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

PROTOCOL

30-Sep-2022

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

PROTOCOL NUMBER	MA-ROC-22-003, Amendment 1
ORIGINAL PROTOCOL DATE	24 Feb 2022
REVISED PROTOCOL DATE	30 Sep 2022
INVESTIGATOR	Multiple
INSTITUTIONAL REVIEW BOARD	Advarra IRB 6100 Merriweather Dr., Suite 600 Columbia, MD 21044
SPONSOR	Aerie Pharmaceuticals, Inc. 2030 Main Street, Suite 1400 Irvine, CA 92614

[redacted]

The information contained in this document is confidential and the proprietary property of Aerie Pharmaceuticals, Inc.

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

PROTOCOL NUMBER	MA-ROC-22-003, Amendment 1
ORIGINAL PROTOCOL DATE	24 Feb 2022
REVISED PROTOCOL DATE	30 Sep 2022

INVESTIGATOR'S SIGNATURE PAGE

I agree to:

1. Implement and conduct this study diligently and in strict compliance with the protocol, Good Clinical Practice, and all applicable laws and regulations.
2. Maintain all information supplied by Aerie Pharmaceuticals, Inc. in confidence and, when this information is submitted to an Institutional Review Board, Independent Ethics Committee, or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety and I agree to all aspects.

Investigator Printed Name	Signature	Date

Investigator's Title

Name of Facility

Location of Facility (City, State)

Acknowledged By:

Signature of Sponsor's Representative	Date
Printed Name and Title	Date

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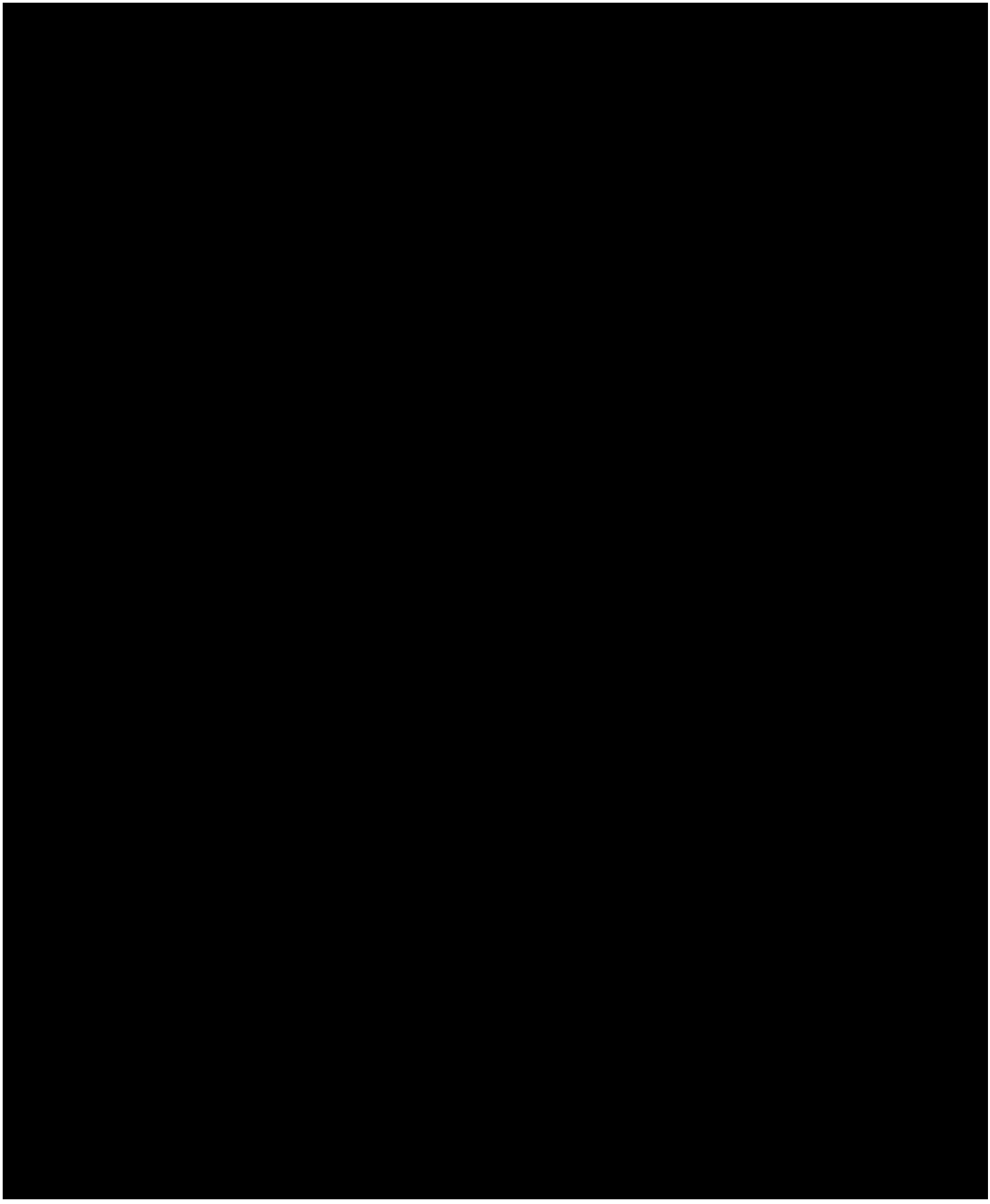

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1. BACKGROUND AND RATIONALE

Glaucoma is a progressive optic neuropathy that causes characteristic loss of visual fields and can eventually lead to blindness. A major risk factor for glaucomatous visual field loss is elevated intraocular pressure (IOP); (The AGIS Investigators 2000). While numerous products are approved for use in the United States to lower IOP, the need for new options with improved efficacy is supported by several clinical studies. Studies such as the Early Manifest Glaucoma Trial (Heijl 2002), the Ocular Hypertension Treatment Study (Kass 2002; Kass 2010), and the Collaborative Normal Tension Glaucoma Study Group (Collaborative Normal-Tension Glaucoma Study Group 1998) support the general conclusion that for delaying disease progression, every millimeter of reduction in IOP is significant. This conclusion holds true not only for ocular hypertensive and glaucoma patients with elevated IOPs but also for glaucoma patients with IOPs in the statistically normal range. In addition, for many individuals with glaucoma, current IOP-lowering medications are not sufficiently effective as monotherapy to achieve target IOP and the majority of glaucoma patients often need more than one drug to reach their target IOP (Lichter 2001). Increasing complexity of the dosing regimen often leads to decreased compliance with dosing.

Thus, the goal for treating patients should be to maximally lower the IOP, to the point that it prevents further damage to the optic nerve and achieve this without sacrificing safety or convenience so as to maintain compliance.

Inhibitors of Rho kinase (ROCK) have emerged as a new class of IOP-lowering agents. Netarsudil 0.02% is a novel Rho kinase and norepinephrine transporter inhibitor developed at Aerie Pharmaceuticals, Inc. Netarsudil lowers IOP through a distinct mechanism of action: increasing trabecular outflow by decreasing acto-myosin–driven cellular contraction and reducing production of extracellular matrix proteins (Kazemi 2018; Lin 2018). In preclinical studies, netarsudil was shown to not only increase trabecular outflow facility (Lin 2018; Wang 2015; Ren 2016; Li 2016), but also to decrease episcleral venous pressure (Kiel 2015) and aqueous humor production (Wang 2015). The mechanisms of action of netarsudil were further explored in a phase 1 study of healthy human volunteers, in whom netarsudil 0.02% QD was demonstrated to lower IOP primarily by increasing outflow facility, but also by reducing episcleral venous pressure (Kazemi 2018).

Prostaglandin analogues are another class of IOP-lowering agents that are highly effective at lowering IOP when dosed once daily in the evening, primarily acting on uveoscleral outflow.

As netarsudil lowers IOP through different mechanisms of action than prostaglandin analogues, netarsudil provides additional IOP-lowering efficacy when used in combination with a prostaglandin analogue. Recently, ROCKLATAN® 0.02%/.005% was approved by the United States Food and Drug Administration for reducing elevated IOP. ROCKLATAN® 0.02%/0.005% is a fixed dose combination of a Rho kinase inhibitor and a prostaglandin F2α analogue indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

Two randomized and controlled clinical trials enrolled subjects with IOP > 36 mmHg and compared IOP lowering effect of ROCKLATAN® dosed once daily (QD) to individually administered netarsudil 0.02% once daily and latanoprost 0.005% once daily. Studies demonstrated 1 to 3 mmHg reductions in IOP greater than monotherapy with either netarsudil 0.02% or latanoprost 0.005% throughout 3 months in one study and reductions were maintained throughout 12 months in the other study (Rocklatan™ Prescribing Information 2019).

2. STUDY OBJECTIVE

The objective of this study is to 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.

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3. 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.

4. STUDY POPULATION

4.1 Number of Subjects

Approximately one hundred and sixty (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 IOP-lowering agent*
- 40 subjects whose Baseline therapy regimen is latanoprost plus 2 additional IOP-lowering agents

  Two additional IOP-lowering 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

4.2 Number of Study Centers

Approximately 22 study centers in the United States will be utilized in this study.

4.3 Subject Eligibility

To be eligible for enrollment into the study, subjects must qualify in at least one eye and meet all inclusion and none of the exclusion criteria detailed in Section 4.3.1 and Section 4.3.2.

4.3.1 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

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- 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

4.3.2 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 (e.g., LASIK, LESEK, RK, PRK) 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 (e.g., ALT, SLT), cataract surgery and minimally invasive glaucoma surgery (MIGS)

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

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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

4.3.3 Subject Withdrawal Criteria

Criteria and procedures for handling subjects who are discontinued from the study are described in Section 9.2. Subjects who are discontinued will not be replaced.

5. STUDY MEDICATION AND OTHER STUDY SUPPLY INFORMATION

5.1 Study Medications

5.1.1 Study Medication Information

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).

Rocklatan® 0.02%/0.005% will be provided by Aerie Pharmaceuticals, Inc. in the marketed containers and available for dispensing at the Baseline Visit (Visit 1, Day 0) and Visit 2 (Week 6).

Detailed information is provided in the Rocklatan® Package Insert (Appendix 4).

5.1.2 Formulations

Netarsudil 0.02%/latanoprost 0.005%

Name:	Rocklatan® (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005%
Active ingredient:	netarsudil dimesylate 0.28 mg and 0.05 mg latanoprost
Other ingredients:	boric acid, mannitol, sodium hydroxide to adjust pH and water for injection, benzalkonium chloride 0.02% (preservative)

5.1.3 Storage, Handling, Dispensing and Reconciliation of Study Medications

The study medication must be stored protected from light and refrigerated at 2º to 8ºC (36º to 46ºF) at the study site in a secure area and administered only to subjects enrolled into the clinical study, at no cost to the subject, in accordance with the conditions specified in the protocol.

Store Rocklatan® 0.02%/0.005% at 2º to 8ºC (36º to 46ºF) until opened. After opening, the product may be kept at 2º to 25ºC (36º to 77ºF) for up to 6 weeks. If after opening the product is kept refrigerated at 2°C to 8°C (36°F to 46°F), then the product can be used until the expiration date stamped on the bottle.

Subjects are to save all used/unused bottles for presentation to designated study staff during office visits.

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Study Medication Supply Records at Study Sites:

It is the responsibility of the investigator to ensure that a current record of study medication disposition is maintained. Records or logs should include:

- Amount received and placed in storage area
- Dates and initials of the person(s) responsible for each product inventory entry/movement
- Amount dispensed to and returned by each subject, including unique subject identifiers
- Amount transferred to another area for dispensing or storage if necessary
- Non-study disposition (e.g., lost, wasted, broken)

Destruction of Study Medication Supplies:

After subjects have completed study medication usage, all study medications (used and unused) will be collected by a designated staff. Only upon direction of sponsor and after reconciliation, all used/unused or undispensed study medication will be destroyed at the study site according to the site's usual medication destruction practices.

5.1.4 Site Personnel Study Medication Instructions

Enrolled subjects will be instructed to stop their current IOP lowering therapy regimen at the Baseline Visit (Visit 1) and to begin self-administering study medication, Rocklatan® 0.02%/0.005%, 1 drop in each eye daily in the evening of the Baseline Visit (Visit 1) (see Section 5.1.5 below). There is no washout period required for subjects.

Instruct subjects that contact lens wear during the study is acceptable. However, subjects must remove their contact lenses before instillation of study medication and not place them in their eye(s) until 15 minutes after instillation.

Instruct subjects to avoid allowing the tip of the bottle to touch the eye to avoid bacterial eye infection which has been reported with the use of multiple-dose containers of topical ophthalmic products.

5.1.5 Subject Dosing and Storage Instructions (Visits 1 & 2)

Baseline Visit (Visit 1) and Follow-Up Visit 2

Visit 1 Study Medication Dosing Instructions

Enrolled subjects will receive 2 bottles of Rocklatan® 0.02%/0.005% at the Baseline Visit (Visit 1) and will be instructed to refrigerate both the unopened bottles (2º to 8ºC [36º to 46ºF]).

During the evening of the day each subject attends his/her Baseline Visit (Visit 1), subjects will remove 1 bottle from refrigeration and commence administering Rocklatan® 0.02%/0.005% 1 drop in each eye daily in the evening until returning to the clinic for Visit 2. The opened bottle of Rocklatan® 0.02%/0.005% may be stored at 2º to 25ºC (36º to 77ºF) for 6 weeks. Subjects will be instructed to completely use up study medication in 1 bottle before removing the second bottle from refrigeration to begin dosing.

Avoid allowing the tip of the bottle to touch the eye to avoid bacterial eye infection which has been reported with the use of multiple-dose containers of topical ophthalmic products.

Contact lenses should be removed prior to using Rocklatan®. Contact lenses can be reinserted 15 minutes following administration of Rocklatan®.

Subjects will return to clinic as instructed by clinic site staff for Visit 2 (Week 6) with all used/unused study medication bottles.

Visit 2 Study Medication Dosing Instructions

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Subjects will receive 2 bottles of Rocklatan® 0.02%/0.005% at Visit 2 (Week 6) and will be instructed to refrigerate both the unopened bottles (2º to 8ºC [36º to 46ºF]).

During the evening on the day each subject attends his/her Visit 2 (Week 6), subjects will remove 1 bottle from refrigeration and commence administering Rocklatan® 0.02%/0.005% 1 drop in each eye daily in the evening until returning to the clinic for the final study visit, Visit 3 (Week 12). The opened bottle of Rocklatan® 0.02%/0.005% may be stored at 2º to 25ºC (36º to 77ºF) for 6 weeks. Subjects will be instructed to completely use up study medication in 1 bottle before removing the second bottle from refrigeration to begin dosing.

Avoid allowing the tip of the bottle to touch the eye to avoid bacterial eye infection which has been reported with the use of multiple-dose containers of topical ophthalmic products.

Contact lenses should be removed prior to using Rocklatan®. Contact lenses can be reinserted 15 minutes following administration of Rocklatan®.

Subjects will return to clinic as instructed by clinic site staff for Visit 3 (Week 12) with all used/unused study medication bottles.

5.2 Additional Study Supplies

The following supplies will be provided to the study site:

- Combined Informed Consent/ Health Insurance Portability and Accountability Act of 1996 (HIPAA) form, as applicable per Institutional Review Board (IRB)
- Screening and Enrollment logs
- Source documents
- Electronic case report form (eCRF) completion guidelines
- Study medication reconciliation logs
- Package insert for Rocklatan® (netarsudil/latanoprost ophthalmic solution) 0.02%/0.005%

6. PRIOR AND CONCOMITANT THERAPIES

6.1 Allowed Medications or Treatments

Therapy considered necessary for a subject's welfare will be given at the discretion of the investigator and documented during the course of the study. The use of any concurrent medication (prescription or over-the-counter, including herbal medications) is to be recorded in a subject's source documentation (charts), as well as in the case report forms (CRFs), noting the date, dosage, frequency, start date, and reason for taking the medication(s).

7. STUDY PROCEDURES

7.1 Subject Entry Procedures

7.1.1 Overview of Entry Procedures

Subjects meeting inclusion and exclusion criteria (Section 4.3.1 and Section 4.3.2, respectively) will be considered for enrollment in this study. [redacted]

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7.1.2 Informed Consent and HIPAA Authorization

Subjects meeting enrollment criteria at the Baseline Visit (Visit 1) will be asked to participate in the study. The study design, follow-up, and participation parameters/criteria will be discussed with each subject. Subjects wishing to participate must provide written informed consent and sign an "Authorization for Use and Disclosure of Health Information for Research" release as a component of the informed consent document (HIPAA authorization) prior to any study-related procedures.

[redacted]

7.2 Study Procedures

The Schedule of Visits/Procedures for this study is included in Appendix 5.

Clinical assessments will be performed throughout the study as detailed in Section 8. All clinical assessments will be performed by the investigator (or designee).

7.3 Overall Instructions

Subject's 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. Evaluations should be performed by the same evaluator throughout the study whenever possible.

7.4 Visit 1 (Day 0): Baseline

Subject's Baseline Visit should occur in the morning (before noon).

The investigator (or designee) will perform/administer the following assessments:

- Written informed consent and HIPAA authorization
- Demographics
- Subject eligibility (inclusion/exclusion criteria)
- Urine pregnancy test (women of childbearing potential only)
- Medical and IOP history
- Prior and concomitant medications and/or procedures review
- Best-corrected visual acuity (Snellen visual acuity chart)
- Biomicroscopy
- IOP assessment (morning measurement in each eye using Goldmann applanation tonometer)
- Corneal pachymetry to measure central corneal thickness
- Enrollment
- Assign subject ID number
- Dispense 2 bottles of Rocklatan® 0.02%/0.005% and have a staff member instruct the subject on use
- Schedule Visit 2 (Week 6) at a similar time in the morning to that of the Baseline Visit

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7.4.1 Women of Childbearing Potential and Acceptable Contraceptive Methods

An adult woman is considered to be of childbearing potential unless she is at least 1-year post-menopause (no menses for 12 months or more without an alternative medical cause) or at least 3 months post-surgical sterilization. Subjects must not intend to become pregnant during the study and must properly use an acceptable effective method of contraception.

If a woman is of childbearing potential, she must have a pregnancy test performed at the visits specified in the Schedule of Visits and Procedures (Appendix 5). Additional pregnancy tests may also be required per local regulatory guidelines. Subjects with positive pregnancy test result must be excluded from the study. Subjects with negative pregnancy test must agree to use an acceptable effective contraception method during the study.

Acceptable contraceptive methods when used consistently and in accordance with both the product label and the instructions of the physician (Clinical Trials Facilitation Group 2014), include:

1. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
2. Progestogen-only hormonal contraception (oral, injectable, or implantable)
3. Intrauterine device (IUD)
4. Intrauterine hormone-releasing system (IUS)
5. Bilateral tubal occlusion
6. Vasectomized partner [1]
7. Sexual abstinence [2]
8. Male or female condom with or without spermicide
9. Cap, diaphragm, or sponge with spermicide

[1] Vasectomized partner is considered to be a highly effective birth control method providing that the partner is the sole sexual partner of the women of childbearing potential and that the vasectomized partner has received a medical assessment of the surgical success

[2] Sexual abstinence is considered to be an acceptable method of contraception when defined as refraining from heterosexual intercourse during the entire period of risk associated with the study interventions. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception.

7.5 Visit 2 (Week 6): Follow-Up

Subject's Visit 2 should occur in the morning (before noon) at a time similar to that of the Baseline Visit.

The investigator (or designee) will perform/administer the following assessments:

- Concomitant medications and/or procedures review
- Best corrected visual acuity (Snellen visual acuity chart)
- Biomicroscopy
- IOP assessment (morning measurement in each eye using Goldmann applanation tonometer)
- Adverse event (AE) assessment
- Collect used/unused study medication containers

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- Dispense 2 bottles of Rocklatan® 0.02%/0.005% and have a staff member instruct the subject on use
- Schedule subject's next visit (Visit 3, Week 12) at a similar time in the morning to that of the Baseline Visit

7.6 Visit 3 (Week 12): Final Visit

Subject's Visit 3 should occur in the morning (before noon) at a time similar to that of the Baseline Visit.

The investigator (or designee) will perform/administer the following assessments:

- Concomitant medications and/or procedures review
- Best corrected visual acuity (Snellen visual acuity chart)
- Biomicroscopy
- IOP assessment (morning measurement in each eye using Goldmann applanation tonometer)

- AE assessment
- Collect used/unused study medication containers
- Complete End of Study (Exit) Form

7.7 Unscheduled Visits

In the event a subject returns for an unscheduled visit, the investigator (or designee) will perform/administer necessary assessments. Information collected from an unscheduled visit will be reported on Interim/Unscheduled Visit CRF(s).

8. CLINICAL ASSESSMENTS

The following clinical assessments will be performed according to the schedule as indicated in the Schedule of Visits/Procedures (Appendix 5). The same investigator (or designee) should complete the evaluations for a given subject throughout the study.

8.1 Efficacy Assessment

8.1.1 Intraocular Pressure

IOP will be measured in both eyes in the morning (before noon) using a Goldmann applanation tonometer affixed to a slit lamp at the Baseline Visit, Visit 2, and Visit 3 (see Appendix 6 for detailed information on this examination).

8.2 Safety Assessments

8.2.1 Adverse Events

At both Visit 2 (Week 6) and Visit 3 (Week 12) the investigator (or designee) will question each subject regarding adverse experiences that may have occurred since a previous visit. Subjects will be queried "How are you feeling?" and all AEs will be recorded in the CRFs including severity, action taken, and relationship to the study medication(s) (see Section 10 for further details).

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Please see “Rocklatan® Package Insert” (Appendix 4) for further details regarding possible adverse experiences associated with the use of study medication.

8.2.2 Best Corrected Visual Acuity

BCVA will be measured for both eyes 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 (see Appendix 6 for detailed information on this examination).

8.2.3 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. All observations will be recorded. (see Appendix 6 for detailed information on this examination).

8.2.4 Pregnancy Testing

A urine human chorionic gonadotropin (hCG) 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.

If pregnancy occurs during the study, the investigator must immediately notify the Ethics Committee/IRB and Aerie. In addition, every attempt will be made to collect data on the pregnancy of female subjects. Signature of a separate consent form will be requested of the pregnant woman. Information on pregnant partners of study subjects will not be collected.

Every attempt will be made to collect data regarding the newborn child born to a female subject with parent/guardian permission. One parent or the legal guardian will be requested to provide permission for the minor to participate in this part of the research

9. END OF STUDY

At the end of each subject’s participation in the study, the investigator (or designee) will complete an End of Study Form (Completion) for all completed and discontinued subjects.

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9.1 Completion of the Study

Each subject who completes the entire Schedule of Visits as specified in this protocol will have completed the study.

9.2 Subject Discontinuation

A subject may be withdrawn from the study prior to completion for any reason and categorized as follows:

- AEs
- Lost to follow-up
- Subject decides it is in his/her best interest to withdraw
- Investigator decides it is in the subject's best interest to be withdrawn
- Noncompliance
- Other (administrative reasons, etc.)

If a subject discontinues from the study for any reason at any point beyond his/her Baseline Visit (Visit 1), he/she should be requested to return for a final visit at which time all Visit 3 (Week 12) procedures should be performed according to the protocol Schedule of Visits/Procedures (see Appendix 5).

Subjects who are prematurely withdrawn or discontinued from the study will not be replaced.

9.3 Study Termination

The study may be terminated by the investigator or the sponsor. If, in the opinion of the investigator, clinical observations made during the study suggest that it may be unwise to continue, the investigator may stop the study. Study termination by the investigator will be reported to the sponsor.

In addition, a written statement fully documenting the reasons for this action will be submitted to the sponsor and the IRB by the investigator within 5 working days.

In the event that the sponsor chooses to discontinue or terminate the study, appropriate notification will be given to the investigator.

10. ADVERSE EVENT DEFINITIONS AND REPORTING

10.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the administration of the study intervention in humans, whether or not considered related to the study medication. AEs include any illness, sign, symptom, or clinically significant laboratory test abnormality that has appeared or worsened during the course of the clinical trial, regardless of causal relationship to the study medication(s) under study.

Study medication is defined as a pharmaceutical form of an active ingredient or vehicle/placebo being tested or used as a reference in the study, whether masked or unmasked. AEs may be either spontaneously reported or elicited during questioning and examination of a subject.

All AEs will be collected from visits 2 and 3 as well as upon subject report after visit 1, and will continue until the final protocol required visit and/or continue through resolution, stabilization, or the Investigator assesses them as chronic or stable or the subject's participation in the trial ends, whichever occurs first. Documentation of AEs will include AE description, start date and stop date, severity, relationship, action(s) taken, seriousness, and outcome.

If a disease is known at the time an AE is reported, this diagnosis should be recorded rather than listing of individual symptoms. However, if a cluster of symptoms cannot be identified as a single diagnosis, each

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individual event should be reported separately. If a diagnosis is subsequently known, it should be reported as follow-up information.

When recording an AE, the following information should be provided on the study AE CRF:

1. Action Taken with Study Intervention:
    - None
    - Study Intervention Discontinued
    - Study Intervention Interrupted
2. AE Outcome:
    - Fatal
    - Not Recovered/Not Resolved
    - Recovered/Resolved
    - Recovered/Resolved with sequelae
    - Recovering/Resolving
    - Unknown/Lost to follow-up

Subjects experiencing AEs that cause interruption or discontinuation of study medication, or those experiencing AEs that are present at the end of their participation in the study should receive follow-up, as appropriate. If possible, report the outcome of any AE that caused permanent discontinuation or that was present at the end of the study, particularly if the AE was considered by the investigator to be related, or possibly/unlikely related to investigational product.

AEs should be followed to resolution or stabilization and reported as serious adverse events (SAEs) if they become serious (Section 10.2).

Adverse drug reactions that are both serious and unexpected (suspected unexpected serious adverse reactions [SUSARs]) will be subject to expedited reporting by the Sponsor to the FDA as required by the relevant regulations.

10.1.1 Severity of Adverse Events

Severity of an AE is defined as a qualitative assessment of the level of discomfort or the degree of intensity of an AE as determined by the Investigator or reported to them by the subject. The assessment of severity is made irrespective of study medication relationship or seriousness of the event and should be evaluated according to the following scale:

Mild: present and noticeable, but not distressing, and no disruption of normal daily activities

Moderate: bothersome, discomfort sufficient to possibly reduce or affect normal daily activity

Severe: incapacitating, with inability to work or perform normal daily activity

A change in increased severity for a reported AE will require a stop date for the previous severity and a new start and stop date for the new severity. For example, a change in severity may go from mild to moderate, or from moderate to severe. In either case, the start and stop dates should be recorded.

Note: A severe AE is not the same as a serious AE. Seriousness of an AE (NOT severity) serves as a guide for defining regulatory reporting obligations (see Section 10.2 for further information on SAEs).

10.1.2 Relationship of Adverse Events

The relationship of the AE(s) to the study medication(s) must be specified by the investigator using the following definitions:

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Not Related: The event is clearly related to other factors, such as subject's clinical condition, therapeutic interventions, concomitant disease, or therapy administered to the subject and does not follow a known response pattern to the product.

Unlikely Related: The event is most probably caused by other etiologies. such as participant's underlying condition, therapeutic intervention, or concomitant therapy; or the delay between administration and the onset of the AE is incompatible with a causal relationship. Therefore, there is not a reasonable possibility that the AE was caused by the study medication.

Possibly Related: The event follows a reasonable, temporal sequence from the time of study medication administration and/or follows a known response pattern to the study medication but could have been produced by other factors, such as the subject's clinical state, therapeutic interventions, or concomitant therapy administered to the subject.

Related: The event follows a reasonable, temporal sequence from the time of study medication administration and/or follows a known response pattern to the study medication and cannot be reasonably explained by other factors, such as subject's clinical state, therapeutic interventions, or concomitant therapy administered to the subject and either occurs immediately following study medication administration, improves on stopping the study medication, reappears on repeat exposure, or there is a positive reaction at the application site.

10.2 Serious Adverse Events

SAEs or reactions are any untoward medical occurrence that, results in any of the following outcomes:

- Results in death
- Is life-threatening (defined as an event in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require non-surgical or surgical intervention to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

Investigators must record all SAEs using the appropriate CRFs.

All SAEs, whether related or unrelated to study medication, must also be immediately reported by investigators to Drug Safety at ProTrials, Contract Research Organization using one of the following mechanisms within 24 hours of learning of the event:

[redacted]

In addition, the governing Ethics Committee/IRB and Aerie Pharmaceuticals, Inc. (sponsor) must also be notified by telephone or confirmed facsimile transmission should an SAE occur.

If only limited information is initially available, follow-up reports are required. Documentation of all SAEs must be maintained in the study files – e.g., Serious Adverse Event Form or equivalent form (e.g., MedWatch Form). Should the investigator become aware of an SAE (regardless of its relationship to investigational product) that occurs within 30 days after stopping the study medication, the SAE must be reported in accordance with procedures specified in this protocol. In the event of death, if an autopsy is

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performed, a copy of the report should be sent to the Ethics Committee/IRB. Aerie will report any SAEs/serious adverse device effects to other investigators, relevant competent authorities, and Ethics Committee/IRB, as required by local health care authorities.

The investigator(s) should always group signs and symptoms into a single term that constitutes a single unifying diagnosis. The investigator's opinion of the relationship of the SAE to study medication, the duration, intensity, frequency, serious criteria, countermeasures taken with study medication, and the outcome of the SAE should be documented.

10.3 Pregnancy

Women of childbearing potential (See Section 7.4.1 for definition of women of childbearing potential) must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Prior to study enrollment, women of childbearing potential must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy.

During the study, all women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). If pregnancy is suspected in any female subject while the subject is receiving study treatment, the study medication must immediately be withheld until the result of pregnancy testing is known. If pregnancy is confirmed, the study therapy will be permanently discontinued and the subject will be withdrawn from the trial. Protocol-required procedures for those subjects that are discontinued from the study must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies).

If pregnancy occurs during the study, the investigator must immediately notify the Ethics Committee/IRB and Aerie. In addition, every attempt will be made to collect data on the pregnancy of female subjects. Signature of a separate consent form will be requested of the pregnant woman. Information on pregnant partners of study subjects will not be collected.

Every attempt will be made to collect data regarding the newborn child born to a female subject with parent/guardian permission. One parent or the legal guardian will be requested to provide permission for the minor to participate in this part of the research

11. STATISTICAL CONSIDERATIONS

11.1 Sample Size

The planned enrollment is approximately 180 subjects.

11.2 Analysis Populations

An intent-to-treat (ITT) population will include all subjects who were enrolled into the study.

A modified intent-to-treat (mITT) population will include all subjects who were treated and had at least 1 follow-up visit with a completed IOP measurement.

A per-protocol (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 safety population will include all subjects who have received at least 1 dose of study medication. This population will be used to summarize safety variables and will summarize subjects as treated.

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11.3 Statistical Methods

Summary tables (descriptive statistics and/or frequency distributions) will be provided for all baseline variables, efficacy variables, and safety variables. 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. Additional analyses may be conducted as described in the Statistical Analysis Plan (SAP). The SAP will be finalized and approved prior to database lock.

11.3.1 Baseline Analyses

Demographic variables (age, sex, race, etc.) will be summarized by overall and baseline IOP lowering therapy participant groups for analysis population.

Baseline characteristics (as recorded on the eCRF) will be summarized by overall and baseline IOP lowering therapy participant groups for analysis population.

11.3.2 Efficacy Analysis

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

Efficacy data will be evaluated for overall, and stratified baseline IOP lowering therapy participant groups.

11.3.2.1 IOP

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.

The primary efficacy variable is percent reduction from baseline IOP in the study eye at Week 12. Percent reduction will be calculated using data from all subjects and within each baseline IOP lowering therapy participant group with complete data at both baseline and final visit. Summary statistics will include mean and median values, standard deviations, minimum and maximum ranges, and frequency distributions.

11.3.3 Safety Analyses

Safety data will be summarized for the Safety population.

11.3.3.1 Adverse Events

All treatment-emergent AEs/SAEs will be summarized with frequency distributions by treatment group, system organ class, and preferred term using version 25.0/Release date: 01Mar22 of the Medical Dictionary for Regulatory Activities (MedDRA) as well as by ocular versus non-ocular. Specific AEs/SAEs occurring with a frequency of 5% or more will be summarized in a separate listing.

Descriptive statistics will also be provided as data summaries.

11.3.3.2 Other Safety Assessments

Other safety variables (as recorded on the eCRF) will be either summarized or listed based on the frequency.

[redacted]

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12. ADMINISTRATIVE CONSIDERATIONS

12.1 Protection of Human Subjects

12.1.1 Informed Consent Regulations

Written informed consent is to be obtained from each subject prior to enrollment into the study, and/or from the subject's legally authorized representative.

12.1.2 Ethics Committee and Independent Review Board Regulations

This study is to be conducted in accordance with Ethics Committee/IRB regulations. The investigator must obtain approval from a properly constituted Ethics Committee/IRB prior to initiating the study and re-approval or review at least annually. Aerie is to be notified immediately if the responsible Ethics Committee/IRB has been disqualified or if proceedings leading to disqualification have begun. Copies of all Ethics Committee/IRB correspondence with the investigator should be provided to Aerie.

12.1.3 Good Clinical Practice Regulations

This protocol is to be conducted in accordance with the applicable Good Clinical Practice regulations and guidelines.

12.2 Changes to Protocol

The investigator should not implement any deviation from or changes to the protocol without approval by Aerie and prior review and documented approval/favorable opinion from the Ethics Committee/IRB of a protocol amendment, except where necessary to eliminate immediate hazards to study subjects, or when the changes involve only logistical or administrative aspects of the study (e.g., change of telephone numbers, etc.).

12.3 Quality Control and Assurance

The progress of this study will be monitored by on-site, written, and telephone communications between personnel at the investigator’s site and the study monitor. The investigator will allow the sponsor or designee to inspect all documents pertinent to the study, including but not limited to: CRFs, subject records (source documents), signed informed consents, records of study medication receipt, storage and disposition and regulatory files related to the study.

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12.4 Subject Confidentiality

Written authorization is to be obtained from each subject prior to enrollment into the study, and/or from the subject's legally authorized representative in accordance with the applicable privacy requirements (e.g., HIPAA).

12.5 Required Study Documents

The investigator will maintain documentation demonstrating Ethics Committee/IRB approval of the study protocol and informed consent at his/her study site.

The investigator is responsible for ensuring that data are properly recorded on each subject's CRFs and related documents. The CRFs are to be submitted in a timely manner and according to an Aerie-specified schedule.

12.6 Record Retention

The investigator must maintain records related to this study for a minimum of 3 years after study completion.

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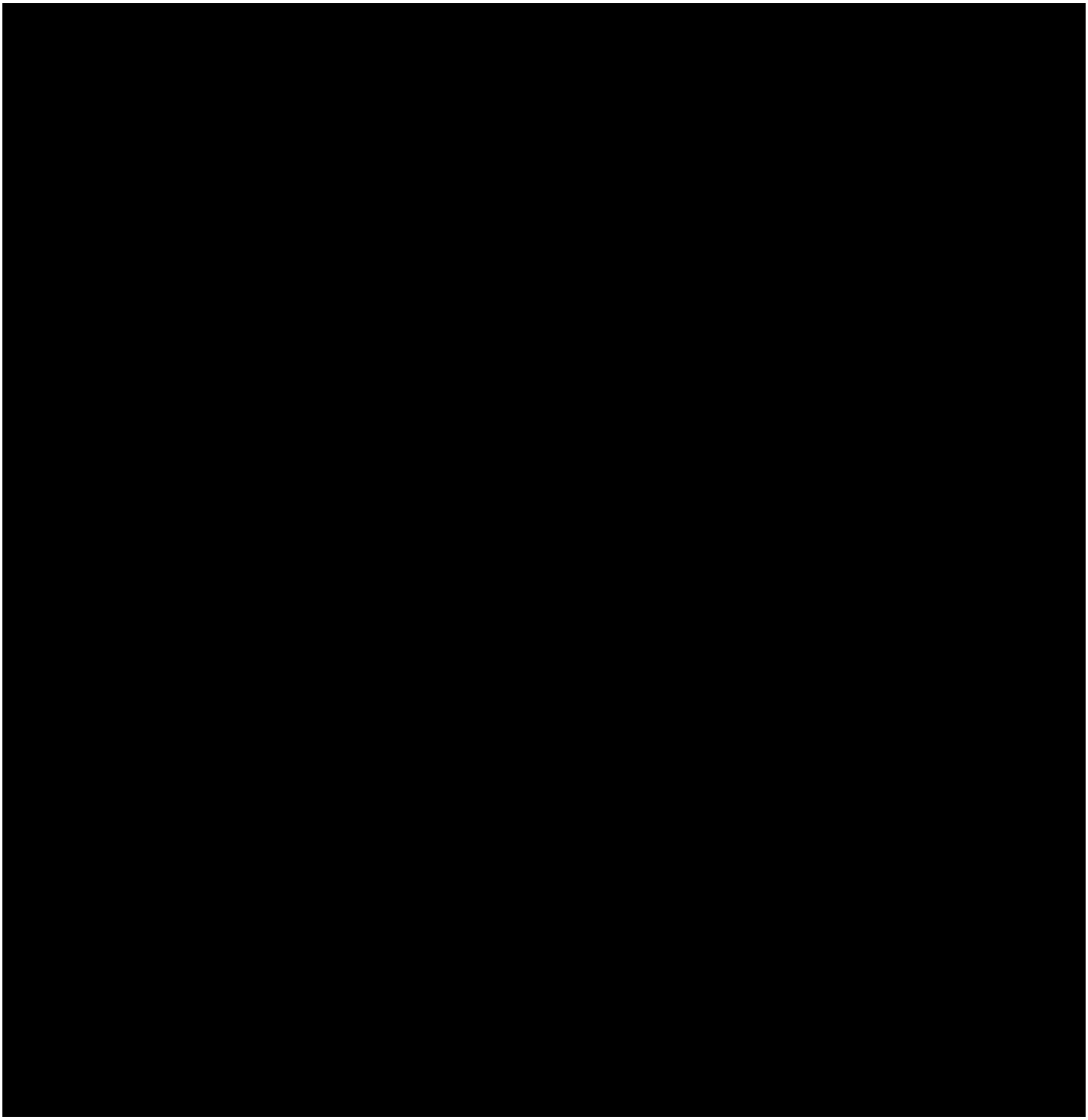

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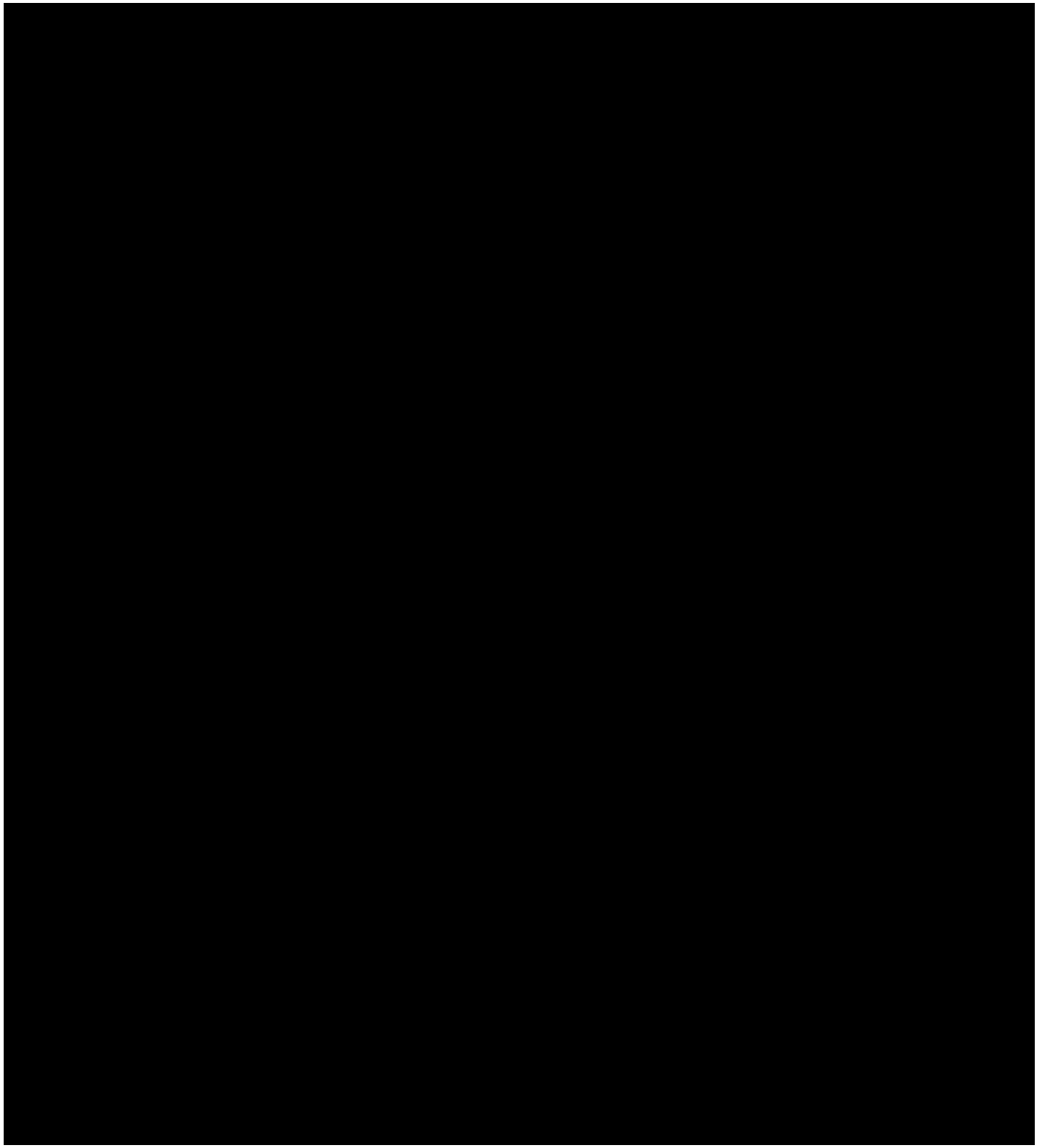

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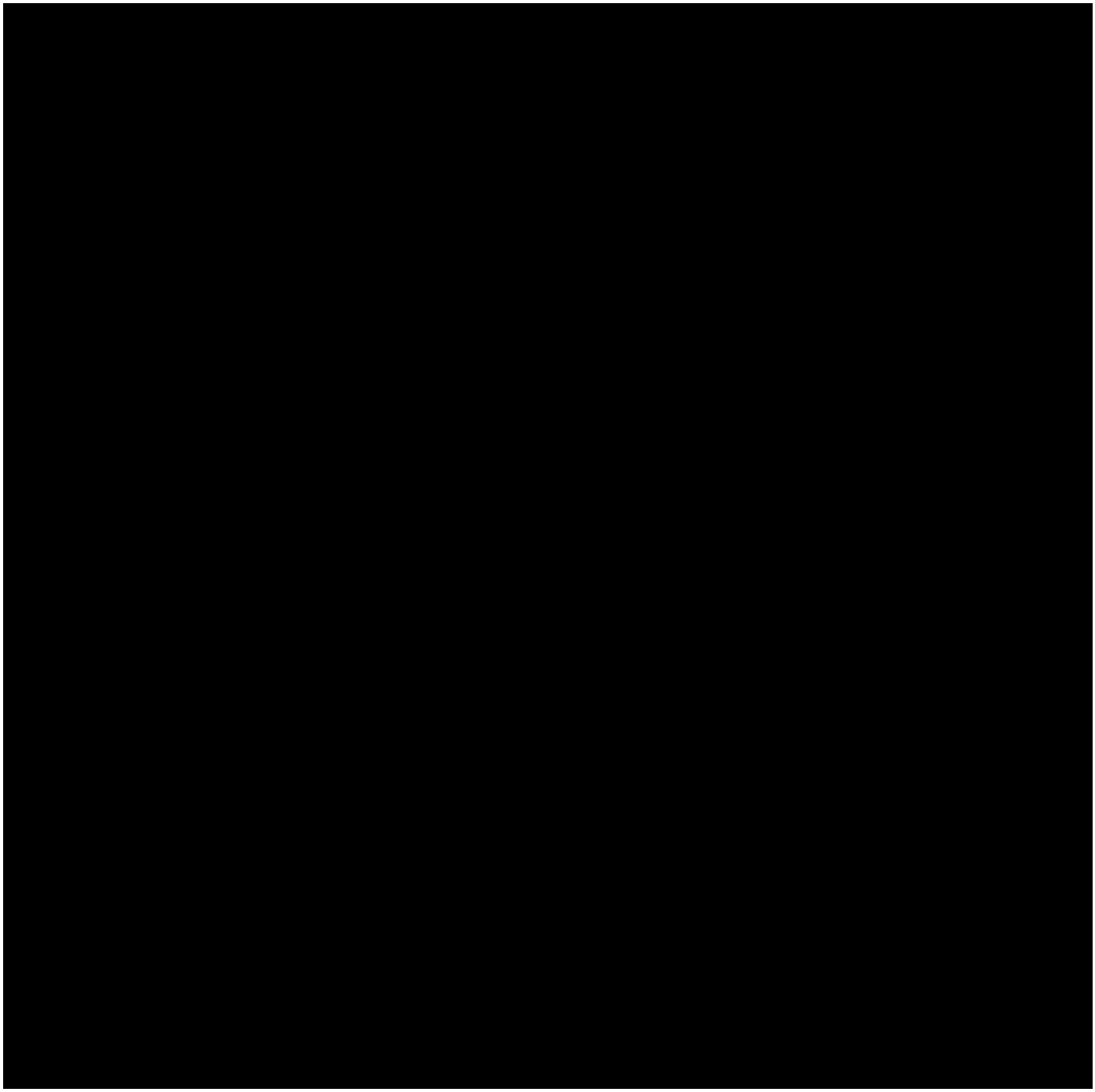

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Appendix 4 STUDY MEDICATION PACKAGE INSERT

Package Insert for Rocklatan™ (netarsudil/latanoprost ophthalmic solution) 0.02%/0.005% will be supplied separately to each study site.

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Appendix 5 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]

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Appendix 6 EXAMINATION PROCEDURES

1. Best Corrected Visual Acuity

At all study visits, BCVA will be assessed in both eyes of each subject using a Snellen visual acuity chart at a distance of 20 feet.

Ensure subject is seated in a position whereby his/her eyes are 20 feet from the chart, which is hung on the wall at eye level. Mark a spot on the floor with a piece of tape to ensure subjects are seated in the exact same position every time they take the test. Also ensure subject is fitted with appropriate lenses as to provide “best correction” each time he/she takes the test. In order to standardize the conditions of the test as much as possible, all visual acuity testing should be performed in the same room under the same lighting conditions for every subject.

Perform the test on the right eye first. Ask the subject to read each letter, line by line, left to right beginning with line #1 on the top of the chart. Subjects should be told that the chart contains only letters, not numbers. If the subject reads a number, he/she should be instructed that the chart only contains letters and for him/her to “try again.” Subjects should be asked to read the letters slowly as to achieve best identification of each letter. There is no time limit for this test. Subjects are not to proceed to the next letter (or line) until they have given a finite answer.

If a subject changes a response (e.g., that should be a “C” not an “O”) before he/she has read the next letter, the change will be accepted. If the subject attempts to change a response after reading the next letter in the series, the change will not be accepted.

When the letters become difficult to read or if the subject identifies a letter as 1 of 2 letters, he/she should be instructed to choose 1 letter and, if necessary, to guess. The examiner should consider the lowest line read with no more than 1 mistake as the extent of a subject’s visual acuity. This visual acuity should then be recorded (in Snellen units, e.g., 20/70) on the appropriate CRF.

Repeat for the left eye.

2. Biomicroscopy

Any findings from the gross examination will be recorded in this section on the CRF. Slit lamp biomicroscopy will be performed by the investigator (or designee) according to the site’s usual practice during the study. Observations for the slit lamp biomicroscopy examination will be graded as follows:

Lids/Lashes (upper and lower)

Erythema

Rating	Score	Description
None	0	Normal, without redness
Trace	+0.5	Minimal flush reddish color, confined to a small region
Mild	+1	A flush reddish color, confined to a small region
Moderate	+2	Diffused reddish color encompassing the entire lid margin
Severe	+3	Deep diffuse reddish color of lid margins and superior or inferior eye lid

Edema

Rating	Score	Description
None	0	Normal. No swelling of the eyelid tissue
Trace	+0.5	Minimal swelling of the lids, above normal, which is regional
Mild	+1	Slight swelling of the lids, above normal, which is regional
Moderate	+2	General swelling

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Severe	+3	Extensive swelling of the eyelids, with or without eversion of upper and/or lower lids

Conjunctiva (Palpebral and Bulbar)

Hyperemia

Rating	Score	Description
None	0	Normal. May appear blanched to reddish-pink without perilimbal injection. Vessels of palpebral or bulbar conjunctiva easily observed
Trace	+0.5	Minimal flush, reddish color predominantly confined to the palpebral or bulbar conjunctiva
Mild	+1	A flush, reddish color predominantly confined to the palpebral or bulbar conjunctiva
Moderate	+2	Bright red color of the palpebral or bulbar conjunctiva
Severe	+3	Deep, bright diffuse redness of the palpebral or bulbar conjunctiva

Edema

Rating	Score	Description
None	0	Normal. No swelling of the conjunctiva
Trace	+0.5	Minimal swelling of the conjunctiva, above normal, which is regional
Mild	+1	Mild swelling of the conjunctiva, above normal, which is regional
Moderate	+2	General swelling of the conjunctiva
Severe	+3	Extensive swelling of the conjunctiva

Follicles

Rating	Score	Description
None	0	No follicles
Trace	+0.5	Minimal number of elevated follicles, with minimal surrounding vasculature
Mild	+1	Few elevated follicles with minimal surrounding vasculature
Moderate	+2	Multiple elevated follicles with moderate surrounding vasculature
Severe	+3	Elevated follicles which may involve the entire conjunctiva, with engorged vasculature

Cornea

Edema

Rating	Score	Description
None	0	No edema
Trace	+0.5	Localized, minimal (trace) epithelial haze
Mild	+1	Dull glass appearance of epithelium that may include fine localized microcystic changes
Moderate	+2	Dull glass appearance of epithelium with large number of cystic changes with or without stromal edema
Severe	+3	Epithelial bullae and/or stromal edema, localized or diffuse, with or without stromal striae

Staining/Erosion

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Rating	Score	Description
None	0	No erosion
Trace	+0.5	Minimal fluorescein staining confined to small focus
Mild	+1	Slight fluorescein staining confined to small focus
Moderate	+2	Regionally dense fluorescein staining (1 mm or greater in diameter) with underlying structure moderately visible
Severe	+3	Marked fluorescein staining or epithelial loss

Anterior Chamber

For the measurements of cells and flare the following settings should be used:

• 1x1 mm slit	• High magnification
• Highest slit lamp voltage	• Low ambient lighting
• Illumination angle of 45 degrees	• Same grader and slit lamp whenever possible

Cells

Rating	Score	Description
None	0	No cells seen
Trace	+0.5	1-5 cells seen
Mild	+1	6-25 cells seen
Moderate	+2	26-50 calls seen
Severe	+3	Too many cells to count

Flare

Rating	Score	Description
None	0	No Tyndall effect
Trace	+0.5	Tyndall effect barely discernible
Mild	+1	Tyndall beam in the anterior chamber has a mild intensity
Moderate	+2	Tyndall beam in the anterior chamber has a moderate-strong intensity
Severe	+3	Tyndall beam is very intense, and the aqueous has a white and milky appearance

Lens Status

Lens status will be described by the observer as phakic, pseudophakic or aphakic.

Lens Appearance (phakic eyes only)

Rating	Score	Description
None	0	No cataract
Trace	+0.5	Trace lens opacity
Mild	+1	Early lens opacity
Moderate	+2	Intermediate lens opacity
Severe	+3	Advanced lens opacity

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3. Intraocular Pressure

NOTE: The examination procedure described below are to be completed for both eyes.

IOP should be measured by the investigator (or designee) in each eye using a Goldmann applanation tonometer affixed to a slit lamp. Measurements will be recorded on an appropriate CRF.

Please ensure tight-fitting neck wear has been loosened prior to initiating the examination. Both eyes will be tested, with the right eye preceding the left.

Instill 1 drop of topical anesthetic (e.g., Ophthetic®) into each eye and wait 4 minutes before continuing with the test procedure.

Test Procedure:

1. With the subject seated, both he/she and the slit lamp should be adjusted so that the subject's head is firmly positioned on the chin rest and against the forehead rest without leaning forward or straining.
2. Look through the binocular viewer of the slit lamp at low power making sure the tension knob is pre-set to the low-pressure value (4-6 mmHg).
3. Follow the image of the fluorescein-stained semicircles while rotating the tension knob until the inner borders of the fluorescein rings touch each other at the midpoint of their pulsation in response to the cardiac cycle.
4. When this image is reached, remove your fingers from the tension knob and record the IOP reading along with the time of day in the CRF.

Please note:

- IOP readings should not be adjusted for corneal thickness.
- The tonometer should be calibrated prior to or at the Baseline Visit (Visit 1) and calibration should be documented.

4. Pregnancy Testing

A urine human chorionic gonadotropin (hCG) 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 childbearing potential.

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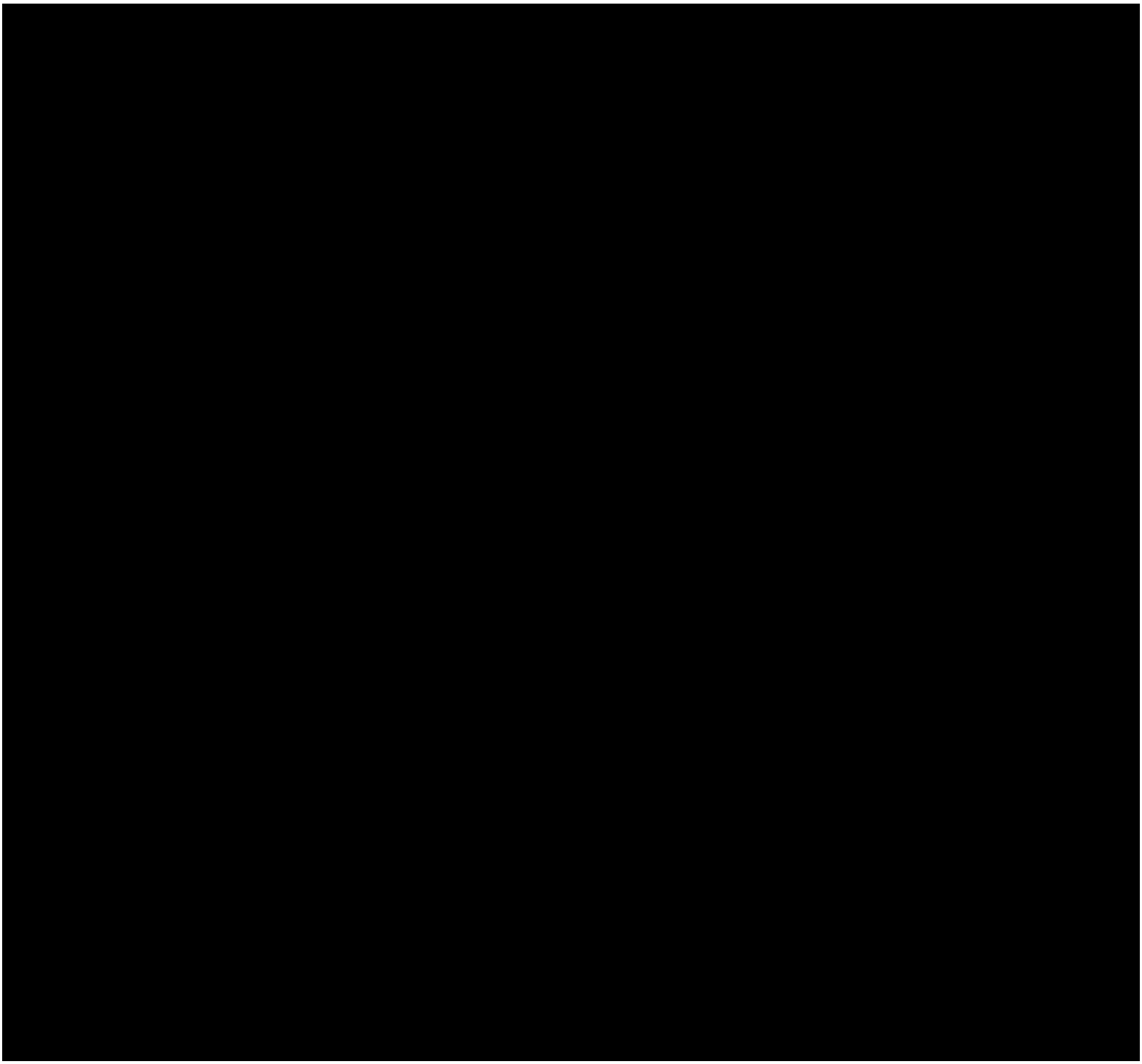
8. Adverse Events

At both Visit 2 (Week 6) and Visit 3 (Week 12), the investigator (or designee) will question each subject regarding adverse experiences that may have occurred since a previous visit. Subjects will be queried “How are you feeling?” and all AEs will be recorded in the CRFs, including severity, action taken, and relationship to study medication.



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