A MULTICENTER, OPEN-LABEL ROCKLATAN® (NETARSUDIL/LATANOPROST OPHTHALMIC SOLUTION) 0.02%/0.005% EVALUATION OF IOP LOWERING EFFICACY AND SAFETY AS REPLACEMENT OF CURRENT MEDICAL THERAPY REGIMEN FOR THE REDUCTION OF ELEVATED INTRAOCULAR PRESSURE IN PATIENTS WITH GLAUCOMA OR OCULAR HYPERTENSION

MORE: Multi-center, Open-label Rocklatan® Evaluation

STUDY ID:

MA-ROC-22-003

STATISTICAL ANALYSIS PLAN

24-FEB-2022

NCT05283395

Aerie Pharmaceuticals
Protocol #: MA-ROC-22-003

Protocol Name: A Multicenter, Open-Label Rocklatan® (Netarsudil/Latanoprost Ophthalmic Solution) 0.02%/0.005% Evaluation of IOP Lowering Efficacy and Safety as Replacement of Current Medical Therapy Regimen for the Reduction of Elevated Intraocular Pressure in Patients with Glaucoma or Ocular Hypertension

[redacted]

Statistical Analysis Plan

SAP Approval

By signing the following, I agree to the contents in the Statistical Analysis Plan and its associated attachments. Once the SAP has been signed, the analyses and programming of the tables, listings, and figures (TLFs) based upon this document can proceed. Any modifications to the SAP and TLFs made after signing may result in a change order.

Approved by:

[redacted]

LIST OF ABBREVIATIONS

Abbreviation	Definition
AA	Alpha Agonists
AE	Adverse event
BB	Beta Blockers
BCVA	Best Corrected Visual Acuity
CAI	Carbonic Anhydrase Inhibitor (CAI)
CI	Confidence interval
CM	Concomitant medication
FDC	Fixed Dose Combination
ITT	Intent to Treat
IOP	Intraocular Pressure
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat Population
PP	Per Protocol
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System Organ Class
TEAE	Treatment emergent adverse event
TLF	Tables, listings, and figures

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1 Protocol Summary

Title	MORE: Multi-center, Open-label Rocklatan® Evaluation A Multicenter, Open-Label Rocklatan® (Netarsudil/Latanoprost Ophthalmic Solution) 0.02%/0.005% Evaluation of Intraocular Pressure (IOP) Lowering Efficacy and Safety as Replacement of Current Medical Therapy Regimen for The Reduction of Elevated Intraocular Pressure in Patients with Glaucoma or Ocular Hypertension
Study Objective	The objective of this study is to evaluate the IOP lowering and number of agents/bottles required to achieve similar or additional IOP lowering with Rocklatan® in subjects on a current regimen of latanoprost alone or latanoprost plus addition of either one or 2 IOP-lowering agents.
Efficacy Analysis	The primary efficacy variable is percent reduction from baseline IOP in the study eye at Week 12.
Safety Analyses	Safety analysis includes assessment of Adverse Events (AEs) and clinical assessments such as Best Corrected Visual Acuity (BCVA), Biomicroscopy, and Pregnancy Testing.

[redacted]

[redacted]

Test Product, Dose, Duration, and Mode of Administration	Enrolled subjects will be instructed to self-instill 1 drop of Rocklatan® (netarsudil/latanoprost ophthalmic solution) 0.02%/0.005% in each eye daily in the evening, beginning the evening of the Baseline Visit (Visit 1) until the Final (Week 12) Visit.
Study Design:	This is a multicenter, prospective, open-label stratified by baseline IOP lowering regimen groups study. Subjects diagnosed with open-angle glaucoma or ocular hypertension will be evaluated at a Baseline Visit (Visit 1, Day 0). Subjects satisfying Visit 1 inclusion/exclusion criteria will be invited to participate in this study. At the Baseline Visit (Visit 1, Day 0), all qualified subjects will be enrolled and dispensed Rocklatan®. Subjects will be instructed to stop their current IOP lowering medical therapy regimen and to begin dosing Rocklatan® in each eye daily in the evening of the Baseline Visit and for the duration of the 12-week study. Subjects will complete 2 follow up visits (Visit 2: 6 weeks [±7 days], Visit 3: 12 weeks [±7 days]), during which efficacy and safety assessments will take place. The subjects will be exited from the study at the end of Visit 3.
Inclusion Criteria	The following are criteria for inclusion in the study. All must be met at the Baseline Visit (Visit 1, Day 0) to be eligible for participation: **1.** Male or female subjects, age 18 or older **2.** Current diagnosis of open-angle glaucoma or ocular hypertension **3.** Subject currently being treated with latanoprost alone or latanoprost plus 1 or 2 additional agents/bottles. Current IOP lowering regimen is stable for at least 30 days prior to Baseline Visit and is one of the regimens listed below:

	• Latanoprost monotherapy • Latanoprost + 1 additional individual IOP-lowering agent * • Latanoprost + 2 additional IOP-lowering agents Two additional agents include two individual IOP-lowering agents* as well as fixed dose combinations** *Additional individual agent(s) include the following IOP lowering classes: beta blocker, alpha agonist, carbonic anhydrase inhibitor. **Fixed-dose combinations combining two active ingredients will be considered as two IOP lowering agents. Note: latanoprost may be brand name or generic drug **4.** Treated IOP ≥ 20 mmHg measured in the morning (before noon) at the Baseline Visit by Goldmann applanation tonometer **5.** Best corrected Snellen visual acuity of 20/100 or better in both eyes **6.** Willingness to follow protocol requirements, including signed informed consent and health information release forms, routine follow-up schedule, completing questionnaires
Exclusion Criteria	The following are criteria for exclusion from the study: **Ophthalmic:** **7.** Have any active ocular disease other than open-angle glaucoma or ocular hypertension that would interfere with study interpretation **8.** Use of fixed dose combination agents as part of the patient's Baseline IOP lowering therapy regimen, if not also on latanoprost **9.** Treatment naïve glaucoma or ocular hypertension patients **10.** Mean central corneal thickness greater than 620 µm in either eye

	11. Have any corneal abnormality preventing reliable applanation tonometry in either eye (e.g., scar, edema, keratoconus) **12.** Active ocular infection/inflammation or history of uveitis **13.** Aphakic or pseudophakic patients with a torn posterior lens capsule, or with known risk factors for macular edema **14.** Visual field loss, which, in the opinion of the investigator, is evidence of end-stage glaucomatous visual field loss **15.** History of corneal refractive laser surgery in the study eye within 3 months prior to Baseline Visit **16.** History of intraocular surgery in the study eye within 3 months prior to Baseline, including glaucoma laser surgery cataract surgery and minimally invasive glaucoma surgery **Systemic:** **17.** Any systemic disease or clinical evidence of any condition which would make the subject, in the opinion of the investigator, unsuitable for the study or could potentially confound the study results **18.** Use of topical, periorbital, intravitreal or systemic steroid within previous 3 months or expected use during the course of the study **19.** Use of systemic medications(s) or therapy that may have a substantial effect on IOP unless such medication(s) or therapy has/have been used for a minimum of 3 months prior to Baseline Visit, is/are expected to remain constant throughout the course of the study and is/are considered necessary for a subjects' welfare **20.** Prior participation in any investigational drug or device study within the last 30 days prior to the Baseline Visit. **21.** Known sensitivity or allergy to the study medication or components **22.** Females who are pregnant, nursing, or planning a pregnancy during the study

	23. Positive pregnancy test at Baseline Visit (women of childbearing potential only) **24.** Women of childbearing potential who are not using a medically acceptable form of birth control
Statistical Methods	Summary tables (descriptive statistics and/or frequency distributions) will be provided for all baseline variables, efficacy variables, safety variables, and any other assessments. Continuous variables will be described by descriptive statistics (n, mean, standard deviation, range, and median). Frequency distributions (counts and percentage) of subjects within each category will be provided for categorical data.
Sample Size	Approximately one hundred and sixty (160) male or female subjects will participate in this study. Approximately 22 study centers in the United States will be utilized.
Stratification	Enrollment will be stratified based on subject's current Baseline IOP lowering therapy regimen: • 60 subjects whose Baseline therapy regimen is latanoprost monotherapy • 60 subjects whose Baseline therapy regimen is latanoprost plus 1 additional individual IOP-lowering agent* • 40 subjects whose Baseline therapy regimen is latanoprost plus 2 additional IOP-lowering agents Two additional agents include two individual IOP-lowering agents* as well as fixed dose combinations** *Additional individual agent(s) include the following IOP lowering classes: beta blocker, alpha agonist, carbonic anhydrase inhibitor. **Fixed-dose combinations combining two active ingredients will be considered as two IOP lowering agents. Note: latanoprost may be brand name or generic dru

2 Statistical Methodology

2.1 General Considerations

The objective of this study is to evaluate the IOP lowering and number of agents/bottles required to achieve similar or additional IOP lowering with Rocklatan® in subjects on a current regimen of latanoprost alone or latanoprost plus addition of either one or 2 IOP-lowering agents.

All statistical analyses will be performed using SAS Version 9.4 or higher. The following summary statistics will be reported for continuous data: the number of eyes or subjects, as applicable, and the mean, median, standard deviation, minimum, and maximum. Confidence intervals (CIs) may be provided where appropriate. For categorical data, the number and percentage of eyes or subjects will be reported. The number of subjects or eyes in the population of interest will be used as the denominator for the percentage at that time point unless otherwise indicated. Percentages will be rounded to one decimal place, and thus may not always add up to exactly 100%. All tests will be performed at two-sided 0.05 level, unless otherwise specified.

For some analyses, results will be separated for the study eye and fellow eye (e.g., non-study eye). If both eyes qualify for study inclusion, the study eye will be the eye with the higher IOP at baseline. If both study eyes are the same at baseline, then the right eye will be considered the study eye.

In general, all summary tables will be supported by a relevant subject data listing including all subjects who received study treatment. The listings will include all data collected, and will be sorted by subject identification, and actual visit date, as applicable, unless otherwise noted.

Concomitant medications (CMs) will be coded using the WHO Drug Dictionary and AEs and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The dictionary versions will be documented in the Data Management Plan for the study.

Study Day 0 (Visit 1) is the day of baseline assessment. Study day is the day relative to Study Day 0. Change from baseline is the post-treatment value minus baseline value.

2.2 Subject Population

2.2.1 Sample Size

Approximately 160 male or female subjects will participate in this study. Enrollment will be stratified based on subject's current Baseline IOP lowering therapy regimen:

- 60 subjects whose Baseline therapy regimen is latanoprost monotherapy
- 60 subjects whose Baseline therapy regimen is latanoprost plus 1 additional individual agent
- 40 subjects whose Baseline therapy regimen is latanoprost plus 2 additional individual agents

2.3 Study Assessment Time Points

The study assessment time points consist of assessments according to the schedule outlined in Table 1.

2.3.1 Schedule of Events

Table 1. Schedule of Visits/Procedures

Procedure / Visit number / Visit[1] / Window	1 Baseline (Day 0)	2 Follow-Up (Week 6) ±7 days	3 Final (Week 12) ±7 days
Informed consent & HIPAA authorization	X		
Demographics	X		
Subject eligibility (inclusion/exclusion)[2]	X		
Urine pregnancy test[3]	(X)		
Medical and IOP history	X		
Prior and concomitant medications and/or procedures review/changes	X	X	X
BCVA[4]	X	X	X
Biomicroscopy	X	X	X
IOP measurement[5]	X	X	X
Pachymetry	X		
AE assessment[6]		X	X
[redacted]			
Dispense study medication bottles	X	X	
Collect used/unused study medication bottles		X	X

X = required, (X) = only if needed.

1. Baseline Visit should occur in the morning (before noon). Subjects should be seen at each follow up visit at a time similar to that of the Baseline Visit.
2. Women of childbearing potential must be willing to practice effective contraception for the duration of this study.
3. Women of childbearing potential only (if applicable).
4. Assessed using Snellen visual acuity chart.
5. Assessed using Goldmann applanation tonometer affixed to a slit lamp. IOP must be measured in the morning at approximately the same time for all visits following completion of the biomicroscopic examination.
6. Adverse Events: Subjects will be queried at each visit "How are you feeling?" and treatment emergent AEs will be documented on the AE form. Additional symptoms reported after baseline and before first dose of open-label treatment will be documented on the medical history form.

[redacted]

2.4 Study Populations for Analysis

The following are the analysis populations to be used:

2.4.1 Intent to Treat (ITT) Population

The ITT population will include all subjects who were enrolled into the study.

2.4.2 Modified Intent to Treat (mITT) Population

The mITT population will include all subjects who were treated and had at least 1 follow-up visit with a completed IOP measurement.

2.4.3 Safety Population

The Safety Population will include all subjects who received any amount of study drug. This population will be used to summarize safety variables and will summarize subjects as treated.

2.4.4 Per-Protocol (PP) Population

The PP population will include all subjects who completed 3 months of treatment without significant protocol violations. Subjects to be excluded from the PP analysis are subjects who have: 1) no efficacy evaluation at baseline, and/or have no follow-up visit; 2) used any prohibited medications during the study period that would interfere with the study objectives; 3) had any prohibited procedures during the study period that would interfere with the study objectives.

A listing of subjects excluded from the mITT and PP populations will be provided.

2.5 Subject Disposition

All subjects enrolled into the study that are issued a subject number will be accounted for in Subject Disposition. Data will be tabulated by overall and baseline IOP lowering therapy participant groups.

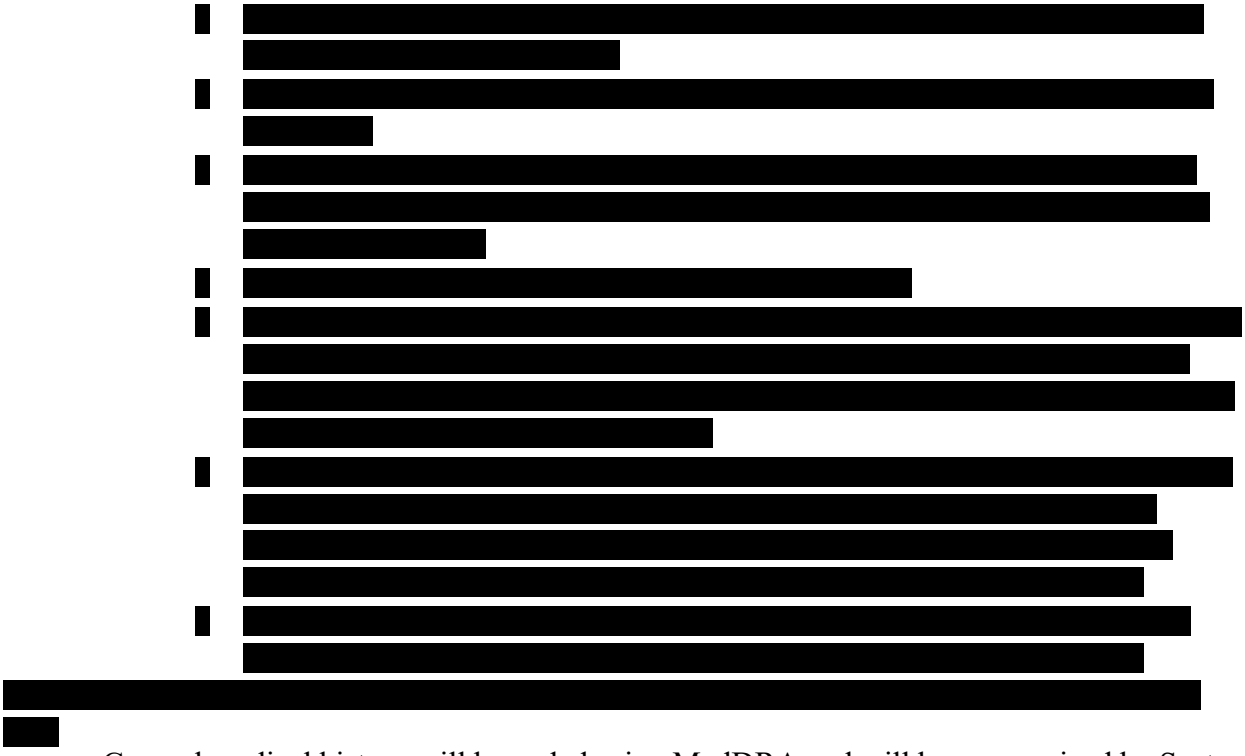
The numbers and percentages of subjects who are enrolled and treated, who comprise each of the analysis populations (e.g., PP, Safety Population, etc.) and who complete the study or withdraw prematurely along with the reason for discontinuation will be presented. The number of subjects enrolled will also be presented by clinical site.

Reasons for any early withdrawals and the last date of dosing completed prior to discontinuation will be provided in a listing.

Protocol deviations (major and minor) will be defined prospectively prior to database lock and will be tabulated by overall and baseline IOP lowering therapy participant groups for the ITT, mITT, and Safety populations. Deviations will also be presented in listings.

2.6 Baseline Characteristics & Medical History

Demographics and baseline characteristics will be summarized by overall and baseline IOP lowering therapy participant groups for all subjects included in the safety population. Where applicable, data will be presented separately for the study eye vs. fellow eye (e.g., non-study eye), else data will be presented by subject. [redacted]



General medical history will be coded using MedDRA and will be summarized by System Organ Class (SOC) and Preferred Term (PT). Prior ocular procedures will also be tabulated by procedure category and procedure name. Data will be stratified by overall and baseline IOP lowering therapy participant groups for all subjects included in the safety population.

Additionally, current use of any IOP lowering medications will be tabulated by medication category and medication name. Data will be stratified by overall and baseline IOP lowering therapy participant groups for all subjects included in the safety population.

All demographic, baseline characteristics, medical history, and IOP medication history will be presented in listings.

2.7 Methods for Handling Missing Data

2.7.1 Imputation Methods

Imputation will only be performed on IOP data for the primary endpoint analysis (Week 12) of the ITT population. No imputation will be performed for any missing Week 6 values. Imputation for missing Week 12 values will be performed using the method of last observation carried forward from Week 6. If there is no Week 6 value, then subjects missing Week 12 and Week 6 data will be excluded from analysis.

2.8 Efficacy Analysis

Efficacy data will be analyzed using [redacted] mITT (without imputation of missing values), [redacted].

If both eyes qualify for study inclusion, analyses will be provided for the worse eye at baseline. If both study eyes are the same at baseline, then data for only the right eye will be analyzed.

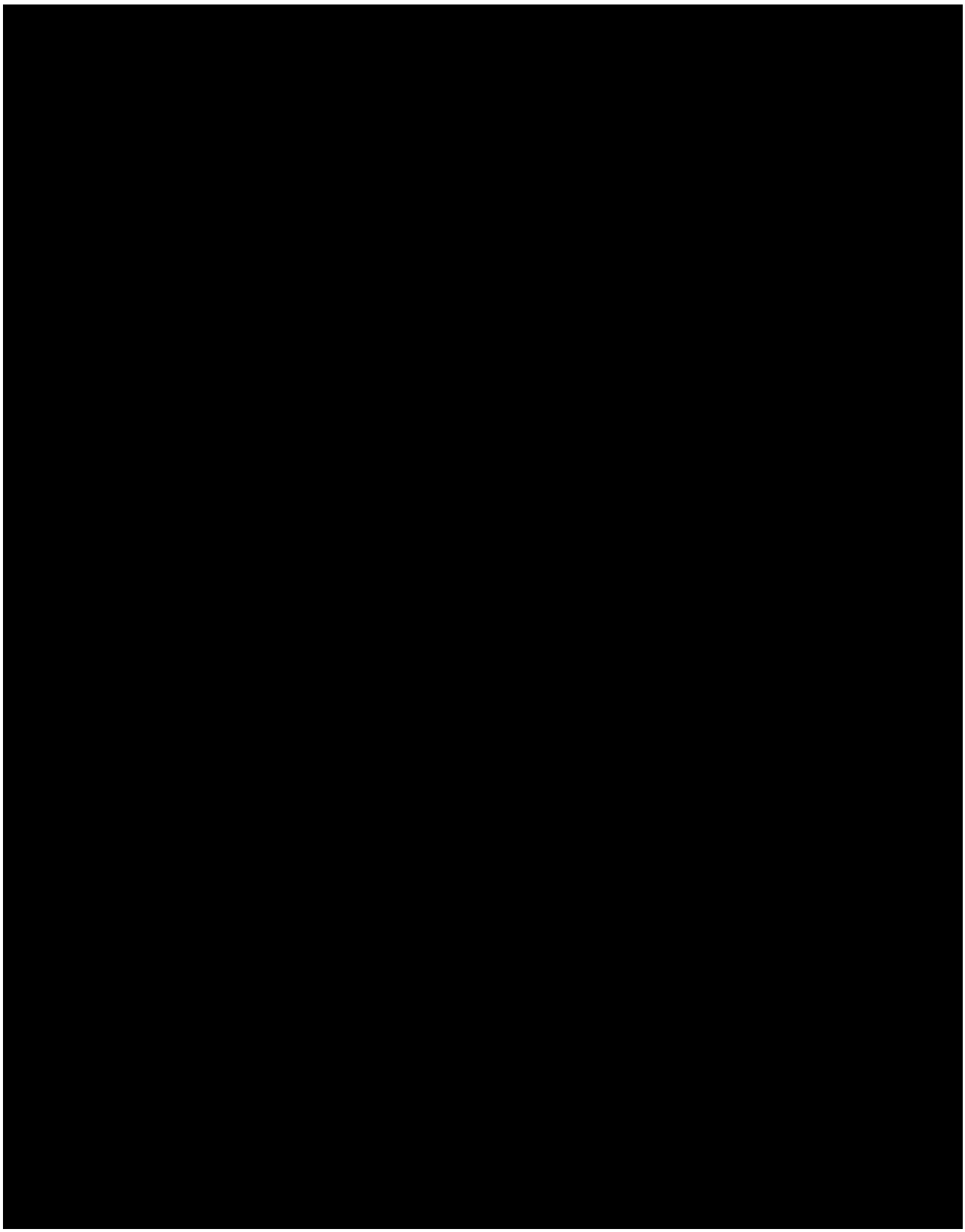
2.8.1 Primary Endpoint

The primary efficacy variable is percent reduction from baseline IOP in the study eye at Week 12 in the mITT population. Percent reduction will be presented by overall and baseline IOP lowering therapy participant groups. Summary statistics will include mean and median values, standard deviations, minimum and maximum ranges for IOP (mmHg), change from baseline IOP, and % change in IOP from baseline at Week 6 and Week 12 Figures will be provided for mean change from baseline and % change from baseline. No imputation of data will be performed.

[redacted]

All collected IOP data will be displayed in listings.

[redacted]



2.10 Safety Analyses

Safety analyses will be based on the Safety Population and be presented by overall subjects and baseline IOP lowering therapy participant groups. Where appropriate, results from the study eye and fellow eye (e.g., non-study eye) will be analyzed separately.

2.10.1 Adverse Events

Adverse events and serious adverse events (SAEs) will be summarized with frequency distributions by overall subjects and baseline IOP lowering therapy participant groups. Results will be summarized by subject rather than eye. If an event occurs in both eyes it will only be counted once in tables. All events will be provided in listings.

Only those adverse events determined to be treatment emergent (TEAE) will be presented. Treatment emergent adverse events are those events with the date of AE onset being greater than or equal to the first date of dosing.

Verbatim terms on the case report forms will be linked to preferred terms and related body systems using the MedDRA Coding Dictionary version 25.0 (Release date: 01Mar22). The number and percentage of subjects who experience treatment-emergent adverse events will be tabulated by SOC and PT by baseline IOP lowering therapy participant group and overall.

Adverse events will be counted only once for a subject within each PT and SOC; thus, since a subject may have more than one PT within an SOC, percentages of PT may not sum to the percentage in the SOC. If a subject reports a PT multiple times with differing severities, only the most severe is counted. If a subject reports a PT multiple times with differing relationships to study medication, only the one related to study drug is counted. Adverse events are defined as having a causality rating of being related, possibly related, unlikely related, or not related.

All reported AEs will be tabulated as described above. [redacted]

Ocular and non-ocular AEs will be tabulated separately. Adverse events judged by the Investigator to be SAEs, SAEs resulting in death, AEs leading to discontinuation, any AEs that occur at a frequency of 5% or greater, and AEs that occurred after date of discontinuation will be summarized in tables or listings. In addition, all TEAEs and treatment related (unlikely, possibly, or related to study medication) AEs will be tabulated by severity.

All safety events and related data will be provided in listings.

2.10.1.1 Serious Adverse Events

The number and percentage of subjects experiencing any SAE will be tabulated by SOC and PT by baseline IOP lowering therapy participant group and overall. Serious AEs will be counted only once for a subject within each PT and SOC. Ocular and non-ocular events will be tabulated separately.

All recorded SAE data will be presented in listings.

2.10.1.2 AEs with a Frequency of 5% or Greater

All events that occur at a frequency of 5% of greater will be tabulated by SOC and PT by baseline IOP lowering therapy participant group and overall. Data will also be provided in a listing.

2.10.1.3 AEs Leading to Discontinuation

All events that lead to discontinuation will be tabulated by SOC and PT by baseline IOP lowering therapy participant group and overall. Data will also be provided in a listing.

2.10.1.4 AEs Occurring after Discontinuation

All events that occurred after the date if subject discontinuation will be provided in a listing and tabulated as necessary. These events are still considered treatment emergent and will also be included in main TEAE listings and tables.

2.10.1.5 Deaths

A listing of subjects who die while on study will be prepared along with the adverse event associated with the cause of death.

2.10.2 Best Corrected Visual Acuity

Monocular Best Corrected Visual Acuity will be measured in each eye by the investigator (or designee) at the Baseline Visit (Visit 1) and at both Visit 2 (Week 6) and Visit 3 (Week 12) using a Snellen Visual Acuity Chart. Parameters (e.g., sphere, cylinder, axis, visual acuity) will be summarized descriptively by baseline IOP lowering therapy participant group and overall at each visit. Results will be presented separately for study eyes versus fellow eyes. Note that in reporting cylinder, all positive measurements will be converted to the negative scale.

2.10.3 Biomicroscopy

Biomicroscopy will be performed according to the site's usual practice by the investigator (or designee) for both eyes at the Baseline Visit and at each follow-up visit by slit lamp examination. Eye structures/surfaces to be assessed include, but are not limited to, lids/lashes, conjunctiva (palpebral and bulbar), cornea, anterior chamber and lens. Parameters will be summarized descriptively by baseline IOP lowering therapy participant group and overall at each visit. Results will be presented separately for study eyes versus fellow eyes.

Observations for the slit lamp Biomicroscopy examination (except lens status) will be graded on a 5-pont scale as follows:

- 0= None
- 0.5 = Trace
- 1.0 = Mild
- 2 = Moderate
- 3 = Severe

Mean grading score of each eye area (e.g., Hyperemia, edema, etc.), as well as a change from baseline (n, %) analysis will be provided at Week 6 and Week 12 visit summaries. Change from baseline will be categorized as follows: No change, Decrease ≥ 0.5, Decrease ≥ 1, Increase ≥ 0.5, and Increase ≥ 1.

The frequency and percentage of subjects with hyperemia that occurred at both Weeks 6 and Week 12, or subjects with any pre-existing hyperemia that worsened at Week 6 and maintained worsening or worsened at Week 12 (Consecutive), as well as subjects with hyperemia that occurred or worsened at only one of the two follow-up visits (Sporadic) will also be summarized.

All biomicroscopy data will be provided in listings.

2.10.4 Pregnancy Testing

A urine human chorionic gonadotropin pregnancy test (only for females of childbearing potential) will be used in this study and performed at the Baseline Visit to immediately confirm non-pregnancy eligibility for women of child-bearing potential. Results will be presented in listings only.

2.10.5 Concomitant Medications & Procedures

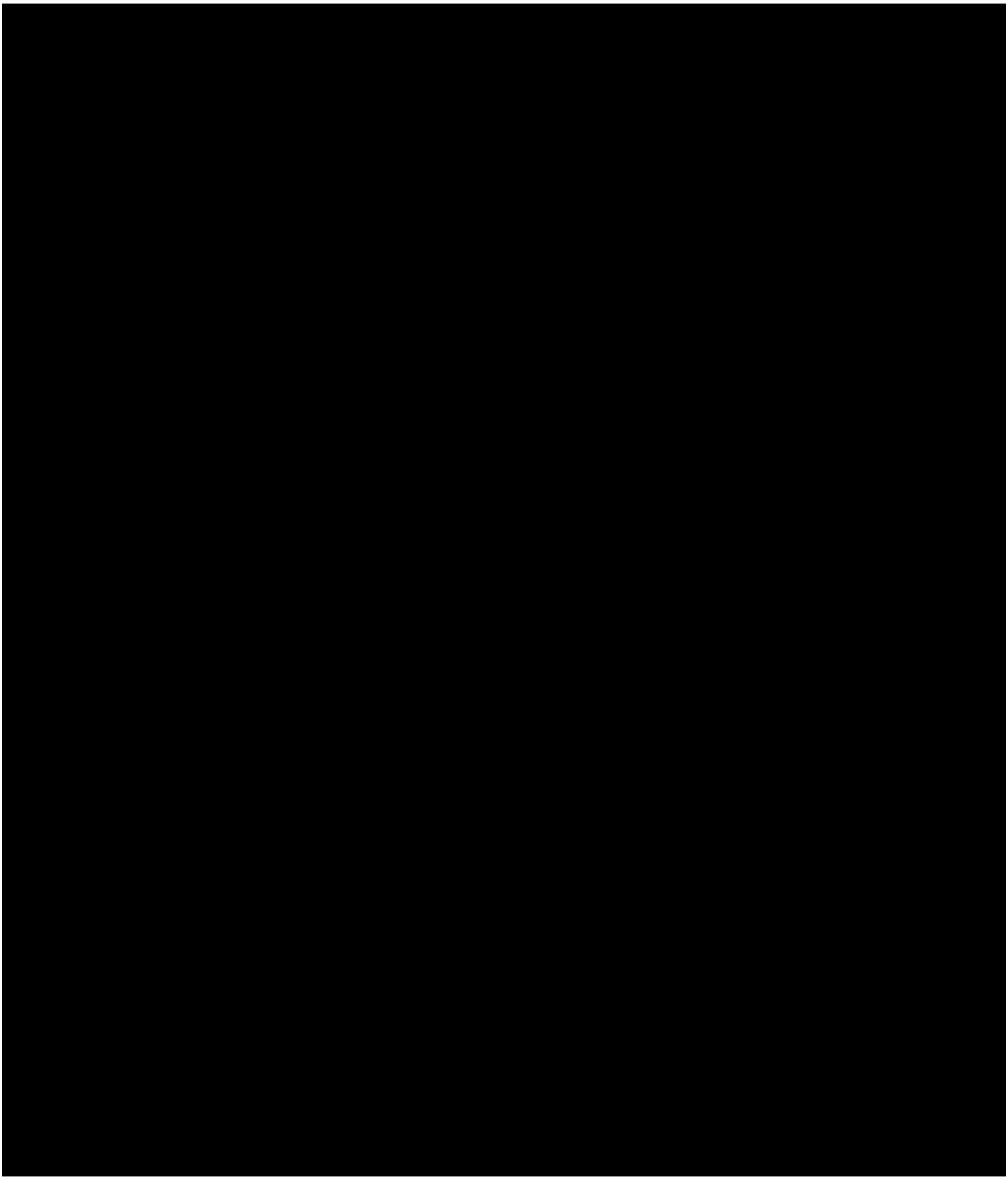
Concomitant medications other than IOP lowering drugs will be coded per the WHO Drug Dictionary Version 1 Mar 2022 and summarized by Drug Class (pharmacological level, ATC3) and Drug Name (chemical substance level, ATC5). Results will be stratified by overall and baseline IOP lowering therapy participant groups. Results will be summarized by subject rather than eye. If a medication occurs in both eyes it will only be counted once in tables. All medications will be provided in listings. Any concomitant procedures will be similarly summarized.

These data will also be provided in subject data listings along with the verbatim drug term and usage details (e.g., dose, frequency, route).

3 Document Version Control

Revision History:

REVISION	RELEASE DATE	AUTHOR	SUMMARY OF CHANGES



[redacted]

[redacted]