated improvement of 2.8 letters also would be needed in the biomarker negative stratum to conclude positivity in that stratum.

4.4 Major Changes to Analysis from Protocol

The following is the list of major changes to analyses planned in the protocol:

- The mITT analysis set is updated including all randomized participants with at least one study treatment as the primary analysis set for efficacy analyses. ITT analysis set is renamed to Randomized analysis set and efficacy analysis in this population is removed since only a few participants were randomized by mistake and didn't receive any study medications.
- Definition of intercurrent events and estimand description are updated to follow the current ICH

E9 guidance. As a result, sensitivity analyses are added imputing missing data assuming MNAR in the active treatment arm to evaluate the assumption on MAR for missing data in the primary analysis. While the supportive estimands for the primary and secondary efficacy endpoints specified in the protocol are removed.

- The overall 2-sided α used for the efficacy analysis at Week 52 is reduced to 0.04806 since one more DMC review than planned on the protocol was conducted before the Week 52 analyses.
- Summary on TEAE will be conducted by ocular AE in study eye, ocular AE in non-study eye, and non-ocular AE. No summary on overall TEAE combining non-ocular and ocular AEs will be provided.

5 ANALYSIS SETS

5.1 Screened Set (SCR)

The **Screened Set (SCR)** will consist of all participants who provided informed consent for this study.

The SCR will be used for summaries of the screened participants including reasons for screen failure.

5.2 Randomized Set

The Randomized Set will include all participants who were randomized into the study, irrespective of whether study medication was administered or not. Participants will be analyzed according to the study treatment arm they were randomized to.

This analysis set will be used to report participant disposition.

5.3 Modified Intent-to-Treat (mITT) Analysis Set

The **modified Intent-to-Treat (mITT) Analysis Set** will include all participants in the randomized set with at least one dose of study medication.

Participants will be analyzed according to the study medication to which they were randomized. This analysis set is the primary analysis set for all efficacy endpoints.

5.4 Safety Analysis Set (SAF)

The Safety Analysis Set (SAF) will include all participants in the mITT analysis set. This analysis set will be employed to analyze the safety endpoints. If there is any doubt whether a participant was treated or not, they will be assumed treated for the purposes of analysis.

Participants will be analyzed according to the study medication actually received for all safety analyses. If participants have received study medication in ways that deviate from their randomized schedule, the following rules will be followed:

- A participant randomized to the control arm who have ever received at least one injection of OPT-302 during the treatment period of interest will be analyzed in the OPT-302 extended dosing arm.
- A participant randomized to one of the OPT-302 dosing arms but never received an injection of OPT-302 during the treatment period of interest will be analyzed in the control arm.

5.5 Per Protocol (PP) Analysis Set

The per-protocol (PP) analysis set will comprise participants in the mITT dataset without major protocol deviations, which will be identified before interim database lock for Week 52 analyses, or other findings that may majorly affect the validity of the assessment of BCVA at Week 52.

Efficacy analyses performed using the PP dataset will be considered as supportive to the mITT analysis. This analysis set is only used for analyses of the primary efficacy endpoint at Week 52.

5.6 Exclusions of data from noncompliant study sites

Participants in the study sites with noncompliance that significantly or potentially significantly affect the reliability of data will be excluded from both mITT and Safety Analysis Sets. As a result, all the data collected from the noncompliant study sites will not be included in any efficacy and safety analyses. The identification of such study sites will be documented before database lock for Week 52 and final analyses.

6 DATA ANALYSIS GENERAL CONVENTIONS

6.1 Identification of Study Eye

For all data where eye is reported (as Right/OD, Left/OS or OU [both]), the eye will be identified as the Study Eye or non-Study Eye for use in analyses by comparing with the Study Eye (Right/OD or Left/OS) recorded on the *Randomization* form. If OU (both) is selected, the data will be considered to relate to both the Study Eye and the non-Study Eye.

6.2 Reference Start Date and Study Day

Reference start date (Day 1) is defined as the day of the first dose of study medication. Study Day will be calculated as the number of days since the reference start date according to the following:

- For dates on or after the reference start date:

  Study Day = date of event – reference start date+1

- For dates prior to the reference start date:

  Study day = date of event – reference start date

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings. Study Day and any corresponding durations will appear missing in the listings.

6.3 Baseline

Unless otherwise specified, Baseline is defined as the last non-missing measurement taken prior to the first dose of study medication (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-Baseline. There is one exception for intraocular pressure (IOP), which was scheduled before and after each injection on each visit. Only the pre-injection IOP before the first injection of medication may be considered as Baseline measurement.

6.4 Change from Baseline

For quantitative measurements, change from Baseline will be calculated as:

- Test Value at Visit X – Baseline Value

and percent change from Baseline will be calculated as

- 100 x Change from Baseline/Baseline.

6.5 Parameters Based on Ophthalmic Imaging from Independent Reading Center (IRC)

Endpoints for SD-OCT, FA and fundus Ophthalmic imaging parameters are provided by IRC. To minimize bias, photography images are read by two independent readers per IRC SOPs. In presence of discrepancy between the two readings, a third reader will adjudicate any disagreements between the initial two readers. The following is the algorithm on how an endpoint will be derived when more than one reading are provided:

- Numerical entries: derived as the mean of the two readers' values, or the median of the three readers' recorded values if a third reader is also available.

- Non-numerical entries: no derivation is needed as only the consensus value is provided from the IRC.

An ophthalmic imaging reading of CD (i.e., can't determine) will be considered as a valid value at baseline, but as missing data for post-baseline assessments. Subgroup analysis will not be performed for participants with baseline value of "CD".

6.6 End of Study Date

The end of study (EoS) date is the date when a participant completes or discontinues the study.

6.7 Last day in the Efficacy Period

The last day in the efficacy period is derived as the following:

- the Week 52 visit date for those who attended Week 52.
- the "date of completion/discontinuation" captured on the EOS eCRF for those who discontinued from the study before Week 52 visit.
- the earlier date of Day 364 or the injection date on the first visit after Week 52 if a participant continued the study in the safety phase but skipped the visit for Week 52.

The Last day in the efficacy period will be used to cut data for the CSR analyses at Week 52. Note that, for those who are continuing in the safety period, the study treatment as well as the post-injection IOP assessments on the last day in the efficacy period are not included in the analyses at Week 52.

6.8 End of Treatment Date, Last Treatment Date, and End of Exposure Date

The end of treatment date is the date when a participant completed or discontinued the study treatment disposition status and based on the "Date of Treatment Completion/Discontinuation" reported on the "End of Product" eCRF. In the case when the End of Product form is not entered for patients who completed the study treatment or discontinued from the study and treatment simultaneously, the following date will be used as end of treatment date:

1) The Week 96 treatment date (or visit date if treatment was interrupted at Week 96 visit) for treatment completers
2) the "Date of completion/discontinuation" on the "Disposition EOS" eCRF form for those who discontinued from study and treatment simultaneously.

The last treatment date is the date when a participant took the last study injection based on the "Dosing Administration" eCRF.

The end of exposure date is the minimum (end of study date, last treatment date + 28 days). For Analyses at W52, the end of exposure date will be the last day in the efficacy period for participants ongoing at W52 (i.e., with treatment on or after Week 52 visit) and the minimum (last day in the efficacy period, last treatment date+28 days) for those who discontinued from the study treatment before W52.

6.9 Derived Timepoints

No visit windows will be derived. All the summary by visit will be based on the reported visit. The discontinuation visit that is not on a scheduled visit will be allocated, based on the study day, to the closet future scheduled evaluation visit.

6.10 Unscheduled Visits

In general, data collected at unscheduled visits will not be used for by-visit summaries but will contribute to analyses based on worst-case value /abnormalities at any time post-Baseline.

All data collected at unscheduled visits will be included in data listings.

6.11 General Method

For categorical variables the number of participants with non- missing data and the number of participants in each category will be presented. Denominators for percentages will exclude participants with missing data unless otherwise stated.

For continuous variables, unless otherwise stated, summaries will include the number of participants with non-missing data, the mean, standard deviation, standard error, 95% CI of the mean (optional), median, range (minimum and maximum).

6.12 Software Version

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

7 STATISTICAL CONSIDERATIONS

7.1 Factors Used in Analysis Models vs. Factors for Randomization Stratification

All participants in the study are randomized based on the following categories of the three stratification factors and the stratum for each participant is entered in the IXRS by investigators.

- Visual acuity at Baseline (> 54 letters vs. ≤ 54 letters)
- Lesion type at Baseline (predominantly classic, minimally classic, or occult)
- Geographical region (North America, South America, Europe/ West Asia, Asia and Pacific)

Note that a participant may belong to a different category if Baseline BCVA or lesion type derived following the Baseline definition in Section 6.3 are used for categorization. The following descriptions will be used in this document to differentiate the two sets of BCVA or lesion type categories:

- The categories entered in the IXRS by investigators for randomization will be referred as
  - stratification stratum for BCVA (> 54 letters vs. ≤ 54 letters)
  - stratification stratum for lesion type (predominantly classic, minimally classic, or occult)
- The categories defined based on the derived Baseline BCVA or Baseline lesion type in the analysis data set will be referred as
  - Baseline BCVA category (> 54 letters vs. ≤ 54 letters)
  - Baseline lesion type (predominantly classic, minimally classic, or occult)

By default, the Baseline BCVA category and Baseline lesion type will be used as factors for all the applicable analysis models or for subgroup analyses.

7.2 Multicentre Studies

Randomization to treatment is not stratified by country, rather region (North America, South America, Europe /West Asia, Asia and Pacific) will be one of the randomization factors.

Country will not be included as a factor in any statistical models, nor will it be a subgroup. However, region, as used in the IXRS, will be included as a factor in some statistical models and as a subgroup (see Section 7.4).

If the number of participants in the regions is such that inclusion of all four regions causes issues with model convergence or parameter estimation, then small regions may be pooled when used as a factor in analyses.

7.3 Multiple Comparisons / Multiplicity

The overall 2-sided alpha of 0.04806 is split 50%:50% to the setting of each pairwise comparison between an OPT-302 dosing regimen arm and the control arm for the testing at Week 52 conducted in the following hierarchical sequence.

- BCVA change from Baseline at W52 in the biomarker positive stratum.
- BCVA change from Baseline at W52 in the overall population.
- The proportion of participants gaining 15 letters or more in BCVA at W52 in the biomarker positive stratum
- The proportion of participants gaining 15 letters or more in BCVA at W52 in the overall population
- The proportion of participants gaining 10 letters or more in BCVA at W52 in the biomarker positive stratum
- The proportion of participants gaining 10 letters or more in BCVA at W52 in the overall population
- CNV area by FA change from Baseline at W52 in the biomarker positive stratum
- CNV area by FA change from Baseline at W52 in the overall population
- The proportion of participants with absence of both SRF and IR Cysts by SD-OCT at W52 in the biomarker positive stratum
- The proportion of participants with absence of both SRF and IR Cysts by SD-OCT at W52 in the overall population

The hierarchical testing procedure described above has been demonstrated in Figure 10-1 for the OPT-302 standard dosing arm compared to the control arm and Figure 10-2 for the OPT-302 extended dosing arm compared to the control arm on Protocol amendment 1. The testing will stop if the immediately preceding comparison failed to show statistical significance at a 2-sided alpha of 0.02403 (updated from 0.024375, which was specified on the protocol Amendment 1 when 5 DMC was assumed). This pre-specified hierarchical testing procedure described above will preserve the overall experimental 2-sided Type-I error rate at 0.04806 (updated from 0.04875 when 5 DMC was assumed on the protocol Amendment 1) for the analyses at W52.

If all the hypotheses in the testing hierarchical sequence listing have been rejected for one OPT-302 dosing regimen comparison to control, the alpha originally allocated to these comparisons will be propagated to the other OPT-302 dosing regimen comparison to control. For example, if the comparisons on all the endpoints under the testing procedure between the OPT-302 standard dosing arm vs. control are significant in the biomarker positive stratum and overall population, the testing on the OPT-302 extended dosing arm vs. control can be tested at 2- sided α=0.04806.

Note that, to achieve a claim for efficacy in the biomarker negative stratum, in addition to requiring positivity in the overall population for a given endpoint, the treatment effect will also be evaluated in the biomarker negative stratum to ensure both clinically relevant and at least as large as would be required for statistical significance in the overall population. For example, an improvement of 2.8 letters in the OPT-302 dosing arm relative to the control in mean change in BCVA from Baseline to Week 52 is expected in the biomarker negative arm is required for the primary endpoint.

7.4 Examination of Subgroups

Subgroup analyses will be conducted as stated in the exploratory analysis sections for the primary

(Section 11.1.4) and the secondary endpoints. It should be noted that the study was not powered to detect treatment differences within subgroups.

The following subgroups will be assessed and described within the exploratory analysis sections:

- Age (< 75 years, ≥ 75 years)
- Sex
- Race (White vs. Other)
- Baseline BCVA category (< 54 letters, ≥ 54 letters)
- Geographical region (North America, South America, Europe/West Asia, Asia and Pacific)
- Baseline CST: > median vs. ≤ median
- Baseline CNV Lesion area: >median vs. ≤ median
- PED present/absent at Baseline.
- SRF present/absent at Baseline.
- Polypoidal Choroidal Vasculopathy (PCV) detected/not detected at Baseline.

For subgroups defined based on medians, these are based on all participants with non-missing Baseline values for the parameter, across all three randomized treatment groups combined, in the corresponding biomarker stratum from the mITT analysis set.

8 DISPOSITION, DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

All the summaries specified in this section are, if not otherwise specified, applicable to both the analyses at W52 and the final analyses and will be provided for the biomarker positive stratum, biomarker negative stratum, and for the overall population.

8.1 Disposition

The SCR set will be used to summarize the number of participants screened (provided informed consent) and the number re-screened. The number of randomized participants and the number of screen failure participants will be summarized, along with main reason for screen failure. This summary is only applicable at the time of analyses at W52.

For analyses at Week 52, the following will be summarized in the randomized set:

- Number of participants in the mITT analysis set
- Number of participants in the SAF
- Number of participants in the PP analysis set and reasons for exclusion for the PP analysis set.
- Number of participants completing the Efficacy Phase and continue in the Safety Phase*
- Number of participants who discontinued from both study treatment and study at Week 52
- Number of participants who discontinued from the study at Week 52 since discontinued study treatment prior to Week 52, among these participants:
    - Number of participants who discontinued OPT-302/sham only
    - Number of participants who discontinued aflibercept only
    - Number of participants who discontinued both OPT-302/sham and aflibercept

- Number of participants discontinuing the study at or prior to Week 52, along with the primary reason for study discontinuation
- Number of participants discontinuing study medication at or prior to Week 52 along with the primary reason for discontinuing study medication.

*Note that a participant will be considered if the participant did not discontinue from study at or prior to W52.

For the final analyses, the following information will be summarized in the randomized set:

- Number of participants in the mITT analysis set
- Number of participants in the SAF
- Number of participants completing Week 100
- Number of participants discontinuing the study treatment and study prior to Week 100, along with the primary reason for study discontinuation

8.2 Protocol Deviations

Protocol deviations will be recorded in the Clinical Trial Management System (CTMS) protocol deviations log for the duration of the study (refer to the Protocol Deviations and Non-compliance Management Plan (PDMP) for the definition of all protocol deviations).

Major protocol deviations will be summarized by the category of deviations and treatment in the randomized set.

A listing of all protocol deviations will be provided.

8.3 Demographic and Baseline Characteristics

Demographic data and other Baseline characteristics will be summarized by treatment and for participants pooled from different treatment arms in the mITT analysis set. No statistical testing for between treatment arms will be carried out for demographic or other Baseline characteristics.

The following demographic and other Baseline characteristics will be reported for this study:

8.3.1 Factors Used to Define Randomization Stratum

- Randomization stratum entered in the IXRS
  - stratification stratum for BCVA (categorized as > 54 letter, ≤ 54 letters)
  - stratification stratum for lesion type (predominantly classic, minimally classic, or occult)
  - Geographical region (North America, South America, Europe/West Asia, Asia and Pacific)
- Baseline BCVA category and Baseline lesion type derived in the analysis data set will also be summarized to show the difference between the two sets of categories.

8.3.2 Demographic Characteristics

- Sex
- Age (years)
  - As a continuous variable
  - Grouped as < 50 years, 50-64 years, 65-74 years, ≥ 75 years
- Race

- Ethnicity, only applicable to participant from US
- Child-bearing potential (yes/no) for female participants only
    - If yes, pregnancy test result

8.3.3 General Baseline Characteristics

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- HbA_{1c} (%)
- Diagnosis of Diabetes (No/Yes) [Type I/Type II/ Type not reported]
- Smoking History (never/ex/current)

8.3.4 Baseline Disease Characteristics

- Study Eye (Oculus Dexter/right eye/OD or Oculus Sinister/left eye/OS)
- Intraocular pressure [IOP]) in the Study Eye and in the Non-study Eye as a continuous variable and in the categories <10, 10 to <15, 15 to <20, 20 to <25 and ≥25 mmHg
- Ophthalmic examination (Study Eye) [Normal; Abnormal, Clinically Non-Significant; Abnormal, Clinically Significant, unless otherwise stated below]
    - Lens (Phakic, Pseudo-phakic, Aphakic)
    - If Lens phakic:
        - Nuclear Grade (0, 1, 2, 3, 4)
        - PSC Grade (0, 1, 2, 3, 4)
        - Cortical Grade (0, 1, 2, 3, 4)
- Visual acuity at Baseline in the Study Eye and Non-Study Eye (continuous, and ≤24, 25-30, 31-40, 41-50, 51-60, >60 letters)
- FA – Study Eye:
    - CNV location (subfoveal, juxtafoveal, extrafoveal, unknown)
    - Total lesion area (mm^2) (continuous and categorized as ≤2.5, >2.5-5.0, >5.0-7.5, >7.5-10, >10.0-20.0, >20.0-30.5, >30.5)
    - Total CNV area (mm^2) (continuous and categorized as ≤2.5, >2.5-5.0, >5.0-7.5, >7.5-10.0, >10.0-20.0, >20.0-30.5, >30.5)
    - Percentage CNV of lesion (continuous and categorized as <50%, 50-<75%, 75-< 100%, 100%)
    - Number of occult lesion participants, and among these participants:
        - Area of occult CNV (mm^2) (continuous and categorized as absent, ≤2.5, >2.5-5.0, >5.0-7.5, >7.5-10.0, >10.0)
        - Percentage occult CNV of lesion

  - Number of predominately classic lesion participants, and among these participants:
    - Area of classic CNV (mm²) (continuous and categorized as absent, ≤2.5, >2.5-5.0, >5.0-7.5, >7.5-10.0, >10.0)
    - Percentage classic CNV of lesion
  - Number of minimally classic lesion participants, and among these participants:
    - Area of classic CNV (mm²) (continuous and categorized as absent, ≤2.5, >2.5-5.0, >5.0-7.5, >7.5-10.0, >10.0)
    - Percentage classic CNV of lesion
  - Presence/absence of haemorrhage, area of haemorrhage (mm²), percentage haemorrhage of the lesion
  - Presence/absence of fibrosis, area of fibrosis (mm²), and percentage fibrosis of the lesion
  - Presence/absence of geographic atrophy, geographic atrophy area (mm²), distance of geographic atrophy from foveal centre (mm), geographic atrophy location (based on distance of geographic activity from foveal centre, categorized as 0 [subfoveal], >0-<0.2 mm [juxtafoveal], 0.2 - <1.0 mm [extrafoveal], ≥1.0 mm [far from fovea])
  - Presence of PCV (possible, no, indeterminate).
- SD-OCT – Study Eye
  - CST (µm) (continuous and categorised as <350, ≥350 and <250, 250- <300, 300-<350, 350-<400, ≥ 400)
  - Central retinal lesion thickness (µm) (continuous and categorised as <200, 200-<250, 250-<300, 300-<350, ≥ 350)
  - CRT (µm) (continuous and categorised as <200, 200- <250, 250-<300, 300-<350, ≥ 350)
  - SRF (present/absent)
  - SRF thickness (µm) (continuous and categorised as <40, 40-<80, 80-<120, 120-<160, ≥ 160
  - Presence/absence of IR cysts
  - PED (present/absent)
  - PED thickness (µm)
  - SHRM height (mm) and SHRM width (mm).
- Wet AMD history in the Study Eye: Time from diagnosis to Day 1 (continuous and categorised as <1 week, 1-2 weeks, >2-4 weeks, >4 weeks)
- Diagnosis of wet AMD in the non-Study Eye (No/Yes [ongoing (concomitant) treatment, prior treatment only/no treatment, unknown])

The following derivation will be done where applicable:

- Weight (in kg) = weight (in lbs) * 0.4536
- Height (in cm) = height (in inches) * 2.54
- BMI (kg/ m^2) = weight (kg)/ height $(m)^2$
- Time from diagnosis to Day 1 (weeks) = (Reference start date* - Date of diagnosis of AMD+1) / 7.

- Diagnosis of diabetes will be determined if a participant has any of the following preferred terms reported on the *Ocular and Relevant Medical History* page of the eCRF.
- In the event of a partial date of diagnosis for the purpose of time from diagnosis to Day1, if the day of diagnosis is missing but month and year are available, the date will be imputed to the 1st of the month, if the day and the month of diagnosis are missing but year is available, the date will be imputed to the 1st of January.

*If the date of 1st dose of study medication is missing, date of randomization will be used.

8.4 Medical History and Prior Ocular History

Medical history and prior ocular history (identified from the answer to the question "Ocular Related?") are captured on the Ocular and Relevant Medical History page of the eCRF and will be summarized by treatment group and overall, in the mITT analysis set. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 27.0 or above.

Prior ocular history (excluding wet AMD history), in the study eye and non-study eye as well as the non-ocular medical history will be tabulated by System Organ Class (SOC) and Preferred Term (PT) and sorted by descending frequency in the overall column.

9 PRIOR AND CONCOMITANT THERAPIES

Prior and concomitant therapies described in this section will be summarized by treatment group and for overall based on the mITT analysis set for both the biomarker positive stratum and the overall population.

Protocol procedural medications, e.g. anticholinergic dilation drops, povidone iodine, local anesthetic eye drops, FA contrast, etc. will not be included in the summary tables. However, these procedural medications, if reported, will be included in the data listings.

All surgeries, procedures and medications (prior and concomitant) will be listed.

9.1 Prior and Concomitant Surgeries and Procedures

Surgery and procedures data will be captured on the Ocular and Non-Ocular Procedures or Surgeries page of the eCRF and coded using MedDRA, version 27.0 or above. Ocular surgeries and procedures will be identified from the answer to the eCRF question "Ocular Related?".

Prior surgeries and procedures are those which started prior to the first dose of study medication.

The concomitant surgery and procedures are those with at least one treatment given between and including the first dose date and the end of exposure date.

See APPENDIX 2 for handling of partial dates for medications. The same rules will apply to partial dates for surgeries and procedures.

The number and percentage of participants with prior ocular surgeries and procedures (in the study and non-study eye, respectively) and non-ocular surgeries and procedures will be summarized by SOC and PT. Similar summaries will be provided for concomitant surgeries and procedures.

Additionally, concomitant procedures on the Study Eye, used to lower intraocular pressure will be summarized by SOC and PT.

Summary tables will be sorted alphabetically by SOC then by PT within SOC based on descending frequency in the overall group.

9.2 Prior and Concomitant Medications

Prior and concomitant medications will be captured on both the Prior relevant recent non-ocular and ocular treatments and Prior and Concomitant Medications page of the eCRF. Ocular medications will be identified

from the answer to the eCRF question “Is the prior Treatment for Ocular or Non Ocular??”.

Prior and concomitant medications will be coded using World Health Organization (WHO) Drug Global dictionary, version B3 March 2024 or later.

The prior and concomitant medication will be defined following the same algorithm specified for the prior and concomitant surgeries and procedures. See APPENDIX 2 for handling of partial dates for medications, in the case where it is not possible to define.

Prior and concomitant medications will be summarized separately by Anatomical Therapeutic Class (ATC) level 2 and preferred drug name overall and by treatment arm based on the safety analysis set. A participant having more than one medication within the same ATC Level 2 or preferred drug name will be counted only once for that ATC Level 2 or preferred drug name. These summaries will be performed for ocular medications in Study Eye and in Non-study Eye, as well as for non-ocular medications.

10 STUDY TREATMENT

All the summaries specified in this section will be provided in Safety Set for the biomarker positive stratum and the overall population.

10.1 Study Treatment Exposure

The number of injections will be summarized as continuous variables for OPT-302, sham for OPT-302, and aflibercept, separately, for the SAF, by treatment group.

The number of injections for OPT-302 (excluding Sham) and for Aflibercept will also be summarized by categories defined below

- The number of injection categories for analysis at W52:
  - OPT-302: 1-3, 5-8, 9-12, and 13
  - Aflibercept: 1-3, 4-5, 6-7 and 8
- The number of injection categories for the final analysis:
  - OPT-302/sham 1-4, 5-8, 9-12, 13-16, 17-20, 21-25
  - Aflibercept: 1-3, 4-7, 8-11, 12-14

The injection fidelity rate, defined as total number of administered injections of aflibercept, OPT-302, and OPT-302 Sham divided by the total number of injections expected to be administered for all the patients in the Safety Analysis Set, will be provided. Twenty-one injections of aflibercept, OPT-302, and OPT-302 sham are expected for each patient in the Efficacy Phase and 39 injections during the overall study treatment period.

Reasons for paused/discontinued study medication will be provided in a data listing.

10.2 Study Treatment Compliance

Compliance to study medication will be presented for the SAF. It will be derived for OPT-302/Sham and aflibercept separately.

For OPT-302/sham, participants are expected to receive 13 injections during the Efficacy Phase and 25 injections during the overall study treatment period for completers. The expected number of OPT-302/sham injections is the total number of scheduled visits on or before the discontinuation from OPT-302/sham treatment.

For aflibercept, participants are expected to receive 8 injections during the Efficacy Phase and 14 injections during the overall study treatment period for completers. The expected number of Aflibercept injections is the total number of visits scheduled for aflibercept injections on or before the discontinuation from aflibercept treatment.

Compliance to study medication, as a percentage will be derived for each participant as:

- (Number of injections received / Expected number of injections) x 100

Compliance (%) will be summarized as a continuous variable by treatment.

11 STATISTICAL METHODS FOR EFFICACY ANALYSIS

All the Efficacy analyses will be performed using mITT analysis set for the biomarker positive stratum and for the overall population if not otherwise specified.

The supportive analyses summarizing the primary and secondary endpoints by visit are specified along with other exploratory efficacy endpoints in Section 11.3.

11.1 Primary Objective

11.1.1 Primary Endpoint and Primary Estimand

The primary endpoint is the change from Baseline to Week 52 in ETDRS BCVA letter score.

The primary estimand is defined as the following:

- Population: the target study population comprises participants with nAMD from the biomarker positive stratum or for the overall population, who also meet the inclusion and exclusion criteria as specified in the study protocol. The analysis population is the mITT analysis set as defined in Section 5.3.
- Variable: the variable of the primary endpoint is the change from Baseline to Week 52 in ETDRS BCVA letter score.
- Intercurrent events:
  - Discontinuation of at least one study treatment due to any reason
  - Use of non-study treatment for nAMD (including anti-VEGF-A therapy) in the study eye or other prohibited therapies.
- Population-level summary: the population-level summary will be the difference of the mean change on primary endpoint between treatment groups.

All intercurrent events will be handled using the treatment policy approach, i.e., all observed data, including those collected after an intercurrent event will be used for analyses. A summary on number of participants with intercurrent events and the type of events will be provided.

Missing Data are assumed to be missing at random (MAR) for the primary analyses.

11.1.2 Statistical hypothesis and Primary Analysis of The Primary Efficacy Endpoint

For the pairwise comparison between the OPT-302 Standard Dosing vs control and the OPT-302 Extended Dosing compared to control, the hypotheses to be tested are as following:

$$H_0: \mu_{opt} = \mu_{sham} \qquad H_a: \mu_{opt} \neq \mu_{sham}$$

where μ_{opt} is the mean change in BCVA in the participants from the OPT-302 standard dosing arm or the OPT-302 extended dosing arm, and μ_{sham} the mean change in BCVA in the participants from the control arm.

Multiplicity adjustment can be found in Section 7.3 Within each pairwise between treatment comparison, if statistical significance is achieved for the biomarker positive stratum, the same model will be used in the subsequent hierarchical testing in the overall population and, if also statistically significant, the treatment effect will be estimated in the biomarker negative stratum. No significance testing of the treatment effect

in the biomarker negative stratum is to be conducted.

A model for repeated measures (MMRM) will be used for the primary analysis of the primary efficacy variable, with the geographical region of the site [North America, South America, Europe/West Asia, Asia and Pacific], Baseline lesion type [predominantly classic, minimally classic, or occult]), Baseline BCVA, analysis visit as a categorical variable, treatment group, and analysis visit by randomized treatment group interaction.

Note that for the analysis of the biomarker positive stratum, Baseline lesion type will, by definition, be a binary variable (minimally classic, or occult) in the MMRM. (APPENDIX 7)

The analysis visits to be included in the model are Weeks 4 and each 4 weeks through to Week 52 (i.e. 13 analysis visits).

In the primary analysis model, all available data from each participant will be included. An unstructured covariance pattern will be used to estimate the variance-covariance of the within-participant repeated measures. Parameters will be estimated using the restricted maximum likelihood approach with the Newton-Raphson algorithm and using the Kenward-Roger method for calculating the denominator degrees of freedom. If the model does not converge, a simpler structure will be used in the order of Toeplitz covariance structure, heterogenous autoregressive (1) structure, and autoregressive (1) structure will be used. However, before moving to a simpler structure, an attempt will be made to get an initial estimate of the covariance using a feasible method such as the Fisher scoring algorithm (Lu, 2010).

Least squares (LS) mean estimates for the change from Baseline to Week 52 for each treatment group will be presented with the corresponding 95% CIs. Pairwise treatment group comparisons (OPT-302 Standard Dosing vs Control and OPT-302 Extended Dosing vs Control) will be estimated by LS mean differences at Week 52, along with two-sided 95% CIs and p-values.

The estimation of the treatment effect in the biomarker negative stratum will be provided using the same MMRM model with the exception that the Baseline lesion type will be excluded from the model since all participants will be of the same lesion type (predominantly classic).

11.1.3 Sensitivity Analysis of the Primary Estimand

Two sensitivity analyses for the primary efficacy estimand in the biomarker positive stratum and in the overall population will be performed to assess the robustness of the primary analysis based on MMRM and evaluate the MAR assumption for missing data in the MMRM analyses.

11.1.3.1 Copy-Reference Multiple Imputation Method (O'Kelly, 2014)

In this sensitivity analysis, missing values will be imputed using the "copy reference method".

Intermittent post Baseline missing data in all treatment groups will be imputed under the assumption of the MAR mechanism using the MCMC algorithm.

Monotone missing data for participants from the control group will be imputed under the assumption of the MAR mechanism, where these participants are assumed to have missing data in line with similar control group participants with complete data, taking into account their values observed.

For participants from the OPT-302 treatment groups, missing data will be imputed from the same MAR-based imputation model estimated from the control group participants, hence the missing data for OPT-302 treatment group participants will drift towards the mean response of the control group. This approach is likely to result in more favorable imputations for the control group compared with a jump (or return) to Baseline assumption, while for the OPT-302 treatment groups, it will not assume a treatment effect beyond that observed.

This imputation will be carried out in two steps. The stratum, such as geographic region, may be removed from the imputation steps in case of model fitting issues caused by strata with scarce data.

Step1: intermediate missing data for BCVA by ETDRS will be multiply imputed under the MAR assumption by treatment group, Baseline lesion type, and geographic region using a multivariate normal imputation model over Baseline value of BCVA and BCVA values at each analysis visit from Weeks 4 through to Week 52. The Markov Chain Monte Carlo (MCMC) method will be used to perform multiple draws from the Bayesian posterior distribution of the parameters of the imputation model, to create partially imputed datasets which have a monotone missing structure. This step will involve 100 imputations.

Step2: All the monotone missing data will then be imputed from data obtained above, using sequential regression models based on control group data (Ratitch, 2013). The regression models will include geographic region, baseline lesion type, baseline BCVA, and post baseline BCVA values prior to the visit to be imputed.

The MCMC method will be used with a single chain, with a burn-in of 2000 iterations and non-informative priors for all parameters. Imputed data will consist of 100 imputed datasets. The random seed number for the MCMC stage will be 3021005 and for the imputation stage it will be 30210051 in Step 2.

For each imputed dataset, the change from Baseline in BCVA at week 52 will be re-derived, and analyzed using an ANCOVA model with factors of treatment, geographical region of the site [North America, South America, Europe/West Asia, Asia and Pacific], Baseline lesion type [predominantly classic, minimally classic, or occult]) as well as a covariate of Baseline BCVA. All of the estimates obtain from the ANCOVA model will be combined (via SAS PROC MINALYZE) using Rubin's rules (Rubin, 1987) to obtain the LS mean estimates within each treatment arm and for between group difference, 95% CIs as well as the *p*-values for between group comparisons (APPENDIX 7).

11.1.3.2 Jump-to-Reference Multiple Imputation Method (O'Kelly, 2014)

In this sensitivity analysis, missing values will be imputed using the "jump to reference method".

The imputation of intermittent missing data will be performed identically to the method described in Step 1 of the Copy Reference approach.

"Jump-to-reference" MI differs to "copy reference" in that observed post-Baseline data for participants with missing data are not used in the imputation, and hence imputed values for participants in the active treatment groups will immediately become similar to values of control group participants, rather than having a trajectory that "drifts" towards that of control group participants as in the "copy reference" approach.

This method for handling missing data is based on a clinical approach where no treatment benefit will be attributed to study treatment at any post treatment time point.

"Jump-to-reference via sequential modelling" imputation will be performed once intermittent missing data have been imputed, assuming MAR.

This imputation will also be carried out in two steps. The first step of the imputation will be as per Step 1 of the Copy Reference approach, but, for Step 2, post-Baseline BCVA analysis visits will not be included in the modelling for those with missing data in the two OPT-302 treatment groups. The random seed number for this imputation stage will be 30210052.

For each imputed dataset, the change from Baseline in BCVA at week 52 will be re-derived, and analyzed using an ANCOVA model with factors of treatment, geographical region of the site [North America, South America, Europe/West Asia, Asia and Pacific], Baseline lesion type [predominantly classic, minimally classic, or occult]) as well as a covariate of Baseline BCVA. All of the estimates obtain from the ANCOVA model will be combined (via SAS PROC MINALYZE) using Rubin's rules (Rubin, 1987) to obtain the LS mean estimates within each treatment arm and for between group difference, 95% CIs as well as the *p*-values for between group comparisons.

11.1.3.3 Tipping point analyses

If one of the OPT-302 treatment groups is not superior to the control group, a tipping point analysis will

be performed to assess the robustness of the significance in the other OPT-302 arm. The tipping point analysis will use an analytical approach similar to the FDA method used in statistical review of Xeljanz(tofacitinib), where treatment effects and p-values are calculated analytically for each assumed difference between dropouts and completers in each treatment arm (FDA, 2019).

11.1.4 Supportive Analysis of the Primary Endpoint

The model described in Section 11.1.2 will be used to analyze the primary efficacy endpoint in the PP analysis set and in the randomized set (in the biomarker positive stratum and the overall population). For the analyses based on randomized set, the worst outcome at each timepoint for the treatment group they belonged to will be used for participants who did not receive treatment.

11.1.5 Exploratory Analyses of Change from Baseline in ETDRS BCVA

All the exploratory analyses will be provided for the biomarker positive stratum and the overall population, respectively.

In addition to the Week 52 timepoints, the change from Baseline in ETDRS BCVA will be evaluated by visit from Week 4 through to Week 52 using the same MMRM model as specified for the primary analyses based on mITT analysis set. From the model, LSMeans for change from Baseline in treatment arm and between treatment differences, alone with the 95% CI will be estimated and presented for each visit. A line plot of LSMeans +/- SE change from Baseline by visit and study treatment will be created.

The following figures will also be produced based on observed data from mITT analysis set:

- Mean (+/- standard error) for observed values of BCVA and change from Baseline over time, with separate lines for each treatment group

Also, subgroup analyses (see Section 7.4) will be performed for the primary endpoint in the biomarker positive stratum and the overall population using mITT analysis set. The data from each subgroup will be fit in the same MMRM as for the primary analyses. The model factors or covariates will be removed if the subgroup is defined based on the same variable, i.e. geographical region will be removed for the subgroup based on geographical region and Baseline BCVA will be removed for the subgroup analyses based on the Baseline BCVA categories. The LSmeans for change from Baseline at Week 52 within each treatment arm and between group difference and its 95% CI between each OPT-302 dosing arm and control for each subgroup level will be provided and presented along with the overall (from the primary efficacy analysis) in forest plots.

11.2 Secondary Objectives

11.2.1 Secondary Endpoints and Estimands

There are four secondary endpoints at Week 52.

11.2.1.1 Proportion of Participants Gaining 15 or More ETDRS BCVA Letters from Baseline to Week 52

For the secondary efficacy endpoint of gaining more than 15 ETDRS BCVA letters compared to Baseline:

- If the change from Baseline is ≥ 15, the participant will be considered to have achieved the endpoint.
- If the change from Baseline is available and is <15, the participant will be considered to have not achieved the endpoint.

The Estimand for this endpoint is the difference in the proportion of Participants Gaining 15 or More ETDRS BCVA Letters from Baseline to Week 52 between one of the OPT-302 dosing regimens vs. control in participants with nAMD from the Biomarker Positive Stratum or the overall population using the mITT analysis set, regardless of any Intercurrent Event (using the treatment policy approach, so all observed data, including those collected after an intercurrent event will be used for analyses). The same intercurrent events

are considered as for the primary endpoint.

11.2.1.2 Proportion of Participants Gaining 10 or More ETDRS BCVA Letters from Baseline to Week 52

For the secondary efficacy endpoint of gaining more than 10 ETDRS BCVA letters compared to Baseline:

- If the change from Baseline is ≥ 10, the participant will be considered to have achieved the endpoint.
- If the change from Baseline is available and is <10, the participant will be considered to have not achieved the endpoint.

The Estimand for this endpoint is the difference in the proportion of participants Gaining 10 or More ETDRS BCVA Letters from Baseline to Week 52 between one of the OPT-302 dosing regimens vs. control in participants with nAMD from the Biomarker Positive Stratum or the overall population using the mITT analysis, regardless of any Intercurrent Event (using the treatment policy approach so all observed data, including those collected after an intercurrent event will be used for analyses). The same intercurrent events are considered as for the primary endpoint.

11.2.1.3 Change in CNV Area by FA from Baseline to Week 52

The endpoint is derived as the CNV area measured by FA at Week 52- Baseline CNV area.

The Estimand for this endpoint is the difference of the mean change in CNV area from Baseline to Week 52 between one of the OPT-302 dosing regimens vs. control in participants with nAMD from the Biomarker Positive Stratum or the overall population using the mITT analysis, regardless of any Intercurrent Event (using the treatment policy approach, so all observed data, including those collected after an intercurrent event will be used for analyses). The same intercurrent events are considered as for the primary endpoint.

11.2.1.4 Proportion of Participants with Absence of Both SRF and IR Cysts by SD-OCT at Week 52

Presence or absence of each of SRF and IR cysts by SD-OCT will be determined by the IRC. The absence of SRF and IR cysts is defined if there is no SRF and no IR cysts. If there is presence of SRF and/or IR cysts at Week 52 the participant will be considered not to have achieved the endpoint. The endpoint is considered as missing if either SRF or IR Cysts has missing information or a reading of CD.

The Estimand for this endpoint is the difference in the proportion of participants with absence of both SRF and IR Cysts at Week 52 between one of the OPT-302 dosing regimens vs. control in participants with nAMD from the Biomarker Positive Stratum or the overall population using the mITT analysis, regardless of any Intercurrent Event (using the treatment policy approach, so all observed data, including those collected after an intercurrent event will be used for analyses). The same intercurrent events are considered as for the primary endpoint.

11.2.2 Missing Data Methods for Secondary Efficacy Variables

Missing data will be handled in the same way as for the primary endpoint and assuming all the missing data are MAR.

11.2.3 Statistical Hypothesis and Analysis Method

The estimands described in Section 11.2.1 will be tested in the sequence as specified in Section 7.3 at 2-sided alpha of 0.02403.

11.2.3.1 Analysis of Binary Secondary Efficacy Endpoint

The missing binary endpoints will be imputed using two different multiple imputation approaches.

For the binary endpoints that are derived by the underneath continuous BCVA values, the missing BCVA values will be imputed assuming MAR by 1) following step 1 specified in Section 11.1.3.1 to impute intermediate missing data using MCMC method; 2) imputing missing data on the monotonized datasets

using MAR-based model that includes randomized treatment group, the randomization strata of geographic region, Baseline lesion type, the Baseline value of BCVA and BCVA values at each analysis visit from Weeks 4 through to Week 52. Imputed data will consist of 100 imputed datasets. The random seed number for the MCMC stage will be 3021005 and for the imputation stage it will be 30210051 in Step 2.

For the binary endpoint based on the presence or absence of SRF and IR Cysts that are directly measured, the missing binary data will be imputed using the fully conditional specification (FCS) multiple imputation approach with the logistic model including randomized treatment group, geographic region, Baseline lesion type, Baseline BCVA category, and responder status (absence of SR fluid and IR cysts or not) at Baseline and each analysis visit from Weeks 4 through to Week 52.

One hundred imputed datasets will be created and the seed to be used for this imputation step will be 3021005.

The binary endpoints will be estimated as rate and the rate difference will be compared using the Mantel-Haenszel (MH) method adjusted for the Baseline BCVA category (> 54 letters *vs.* ≤ 54 letters) and Baseline lesion type (predominantly classic, minimally classic, or occult) on each multiple imputed dataset. The comparisons of Standard Dosing vs Control and Extended Dosing vs Control will be conducted separately. (APPENDIX 7)

SAS procedure PROC MIANALYZE will be used to derive the estimates of proportions (95% CI), difference in proportions (95% CI), and the p-value for between group comparison on difference in proportions from the multiple imputed datasets.

The estimation of the treatment effect in the biomarker negative stratum will be provided using the MH method without the Baseline lesion type stratum since all participants will be of the same lesion type (predominantly classic).

11.2.3.2 Analysis of Continuous Secondary Efficacy Endpoint

For the continuous secondary endpoint of CNV change from Baseline at Week 52, the same MMRM as described for the analysis of the primary efficacy endpoint will be performed. Note that Baseline BCVA will be replaced by the Baseline BCVA category (> 54 letters *vs.* ≤ 54 letter), and the Baseline CNV area will be added in the MMRM model. The MMRM model is implicitly imputing data assumed to be MAR.

For the secondary endpoint of change in CNV area by FA, there are only three post-Baseline analysis visits to be included in the MMRM: Week 12, Week 24, and Week 52.

The estimation of the treatment effect in the biomarker negative stratum will be provided using the same MMRM model with the exception that the Baseline lesion type will be excluded from the model since all participants will be of the same lesion type (predominantly classic).

11.2.4 Sensitivity Analysis of the Secondary Estimand

Sensitivity analysis assuming missing data are MNAR will be used to assess the robustness of the MAR assumption for the primary analysis of the secondary endpoints in the biomarker positive stratum and in the overall population.

The binary endpoints on BCVA improvements will be derived based on the underneath continuous BCVA from data imputed data using Copy-reference multiple imputation method as described in Section 11.1.3.1. The same analyses will be conducted following the MH method and combined based on Rubin's rule as specified in Section 11.2.3.1.

The binary endpoint of the presence or absence of SRF and IR Cysts at Week 52 will impute the missing data as non-responders. The analyses will be conducted following the same MH method as specified in Section 11.2.3.1.

For the continuous endpoint of CNV area, the missing data imputation using copy-reference method for

continuous variables will be done in the same way as described in Section 11.1.3.1 The imputation model includes randomized treatment group, the randomization strata of geographic region, Baseline lesion type, Baseline BCVA category (> 54 letters *vs.* ≤ 54 letter), Baseline CNV area, and CNV area values at each analysis visit. The change from Baseline in CNV area at Week 52 will be derived from each imputed dataset and analyzed using an ANCOVA model with factors of geographical region of the site [North America, South America, Europe/West Asia, Asia and Pacific], Baseline lesion type [predominantly classic, minimally classic, or occult]), Baseline BCVA category (> 54 letters *vs.* ≤ 54 letter) as well as a covariate of Baseline CNV area. All of the estimates obtain from the ANCOVA model will be combined (via SAS PROC MINALYZE) using Rubin's rules (Rubin, 1987) to obtain the LS mean estimates, 95% CIs and *p*-values.

11.2.5 Exploratory Analyses of the Secondary Efficacy Endpoints

All the exploratory analyses will be provided based on the mITT analysis set for the biomarker positive stratum and the overall population, respectively.

11.2.5.1 Exploratory Analyses of Binary Secondary Endpoints

Subgroup analyses (see Section 7.4) will be performed based on the same primary analysis of binary secondary endpoints. The analysis described in Section 11.2.3 (MH method on imputed datasets assuming data MAR) will be run separately for each subgroup level. For analyses with small subgroups where there is stratum without participants, the method will be simplified by removing the Baseline lesion type stratum. For each OPT-302 treatment group vs control, forest plots will be provided displaying the difference in proportions and 95% CI for each subgroup level and overall (from the primary analysis of the corresponding secondary endpoint).

11.2.5.2 Exploratory Analyses of Continuous Secondary Endpoint

In addition to the Week 52 timepoints, the change from Baseline in CNV area by FA will be evaluated by visit up to Week 52 using the same MMRM model as specified for the primary analyses. From the model, LSMeans for change from Baseline in treatment arm and between treatment differences, alone with the 95% CI will be estimated and presented for each visit.

The following line plots will also be produced:

- LSMeans (+/- SE) change from Baseline in CNV area by FA by visit and study treatment
- Mean (+/- standard error) for observed values of CNV and change from Baseline over time, with separate lines for each treatment group.

Subgroup analyses (see Section 7.4) will be performed based on the primary analysis of CNV area by FA. The data from each subgroup will be fit in the same MMRM as for the primary analyses but removing the factors derived based on the same variables for subgroup definition. The appropriate estimates for the LS mean difference in change from Baseline at Week 52, between each OPT- 302 treatment group and control, along with its 95% CI will be presented. Forest plots will be provided displaying the LS mean difference and its 95% CI for each subgroup level and overall (from the primary analysis of CNV change from Baseline).

11.3 Exploratory Efficacy Endpoints and Analyses

All the exploratory efficacy endpoints will be summarized by visit and treatment on the mITT analysis set based on observed data for the biomarker positive stratum and the overall population. No between group comparisons will be conducted. All the outputs will be created for the analyses at W52 as well as for the final analyses.

11.3.1 Continuous Exploratory Efficacy Endpoints

The following exploratory efficacy endpoints will be evaluated:

- ETDRS BCVA and change from Baseline
- CNV area, change and percent change from Baseline by FA
- Total Lesion Area, change and percent change from Baseline by FA
- Geographic Atrophy (GA) Area, change and percent change from Baseline by FA
- CST, change and percent change from Baseline by SD-OCT
- Central Retinal Thickness (CRT), change and percent change from Baseline by SD-OCT
- Pigment Epithelial Detachment (PED) thickness, change and percent change from Baseline by SD-OCT

For each of the endpoints listed above, the observed values, change from Baseline, and, if applicable, percent change from Baseline at each analysis visit will be summarized descriptively, using the number of observations (n), mean, standard deviation (SD), median, minimum, maximum, as well as the 95% CI for the mean by treatment and visit.

11.3.2 Binary Exploratory Efficacy Endpoints

The following exploratory efficacy endpoints will be evaluated:

- Gaining 5, 10, 15 or More ETDRS BCVA Letters from Baseline
- With 70 or more and 80 or more ETDRS BCVA letters
- With absence of SRF and IR Cysts by SD-OCT
- With absence of SRF by SD-OCT
- With absence of IR Cysts by SD-OCT in participants with IR cysts present at Baseline
- With Pigment Epithelial Detachment (PED) by SD-OCT
- With at least one Geographic Atrophy (GA) lesion area by FA
- With fibrosis present by FA
- With presence of Polypoidal Choroidal Vascularization (PCV) by FA

For each of the binary efficacy endpoint, the number and percentage of participants achieving the endpoint among the participants with non-missing data at the corresponding visit will be provided by visit and treatment arm. The 95% CI using Clopper-Pearson exact method for the percentage of participants achieving the endpoint will be provided within each treatment group.

12 REPORTED OUTCOME (PRO) ANALYSES

Quality of Life will be assessed using the National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) and the EQ-5D-5L questionnaire.

Analyses of PRO outcomes will be performed on the mITT analysis set based on observed data for the biomarker positive stratus and for the overall population. There will be no between treatment arm comparison for any of the PRO endpoints.

12.1 The NEI VFQ-25 Composite Score

The composite score of the NEI VFQ-25 will be derived following the rules provided in APPENDIX 3. The observed and change from Baseline in the composite score will be summarized at Weeks 52 and Week 100.

12.2 The EQ-5D-5L Score

The EQ-5D-5L is a health Status instrument for self-reported assessment of 5 domains of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each domain is rated by selecting 1 of 5 standardized categorizations ranging from no problem to extreme problem. The final question is a visual analogue scale (VAS) to rank health status from best health imaginable (100) to worst health imaginable (0).

A unique EQ-5D-5L health state is defined by combining 1 level from each of the 5 dimensions: this defines a profile that is primarily reported as a 5-digit number, for instance 11221. A total of 3125 possible health states are defined in this way. For example, state 11111 indicates no problems on any of the 5 dimensions, while state 12345 indicates no problems with mobility, slight problems with washing or dressing, moderate problems with doing usual activities, severe pain or discomfort and extreme anxiety or depression.

The instrument was specifically designed to provide an overall single number, called a weighted index, for each of the health states resulting from the combination of item responses. The weighted index constitutes a measure of utility, an economics term used to describe consumer preferences or in the present case patient preferences for different health related quality of life states. The weighted index can only be derived from patients who have provided a complete 5-response profile. A higher index indicates better QoL.

The EQ-5D-5L utility index value will be derived using a value set for the United Kingdom. In August 2017 (updated in October 2019), the UK's National Institute of Health and Care Excellence (NICE) published a position statement (https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l) advising companies, academic groups and others preparing evidence submissions to NICE not to use the EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L) England validation set to derive utility values for their evidence submissions. In their position statement, NICE recommends the mapping function developed by van Hout et al (van Hout, 2012) to be used (SAS code presented in APPENDIX 4).

The observed EQ-5D-5L score (index score and the VAS) and change from Baseline to Week 52 and to Week 100 will be summarized by treatment arm.

For each of the 5 separate dimensions of the EQ-5D shifts from Baseline to Week 52 and to Week 100 will be provided by treatment arm.

13 PHARMACOKINETIC

Details of Pharmacokinetic analysis will be detailed in a separate SAP.

14 SAFETY OUTCOMES

All summaries of safety data will be based on the Safety Analysis Set for the overall population. Summaries will be performed for the analyses at W52 including all data from the Efficacy Phase, and for the final analyses including all data from the Efficacy and Safety Phases Combined.

There will be no statistical comparisons between the treatment groups for safety data.

14.1 Adverse Events

All AEs will be categorised as either ocular AEs (further split by Study Eye and non-Study Eye) or non-ocular AEs and will be coded according to the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) coding system. The ocular AEs will be defined via the question "Is this Ocular Event?" on the Adverse Events page of the eCRF lock.

Treatment emergent AEs (TEAEs) are defined as AEs that started or worsened in severity on or after the date of first dose of study medication up to the end of exposure date (Section 6.8). Adverse events which started on the same day as the first dose of study medication will be classified as TEAEs unless the "AE Start Timepoint" on the Adverse Events Page of the eCRF is "Prior to administration of study product". An

AE which started on the W52 visit date will be included in the analyses at W52 .

See APPENDIX 2 for handling of partial dates or missing dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case, i.e. treatment emergent.

All summaries on TEAEs specified in this section below will be provided for ocular AEs in Study Eye; ocular AEs in non-Study Eye, and non-ocular AEs, respectively, by treatment group.

14.2 Overall AE summary

The number and percentage of participants with TEAEs within each of the following categories will be summarized:

- All TEAEs, overall and by maximum intensity
- TEAEs related to study treatment (related to either study medication or IVT injection procedure)
- TEAEs related to study medication
- TEAEs related to intravitreal (IVT) injection procedure
- Serious TEAEs
- Serious TEAEs related to study treatment (related to either study medication or IVT injection procedure)
- Serious TEAEs related to study medication
- Serious TEAEs related to IVT injection procedure
- Severe TEAEs (i.e., with intensity greater or equal to 3)
- TEAEs leading to study medication discontinuation
- TEAEs leading to discontinuation from the study
- TEAEs with outcome of death

14.2.1 AE Category Definition

Relationship to study treatment

Relationship to study treatment will be assessed by the Investigator and classified as study medication related (broken down further as “possibly related”, “probably related” or “definitely related” (increasing severity of relationship)), IVT injection related or not related.

TEAEs with a missing relationship to study treatment will be regarded as “related” to study medication for the purpose of TEAE summaries but the relationship to study treatment will be presented as missing in listings of AEs.

Intensity

Intensity will be derived as a combination of AE severity and/or CTCAE grades by the investigator according following:

- Grade 1 (mild) through to Grade 5 (Fatal) as per the current version of the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0).
- Severity graded by the investigator as Mild, Moderate, Severe, life-threatening, or fatal.

Intensity will take worst grade from CTCAE and severity. For example, if an TEAE is CTCAE Grade 1 (mild) but severity is graded as Moderate by investigator, the TEAE intensity will be Grade 2 (moderate).

TEAEs with a missing CTCAE grade will have its intensity determined by investigator's graded severity, vice versa. TEAE with both missing CTCAE and severity grades will have its intensity classified as CTCAE Grade 3 (severe) for the purpose of TEAE by intensity summaries. The missing CTCAE grade and severity grade are not imputed in the listing.

If a participant reports a TEAE more than once within a SOC/ PT, the TEAE with the worst-case intensity (highest grade) will be used in summaries of TEAEs by intensity.

Serious Adverse Events

Serious AEs (SAEs) are those events recorded as "Yes" to the question" Serious Event?" on the *Adverse Events* page of the eCRF.

TEAEs Leading to Discontinuation of Study Medication

TEAEs leading to permanent discontinuation of study medication will be identified by using the "Action Taken with study treatment" of "Study drug permanently discontinued" from the *Adverse Events* page of the eCRF.

TEAEs Leading to Discontinuation from The Study

AEs leading to permanent discontinuation from the study will be identified by using the answer to the question "Did the participant discontinue the study as a result of this AE?" from the *Adverse Events* page of the eCRF.

Adverse Events Leading to Death

TEAEs leading to Death are those events which are recorded with "Outcome" of "Fatal" on the *Adverse Events* page on the eCRF. A listing of TEAEs leading to death will be prepared.

14.2.2 TEAEs summary by SOC and PT

TEAEs will be summarized by SOC and PT, where each participant is counted once for each event, in the following tables:

- All TEAEs, overall and by maximum intensity
- TEAES related to study medication
- TEAEs related to IVT injection procedure
- TEAEs related to study medication by maximum intensity
- Severe TEAEs (i.e., with intensity greater or equal to 3)
- TEAEs leading to study medication discontinuation
- TEAEs leading to discontinuation from the study
- TEAEs with outcome of death
- Serious TEAEs
- Serious TEAEs related to study medication
- Serious TEAEs related to IVT injection procedure

AEs listings will be created including both TEAEs and non-TEAEs. This listing will include study treatment group with variables describing the nature, duration, and resolution of the event.

14.2.3 Adverse Events of Special Interest

TEAEs of special interest will include the following AE clusters: intraocular inflammation (Study Eye),

cataract (Study Eye), raised intraocular pressure (Study Eye), arteriothrombotic events, and Anti-Platelet Trialists' Collaboration (APTC) events, etc. The AE clusters will be identified using applicable MedDRA Terms and additional specific and relevant MedDRA Preferred Terms.

On an ongoing basis during the study, a masked review of MedDRA coded AEs will be performed and the MedDRA terms for AEs of special interest will be identified. The list of AEs of special interest will be finalized prior to the database locks for the analyses at W52 and the final analyses, respectively.

The overall count of events, number and percentage of participants overall, and by AE cluster, SOC, and PT will be provided for AEs of special interest. The AESI will not be further categorized and summarized as ocular events in study eye vs. non-study eye or non-ocular events since the definition of AESI has already specified the applicable categories.

14.2.4 Adverse event reporting for Clinical Trial Safety Disclosure

For the legal requirements of ClinicalTrials.gov and EU CTR, two required tables 1) on TEAEs which are not serious adverse events with an incidence greater than X% (1-5% as appropriate), and 2) on deaths and SAEs suspected to be related to study treatment (related to study medication and/or injection) will be provided by SOC and PT on the SAF population after final DBL.

14.2.5 Deaths

If any participants die during the study as recorded on the Death Details page of the eCRF, the number and participants who died will be summarized by treatment group along with the primary cause of death. Data recorded on this eCRF page will be presented in a data listing.

14.3 Loss of BCVA Letters Compared to Baseline in the Study Eye

For the four safety endpoints of losing either 5 or more, 10 or more, 15 or more or 30 or more BCVA letters compared to Baseline:

- If the change from Baseline is available and is $\leq$ -x or the absolute BCVA letters =0 the participant will be considered to have met the safety endpoint.
- If the change from Baseline is available and is > -x the participant will be considered to have not achieved the endpoint.

where x= 5, 10, 15 or 30.

The number and percentage of participants losing x or more BCVA letters compared to Baseline will be provided by visit.

14.4 Laboratory Evaluations

The parameters to be collected and reported for haematology and biochemistry are provided in APPENDIX 5 of this SAP.

All the parameters will be presented using SI Units.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following summaries will be provided for laboratory data for the analysis at W52:

- Actual and change from Baseline to Week 52
- Incidence of post-Baseline abnormal values based on the worst post-Baseline measurement among the patients with normal assessments at Baseline

The following summaries will be provided for laboratory data for the final analysis:

- Actual values and change from Baseline to Week 52, Week 100
- Incidence of post-Baseline abnormal values based on the worst post-Baseline measurement in the subset of patients with normal measurement at baseline.

The abnormal values for quantitative laboratory measurements are defined based on the relevant laboratory reference ranges in SI units as following:

- Low: Below the lower limit of the laboratory reference range
- Normal: Within the laboratory reference range (upper and lower limit included)
- High: Above the upper limit of the laboratory reference range.

Laboratory measurements will be graded using the CTCAE toxicity grading system as defined in APPENDIX 6.

A listing will be created for Hematology, Chemistry, and Urinalysis parameters, respectively and abnormal values will be denoted in data listings as low or high relative to reference range as well as the CTCAE grades if applicable.

14.5 Vital Signs

The following vital signs measurements, recorded prior to study medication administration, and after a period of approximately 5 minutes rest in a seated or semi-recumbent position will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Temperature (ºC)

The following summaries will be provided for vital signs data:

- Actual values and change from Baseline by analysis visit
- Incidence of markedly abnormal values by analysis visit and at any time post-Baseline

A listing for vital signs will be provided and abnormal values will be denoted in the listing as low or high.

Temperatures recorded in Fahrenheit will be converted to Celsius as follows:

- Temperature in Celsius = (Temperature in Fahrenheit minus 32) / 1.8.

Markedly abnormal quantitative Vital Signs measurements will be identified in accordance with the following predefined markedly abnormal criteria:

Table 2 Abnormal Vital Signs Criteria

Variable	Unit	Low	High
Systolic Blood Pressure	mmHg	≤ 90 AND change from Baseline ≤ -20	≥ 180 AND change from Baseline ≥ 20
Diastolic Blood Pressure	mmHg	≤ 50 AND change from Baseline ≤ -15	≥ 105 AND change from Baseline ≥ 15

Variable	Unit	Low	High
Pulse Rate	bpm	≤ 50 AND change from Baseline ≤ -15	≥ 120 AND change from Baseline ≥ 15
Body temperature	˚C	NA	≥ 38.3 AND change from Baseline ≥ 1.1

14.6 Physical Examination

A standard physical examination will be performed at the screening evaluation. All relevant medical conditions identified will be recorded on the Medical History page of the eCRF.

Thereafter a physical examination will only be performed during or at the end of the study if required to assess an emergent AE. Any clinically significant abnormalities detected during a physical examination that has been conducted post-randomization, and not present during the screening examination, will be documented as an AE.

As a result, physical examination data will not be summarized or listed separately to medical history and AEs.

14.7 Ophthalmic Examination and Tonometry

14.7.1 Slit Lamp Biomicroscopy

The number and percentage of participants with results per category will be summarized by eye (study and non-study), treatment group and visit for all ophthalmic variables.

The results of the following ophthalmic variables will be summarized and provided in a data listing:

- Ophthalmic examination (Study Eye) [Normal; Abnormal, Clinically Non-Significant; Abnormal, Clinically Significant, unless otherwise stated below]
    - Pupil dilated (yes/no)
    - Motility
    - Eye Lids
    - Conjunctiva
    - Sclera
    - Cornea
    - Anterior chamber activity: cells (0, trace [1-4 cells], 1+ [5-10 cells], 2+ [11-20], 3+ [21-50], 4+ [>50])
    - Iris
    - Pupil
    - Lens (Phakic, Pseudo-phakic, Aphakic)
    - If Lens phakic:
        - Nuclear Grade (0, 1, 2, 3, 4)
        - PSC Grade (0, 1, 2, 3, 4)
        - Cortical Grade (0, 1, 2, 3, 4)
    - Vitreous

- Macular
- Retina, including Peripheral Retina
- Optic Nerve

14.7.2 Intraocular Pressure (IOP)

IOP in the study eye will be summarized by visit and treatment group, including all pre-injection, "IOP after aflibercept injection" and "IOP after OPT-302/sham injection" measurements. When there are more than one pre-injection IOP at a given visit, the measurement closest to the first injection will be used for analyses. Observed values of IOP at Baseline and all post-Baseline timepoints will be summarized. Changes of IOP between any post-injections and pre-injection, and changes between pre-injection and Baseline assessment will be summarized as continuous variables by visit.

The line plots for the Mean (+/- standard error) of pre-injection IOP and change from Baseline in pre-injection over time will be provided

The counts and percentages of the following treatment-emergent findings in pre-injection IOP in the study eye will be summarized for the efficacy period and for the overall study treatment period. All the IOP assessments collected on unscheduled visits or reported as pre-injection IOP on scheduled visits during the treatment period are analyzed as pre-injection IOP.

- Participants with post Baseline pre-injections IOP >=30 mmHg
- Participants with post Baseline pre-injection IOP change from Baseline >=10mmHg increase on two consecutive visits. Any two consecutive visits, including unscheduled visits, on different dates are considered.

14.8 Anti-Drug Antibodies

These data will be analyzed and reported separately by the Sponsor.

15 IMPACT OF COVID-19

Data relating to missing assessments due to the impact of the Covid-19 pandemic are to be captured on the COVID-19 IMPACT FULL page of the eCRF. The data, including the visit(s) missed, the reason for missing data, the method of contact and whether any assessments were performed via an alternate method of contact, will be listed.

16 REFERENCES

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17 APPENDICES

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

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

Descriptive Statistics

If the original data has N decimal places, then the summary statistics will have the following decimal places:

- Minimum and maximum: N;
- Mean, median, lower, and upper bounds of two-sided 95% CI: N + 1.
- SD and SE: N + 2

Percentages

Percentages will be reported to one decimal place. Rounding will be applied, except for percentages < 0.1 but > 0.0 which will be presented as '< 0.1' and percentages < 100.0 but >99.9 which will be presented as '>99.9'.

Where counts are zero, no percentages will appear in the output.

p-values

p-values will be reported to six decimal places. Rounding will be applied, except for the p-values < 0.001 which will be presented as '< 0.001' and p-values < 1.000 but > 0.999 which will be presented as '> 0.999.'

Dates & Times

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

Spelling Format

English UK.

Presentation of Treatment Groups

For outputs, treatment groups will be represented as follows and in the given order:

Table 3 Treatment Groups Naming Convention

Treatment Group	For Tables and Graphs	For Listings (include if different to tables)
OPT-302 Standard Dosing	Standard Dosing OPT-302 + Aflibercept	Standard Dosing
OPT-302 Extended Dosing	Extended Dosing OPT-302 + Aflibercept	Extended Dosing
Control	Sham + Aflibercept	Control
Not Treated		Randomized and Not Treated
Not Randomized		Not Randomized

Presentation of Visits

For summary by analysis visits (including derived Baseline visit), analysis visits will be represented as follows and in that order. The listing will be based on reported visit and, if applicable, the record used as Baseline will be flagged on the listing.

Table 4 Visits Naming Convention

Long Name (default)	Short Name
Baseline	BL
Week 4	W4 (V3)
Week 8	W8 (V4)
Week X (X=12 to 100 in increments of 4)	WX (VY) (X=12 to 100 in increments of 4; Y=(X/4) + 2
Discontinuation	ED
Week 52/ Discontinuation +	W52/ED
End of Study +	EOS

Listings

All listings will be ordered by the following (unless otherwise indicated in the template):

- Randomized treatment group (or treatment received if it's a safety output), in the following order:
  - OPT-302 Standard Dosing
  - OPT-302 Extended Dosing
  - Control
- Site-participant ID,
- Date (where applicable),

For listings where randomized and non-treated participants, or non-randomized participants are included, these will appear in a category after the randomized treatment groups labelled 'Not Randomized'.

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

Table 5 Algorithm for Treatment Emergence of Adverse Events

START DATE	STOP DATE	ACTION
Known	Known/Partial/ Missing	If AE start date < study medication start date, then not TEAE If AE start date ≥ study medication start date and ≤ TEAE period end date*, then TEAE If AE start date > TEAE period end date*, then not TEAE.
Partial, but known components show that it is definitely or after study medication start date or that it is definitely after the TEAE period end date*	Known/Partial/ Missing	Not TEAE
Partial, could be on or after study medication start date AND before the TEAE period end date* OR Missing	Known	If AE stop date < study medication start date, then not TEAE If AE stop date ≥ study medication start date, then TEAE
	Partial	Impute stop date as latest possible date (*i.e.* last day of month if day unknown or 31st December if day and month are unknown), then: If AE stop date < study medication start date, then not TEAE If AE stop date ≥ study medication start date, then TEAE
	Missing	Assumed TEAE

*See Section 14.1 for the definition of the TEAE period end date.

Table 6 Algorithm for Prior / Concomitant Medications

START DATE	STOP DATE	ACTION
Known	Known	If medication stop date < study medication start date, assign as prior. If medication stop date ≥ study medication start date and medication start date ≤ concomitant period end date*, assign as concomitant
	Partial	Impute stop date as latest possible date (*i.e.* last day of month if day unknown or 31st December if day and month are unknown), then: If medication stop date < study medication start date, assign as prior If medication stop date ≥ study medication start date and medication start date ≤ concomitant period end date*, assign as concomitant
	Missing	If stop date is missing could never be assumed a prior medication If start date ≤ concomitant period end date*, assign as concomitant
Partial	Known	Impute start date as earliest possible date (*i.e.* first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study medication start date, assign as prior If stop date ≥ study medication start date and start date ≤ concomitant period end date*, assign as concomitant
	Partial	Impute start date as earliest possible date (*i.e.* first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (*i.e.* last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study medication start date, assign as prior If stop date ≥ study medication start date and start date concomitant period end date*, assign as concomitant
	Missing	Impute start date as earliest possible date (*i.e.* first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date ≤ study medication last dose date, assign as concomitant If start date > study medication last dose date, assign as post treatment
Missing	Known	If stop date < study medication start date, assign as prior If stop date ≥ study medication start date, assign as concomitant
	Partial	Impute stop date as latest possible date (*i.e.* last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study medication start date, assign as prior If stop date ≥ study medication start date, assign as concomitant
	Missing	Assign as concomitant

*Defined in Section 9.2

Note that the same rules will apply to partial dates for surgeries and procedures.

APPENDIX 3. NEI VFQ-25 SCORE CALCULATIONS

The scoring of NEI VFQ-25 with or without optional items will be based on the following two-step process:

Step 1. NEI VFQ-25 Scoring rules

Original numeric values from the survey will be re-coded following the scoring rules outlined in Table 7 (Mangione, 2000) All items will be scored so that a high score represents better functioning. Each item will then be converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively. In this format scores represent the achieved percentage of the total possible score, *e.g.* a score of 50 represents 50% of the highest possible score.

Table 7 Scoring Key: Recoding of Items

Item Numbers	Change original response category [a]	To recoded value of:
1, 3, 4, 15c[b]	1	100
	2	75
	3	50
	4	25
	5	0
2	1	100
	2	80
	3	60
	4	40
	5	20
	6	0
5 through 14, 16, 16a, A3 through A9[c]	1	100
	2	75
	3	50
	4	25
	5	0
	6	*
17 through 25, A11a, A11b, A12, A13	1	0
	2	25
	3	50
	4	75
	5	100
A1, A2	0	0
	to	to
	10	100

(a) Precoded response choices as printed in the questionnaire.

(b) Item 15c has four response levels, but is expanded to five levels using item 15b:

a. If 15b=1, then 15c should be recoded to "0"

b. If 15b=2 or 3, then 15c should be recoded to missing.

(c) "A" before the item number indicates that this item is an optional item from the Appendix of the questionnaire. If optional items are used, the NEI-VFQ developers encourage users to use all items for a given sub-scale.

*Response choice "6" indicates that the person does not perform the activity because of non-visual related problems. If this choice is selected the item is coded as "missing".

Step 2. Sub-scale Scoring

The means of the recoded values within each sub-scale will be derived to create 12 sub-scale scores. Items that were left blank (missing data) will not be taken into account when calculating the sub-scale scores. Sub-scale scores will be generated if at least one item within that sub-scale is answered. Hence, scores represent the average for all items in the sub-scale that the respondent answered.

Table 8 (Mangione, 2000) shows the derivation of 12 vision-targeted subscales:

Table 8 Averaging of Items to Generate NEI VFQ-39 Sub-Scales (VFQ-25 + Optional Items)

Sub-Scale	Number of Items	Items to be Averaged
General Health	2	1, A1
General Vision	2	2, A2
Ocular Pain	2	4, 19
Near Activities	6	5, 6, 7, A3, A4, A5
Distance Activities	6	8, 9, 14, A6, A7, A8
Vision-Specific Social Functioning	3	11, 13, A9
Vision-Specific Mental Health	5	3, 21, 22, 25, A12
Vision-Specific Role Difficulties	4	17, 18, A11a, A11b
Vision-Specific Dependency	4	20, 23, 24, A13
Driving	3	15c, 16, 16a
Color Vision	1	12
Peripheral Vision	1	10

Composite Score Calculation:

To calculate an overall composite score for the NEI VFQ-25, the vision-targeted sub-scale scores are simply averaged, excluding the general health-rating question. By averaging the sub-scale scores rather than the individual items, equal weight is given to each sub-scale.

APPENDIX 4. EQ-5D-L INDEX SCORING

The EQ-5D-L index score based on UK population norms will be derived using the mapping function developed by van Hout *et al* (van Hout, 2012).

APPENDIX 5. LABORATORY PARAMETERS

Haematology:

- Red blood cells (RBC)
- Haemoglobin
- Haematocrit
- Mean corpuscular volume (MCV)
- Mean corpuscular haemoglobin (MCH)
- Platelets
- White blood cells (WBC) with differential:
    - absolute count or percentage of neutrophils, eosinophils, basophils, lymphocytes, and monocytes

Biochemistry:

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Albumin
- Calcium
- Magnesium
- Phosphorous
- Glucose
- Glycated haemoglobin (HgbA1c) – at screening only
- Blood urea nitrogen (BUN)
- Creatinine
- Creatinine kinase
- Total bilirubin
- Aspartate transaminase (AST)
- Alanine transaminase (ALT)
- Alkaline phosphatase

Urinalysis:

- Blood
- Nitrite
- Protein

APPENDIX 6. CTCAE TOXCITY GRADING VERSION 5 FOR LABORATORY PARAMETERS

Table 9 CTCAE Toxcity Grading Version 5 for Laboratory Parameters

From https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (accessed on 22-Apr-2020)

CTCAE Term	Laboratory Test	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	Hemoglobin (g/L)	≥ LLN	≥ 100 g/L - < LLN	≥ 80 - < 100 g/L	< 80 g/L	n/a
Hemoglobin increased	Hemoglobin (g/L)	No increase from Baseline	Increase from Baseline > 0 - ≤ 20 g/L	Increase from Baseline > 20 - ≤ 40 g/L	Increase from Baseline > 40 g/L	n/a
Platelet count decreased	Platelet count (x10E9/L)	≥ LLN	≥ 75 x 10E9/L – < LLN	≥ 50 - < 75 x 10E9/L	≥ 25 - < 50 x 10E9/L	< 25 x 10E9/L
White blood cell (WBC) decreased	WBC (x 10E9/L)	≥ LLN	≥ 3.0 x 10E9/L – < LLN	≥ 2.0 - < 3.0 x 10E9/L	≥ 1.0 - < 2.0 x 10E9/L	< 1.0 x 10E9/L
Leukocytosis	WBC (x 10E9/L)	≤ 100 x 10E9/L	n/a	n/a	> 100 x 10E9/L	n/a
Absolute neutrophils count decreased	Absolute neutrophils count (x 10E9/L)	≥ LLN	≥ 1.5 x 10E9/L – < LLN	≥ 1.0 - < 1.5 x 10E9/L	≥ 0.5 - < 1.0 x 10E9/L	< 0.5 x 10E9/L
Eosinophilia	Absolute eosinophils	≤ ULN or ≤ Baseline	> ULN and > Baseline	n/a	n/a	n/a
Absolute lymphocytes count decreased	Absolute lymphocytes count (x 10E9/L)	≥ LLN	≥ 0.8 x 10E9/L – < LLN	≥ 0.5 - < 0.8 x 10E9/L	≥ 0.2 - < 0.5 x 10E9/L	< 0.2 x 10E9/L
Absolute lymphocytes count increased	Absolute lymphocytes count (x 10E9/L)	≤ 4 x 10E9/L	n/a	> 4 – ≤ 20 x 10E9/L	> 20 x 10E9/L	n/a
Hypernatremia	Sodium (mmol/L)	≤ ULN	> ULN – ≤ 150 mmol/L	> 150 – ≤ 155 mmol/L	> 155 – ≤ 160 mmol/L	> 160 mmol/L
Hyponatremia	Sodium (mmol/L)	≥ LLN	≥ 130 mmol/L – < LLN	≥ 125 - < 130 mmol/L	≥ 120 - < 125 mmol/L	< 120 mmol/L

CTCAE Term	Laboratory Test	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hyperkalemia	Potassium (mmol/L)	≤ ULN	> ULN – ≤ 5.5 mmol/L	> 5.5 – ≤ 6.0 mmol/L	> 6.0 – ≤ 7.0 mmol/L	7.0 mmol/L
Hypokalemia	Potassium (mmol/L)	≥ LLN	≥ 3.0 mmol/L – < LLN	n/a	≥ 2.5 - < 3.0 mmol/L	< 2.5 mmol/L
Blood bicarbonate decreased	Bicarbonate	≥ LLN	< LLN	n/a	n/a	n/a
Hypoalbuminemia	Albumin (g/L)	≥ LLN	≥ 30 g/L - < LLN	≥ 20 - < 30 g/L	< 20 g/L	n/a
Hypercalcemia	Ionized calcium (mmol/L)	≤ ULN	> ULN – ≤ 1.5 mmol/L	> 1.5 – ≤ 1.6 mmol/L	> 1.6 – ≤ 1.8 mmol/L	> 1.8 mmol/L
Hypocalcemia	Ionized calcium (mmol/L)	≥ LLN	≥ 1.0 mmol/L – < LLN	≥ 0.9 - < 1.0 mmol/L	≥ 0.8 - < 0.9 mmol/L	< 0.8 mmol/L
Hypermagnesemia	Magnesium (mmol/L)	≤ ULN	> ULN – ≤ 1.23 mmol/L	n/a	> 1.23 – ≤ 3.30 mmol/L	> 3.30 mmol/L
Hypomagnesemia	Magnesium (mmol/L)	≥ LLN	≥ 0.5 mmol/L – < LLN	≥ 0.4 - < 0.5 mmol/L	≥ 0.3 - < 0.4 mmol/L	< 0.3 mmol/L
Hypoglycemia	Glucose (mmol/L)	≥ LLN	≥ 3.0 mmol/L – < LLN	≥ 2.2 - < 3.0 mmol/L	≥ 1.7 - < 2.2 mmol/L	< 1.7 mmol/L
Creatinine increased	Creatinine (µmol/L)	≤ ULN	> ULN – ≤ 1.5 x ULN	> 1.5 – ≤ 3.0 x ULN or > 1.5 – ≤3.0 x Baseline	> 3.0 – ≤ 6.0 x ULN Or > 3.0 x Baseline	> 6.0 x ULN
Blood bilirubin increased	Total bilirubin	≤ ULN if Baseline normal; ≤ Baseline if Baseline abnormal	> ULN – ≤ 1.5 x ULN if Baseline normal; > Baseline - ≤ 1.5 x Baseline if Baseline abnormal	> 1.5 – ≤ 3.0 x ULN if Baseline normal; > 1.5 - ≤ 3.0 x Baseline if Baseline abnormal	> 3.0 – ≤ 10.0 x ULN if Baseline normal; > 3.0 - ≤ 10.0 x Baseline if Baseline abnormal	> 10.0 x ULN if Baseline normal; > 10.0 x Baseline if Baseline abnormal

CTCAE Term	Laboratory Test	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Alkaline phosphatase (ALP) increased	ALP	≤ ULN if Baseline normal; ≤ 2.0 x Baseline if Baseline abnormal	> ULN – ≤ 2.5 x ULN if Baseline normal; > 2.0 - > ≤ 2.5 x Baseline if Baseline abnormal	> 2.5 – ≤ 5.0 x ULN if Baseline normal; > 2.5 – > ≤ 5.0 x Baseline if Baseline abnormal	> 5.0 – ≤ 20.0 x ULN if Baseline normal; > 5.0 – ≤ 20.0 x > Baseline if Baseline abnormal	> 20.0 x ULN if Baseline normal; > 20.0 x Baseline if Baseline abnormal
Aspartate transaminase (AST) increased	AST	≤ ULN if Baseline normal; ≤ 1.5 x Baseline if Baseline abnormal	> ULN – ≤ 3.0 x ULN if Baseline normal; > 1.5 - ≤ 3.0 x Baseline if Baseline abnormal	> 3.0 – ≤ 5.0 x ULN if Baseline normal; > 3.0 – ≤ 5.0 x Baseline if Baseline abnormal	> 5.0 – ≤ 20.0 x ULN if Baseline normal; > 5.0 – ≤ 20.0 x Baseline if Baseline abnormal	> 20.0 x ULN if Baseline normal; > 20.0 x Baseline if Baseline abnormal

APPENDIX 7. SAMPLE SAS CODE

Table 10 Variables Description

Variable Name	Variable Description
DATAIN	data set
TRTP	Treatment group
TRTPN	Treatment group in numeric value
AVISITN	Scheduled visit
LESIONTY	Baseline lesion type
STRAT3	Geographical region of the site
BCVACAT1	Baseline BCVA Category
Base	Baseline BCVA
USUBJID	Participant ID
CHG	Change from baseline
IMPUTATION	Number of imputations
CASE	Number of participants met criteria by TRTPN, LESIONTY and BCVACAT1
TOTAL	Number of participants by TRTPN, LESIONTY and BCVACAT1

1. Mixed Model for Repeated Measures:

```
PROC MIXED DATA=DATAIN METHOD=REML;
CLASS TRTP(REF="CONTROL") USUBJID AVISITN LESIONTY STRAT3;
MODEL CHG = TRTP AVISITN  LESIONTY STRAT3 TRTP*AVISITN BASE / DDFM=KR;
REPEATED AVISITN/ SUBJECT=USUBJID TYPE=UN;
LSMEANS TRTP*AVISITN /SLICE=AVISITN CL PDIFF OM ALPHA = 0.05;
ODS OUTPUT CONVERGENCESTATUS = CONVSTAT LSMEANS=LSMEANS0 DIFFS=DIFFS
     (WHERE=(_TRTP ="CONTROL" AND AVISITN=_AVISITN));
RUN;
```

2. ANCOVA Model for Multiple Imputation:

```
PROC MIXED DATA=DATAIN;
BY _IMPUTATION_;
CLASS TRTP(REF="CONTROL") LESIONTY STRAT3;
MODEL CHG = TRTP LESIONTY STRAT3 BASE / SOLUTION;
LSMEANS TRTP /CL DIFF ALPHA = 0.05;
ODS OUTPUT LSMEANS=LSM  DIFFS=LSMDIFFS (WHERE=(_TRTP ="CONTROL"));
RUN;

     PROC SORT DATA=LSM; BY TRTP _IMPUTATION_; RUN;
PROC SORT DATA=LSMDIFFS; BY TRTP _IMPUTATION_; RUN;

/* LS Mean of Change from Baseline*/
PROC MIANALYZE PARMS(CLASSVAR=FULL) = LSM EDF=888 ALPHA=0.05;
*note: EDF is complete-data degrees of freedom, can get from LSMDIFFS;
BY TRTP;
MODELEFFECTS TRTP;
ODS OUTPUT PARAMETERESTIMATES= MI_LSM;
RUN;

/*Difference in LS Means vs. Control*/
PROC MIANALYZE PARMS(CLASSVAR=FULL) = LSMDIFFS EDF= 888 Alpha=0.05;
*note: EDF is complete-data degrees of freedom, can get from LSMDIFFS;
BY TRTP;
MODELEFFECTS TRTP;
ODS OUTPUT PARAMETERESTIMATES= MI_DIFF;
```

```
RUN;
```

3. MH with Multiple Imputation

```
PROC STDRATE DATA=DATA3 METHOD=MH STAT=RISK EFFECT=DIFF;
BY _IMPUTATION_;
WHERE TRTPN IN (1, 3);
POPULATION GROUP=TRTPN EVENT=CASE TOTAL=TOTAL;
STRATA LESIONTY STRAT2 / ORDER=DATA EFFECT;
ODS OUTPUT STDRISK=RATE EFFECT=RISKDIFF;
RUN;

/* MH Estimate of Rate */
PROC SORT DATA=RATE; BY TRTPN _IMPUTATION_; RUN;

PROC MIANALYZE DATA= RATE;
MODELEFFECTS  STDRISK;
STDERR STDERR;
BY TRTPN;
ODS OUTPUT PARAMETERESTIMATES= MI_PROP1;
RUN;

/* MH Estimate of Risk Difference vs Control */
PROC MIANALYZE DATA= RISKDIFF;
MODELEFFECTS RISKDIFF;
STDERR STDERR;
ODS OUTPUT PARAMETERESTIMATES= MI_PROP2;
RUN;
```