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Opus Genetics, Inc.

STATISTICAL ANALYSIS PLAN

Protocol Title:	Randomized, Double-Masked, Placebo-Controlled, Multicenter, Phase 3 Study of the Efficacy and Safety of Phentolamine Ophthalmic Solution (POS) 0.75% in Participants With Presbyopia
Study Number:	OPI-NYXP-302 (VEGA-3)
Phase:	Phase 3
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2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Only abbreviations and terms relevant to the SAP are repeated herein. The reader is referred to the protocol for the complete and comprehensive list of abbreviations and definitions of terms for the study.

Abbreviation/Term	Definition
ADaM	Analysis Data Model
AE	adverse event
ANCOVA	analysis of covariance
ARP	All Randomized Population
ATC	Anatomical Therapeutic Chemical
BCDVA	best-corrected distance visual acuity
BP	blood pressure
bpm	beats per minute
CDISC	Clinical Data Interchange Standards Consortium
CFS	corneal fluorescein staining
CI	confidence interval
CSR	clinical study report
DCIVA	distance-corrected intermediate visual acuity
DCNVA	distance-corrected near visual acuity
eCRF	electronic Case Report Form
EDC	electronic data capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
HR	heart rate
IOL	multifocal intraocular lenses
IOP	intraocular pressure
LSM	least-squares mean
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-to-Treat
OD	oculus dexter (right eye)
OTC	over-the-counter
OU	oculus uterque (both eyes)
PD	pupil diameter

Abbreviation/Term	Definition
PMM	Pattern-Mixture Model
POS	Phentolamine Ophthalmic Solution
PP	Per Protocol
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SDTM	study data tabulation model
SE	standard error
SOC	system organ class
SP	Safety Population
TBUT	tear break-up time
TEAE	treatment-emergent adverse event
TFL	tables, figures, and listings
VA	visual acuity
WHO-DD	World Health Organization Drug Dictionary

3. INTRODUCTION

3.1. Preface

This document presents a statistical analysis plan (SAP) for Opus Genetics, Inc. Protocol OPI-NYXP-302 (VEGA-3) (*Randomized, Double-Masked, Placebo-Controlled, Multicenter, Phase 3 Study of the Efficacy and Safety of Phentolamine Ophthalmic Solution (POS) 0.75% in Participants With Presbyopia*).

Reference materials for this statistical plan include the protocol OPI-NYXP-302 Amendment 2 (19 July 2024) and Case Report Forms (CRFs; Version 13 August 2024).

The SAP described hereafter is an *a priori* plan. The SAP will be finalized and approved prior to unmasking of any study data.

For the reasons stated here, the conduct of the study in the field is considered to be independent of any study outcome that might materialize upon enactment of the currently proposed statistical plan.

3.2. Purpose of Analyses

The VEGA-3 study is a randomized, double-masked, placebo-controlled, multicenter study of the safety and efficacy of 0.75% Phentolamine Ophthalmic Solution (POS) in participants with presbyopia.

Post-hoc exploratory analyses not identified in this SAP may be performed to further examine the study data. These analyses will be clearly identified, where appropriate, in the final clinical study report (CSR). Additional analyses not prospectively identified in this SAP may also be completed for publications, or regulatory or funding inquiries. These analyses, if performed, may not be reported in the CSR but will be fully detailed in the document containing the additional analyses.

3.3. Summary of Statistical Analysis Changes to the Protocol

Only the primary efficacy endpoint will be analyzed by light/dark irides type; the protocol (Section 8.2) states that all efficacy endpoints will be analyzed by irides type. Otherwise, the analyses described in this analysis plan are consistent with the analyses described in the study protocol.

4. STUDY OBJECTIVES AND ENDPOINTS

Study objectives and endpoints defined in the protocol include safety and efficacy endpoints. Objectives and pre-specified endpoints are as follows:

4.1. Study Objectives

The objectives of this study are as follows:

Primary objective

To evaluate the efficacy of POS to improve distance-corrected near visual acuity (DCNVA) without loss of best-corrected distance visual acuity (BCDVA) compared to placebo in participants with presbyopia

Secondary objectives

- To evaluate additional efficacy measures, such as visual acuity (VA) and pupil diameter (PD), across multiple time points and visits for POS in participants with presbyopia
- To evaluate tachyphylaxis of the DCNVA response to POS after 6 weeks of dosing
- To evaluate the effect of iris color, baseline PD, and baseline DCNVA on the efficacy of POS in participants with presbyopia
- To evaluate the ocular and systemic safety of POS in participants with presbyopia
- To evaluate participant-reported outcomes of POS in participants with presbyopia

4.2. Study Endpoints

4.2.1. Primary Endpoint

The primary efficacy endpoint is the percentage of participants with ≥ 15 letters of improvement in binocular **DCNVA** and with < 5 letters of loss in binocular **BCDVA** from baseline comparing POS-treated participants to placebo-treated participants at 12 hours post-dose at Visit 4 (Day 8).

This comparison will be analyzed first using a hierarchical testing method.

4.2.2. Secondary Endpoints

Efficacy:

Secondary efficacy endpoints will include the following:

- Percentage of participants with ≥ 15 letters of improvement in binocular **DCNVA** and with < 5 letters of loss in binocular **BCDVA** from baseline at Day 1 (1 hour post-dose), Day 3, and Week 6

- Percentage of participants with ≥ 5, ≥ 10, and ≥ 15 letters of improvement in **DCNVA** from baseline (monocular and binocular) at Day 1 (0.5 hours and 1 hour post-dose), Day 3, Day 8, and Week 6
- Change in **DCNVA** from baseline (monocular and binocular) at Day 1 (0.5 hours and 1 hour post-dose), Day 3, Day 8, and Week 6
- Change in mean binocular **DCNVA** from baseline at Week 6 compared to the best prior observed change from baseline in mean binocular **DCNVA** in participants treated with POS
- Percentage of participants with **DCNVA** ≤ 20/15, ≤ 20/20, ≤ 20/25, ≤ 20/32, ≤ 20/40, ≤ 20/50, ≤ 20/63, ≤ 20/80, ≤ 20/100, ≤ 20/125, and ≤ 20/160 at Day 1 (0.5 hours and 1 hour post-dose), Day 3, Day 8, and Week 6
- Percentage of participants with ≥ 5, ≥ 10, and ≥ 15 letters of improvement in binocular distance-corrected intermediate visual acuity **(DCIVA)** from baseline at Day 1 (1 hour post-dose), Day 3, Day 8, and Week 6
- Change in binocular **DCIVA** from baseline at Day 1 (1 hour post-dose), Day 3, Day 8, and Week 6
- Percentage of participants with loss or improvement in **BCDVA** from baseline (monocular and binocular) at Day 1 (1 hour post-dose), Day 3, Day 8, and Week 6
- Change in **BCDVA** from baseline (monocular and binocular) at Day 1 (1 hour post-dose), Day 3, Day 8, and Week 6
- Change and percent change in **PD** from baseline at Day 3 and Day 8
- Percentage of participants with **PD** of < 3.5, < 3.0, < 2.5, < 2.0, and < 1.5 mm at Day 3 and Day 8
- Percentage of participants with **PD** of 1.5 to < 2.0 mm, 2.0 to < 2.5 mm, 2.5 to < 3.0 mm, 3.0 to < 3.5 mm, and 2.4 to ≤ 3.5 mm at Day 3 and Day 8
- Percentage of participants with baseline **DCNVA** ≤ 20/63, ≤ 20/80, ≤ 20/100, ≤ 20/125, and ≤ 20/160, with a ≥ 10-letter and ≥ 15-letter improvement in **DCNVA** at Day 1 (0.5 hours and 1 hour post-dose), Day 3, Day 8, and Week 6
- Percentage of participants with baseline **DCNVA** from 20/50 to 20/63, 20/50 to 20/80, 20/50 to 20/100, 20/50 to 20/125, and 20/50 to 20/160, with a ≥ 10-letter and ≥ 15-letter improvement in **DCNVA** at Day 1 (0.5 hours and 1 hour post-dose), Day 3, Day 8, and Week 6
- Change from baseline in overall and component participant-reported outcomes at Day 3, Day 8, and Week 6

[redacted]

All of the efficacy endpoints will be analyzed overall and by light/dark irides at all timepoints. Participants will also be analyzed by binocular, study eye, and fellow eye, where applicable.

Safety:

- Adverse events
- Intraocular pressure (IOP)
- Best-corrected distance VA
- Slit lamp biomicroscopy
- Automated corneal specular microscopy (at select sites)
- Undilated ophthalmoscopy
- Vital signs (heart rate [HR] and blood pressure [BP])
- Urine pregnancy test (for females of childbearing potential)

[redacted]

5. STUDY METHODS

5.1. General Study Design and Plan

This is a randomized, placebo-controlled, double-masked, Phase 3 study in approximately 545 participants with presbyopia.

On Day -7 to -1 (Screening), participants will be assessed for eligibility. On Day 1 (Baseline), participants will be reassessed for all VA measurements and, if eligibility is met, will be randomized 3:2 to 1 of 2 treatment arms:

- Daily evening POS (n=327)
- Daily evening placebo (ie, POS vehicle; n=218)

Randomization will be stratified by iris color (light/dark irides).

The study eye is defined as the eligible eye with the worse baseline DCNVA at Visit 2 (Day 1; Baseline). If both eyes have the same baseline DCNVA, then the eye with the better BCDVA will be the study eye. If both DCNVA and BCDVA are equivalent between eyes, the study eye will be the right eye. The study eye and fellow eye will both be evaluated with all assessments. For all assessments other than VA, the baseline values will be determined during screening assessments at Visit 1. For PD and VA measurements, assessments at Visit 2 will be used to determine baseline values.

Study medication will be administered as a single drop in each eye by site staff on Day 1 (Visit 2; Baseline). Starting Day 2, study medication will be self-administered by the participant for approximately 48 weeks as a single drop in each eye in the evening near bedtime. On the evening prior to each office visit, participants should dose as close as possible to 12 hours prior to the scheduled time for each office visit (Visits 3 through 12).

The study is also designed to examine tachyphylaxis of the therapeutic response to POS for binocular DCNVA. This will be achieved by comparing change from Baseline at Week 6 in the POS group to the best change from baseline achieved prior to Week 6 for binocular DCNVA.

The schedule for assessments and timing of events is presented in Table 1.

Table 1 Visit Schedule and Assessments

Visit	1	2			3	4	5	6	7	8	9	10	11	12
	Screening	Baseline Day 1			Day 3	Day 8	Week 6	Week 12	Week 18	Week 24	Week 30	Week 36	Week 42	Week 48/EOS
Window	Day -7 to -1	N/A			N/A	± 1 d	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d
Time		0	0.5	1										
Informed consent	X													
Participant ID # assigned	X													
Medical/Ophthalmic history	X													
Demographics	X													
Prior/Concomitant medications [a]	X	X			X	X	X	X	X	X	X	X	X	X
Urine pregnancy test [b]	X	X						X		X		X		X
HR/BP [c]	X					X	X	X	X	X	X	X	X	X
Manifest refraction and near add	X					X		X		X		X		X
PD (photopic) [d]	X	X			X	X								
DCNVA (photopic) [e]	X	X [k]	X	X	X	X	X							
DCIVA (photopic) [e]	X	X		X	X	X	X							
BCDVA (photopic) [e]	X	X [k]		X	X	X	X	X	X	X	X	X	X	X
Best-corrected near VA (photopic)	X	X [k]												
Slit lamp biomicroscopy	X				X	X	X	X	X	X	X	X	X	X
Automated corneal specular microscopy [f]	X				X	X		X		X		X		X
TBUT and CFS [g]	X													
IOP [h]	X				X	X		X		X		X		X
Ophthalmoscopy [i]	X				X	X	X	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization [j]		X												
Participant questionnaire		X			X	X	X							
In-office treatment: POS or placebo		X												
Treatment/Participant diary dispensing [l]				X			X	X	X	X	X	X	X	
Return of study medication [m]							X	X	X	X	X	X	X	X

AE, adverse event; BCDVA, best-corrected distance visual acuity; BP, blood pressure; CFS, corneal fluorescein staining; D, diopter; DCIVA, distance-corrected intermediate visual acuity; DCNVA, distance-corrected near visual acuity; EOS, End of Study; HR, heart rate; IOP, intraocular pressure; N/A, not applicable; PD, pupil diameter; POS, phentolamine ophthalmic solution; TBUT, tear break-up time; VA, visual acuity.
[a] This includes asking if participants have been diagnosed with dry eye, take prescription drops for dry eye, or take artificial tear drops routinely for dry eye. Investigators will note changes to concomitant medications at any time throughout the study.
[b] Urine pregnancy test is for females of childbearing potential only.
[c] HR and BP can be measured manually or with available digital devices.
[d] PD will be measured using a NeurOptics VIP-300 or VIP-400 pupillometer (mm).
[e] Binocular VA assessments will be conducted first, followed by assessment of each eye individually at Screening; thereafter, study eye will be assessed first, followed by fellow eye and then binocular.
[f] Automated corneal specular microscopy will be performed at select sites only.
[g] Dry eye test will include both TBUT (performed first) and CFS.
[h] IOP will be assessed using Tono-Pen or Goldmann applanation tonometry.
[i] Direct or indirect ophthalmoscopy will be performed without dilation. Use of 90 D lens (indirect) is allowed.
[j] A randomization number is assigned after the participant is qualified.
[k] Participants must requalify for inclusion criteria #5, #6, and #7 at Baseline Time 0 min to be eligible for the study.
[l] All participants will be reminded to instill treatment approximately 12 hours prior to the scheduled time of their next office visit.
[m] Participants should return both used (empty) and unused vials/

5.2. Inclusion – Exclusion Criteria and General Study Population

5.3. Participant Inclusion Criteria

Participants must meet all of the following criteria:

1. Males or females ≥ 45 and ≤ 64 years of age
2. Able to comply with all protocol-mandated procedures independently and to attend all scheduled office visits
3. Able and willing to give signed informed consent
4. Able to self-administer study medication throughout the study period

Inclusion criteria #5, #6, and #7 must all be met at both Screening and Baseline Visits:

5. Best-corrected distance VA of 55 ETDRS letters (20/20 Snellen equivalent) or better in photopic conditions in each eye
6. Distance-corrected near VA of 50 ETDRS letters (20/50 Snellen equivalent) or worse but not <35 ETDRS letters (20/100 Snellen equivalent) in photopic conditions in each eye and binocularly
7. For participants who depend on reading glasses or bifocals, binocular best-corrected near VA of 65 ETDRS letters (20/25 Snellen equivalent) or better
8. Photopic PD of ≥ 4 mm in the study eye at Screening

5.4. Participant Exclusion Criteria

Excluded from the study will be individuals with any of the following characteristics:

Ophthalmic (in either eye):

1. Use of any topical prescription (including Vuity® or Qlosi™) or over-the-counter (OTC) ophthalmic medications of any kind within 7 days of Screening until study completion, with the exception of lid scrubs with OTC products (eg, OCuSOFT® lid scrub, SteriLid®, baby shampoo, etc.) and artificial tears as specified in Exclusion Criterion #2 below
2. Use of any OTC artificial tears (preserved or unpreserved) during visit days or 15 min before or after instillation of study medication
3. Use of Ryzumvi™ (POS) within 7 days prior to Screening
4. Use of any dry eye product, such as topical ophthalmic therapy for dry eye (eg, generic cyclosporine, Restasis®, Xiidra®, Cequa®, and Eysuvis®) or intranasal dry eye product (eg, Tyrvaya®) or other devices within 12 months prior to Screening

5. Tear break-up time of < 5 seconds or corneal fluorescein staining (CFS) Grade ≥ 2 in the inferior zone or Grade ≥ 1 in the central zone using the National Eye Institute scale
6. Clinically significant ocular disease (eg, cataract, glaucoma, corneal edema, uveitis, retinal degeneration, loss of visual field, or any macular pathology) that, in the judgment of the Investigator, might interfere with study procedures
7. Recent or current evidence of ocular infection or inflammation in either eye (such as current evidence of clinically significant blepharitis, conjunctivitis, keratitis, etc.). Participants must be symptom free for at least 7 days prior to Screening
8. Any history of herpes simplex or herpes zoster keratitis
9. Known allergy, hypersensitivity, or contraindication to any component of the phentolamine or vehicle formulations
10. Prior participation in a study involving the use of POS for the treatment of presbyopia or night vision disturbance
11. History of cauterization of the punctum or punctal plug (silicone or collagen) insertion or removal
12. Ocular trauma within 6 months prior to Screening
13. Ocular surgery or any ocular laser treatment within 6 months prior to Screening. Any history of radial keratotomy is prohibited
14. Participants with surgical monovision, multifocal, or extended depth-of-focus multifocal intraocular lenses (IOL). Monofocal IOLs are acceptable if in place > 6 months prior to Screening
15. Monofocal IOL in place > 6 months prior to Screening with any posterior capsule opacification
16. History of any traumatic (surgical or nonsurgical) or nontraumatic condition affecting the pupil or iris (eg, irregularly shaped pupil, neurogenic pupil disorder, iris atrophy, iridotomy, iridectomy, iritis, etc.)
17. Unwilling or unable to discontinue use of contact lenses at least 1 hour prior to Screening for soft contact lenses or at least 8 hours prior to Screening for hard gas permeable contact lenses, and at least 8 hours (for both types of lenses) prior to all other office visits

Systemic:

18. Known hypersensitivity or contraindication to alpha- and/or beta-adrenoceptor antagonists (eg, chronic obstructive pulmonary disease or bronchial asthma; abnormally low BP or HR; second- or third-degree heart blockage or congestive heart failure)
19. Known hypersensitivity or contraindication to any systemic cholinergic parasympathomimetic agent

20. Clinically significant systemic disease (eg, uncontrolled diabetes, myasthenia gravis, cancer, hepatic, renal, endocrine, or cardiovascular disorders) that might interfere with the study as deemed by the judgment of the Investigator
21. Initiation of treatment with, or any changes to, the current dosage, drug, or regimen of any systemic adrenergic or cholinergic drugs within 7 days prior to Screening or during the study; however, Flomax® (tamsulosin) is specifically excluded
22. Participation in any investigational study within 30 days prior to Screening
23. Females of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. Acceptable methods include the use of at least one of the following: intrauterine device, hormonal contraception (oral, injection, patch, implant, ring), barrier with spermicide (condom, diaphragm), or abstinence. A female is considered to be of childbearing potential unless she is 1 year postmenopausal or 3 months post–surgical sterilization. All females of childbearing potential, including those with post−tubal ligation, must have a negative urine pregnancy test result at Visit 1 (Screening)
24. Resting HR outside the range of 50 to 110 beats per minute (bpm) following at least a 5-min rest period in the sitting position at Visit 1 (Screening). Heart rate may be repeated **only once** if outside the specified range, following another 5-min rest period in the sitting position
25. Hypertension with resting diastolic BP > 105 mmHg or systolic BP > 160 mmHg following at least a 5-min rest period in the sitting position at Visit 1 (Screening). Blood pressure may be repeated **only once** if outside the specified range, following another 5-min rest period in the sitting position.

5.5. Randomization and Masking

A randomization code for allocating participants to each treatment group will be prepared by an unmasked biostatistician not connected with the study. Approximately 545 participants will be randomized in a 3:2 ratio to 1 of 2 treatment arms (POS or placebo). Randomization will be stratified by iris color (light/dark irides).

Study medications will be masked to Investigators, site staff, study participants, clinical research organizations involved in the study, and Opus Genetics. Only in case of medical emergency or occurrence of SAEs will the randomization code be unmasked by the Medical Monitor and made available to the Investigator, Opus Genetics, and/or other personnel involved in the monitoring or conduct of this study.

6. SAMPLE SIZE

Using $\alpha = 0.05$ significance and a two-tailed test, 525 evaluable participants (313 participants each in the POS arm and 212 participants in the placebo arms) who are evaluable for efficacy will provide greater than 90% power to detect a difference of 11.5% between treatments in percentage of participants with ≥ 15 letters of improvement in photopic binocular DCNVA and with < 5 letters of loss in photopic binocular BCDVA from baseline at 12 hours post-dose at Visit 4 (Day 8). [redacted] An additional 20 participants will be enrolled to account for dropouts.

7. GENERAL CONSIDERATIONS

7.1. Analysis Populations

The following analysis populations will be defined for this study.

7.1.1. Modified Intention-to-Treat (mITT)

The mITT Population will include all randomized participants who received at least 1 dose of study medication. The mITT Population will be used for the primary endpoint analysis and to analyze efficacy endpoints, with participants included in their randomized treatment regardless of the treatment they actually received.

7.1.2. Per Protocol Population (PP)

The PP Population will include all participants in the mITT Population who received at least 80% of expected doses of study medication through Day 8, have Baseline and Day 8 DCNVA and BCDVA measurements, and have no major protocol deviations considered to have significant impact on treatment outcome. The PP Population will be used to analyze efficacy endpoints, with participants included in their randomized treatment group regardless of the treatment they received.

7.1.3. All Randomized Population (ARP)

The ARP will include all randomized participants. This population is also known as the Intention-to-Treat (ITT) Population. The ARP may be used in confirmatory efficacy analyses, with participants included in their randomized treatment regardless of the treatment they actually received.

7.1.4. Safety Population (SP)

The SP will include all randomized participants who have received at least 1 dose of study medication. The Safety Population will be used to summarize safety variables, using the actual treatment a participant received.

7.2. Covariates and Subgroups

7.2.1. Planned Covariates

Planned covariates include irides type (light, dark) and baseline values for the given assessment.

7.2.2. Planned Subgroups

A subgroup analysis by irides type (light, dark) will be completed for the primary efficacy endpoint.

Other possible subgroups include age (≥ 45 to ≤ 54 and ≥ 55 to ≤ 64), sex, and race.

7.3. Management of Analysis Data

7.3.1. Data Handling

Data from unscheduled visits will not be included in the analysis of efficacy or safety, but will be listed. Nominal visits will be used, with no additional analysis visit windowing except for the early termination data (Section 7.3.3).

7.3.2. Missing Data

The primary efficacy endpoint is the percent of participants with ≥ 15 letters of improvement in binocular DCNVA and with < 5 letters of loss in binocular BCDVA from baseline comparing POS-treated participants to placebo-treated participants at 12 hours post-dose at Day 8. For the analysis of the primary efficacy and selected secondary endpoints, imputation will be performed for missing efficacy data as specified in Section 7.3.2.3 for the analysis using the mITT, as well as either PP population, if required. Confirmatory analyses may be performed using the ARP, also using imputation for missing data.

Otherwise, there will be no substitutions made to accommodate missing data points for efficacy data. All data recorded on the CRF will be included in data listings that will accompany the CSR.

Safety data will be imputed in limited situations. If the severity of an AE is missing, then the severity will remain missing. If relationship of the AE to study drug is missing, the relationship will remain missing. Missing or partial dates for AEs or concomitant medications will be imputed as described in Section 7.3.2.1. Otherwise, all summaries of safety endpoints will be completed using observed cases in the SP; no imputation will be completed.

7.3.2.1. Handling of Missing Date Values

Partial or Missing Dates

The following conventions will be used to impute missing portions of dates for AEs and concomitant medications, if warranted. Note that the imputed values outlined here may not always provide the most conservative date. In those circumstances, the imputed value may be replaced by a date that will lead to a more conservative analysis.

A. Start Dates

1) If the year is unknown, then the date will not be imputed and will be assigned a missing value.
2) If the month is unknown, then:
    i) If the year matches the first dose date year, then impute the month and day of the first dose date.

ii) Otherwise, assign 'January.'

3) If the day is unknown, then:

i) If the month and year match the first dose date month and year, then impute the day of the first dose date.

ii) Otherwise, assign the first day of the month.

B. Stop Dates

1) If the year is unknown, then the date will not be imputed and will be assigned a missing value.

2) If the month is unknown, then assign 'December.'

3) If the day is unknown, then assign the last day of the month.

7.3.2.2. Missing Baseline Data

Every effort will be made to ensure that accurate baseline information on the participants is collected. In the event that a participant is missing baseline information that is required for the primary efficacy analyses, the participant will be included in the SP for assessment of safety and excluded from the primary analyses. Each case of missing baseline data will be evaluated for potential inclusion for each endpoint. All baseline data will be observed cases, without imputation.

7.3.2.3. Imputation Methods

Imputation for efficacy data will be performed for the primary efficacy endpoint using the mITT, as well as the PP population, if required. Imputation for selected secondary efficacy endpoints may also be performed.

Multiple imputation will be employed to analyze incomplete data sets under the assumption that the mechanism responsible for the missing data is at worst characterized as missing at random (MAR). Multiple imputation is a simulation-based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These completed datasets can then be analyzed using standard analysis methods. Rubin [2] presented rules for how to combine the multiple sets of estimates to produce overall estimates, confidence intervals (CIs), and tests that adequately incorporate missing data uncertainty.

To implement this approach for the primary endpoint, missing values for binocular DCNVA and BCDVA will be imputed based on an underlying joint normal distribution using a Markov Chain Monte Carlo (MCMC) method.

The imputations will be done separately for each treatment group and will include the following variables in the imputation model: binocular DCNVA or BCDVA at baseline, Day 1 (1 hour post-dose), Day 3, Day 8, and Week 6. No imputation will be performed after Week 6.

The number of imputations will be set to 20. The change from baseline for binocular DCNVA or BCDVA will be calculated from these imputed datasets. When all binocular DCNVA and BCDVA values are imputed, the primary efficacy endpoint, which is a dichotomous variable based on binocular DCNVA and BCDVA, will be evaluated for each imputed dataset using logistic regression. See Section 9.1 for details on these models. The estimates and 95% CIs of the difference of proportions based on the 20 imputed datasets are then combined by applying Rubin's rules for multiple imputed datasets. T-tests are also provided. SAS Proc MI, Proc NLMIXED, and Proc MIANALYZE will be utilized for these analyses. The difference of proportions with the corresponding 95% CI will also be presented.

This approach will be implemented for secondary endpoints in a similar fashion, with the variable and visits changed to fit the endpoint definition. Continuous secondary endpoints will be analyzed using analysis of covariance (ANCOVA) instead of logistic regression; see Section 9.1 for details on these models.

A sensitivity analysis will be employed on the primary efficacy endpoint using a control-based Pattern-Mixture Model (PMM). In this analysis, intermittent missing binocular DCNVA and BCDVA data (Day 1 [1 hour post-dose], Day 3, and Day 8) will be imputed using MCMC methods, assuming MAR, within each treatment group. SAS PROC MI will be utilized for this step using the MCMC impute=monotone option. In accordance with the PMM method, all data from the placebo group and only data from participants in the POS group who have missing data will be included in the multiple imputation used to fill in the intermittent missing data. Treatment will not be included as a factor in the multiple imputation.

The remaining missing binocular DCNVA and BCDVA values with a monotone missing data pattern will then be imputed. The missing values in the POS group will not be constructed from the observed data in the POS group, but rather from the observed data in the placebo group. This model will also be used to impute missing efficacy measurements in the placebo group. The MNAR statement in SAS PROC MI will be used to impute all missing values. The imputed values will be converted into responder (yes/no) variables according to the definition of the primary efficacy endpoint. This will be performed for 20 datasets.

When all binocular DCNVA and BCDVA values have been imputed, the primary efficacy endpoint will be derived and the observed outcome (yes/no) at Day 8 for each imputed dataset will be evaluated using logistic regression. The estimates and 95% CIs of the difference of proportions based on the 20 imputed datasets are then combined by applying Rubin's rules for multiple imputed datasets (as described above), and the difference of proportions with the corresponding 95% CI will be presented.

Assuming the primary efficacy analysis shows a significant difference between treatment groups at Day 8, a tipping point analysis will also be used as a sensitivity analysis. This analysis will apply multiple imputation assuming MAR, but will also employ increasingly negative shifts to be added to imputed binocular DCNVA data from the POS group, crossed with increasingly positive shifts to be added to the imputed binocular DCNVA data from the

placebo group. Simultaneously, increasingly negative shifts will be added to imputed binocular BCDVA data from the POS group, crossed with increasingly positive shifts to the imputed binocular BCDVA data from the placebo group. The imputed values will be converted into responder (yes/no) variables according to the definition of the primary efficacy endpoint, and analyzed as described above. The analysis with no shifts will correspond to the original multiple imputation strategy assuming MAR described above. The most extreme shift will ensure that participants with missing binocular DCNVA and/or BCDVA data in the POS arm are considered as nonresponders while similar participants in the placebo arm are considered as responders.

7.3.3. Handling of Early Termination Visit Information

In the event that a participant is terminated early from the study, the early termination data will be assigned to the closest scheduled visit and/or time point. If the closest visit or time point has valid data, the early termination data will be assigned to the next available visit or time point.

7.3.4. Pooling of Investigational Sites

The data from all study centers will be pooled together for all planned analyses.

7.3.5. Coding Conventions for Events and Medications

All AEs and medical history will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA Version 27.0) system for reporting (preferred term and body system).

Prior and concomitant medications will be coded using WHO-DD (World Health Organization Drug Dictionary) (Version 2024MAR).

7.3.6. Analysis Software

Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher) for Windows. If the use of other software is warranted, the final CSR will detail what software was used and for what purposes.

7.3.7. Study Data

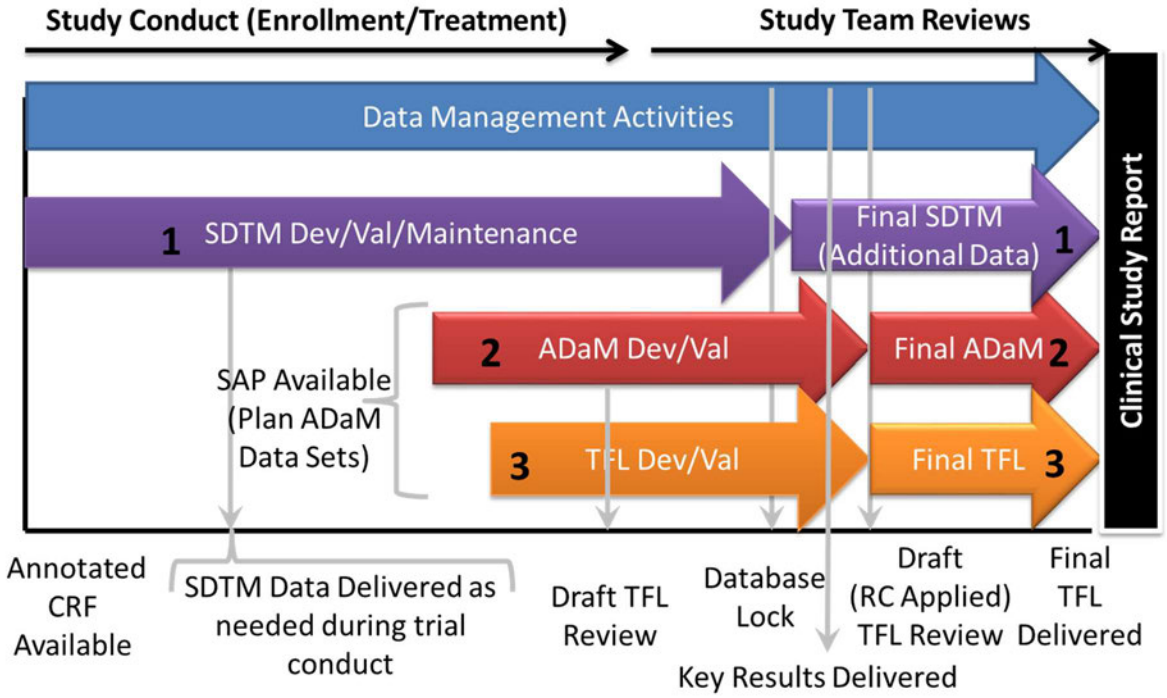
Study data identified in the schedules for time and events (

Table 1) are collected, and source verified, on the Fountayn electronic data capture (EDC) system.

All study data will be formulated into regulatory-compliant data sets to provide transparency, traceability, and integrity of trial analysis results from the collection source. Observed study data will be mapped to the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) and serve as the source data from the trial. All study analyses will be completed using analysis data sets that are derived from the SDTM and follow the CDISC Analysis Data Model (ADaM) architecture.

The methods for programming the CDISC SDTM and ADaM data sets are described in Figure 1.

Figure 1 SDTM, ADaM, and TFL Development and Validation



Where:

1. Development, validation, and maintenance of SDTM domains
2. Development and validation of ADaM data sets, with input source the appropriate SDTM domains.
3. Development and validation of tables, figures, and listings (TFL), with input data source the SDTM domains and analysis specific ADaM data sets.

7.4. Planned Study Analyses

7.4.1. Statistical Summaries: Descriptive and Inferential

Categories for data presentation and analysis will consist of each treatment group: POS and placebo.

All statistical tests will be two-sided and a difference resulting in a p-value of less than or equal to 0.05 will be considered statistically significant. The p-values for the analysis of secondary efficacy endpoints and safety endpoints will be considered descriptive, unless the endpoint is used for the hierarchical testing method. All p-values will be rounded to and displayed in four decimals. If a p-value less than 0.0001 occurs, it will be shown in tables as <0.0001.

Descriptive summaries of variables will be provided where appropriate. For continuous variables, the number of non-missing values (n), mean, standard deviation, median, minimum, and maximum will be tabulated by treatment group. For categorical variables, the counts and proportions of each value will be tabulated by treatment group. Expansion of descriptive table categories within each treatment may occur if such elaborations are thought to be useful.

All study-related data collected will be presented in listings. Study-related data not participant to analysis according to this plan will not appear in any tables or graphs but will be included in the data listings.

7.4.2. Interim Analyses and Data Monitoring

The primary efficacy analysis of study data will be conducted after all participants complete Week 6 of the study. All efficacy and safety endpoints though Week 6, as well as the endpoint for tachyphylaxis, will be analyzed. Most study staff, including the study biostatisticians and statistical programmers, will be unmasked when all clinical data through the Week 6 visit are collected and cleaned, and will perform the primary analysis. Other study personnel, including investigational site staff, the study monitor, and medical monitor will remain masked to individual treatment assignments until database lock for final analysis. Another interim analysis of safety endpoints will be conducted after all participants complete Month 6 (Week 24) of the study.

7.4.3. Final Analysis and Publication of Study Results

The final analysis will be completed after all participants have completed the study.

7.5. Multiple Testing Procedures

A hierarchical analysis will formally test a family of endpoints beyond the primary efficacy endpoint. The full hierarchy is in Section 12.3.

Otherwise, there will be no adjustments for multiplicity and no formal multiple testing procedures are to be implemented with this analysis plan.

7.6. Baseline Values

Baseline values are the values obtained at Visit 1, 0 Hour, prior to any treatment administration. If the Visit 1, 0 Hour assessments are missing or were not scheduled to be collected at that time point, a value collected prior to treatment administration, such as at the Screening visit, will be used for the baseline value.

8. SUMMARY OF STUDY DATA

8.1. Participant Disposition

A summary of the analysis sets includes the number and percentage of participants by treatment group and overall for the following categories: participants in the ARP, participants in the SP, participants in the mITT Population, and participants in the PP Population. All percentages will be based on the number of participants in the ARP.

End of trial information will also be summarized in these tables, including the number of participants completing the study, the number of participants who prematurely discontinued the study with reasons for withdrawal, the number of participants completing the study medication dosing, and the number of participants who prematurely discontinued the study medication with reasons for study medication discontinuation.

A by-participant data listing of study completion information including the reason for premature study withdrawal, if applicable, will be presented.

8.2. Protocol Deviations

Major protocol deviations, as determined by a Sponsor masked review of the data prior to database lock and unmasking of the study, may result in the removal of a participant's data from the PP Population. The Sponsor or designee will be responsible for producing the final deviation file; this file will include a description of the protocol deviation and clearly identify whether this violation warrants exclusion from the PP Population. This file will be finalized prior to database lock.

All protocol deviations will be presented in a by-participant data listing, with a flag to indicate if a deviation was considered major and/or exclusionary.

8.3. Demographics and Baseline Characteristics

Participant demographic data and baseline characteristics will be tabulated and summarized descriptively by treatment group, and overall. The demographic data and baseline characteristics will be summarized for the mITT Population, PP Population, SP, and ARP. If the mITT population is equivalent to any of the other populations, then only the mITT version will be generated rather than repeating equivalent summaries.

The demographics consist of age (year), sex, race, ethnicity, and study eye, iris type (light, dark). A participant's age in years is calculated using the date of the informed consent and date of birth. Age will be summarized using descriptive statistics. The number and percentage of participants by sex, race, ethnicity, study eye, and iris type will also be reported. Percentages will be based on the total number of participants in the study population presentation.

The following baseline characteristics will be summarized for study eye, fellow eye, and binocular (if applicable), using descriptive statistics:

- BCDVA
- DCNVA
- DCIVA
- Pupil diameter
- IOP

All demographic and baseline information will be presented in by-participant listings.

8.4. Medical History

The number and percent of participants with individual medical histories will be summarized for all participants by treatment group and overall. Non-ocular and ocular medical history will be summarized separately.

Medical history will be coded using the MedDRA Version 27.0. The number and percentage of participants with any medical history will be summarized overall and for each system organ class (SOC) and preferred term (PT). Percentages will be calculated based on number of participants in the SP.

Participant medical history data including specific details will be presented in by-participant listings.

8.5. Prior and Concomitant Medications

The number and percentages of all concomitant medications will be summarized by treatment group, Anatomical Therapeutic Chemical (ATC) level 4, and PT. The total number of concomitant medications and the number and percentages of participants with at least 1 concomitant medication will be summarized by treatment group and overall. All summaries will be performed using the SP.

A concomitant medication is defined as any medication taken on or after the day of first exposure to study drug.

Prior medications are defined as any medication that has a start and stop date prior to the day of first exposure to any study drug, collected from up to 30 days prior to Screening. The total number of prior medications and the number and percentages of participants with at least 1 prior medication will be summarized by treatment group and overall.

8.6. Treatment Exposure and Compliance

Continuous descriptive summaries for total exposure to study medication (in days) and percentage compliance through Week 6, through Week 24, and for the entire study will be presented for the SP by treatment group.

Additionally, categorical summaries of compliance (participants with compliance rates of <80% and ≥80%) will be presented by treatment group.

Exposure to study drug will be determined by the visit date at the end of the treatment period – date of first study medication administration + 1. For participants who discontinued study medication during the treatment period, the visit date at the end of the period will be replaced by the medication discontinuation date. Compliance will be determined by dividing the number of used vials returned, plus the in-office treatment administration on Day 1, by the exposure to study medication during the treatment period.

9. EFFICACY ANALYSES

Unless otherwise noted, efficacy will be assessed using the mITT Population, with participants included in their randomized treatment regardless of the treatment they actually received. For the analysis of the primary efficacy endpoint, imputation will be performed for missing data as described in Section 7.3.2.3. If the analysis using the mITT Population shows a positive effect for POS at the 0.05 level of significance, the primary endpoint will be considered met. The primary efficacy endpoint and selected secondary efficacy endpoints will also be evaluated using the PP Population.

A hierarchical approach will be applied to formally test the significance of endpoints of interest beyond primary efficacy. Select efficacy endpoints will be tested in a predefined sequence until the first nonsignificant test. The primary efficacy endpoint will be first in the sequence. See Section 12.3 for the full sequence of endpoints.

All efficacy assessment data, regardless of whether they are included in the analysis, will be presented in by-participant listings.

9.1. Clinical Efficacy

All efficacy data will be summarized by treatment group (POS or placebo) and visit. Efficacy assessments collected after the Week 6 visit will be summarized using descriptive statistics.

9.1.1. Primary Efficacy Estimand

The primary efficacy estimand, corresponding to the primary efficacy endpoint, is defined by the following components:

by the following components:

1. The *population* is restricted to the mITT Population
2. The *variable* for the primary endpoint is percent of participants with ≥ 15 ETDRS letters of improvement in binocular DCNVA and with < 5 letters of loss in binocular BCDVA from baseline comparing POS-treated participants to placebo-treated participants at 12 hours post-dose at Day 8
3. The *intercurrent events* of treatment discontinuation or use of prohibited concomitant medications will be handled according to the treatment policy strategy, irrespective of premature discontinuation of randomized treatment
4. The *population-level summary* is the difference in percent of participants with ≥ 15 ETDRS letters of improvement in binocular DCNVA and with < 5 letters of loss in binocular BCDVA from baseline comparing POS-treated participants to placebo-treated participants at 12 hours post-dose at Day 8, analyzed using a logistic regression model with treatment and light/dark irides as factors and the baseline binocular DCNVA as a covariate

5. *Treatment:* There will be 1 active treatment arm (POS) and 1 control arm (placebo)

9.1.2. Primary Efficacy Analysis

The primary efficacy endpoint will be analyzed using a logistic regression model with treatment and light/dark irides as factors and the standardized baseline DCNVA as a covariate, which is derived from the baseline DCNVA by subtracting the mean of all baseline DCNVA values and dividing by the standard deviation. The percentage of participants in each treatment group meeting the criteria, the difference of proportions with 95% CI, and p-value will be provided. Example SAS code is as follows:

```
PROC NLMIXED DATA=DCNVA_RESP;
      BY _IMPUTATION_;
      PARMS B0=0 B2=1 B2=1 B3=1;
      XB = B0 + B1*TRTN + B2*IRIDES + B3*B_DCNVA;
      P = EXP(XB)/(1+EXP(XB));
      MODEL RESP ~ BINARY(P);
      ESTIMATE 'DIFF_PROP' LOGISTIC(B0+B1+0.5*B2+0*B3) -
LOGISTIC(B0+0.5*B2+0*B3);
RUN;
```

Sensitivity analyses for the primary efficacy endpoint include the control-based PMM and the tipping point analysis described in Section 7.2.3. Analyses of subgroups, including by irides type, will be performed (see Section 7.2.2 for all subgroups).

9.1.3. Secondary Efficacy Estimands

Secondary efficacy estimands will have the same population, intercurrent events, and treatment as the primary estimand. For secondary categorical endpoints, the population-level summary will also match the primary estimand; only changes to the variable (eg, visit, type of assessment) will be required to match the particular secondary endpoint.

Secondary efficacy estimands for continuous endpoints will also vary depending on the assessment, visit, and time point. For change from baseline endpoints, the population-level summary is the change from Baseline in the assessment at the required visit, analyzed using ANCOVA with treatment and light/dark irides as factors and the baseline assessment as a covariate.

The following is an example of a secondary efficacy estimand with a change from baseline endpoint:

1. The *population* is restricted to the mITT Population
2. The *variable is* change from Baseline (Day 1 pre-dose) in DCNVA in the study eye at Day 8

3. The *intercurrent event* of treatment discontinuation or use of prohibited concomitant medications will be handled according to the treatment policy strategy, irrespective of premature discontinuation of randomized treatment
4. The *population-level summary* is the change from Baseline in DCNVA in the study eye at Day 8, analyzed using ANCOVA with treatment and light/dark irides as factors and the baseline DCNVA in the study eye as a covariate
5. *Treatment:* There will be 1 active treatment arm (POS) and 1 control arm (placebo)

9.1.4. Secondary Efficacy Analysis

Secondary efficacy endpoints are indicated in Section 4.2.2. Secondary efficacy endpoints will be analyzed by study eye, fellow eye, and binocular (if available) using the mITT Population, and the PP population for selected endpoints.

Each of the continuous secondary efficacy endpoints will be analyzed using the ANCOVA model specified in the secondary efficacy estimand, with change from baseline as the dependent variable, treatment, and light/dark irides as factors, and the respective baseline value included as the covariate. The output from each ANCOVA will include the LSM and SE for both treatment groups, along with the placebo-corrected LSM, its 95% CI and associated p-value.

For each of the secondary endpoints related to percent of participants achieving certain criteria, the analysis will be performed using a logistic regression model with treatment and light/dark irides as factors, and the respective baseline as a covariate. For each analysis, the percentage of participants in each treatment group meeting the criteria, and the difference in percentage with 95% CI and p-value, will be provided.

Secondary endpoints using Snellen measurements will be converted from letters read as follows:

Table 2 Snellen Equivalents to VA Assessment Letters Read

DCNVA/DCIVA letters	Snellen	BCDVA letters
≥75	20/15	≥60
70 - 74	20/20	55 - 59
65 - 69	20/25	50 - 54
60 - 64	20/32	45 - 49
55 - 59	20/40	40 - 44
50 - 54	20/50	35 - 39
45 - 49	20/63	30 - 34
40 - 44	20/80	25 - 29
35 - 39	20/100	20 - 24
30 – 34	20/125	15 - 19
25 - 29	20/160	10 - 14
<25	20/200	<10

To test for tachyphylaxis, a mixed model for repeated measures will be applied with change from baseline in binocular DCNVA as the dependent variable, treatment, visit, and light/dark irides as factors, and the respective baseline value included as the covariate. Interactions between factors will be tested, and, if significant, interaction terms may be added to the model. All visits through Week 6 where binocular DCNVA is assessed will be included in the model. An unstructured covariance type will be used. The LSM of the difference between the change from baseline in binocular DCNVA at Week 6 and the best change in binocular DCNVA during the first month of the study, the 90% CI, and associated p-value from a test with null hypothesis of binocular DCNVA at Week 6 – binocular DCNVA at the visit/time point ≥ -5 and alpha = 0.05, will be presented.

Finally, select participant-reported outcomes in the post-baseline version of the questionnaire will be analyzed. The results for individual questions will be analyzed using an ANCOVA model with numeric observed response as the dependent variable (ranging from 1 [poor outcomes] to 5 [good outcomes]) treatment as a factor, and baseline response as a covariate (if available). The overall score will be derived as the sum of questions #1-8 and #10-14 in the post-baseline questionnaire; if there are missing or not applicable responses, the overall score will be based on the sum of all non-missing questions and standardized to the number of possible points for the original overall score, assuming all questions are answered. The outcomes in the baseline version of the questionnaire will be summarized descriptively by treatment group.

10. SAFETY ANALYSES

All safety analyses will be conducted using the SP unless specified otherwise below. All safety analyses will be completed using the actual treatment a participant received. Observed case data will be used; no imputation will be performed for missing safety data except for the limited situations described in Section 7.3.2.

All safety data will be presented in by-participant listings. Unscheduled assessments will not be summarized but will be included in the listings.

10.1. Adverse Events

AEs will be coded using MedDRA, Version 27.0. Treatment-emergent adverse events (TEAEs) are defined as any AE that begins or worsens after initiation of the investigational product and through the participant's last study visit (study completion or early termination).

If the onset of an AE is on or after the date of first dose of study medication or is increasing in severity after first dose of study medication, then the AE will be considered treatment emergent.

Only TEAEs will be summarized; all AEs (TEAE, non-TEAE) will be included in a by-participant listing.

The number and percent of participants with any TEAEs will be summarized by SOC and PT by treatment group and overall. At each level of tabulation (e.g., at the PT level), participants will be counted only once if they had more than one such event reported during the AE collection period.

Note that in MedDRA, ocular events are coded to the SOC of "Eye Disorders". Thus, using SOC in the summaries will provide a separation of ocular and non-ocular adverse events.

The following summary tables will be presented for TEAE data:

- Overall summary of TEAEs
- Summary table of TEAEs by SOC and PT
- Summary table of TEAEs by SOC, PT, and by greatest relationship level to study drug (not related, unlikely related, possibly related, probably related, definitely related, or unknown)
- Summary table of TEAEs by SOC, PT, and maximum severity (mild, moderate, severe)
- Summary table of serious TEAEs by SOC and PT
- Summary table of TEAEs leading to withdrawal from the study by SOC and PT
- Summary table of TEAEs leading to study medication discontinuation by SOC and PT

10.2. Deaths, Serious Adverse Events and Other Significant Adverse Events

10.2.1. Deaths

The AE listing will include all AEs, including deaths, regardless of causality; one of the columns in the listing will specify whether the AE was fatal.

10.2.2. Serious Adverse Events

The AE listing will include all AEs, including SAEs; one of the columns in the listing will specify whether the AE was an SAE.

10.2.3. Adverse Events Leading to Withdrawal from the Study

The AE listing will include all AEs, including AEs leading to withdrawal from the study; one of the columns in the listing will specify whether the AE led to withdrawal from the study.

10.2.4. Adverse Events Leading to Discontinuation of Study Medication

The AE listing will include all AEs, including AEs leading to discontinuation of study medication; one of the columns in the listing will specify whether the AE led to discontinuation of study medication.

10.3. IOP

Observed values and changes from baseline in IOP will be summarized using descriptive statistics at each visit for each treatment group and overall. Separate summaries will be created for the study eye and the fellow eye.

10.4. BCDVA

The percentage of participants with ≥ 5, ≥ 10, and ≥ 15 letters of improvement or loss in BCDVA from baseline at each visit will be summarized by treatment group. Separate summaries will be created for the study eye, the fellow eye, and binocular.

10.5. Biomicroscopy and Ophthalmoscopy

Results from biomicroscopic and ophthalmoscopic examinations at each visit will be summarized by treatment group. Separate summaries will be created for the study eye and the fellow eye.

10.6. Corneal Specular Microscopy

Observed values and change from baseline in median endothelial cell count (ECC) from the automated corneal specular microscopy will be summarized by treatment group at each visit (if available). Separate summaries will be created for the study eye and the fellow eye.

10.7. Vital Signs

Descriptive statistics of observed values will be presented for vital sign data at each visit including systolic BP (mmHg), diastolic BP (mmHg), and HR (bpm) by treatment group and overall. Changes from baseline (collected at the Screening visit) to each scheduled post-baseline time point will be presented.

10.8. Other Screening and Safety Measures

Urine pregnancy tests for females of childbearing potential will be presented in by-participant listings. Dry eye tests (tear break-up time and corneal fluorescein staining), performed only at Day 1, will also be listed.

11. REFERENCES

[1] ICH E9 Expert Working Group. Statistical Principles for Clinical Trials: ICH Harmonized Tripartite Guideline, September 1998

[2] Rubin, D.B. *Multiple Imputation for Nonresponse in Surveys*. John Wiley & Sons Inc., New York, 1987

12. APPENDICES

12.1. List of Planned Tables, Figures, and Listings

The list of planned TFLs will be provided in a separate document, with shells for each planned output.

12.2. Testing Hierarchy

