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Protocol Number: OPT-302-1004

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

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STATISTICAL ANALYSIS PLAN

ShORe

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

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0 for Protocol OPT-302-1004 (ShORe)

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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MODIFICATION HISTORY

Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
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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
BCVA	Best-corrected Visual Acuity
BMI	Body Mass index
CD	Can't Determine
CI	Confidence Interval
CRF	Case Report Form
CNV	Choroidal Neovascularisation
CRT	Central Retinal Thickness
CST	Central Subfield Thickness
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein Angiography
IOP	Intraocular Pressure
IR	Intra-retinal
IRC	Independent Reading Centre
IRF	Intra-retinal Fluid
IVT	Intravitreal
IXRS	Interactive Randomization System
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
mITT	Modified Intent to Treat (analysis population)
MMRM	Mixed Model for Repeated Measures
N/A	Not Applicable
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

Abbreviation	Description
PK	Pharmacokinetic(s)
PROs	Participant Reported Outcomes
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SE	Standard Error
SOC	System Organ Class
SOP	Standard Operating Procedure
SRF	Sub-retinal Fluid
TEAE	Treatment-Emergent Adverse Event

2 INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods, rules and conventions to be used in the presentation and analysis of efficacy and safety data in the abbreviated Clinical Study Reports (CSR) for study OPT-302-1004. The study was terminated early due to lack of efficacy.

The SAP will be finalized before the date base lockfor the analysis. Any changes to the SAP after approval will be documented. This SAP is based on study protocol version 2.0 (Amendment 1) dated 19 Dec 2023.

3 STUDY OBJECTIVES

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 0.5 mg ranibizumab, 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 0.5 mg ranibizumab 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 0.5 mg ranibizumab 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.

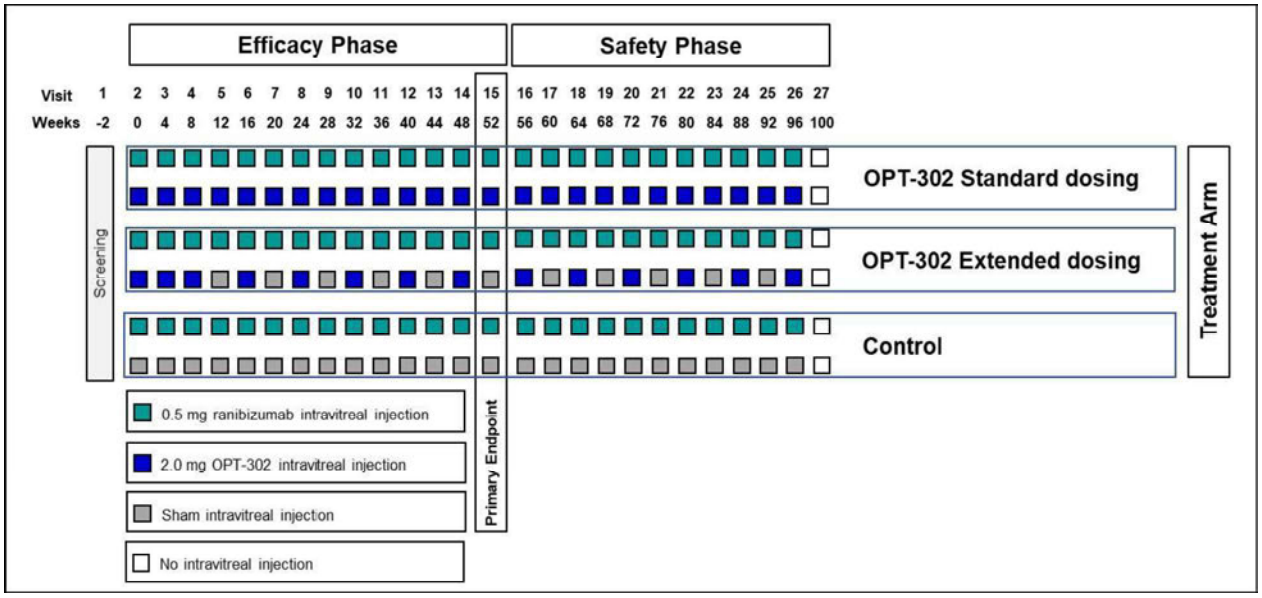
4 STUDY DESIGN

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 0.5 mg ranibizumab followed by Standard Dosing 2.0 mg OPT- 302, referred as **OPT-302 standard dosing** arm in the following sections of the document
- intravitreal 0.5 mg ranibizumab followed by Extended Dosing 2.0 mg OPT-302, referred as **OPT-302 extended dosing arm** in the following sections of the document
- intravitreal 0.5 mg ranibizumab 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.

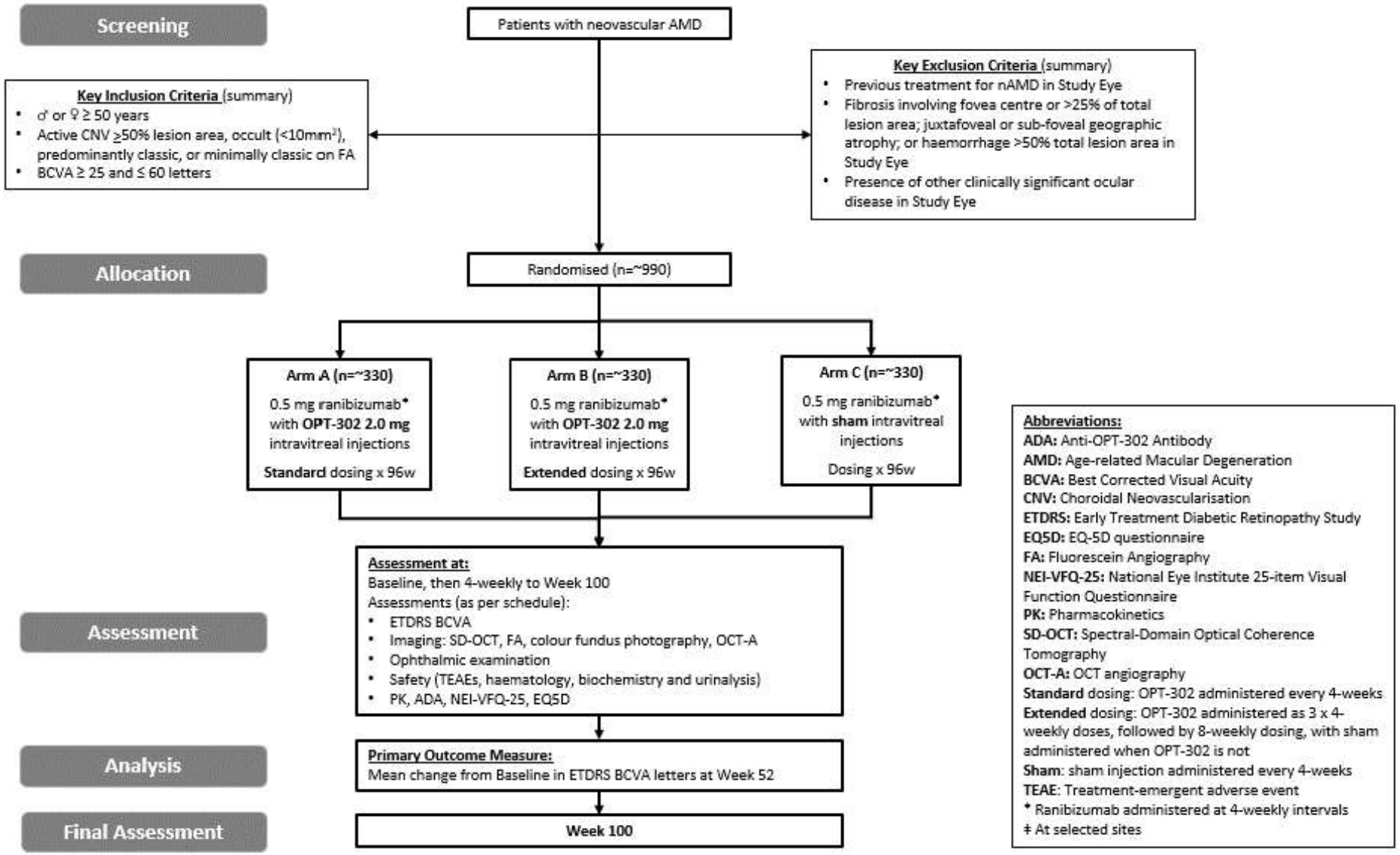
During the Efficacy Phase (Baseline to Week 52), study medication will be administered according to the randomization schedule, commencing at the Baseline visit through to Week 48. The primary endpoint will be determined at Week 52 (Visit 15). Once all study assessments have been completed at Week 52, 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, ranibizumab 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 ranibizumab 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 analysis. To be precise, implementing a Fleming-Harrington-O'Brien[1] 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 ranibizumab 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 et al**Error! Reference source not found.**), 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.

- Treatment comparison will be provided for the primary endpoint at Week 52 for description purpose only, no formal hypothesis testing will be performed.
- The secondary efficacy endpoints and Central Subfield Thickness (CST) will be summarized descriptively.
- Proportion of participants losing 15 or more ETDRS BCVA letters from Baseline to Week 52 and end of study will be summarized.
- 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.
- Analysis of other safety parameters will not be presented

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 has 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.

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 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).

6.8 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 closest future scheduled evaluation visit.

6.9 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.

6.10 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).

6.11 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 statistical models.

7.2 Hypotheses testing

All statistical summaries are descriptive, no hypotheses testing will be performed.

8 DISPOSITION, DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

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 the main reason for screen failure.

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 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 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:

8.2.1 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.

8.2.2 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

8.2.3 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)

8.2.4 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)
- Study eye total lesion area (mm^2) by FA (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)
- Study eye CST (μm) by SD-OCT (continuous and categorised as <350, ≥350 and <250, 250-<300, 300-<350, 350-<400, ≥ 400)
- 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, the date of randomization will be used.

9 STUDY TREATMENT

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

9.1 Study Treatment Exposure

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

10 STATISTICAL METHODS FOR EFFICACY ANALYSIS

10.1 Primary Endpoint

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

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

10.1.1 Statistical Analysis

A model for repeated measures (MMRM) will be used for the analysis of the primary endpoint, the model will include study treatment, study visit and their interaction, baseline BCVA, geographical region [North America, South America, Europe/West Asia, Asia and Pacific], and baseline lesion type [predominantly classic, minimally classic, or occult]).

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, heterogeneous autoregressive (1) structure, and autoregressive (1) structure will be used.

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 MMRM analysis will be performed using mITT analysis set for the biomarker positive stratum and for the overall population. ETDRS BCVA letter score in study along with the change from baseline will be summarized by visit for the overall population.

10.2 Secondary Endpoints

There are four secondary endpoints:

- Proportion of participants gaining 15 or more ETDRS BCVA letters from Baseline to Week 52
- Proportion of participants gaining 10 or more ETDRS BCVA letters from Baseline to Week 52
- Change in CNV area by FA from Baseline to Week 52
- Proportion of participants with absence of both SRF and IR cysts by SD-OCT at Week 52

The secondary endpoints will be tabulated using summary statistics by visit using the overall mITT analysis set.

10.3 Exploratory Endpoint

Mean change in study eye CST by SD-OCT from Baseline by visit up to week 52 will be analyzed using the same MMRM model as the primary endpoint(overall mITT set only), with baseline BCVA replaced by the Baseline BCVA category (> 54 letters *vs.* ≤ 54 letter), and baseline CST included in the model.

11 SAFETY OUTCOMES

All safety analyses will be done in the overall population using the Safety Analysis Set.

11.1 Adverse Events

All AEs will be categorized 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 6.7). 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".

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.

11.2 Overall AE summary

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

- All TEAEs
- 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
- TEAEs leading to study medication discontinuation
- TEAEs leading to discontinuation from the study
- TEAEs with outcome of death

11.2.1.1 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.

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.

11.2.2 TEAEs summary by SOC and PT

The overall count of events, number and percentage of participants overall, and by SOC and PT, will be provided for each of the following categories:

- All TEAEs
- TEAEs with outcome of death
- Serious TEAEs

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.

11.2.3 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.

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.

11.2.4 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.

11.2.5 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.

11.3 Loss of ETDRSA BCVA letters

Proportion of participants losing 15 or more ETDRS BCVA letters in the study eye from Baseline will be summarized at Week 52 and end of study(week 100). The summary will be based on the observed values at the visit, as well as using last observation carried forward for those with missing values.

12 REFERENCES

1. Fleming T, Harrington D, O'Brien C. Designs For Group Sequential Tests. *Controlled Clinical Trials.* 1984;5:348-361

13 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 2 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 + Ranibizumab	Standard Dosing
OPT-302 Extended Dosing	Extended Dosing OPT-302 + Ranibizumab	Extended Dosing
Control	Sham + Ranibizumab	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 3 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

Table 4 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 11.1 for the definition of the TEAE period end date.

SAMPLE SAS CODE

Table 5 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
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;
```