A prospective, double-masked, randomized, multi-center, active-controlled, parallel-group 12-month study assessing the safety and ocular hypotensive efficacy of PG324 Ophthalmic Solution compared to AR-13324 Ophthalmic Solution, 0.02% and Latanoprost Ophthalmic Solution, 0.005% in subjects with elevated intraocular pressure

NCT02558400

12June2017

Clinical Study Protocol: PG324-CS301

Study Title:	A prospective, double-masked, randomized, multi-center, active-controlled, parallel-group 12-month study assessing the safety and ocular hypotensive efficacy of PG324 Ophthalmic Solution compared to AR-13324 Ophthalmic Solution, 0.02% and Latanoprost Ophthalmic Solution, 0.005% in subjects with elevated intraocular pressure
Study Number:	PG324-CS301
Study Phase:	3
Product Name:	PG324 (AR-13324, 0.02% and latanoprost, 0.005%) Ophthalmic Solution
Indication:	Reduction of intraocular pressure in subjects with open-angle glaucoma or ocular hypertension
Investigators:	Multi-center
Sponsor:	Aerie Pharmaceuticals, Inc.
Sponsor Contact:	135 US Highway 206, Suite 15 Bedminster, NJ 07921 (908) 470-4320
Medical Monitor:	Richard A. Lewis, M.D.

	Date
Original Protocol (Rev 0):	10 June 2015
Amendment 1 (Rev 1):	24 June 2015
Amendment 2 (Rev 2):	12 April 2016
Amendment 3 (Rev 3):	05 January 2017
Amendment 4 (Rev 4):	12 June 2017

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CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A prospective, double-masked, randomized, multi-center, active controlled, parallel-group 12-month study assessing the safety and ocular hypotensive efficacy of PG324 Ophthalmic Solution compared to AR-13324 Ophthalmic Solution, 0.02% and Latanoprost Ophthalmic Solution, 0.005% in subjects with elevated intraocular pressure

Study No: PG324-CS301

Original Protocol Date: 10 June 2015

Protocol Version No: Rev 4

Protocol Version Date: 12 June 2017

Role	Contact information
Author, Clinical Operations	[redacted]
Aerie Management and Sponsor Safety Officer	[redacted]

Medical Monitor

Clinical Laboratory

Biostatistics and Data Management

Amendment #1: 24 June 2015

Changes made include minor clarifications on procedures, correction of typographical errors, and correct application of inclusion criteria by study visit. [redacted] Specifically:

- Synopsis:

[redacted]

- Synopsis and Section 4.2:

[redacted]

- Section 3.1:

[redacted]

- Section 4.3:

[redacted]

- Section 5.5:

- Section 5.7.2:

- Section 6.3:

- Section 6.8.2:

- Section 6.9.11:

- Section 6.17.2

- Section 6.17.3:

- Section 7.1.2:

- Section 7.1.3:

- Sections 7.1.4:

[redacted]

- Section 7.1.5:

[redacted]

- Section 7.1.6:

[redacted]

- Section 7.1.8:

[redacted]

- Section 7.1.9:

- Section 7.1.12:

- Section 7.1.15:

- Section 7.1.17:

- Section 7.1.18:

- Section 7.1.20:

- Section 7.1.21:

- Section 7.1.23:

- Section 7.2:

- Section 7.3:

- Section 7.4:

[redacted]

- Appendix 1, footnote 8:

[redacted]

- Appendix 1, Footnotes 10 and 11:

[redacted]

- Appendix 2, Subsection 3. Clinical Laboratories:

[redacted]

None of these protocol changes impact patient safety or exposure to investigational product.

Amendment #2: 12 April 2016

Changes made include clarifications on procedures, correction of typographical errors, correct application of inclusion criteria by study visit, and other minor clarifications. [redacted] Specifically:

- Updated the Sponsor contact information [redacted]
- [redacted]

  Synopsis and Section 4.2 (Inclusion Criterion 3):

  [redacted]

  Synopsis and Section 4.3 (Exclusion Criterion 3):

  [redacted]

  Section 4.2:

  [redacted]

Sections 7.1.2 – 7.1.5:

[redacted]

Section 7.1.2:

[redacted]

Section 7.1.3:

[redacted]

Section 7.1.4:

[redacted]

Section 7.1.5:

[redacted]

[redacted]

Section 9.4.1:

[redacted]

- [redacted]

Section 5.7.1:

[redacted]

[redacted]

Section 6.5.2:

[redacted]

Sections 7.1.1 and 9.4.3:

[redacted]

- [redacted]

Section 5.6:

[redacted]

- For SAEs and related procedures, removed a portion of the description and expanded description of pregnancy reporting procedures as a distinct part of safety reporting procedures [redacted]

[redacted]

- Added 3 references to protocol reference list

[redacted]

- Added abbreviations to bottom of Appendix 1 Table
- [redacted]

[redacted]

- The package insert for the comparator product latanoprost ophthalmic solution, 0.005% has replaced the November 2012 package insert with the more recent February 2015 package insert from the manufacturer, Bausch & Lomb Incorporated (Tampa, FL) (Appendix 3).

Amendment #3: 05 January 2017

Changes made include an extension to the study adding two additional observational visits after Month 12. Also minor changes in pagination and punctuation were made. [redacted]

Specifically:

Clinical Protocol Approval Form:
Updated the Sponsor contact information for Clinical Operations

Synopsis:
Added Intraocular Pressure to the list of Safety Assessments
Added a description of the extension visits to the study design, efficacy and safety assessments, and statistical methods:

[redacted]

Subjects who agree to participate in this study and are enrolled in the study will attend a total of 9 study visits **with the option of participating in 2 additional study visits over a 2-month extension period for a total of 11 visits.** [redacted]

Following completion of the Month 12 study visit procedures, subjects will **be offered the opportunity to participate in a 2-month observational (i.e., non-interventional) trial extension.** [redacted]

[redacted]

Efficacy Assessments:
Added: **The primary efficacy assessment for the extension visits will be the IOP measurement at each extension visit.** [redacted]

Safety Assessments:

Added: **The safety assessments for the extension visits will include visual acuity, objective findings of biomicroscopic examinations (i.e., anterior segment examinations including evaluation of cornea, conjunctiva, and lens), and findings of dilated ophthalmoscopic examination (retina, vitreous, macula, choroid, optic nerve).**

[redacted]

Section 1.1 Investigational Product

[redacted]

Section 2.2 Secondary Objectives

[redacted]

Section 3.1 Overall Study Design and Plan

Added **bolded text**:

Following completion of the 12-month treatment and evaluation period, subjects will be offered the opportunity to continue for an additional 2 months in a non-interventional, observation extension trial.

[redacted]

[redacted]

Section 4.3 Exclusion criteria
Ophthalmic exclusion criteria: Added "**Shaffer scale**" to the "Grade 2 or less".

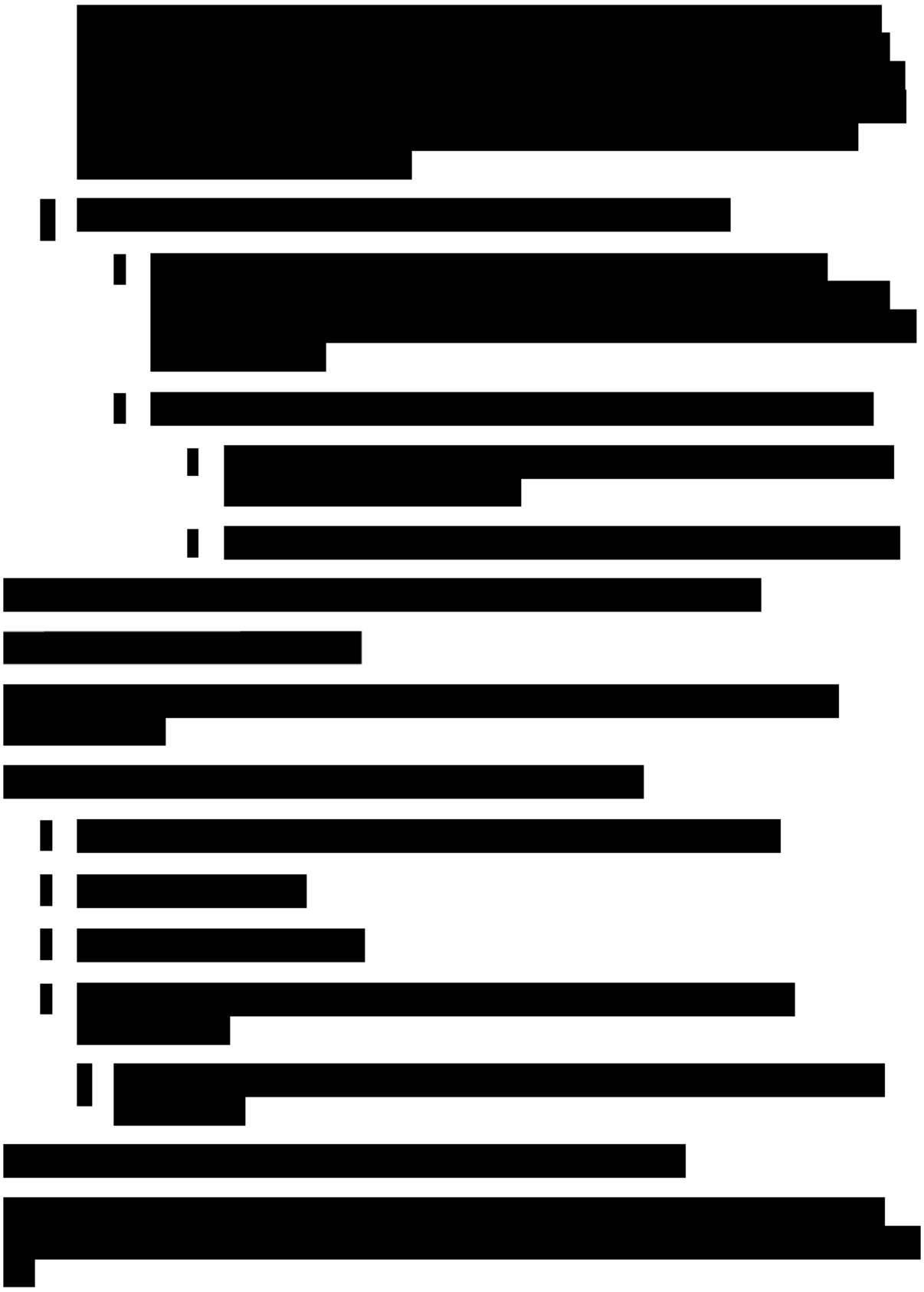
Section 6.1 Informed Consent
Added **bolded text**:
Prior to any study procedures **in the treatment period (Screening through Visit 9 [Day 365])…**

For subjects opting to participate in the extension visits, they must complete a new informed consent form prior to any study procedures being conducted in the observational period.

[redacted]

Section 6.6 Assessment of Safety
Added: **The safety assessments for the extension visits will include visual acuity, objective findings of biomicroscopic examinations (i.e., anterior segment examinations including evaluation of cornea, conjunctiva, and lens), and findings of dilated ophthalmoscopic examination (retina, vitreous, macula, choroid, optic nerve).**

[redacted]



[redacted]

Section 9.4.1 General considerations

[redacted]

[redacted]

Section 10.6 Subject Information and Consent
Added **bolded text:**
Informed consent must take place before any study specific procedures are initiated **in the treatment period of the study (Screening through Visit 9 [Month 12, Day 365]) and again before any study specific procedures are initiated in the extension visits (Visit 10 [Month 13, Day 395] through Visit 11 [Month 14, Day 425])**. [redacted]

Appendix 1 Schedule of Visits and Examinations
Added columns for Observational Period Visits 10 and 11.

[redacted]

Amendment #4: 12 June 2017

The primary purpose for this amendment is to add an interim database lock when all subjects have completed 12 months treatment. [redacted]

Additional wording was changed per section, [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Section 9.4.2 – Interim Analyses

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

SYNOPSIS

Sponsor:

Aerie Pharmaceuticals, Inc.

Name of Finished Product:

PG324 (AR-13324, 0.02% and latanoprost, 0.005%) Ophthalmic Solution

Name of Active Ingredients:

AR-13324 and latanoprost

Study Title:

A prospective, double-masked, randomized, multi-center, active controlled, parallel-group 12-month study assessing the safety and ocular hypotensive efficacy of PG324 Ophthalmic Solution compared to AR-13324 Ophthalmic Solution, 0.02% and Latanoprost Ophthalmic Solution, 0.005% in subjects with elevated intraocular pressure

Study Number: PG324-CS301

Study Phase: Phase 3

Primary Objectives:

To evaluate:

- The ocular hypotensive efficacy of PG324 Ophthalmic Solution relative to each of its active components, AR-13324, 0.02% and Latanoprost, 0.005% at 08:00, 10:00, and 16:00 hours at Week 2, Week 6, and Month 3
- The ocular and systemic safety of PG324 Ophthalmic Solution during a 12-month treatment period

Secondary Objectives:

To evaluate:

- Mean IOP within a treatment group at each post-treatment time point
- Mean diurnal IOP within a treatment group at each post-treatment visit
- Mean change from diurnally adjusted baseline IOP at each post-treatment time point
- Mean change from baseline in diurnal IOP at each post-treatment visit
- Mean percent change from diurnally adjusted baseline IOP at each post-treatment time point
- Mean percent change from baseline in diurnal IOP at each post-treatment visit
- Percentages of subjects achieving pre-specified mean, mean change, and percent mean change in diurnal IOP levels

[redacted]

Study Design: This will be a 12-month, double-masked, randomized, multi-center, active-controlled, parallel-group safety and efficacy trial in subjects at least 18 years of age for reduction of intraocular pressure (IOP) with PG324 Ophthalmic Solution compared to each of its active components, AR-13324, 0.02% and Latanoprost, 0.005%. All investigational products will be dosed QD (PM). Subjects eligible to be enrolled in this study will be those with a diagnosis of either open angle glaucoma (OAG) or ocular hypertension (OHT). Subjects who agree to participate in this study and are enrolled in the study will attend a total of 9 study visits with the option of participating in 2 additional study visits over a 2-month extension period for a total of 11 visits. The study visits include: a Screening Visit, Qualification Visit #1, Qualification Visit #2/Day 1 (baseline), Week 2 (Day 15), Week 6 (Day 43), and Month 3 (Day 90), Month 6 (Day 180), Month 9 (Day 270), and Month 12 (Day 365), [redacted] Subjects will be required to

washout of any ocular hypotensive medication in use (if any) for a minimum prescribed period (5 days-4 weeks, depending on the medication) prior to attending Qualification Visit #1. Subjects eligible to be enrolled in this study must meet all inclusion criteria and none of the exclusion criteria at each of the Screening Visit and Qualification Visits #1 and #2. Among multiple procedures, subjects will receive an eye examination including IOP measurements at Qualification Visits #1 and #2 and, if deemed eligible, will be enrolled at Qualification Visit #2 and assigned to 1 of 3 investigational products in a 1:1:1 ratio according to a computer-generated randomization list. Randomization will take place using IWRS methodology and will stratify subjects by site and by maximum baseline IOP (< 25 mmHg vs ≥ 25 mmHg). Enrolled subjects will dose the assigned investigational product in both eyes QD in the evening beginning on Day 1 and up to and including the evening prior to the Month 12 visit. Procedures conducted at each visit will include safety and efficacy measurements, including IOP at the following time points: 08:00, 10:00, and 16:00 hours. Subjects will be seen in the clinic for safety and efficacy assessments during the treatment period at Weeks 2 and 6, and Month 3; subsequent study visits at Month 6, Month 9, and Month 12 will focus primarily on safety and will include measurement of IOP at 08:00, 10:00, and 16:00 hrs. Following completion of the Month 12 study visit procedures, subjects will be offered the opportunity to participate in a 2-month observational (i.e., non-interventional) trial extension. [redacted] For subjects who discontinue early, every possible effort will be made to assure there is an exit visit that includes all required examinations listed for Visit 9.0 (Day 365) and dilated ophthalmoscopy.

Inclusion criteria:

Subjects have to meet all of the following criteria at screening and qualification visits to enter into the study:

1. Must be 18 years of age or older
2. Diagnosis of open angle glaucoma (OAG) or ocular hypertension (OHT) in both eyes (OAG in one eye and OHT in the fellow eye is acceptable)
3. Unmedicated (post-washout) IOP > 20 mmHg and < 36 mmHg in both eyes at 2 qualification visits at 08:00 hour, 2-7 days apart. At the second qualification visit, have IOP > 17 mmHg and < 36 mmHg in both eyes at 10:00 and 16:00 hours. Both eyes must qualify at all qualification visit time points. **Note: For purposes of determining eligibility of subjects to be enrolled, any non-integral mean IOP number should not be rounded.**
4. Best corrected visual acuity +1.0 logMAR or better by ETDRS chart in each eye (equivalent to 20/200 or better Snellen visual acuity in each eye)
5. Be able and willing to give signed informed consent and follow study instructions

Exclusion criteria:

Subjects meeting any of the following criteria during screening or qualification evaluations (eg, at the time of randomization) will be excluded from entry into the study:

Ophthalmic:

1. Clinically significant ocular disease (eg, corneal edema, uveitis, or severe keratoconjunctivitis sicca) which might interfere with interpretation of the study efficacy endpoints or with safety assessments, including subjects with glaucomatous damage so severe that washout of ocular hypotensive medications (if needed) for up to 1 month is not judged safe as it would put the subject at risk for further vision loss (see Section 6.15 for further details)
2. Pseudoexfoliation or pigment dispersion component glaucoma, history of angle closure glaucoma, or narrow angles (i.e., Grade 2 or less [Shaffer scale]; extreme narrow angle with complete or partial closure). Note: Previous laser peripheral iridotomy is NOT acceptable
3. Intraocular pressure ≥ 36 mmHg (unmedicated) in either eye (individuals who are excluded for this criterion are not allowed to attempt requalification), or use of more than two ocular hypotensive medications within 30 days of screening. Note: fixed dose combination medications, for the purpose of this exclusion criterion, count as one medication.

4. Known hypersensitivity to any component of the formulation, to latanoprost, or to topical anesthetic
5. Previous glaucoma intraocular surgery, including SLT or ALT in either eye
6. Refractive surgery in either eye (eg, radial keratotomy, PRK, LASIK, corneal cross-linking, etc.)
7. Ocular trauma within the six months prior to screening, or ocular surgery or non-refractive laser treatment within the three months prior to screening
8. Recent or current evidence of ocular infection or inflammation in either eye. Current evidence of clinically significant blepharitis, keratitis, or conjunctivitis. Additionally, current evidence or **history** of herpes simplex or zoster keratitis in either eye at screening is excluded.
9. Used ocular medication in either eye of any kind within 30 days of screening and throughout the study, with the exception of a) ocular hypotensive medications (which must be washed out according to the provided schedule), b) lid scrubs (which may be used prior to, but not after screening), c) lubricating drops for dry eye (which may be used throughout the study), or d) non-corticosteroid or non-vasoconstrictor containing allergy drops and allergy drops that do not have a redness reliever effect as prescribed by the Investigator
10. Mean central corneal thickness greater than 620 μm at screening
11. Any abnormality preventing reliable applanation tonometry of either eye (eg, keratoconus, etc.)

Systemic:

12. Clinically significant abnormalities in laboratory tests at screening
13. Clinically significant systemic disease (eg, uncontrolled diabetes, myasthenia gravis, hepatic, renal, endocrine or cardiovascular disorders) which might interfere with the study
14. Participation in any investigational study within 60 days prior to screening
15. Systemic medication that could have a substantial effect on IOP within 30 days prior to screening, or anticipated during the study, including any corticosteroid-containing drug regardless of route of administration.
16. Women of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. An adult woman is considered to be of childbearing potential unless she is one year post-menopausal or three months post-surgical sterilization. All females of childbearing potential must have a negative urine pregnancy test result at the screening examination and must not intend to become pregnant during the study.

Study Population:

A total of approximately 690 subjects will be enrolled in this study at approximately 60 clinical sites, comprising a total of approximately 230 subjects per treatment arm for each of 3 treatment arms. Subjects who are enrolled in this study will be those at least 18 years of age with diagnosed open angle glaucoma (OAG) or ocular hypertension (OHT), each of whom meets all inclusion criteria and none of the exclusion criteria.

Investigational Products, Dose, and Mode of Administration:

- PG324 Ophthalmic Solution, 1 drop QD (PM), OU
- AR-13324 Ophthalmic Solution, 0.02%, 1 drop QD (PM), OU
- Latanoprost Ophthalmic Solution, 0.005%, 1 drop QD (PM), OU

Duration of Treatment: Subjects will dose for approximately 365 days

Efficacy Assessments:

The primary efficacy variable will be:

- IOP measurements at 8:00, 10:00, and 16:00 hours at Week 2 (Day 15), Week 6 (Day 43), and Month 3 (Day 90) by Goldmann Applanation Tonometry

The primary efficacy outcome will be the comparison of PG324 Ophthalmic Solution relative to each of its active components, AR-13324, 0.02% and latanoprost, 0.005%, for:

- Mean IOP for all subjects within a treatment group at 08:00, 10:00, and 16:00 hrs at the Week 2, Week 6, and Month 3 study visits

Secondary efficacy outcomes will include a summary of the following comparisons of PG324 Ophthalmic Solution relative to each of its active components (AR-13324, 0.02% and latanoprost, 0.005%) for:

- Mean IOP within a treatment group at each post-treatment time point
- Mean diurnal IOP within a treatment group at each post-treatment visit
- Mean change from diurnally adjusted baseline IOP at each post-treatment time point
- Mean change from baseline in diurnal IOP at each post-treatment visit
- Mean percent change from diurnally adjusted baseline IOP at each post-treatment time point
- Mean percent change from baseline in diurnal IOP at each post-treatment visit
- Percentages of subjects achieving pre-specified mean, mean change, and percent mean change diurnal IOP levels

Other secondary efficacy analyses will be carried out as described in the study Statistical Analysis Plan.

[redacted]

Safety Assessments:

The primary safety assessments in both eyes of enrolled subjects at study visits will be:

- Ocular symptoms/adverse events
- Intraocular pressure
- Ocular comfort test
- Pachymetry
- Gonioscopy
- ETDRS corrected visual acuity
- Pupil size
- Objective findings of biomicroscopic examinations (ie, anterior segment examinations including evaluation of cornea, conjunctiva, and lens)
- Visual field and cup-disc ratio measurements
- Dilated ophthalmoscopy

Other safety assessments will be:

- Systemic safety assessments as measured by heart rate, blood pressure, and clinical laboratory evaluations (including hematology and clinical chemistry)
- Pregnancy testing (for women of child bearing potential)

[redacted]

Statistical Methods:

The primary analysis of the primary efficacy outcome will employ a linear model with mean IOP at the given visit (Week 2, Week 6, and Month 3) and time point (08:00, 10:00, and 16:00 hours) as the response, baseline IOP as a covariate, and treatment as a main effect factor, using the intent to treat population and with multiple imputation techniques used to impute missing data. Each time point within each visit will be modeled separately. The least squares mean differences (test – control) between PG324 Ophthalmic Solution and each

of Latanoprost Ophthalmic Solution, 0.005% and AR-13324 Ophthalmic Solution, 0.02% will be presented as well as 2 sided p-values and 95% confidence intervals. Inference will be made on the p-value < 0.05 for all time points at the Week 2, Week 6, and Month 3 Visits.

One-hundred ninety six (196) subjects per arm completing 3 months of treatment yields at least 90% power to conclude statistical superiority of PG324 to latanoprost and > 99% power to conclude statistical superiority of PG324 to AR-13324 at all nine pre-specified time points (08:00, 10:00, and 16:00 hrs at each of the Week 2, Week 6, and Month 3 visits), assuming a two-sided alpha = 0.05, a true mean difference of 1.5 mmHg (to latanoprost) and 2.0 mmHg (to AR-13324), a common standard deviation of 3.5 mmHg at each time point, and independence among time points. Power increases as the correlation among time points increases. Therefore, 196 subjects per arm yield at least 90% power to conclude superiority to both controls over all nine time points. Approximately 230 subjects will be enrolled per arm to yield 196 subjects completing 3 months of treatment, assuming an early discontinuation rate of about 15%.

[redacted]

Date of Original Approved Protocol (Rev 0): 10 June 2015

Date of Most Recent Protocol Amendment (if applicable): 12 June 2017

Prepared in: Microsoft Word 2010

TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
ALT	Argon laser trabeculoplasty
BCVA	Best corrected visual acuity
BOCF	Baseline observation carried forward
BP	Blood Pressure
C	Centigrade
CFR	Code of Federal Regulations
CRF	Case report form
CRO	Contract research organization
CV	Curriculum vitae
DHHS	Department of Health and Human Services
EDC	Electronic data capture
eCRF	electronic case report form
ETDRS	Early Treatment of Diabetic Retinopathy Study
F	Fahrenheit
FAX	Facsimile communication
FDA	Food and Drug Administration
FDC	Fixed dose combination
FP	Prostaglandin $F_{2\alpha}$
GCP	Good clinical practice
hCG	human chorionic gonadotropin
hr	Hour
HR	Heart rate
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IOP	Intraocular Pressure
IRB	Institutional Review Board
ITT	Intent-To-Treat
IWRS	Interactive Web-based response system
kg	Kilogram
L	Liter
LASIK	Laser-assisted in-situ keratomileusis

LOCF	Last observation carried forward
logMAR	Logarithm of the minimum angle resolvable
M.D.	Medical doctor
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Milliliter
mm	Millimeter
mmHg	Millimeters Mercury
mOsmol	milliOsmoles
OAG	Open angle glaucoma
OHT	Ocular hypertension
OTC	Over-the-counter
OU	Both eyes
pH	$-\log_{10}$ [hydrogen ion concentration in moles/liter]
PM	Post meridian (ie, after noon)
PP	Per protocol
PRK	Photorefractive keratectomy
PT	Preferred term
QD	Once daily
ROCK	Rho kinase
Rx	Prescription
SAE	Serious Adverse Event
SITA	Swedish interactive threshold algorithm
SLT	Selective laser trabeculoplasty
SOC	System/Organ/Class
SSAR	Serious Suspected Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
t1/2	Half-life
US	United States

1. INTRODUCTION

1.1 Investigational Product

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 (AGIS 2000).

The need for improved efficacy of glaucoma medications is supported by several clinical studies. Studies such as the Early Manifest Glaucoma Trial (Heijl 2002), the Ocular Hypertension Treatment Study (Kass 2010), and the Collaborative Normal Tension Glaucoma Study Group (Collaborative Normal-Tension Glaucoma Study Group 1998) support the general conclusion that every millimeter of reduction in intraocular pressure (IOP) is significant for delaying disease progression. This conclusion holds true not only for ocular hypertensive and glaucoma subjects with elevated IOPs but also for glaucoma subjects with IOPs in the normal range. Thus the goal for treating subjects should be to achieve the lowest possible IOP, preferably without sacrificing safety or convenience.

For many glaucoma subjects, current glaucoma medications are not sufficiently effective as monotherapy to achieve target IOP. These subjects are often prescribed two or more medications, which increases the complexity of the dosing regimen and often leads to decreased subject compliance. Fixed-dose combination (FDC) products such as Cosopt® and Combigan® Ophthalmic Solutions simplify dosing regimens by providing two medications in a single bottle, but these products still require twice-daily dosing. The ideal FDC product would provide the same efficacy as co-administration of two medications with the convenience of a once-daily eye drop.

Inhibitors of Rho kinase (ROCK) have emerged as a new class of potential glaucoma medication and are currently being tested in the clinic (Chen 2011; Kopczynski 2014). AR-13324 is a novel Rho kinase and norepinephrine transporter inhibitor developed at Aerie Pharmaceuticals, Inc. Its physicochemical characteristics were engineered specifically for efficient topical ocular delivery. In both rabbit and monkey studies, AR-13324 produces large reductions in IOP with a longer duration of action than reported for previously characterized Rho kinase inhibitors. AR-13324 Ophthalmic Solution has been shown to provide significant IOP lowering when dosed once-daily in the evening (Study Report AR-13324-CS202). The related Rho kinase inhibitor AR-12286 appears to reduce IOP through increasing trabecular outflow (Williams 2011), and AR-13324 appears to reduce IOP potentially through several mechanisms: increasing trabecular outflow (as with AR-12286), decreasing aqueous humor production (Wang 2015), and reducing episcleral venous pressure (Kiel, 2015). The ability to reduce aqueous production may be related to AR-13324 *in vitro* inhibitory activity against monoamine transporters, including the norepinephrine transporter.

Prostaglandin analogues are highly effective at lowering IOP when dosed once daily in the evening. [redacted]

[redacted] a fixed-dose combination of AR-13324 (0.01% or 0.02%) and latanoprost (0.005%) dosed once daily (PM) was investigated in a double-masked, parallel-group study. In that study, the fixed-dose combination PG324 provided clinically and statistically superior ocular hypotensive efficacy relative to its individual active components at the same concentrations (Study Report PG324-CS201). The only safety finding of note was transient asymptomatic conjunctival hyperemia which was of trace or mild severity approximately 80% of the time when it occurred.

The present investigation is designed to evaluate PG324 in a controlled study compared to AR-13324 Ophthalmic Solution, 0.02% and Latanoprost Ophthalmic Solution, 0.005% in a study of 12 months duration, with an optional 2-month non-interventional observation follow-up period (extension visits).

1.2 Findings from Nonclinical and Clinical Studies

Detailed information on nonclinical and clinical studies completed with AR-13324 and PG324 is provided in the Investigator's Brochure.

1.3 Risks and Benefits to Human Subjects

As no other fixed dose combinations of this class are approved, and only early stage clinical experience is available, the risks and benefits are not well understood at this time. Given the pharmacology of this class of agents and the results of previously completed Phase 1, Phase 2, and Phase 3 clinical studies by the Sponsor (AR-13324-CS101, AR-13324-CS201, AR-13324-CS202, AR-13324-CS301, and PG324-CS201), it is expected that adverse events seen in clinical trials individually with latanoprost and AR-13324 containing ophthalmic formulations may be observed with PG324. No clinical experience is available in the pediatric population with AR-13324. However, based on the pharmacologic class, topical nature, and negligible systemic bioavailability of the pharmacologically active components of PG324 (Appendix 3 and AR-13324-CS101), the safety profile in the pediatric subject population may be similar to the adult population. The reader should refer to the Investigator's Brochure and Appendix 3 for more detailed information on potential risks due to use of AR-13324 and PG324 ophthalmic solutions.

The major potential benefit from exposure to PG324 is reduction in IOP in subjects with open angle glaucoma or ocular hypertension. An important clinical result of reduced IOP could be slowing of glaucoma disease progression and preservation of vision in subjects for longer times when measured over periods of months to years.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are:

- To evaluate the ocular hypotensive efficacy of PG324 Ophthalmic Solution relative to each of its active components, AR-13324, 0.02% and latanoprost, 0.005% at 08:00, 10:00, and 16:00 hours at Week 2, Week 6, and Month 3
- To evaluate the ocular and systemic safety of PG324 Ophthalmic Solution during a 12-month treatment period

2.2 Secondary Objectives

The secondary objectives of this study include evaluation of:

- Mean IOP within a treatment group at each post-treatment time point
- Mean diurnal IOP within a treatment group at each post-treatment visit
- Mean change from diurnally adjusted baseline IOP at each post-treatment time point
- Mean change from baseline in diurnal IOP at each post-treatment visit
- Mean percent change from diurnally adjusted baseline IOP at each post-treatment time point
- Mean percent change from baseline in diurnal IOP at each post-treatment visit
- Percentages of subjects achieving pre-specified mean, mean change, and percent mean change in diurnal IOP levels

[redacted]

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a multi-center, randomized, double-masked, parallel group, active agent-controlled study. The study is being conducted to evaluate safety and efficacy of an investigational fixed dose combination (FDC) product (PG324 Ophthalmic Solution) for reduction of IOP in subjects with elevated IOP due to a diagnosis of open angle glaucoma or ocular hypertension. Acknowledging the application of the Combination Rule of the U.S. Food and Drug Administration (21 CFR 300.50), efficacy of the FDC PG324 in this study will be assessed relative to the efficacy of each of the pharmacologically active components in PG324:

- AR-13324 Ophthalmic Solution, 0.02%
- Latanoprost Ophthalmic Solution, 0.005%.

Participating subjects who have signed an informed consent form will attend up to 9 study visits. The study duration for an enrolled subject will be approximately 55 weeks from screening (Visit 1) to the last visit (Visit 9 [Day 365±7]). Visit 1 will be the Screening Visit and will occur up to approximately 28 days prior to Visit 2. Visit 2 will be the first of 2 qualification visits. After undergoing a screening visit and repeat qualification visits, eligible subjects who have met all inclusion/exclusion criteria will be enrolled and assigned at Qualification Visit #2 to one of 3 treatment groups, with group assignment to one of the following treatment groups determined by a computer-generated randomization code:

- PG324 Ophthalmic Solution
- AR-13324 Ophthalmic Solution, 0.02%
- Latanoprost Ophthalmic Solution, 0.005%

Enrolled subjects will return on Week 2, Week 6, Month 3, Month 6, Month 9, and Month 12 for efficacy and/or safety assessments. Efficacy assessments for the first 3 months of the 12-month treatment period will focus on careful monitoring of IOP at each study visit at three different times (08:00, 10:00, and 16:00 hours) during each study visit. These data will be used to evaluate the primary efficacy endpoint of mean IOP at 08:00, 10:00, and 16:00 hours at the Week 2, Week 6, and Month 3 study visits. Subsequent study visits at Month 6, Month 9, and Month 12 will focus primarily on safety and will include measurement of IOP at 08:00, 10:00 and 16:00 hrs.

At each study visit, multiple ocular and systemic safety assessments will be conducted, including some or all of the following: systemic safety assessments (heart rate, blood pressure, and clinical laboratory evaluations [including hematology]), pregnancy testing (for women of child bearing potential), ocular symptoms/adverse events, ocular comfort, ETDRS corrected visual acuity, pupil size, objective findings of biomicroscopic examinations (ie, anterior segment examinations including evaluation of cornea, conjunctiva, and lens), visual field and cup-disc ratio measurements, and dilated ophthalmoscopic examination,.

Approximately 690 subjects will be enrolled in this study and will be assigned in a 1:1:1 ratio to treatment with PG324, AR-13324, 0.02%, or latanoprost, 0.005% ophthalmic solutions.

All investigational products will be instilled QD as a single drop OU in the evening, beginning with the day of Qualification Visit #2. Significant effort will be made to ensure adequate masking of all investigational products for both subjects and clinical staff. All doses will be administered by the study subjects. For subjects deemed unable to self-administer the doses, a guardian or caregiver will be asked to administer the medication.

[redacted]

[redacted]

3.2 Rationale for Study Design and Control Group

In order to best evaluate the contributions of AR-13324 and latanoprost to the ocular hypotensive efficacy of PG324 [redacted] a parallel group, double-masked, three-arm study design was selected. The PG324 dose selected for this study is based on a recently completed Phase 2 study (PG324-CS201). The treatment period and dosing frequency is selected on the basis of nonclinical safety studies with PG324 and regulatory requirements for demonstration of ocular hypotensive efficacy.

[redacted]

3.3 Expected Duration of Subject Participation

Subjects on prior hypotensive medications are required to undergo a minimum washout period. All subjects will undergo about 365 days of QD treatment with the study medication. Treatment duration with investigational product for this study will start on the evening of Visit 3 (Qualification Visit #2; Day 1) and end on the evening before Visit 9 (Day 365±7). [redacted]

4. STUDY POPULATION SELECTION

4.1 Study Population

A total of approximately 690 subjects will be enrolled in this study at approximately 60 clinical sites, comprising a total of approximately 230 subjects per treatment arm for each of 3 treatment arms. Subjects who are enrolled in this study will be those at least 18 years of age with diagnosed open angle glaucoma (OAG) or ocular hypertension (OHT), each of whom meets all inclusion criteria and none of the exclusion criteria.

4.2 Inclusion Criteria

Subjects must qualify in both eyes. See Section 9 for more information on statistical analysis of the study eye. ALL TREATMENTS WILL BE DOSED TO BOTH EYES (OU).

Subjects have to meet all of the following criteria at screening and qualification visits to enter into the study:

1. Must be 18 years of age or older

2. Diagnosis of open angle glaucoma (OAG) or ocular hypertension (OHT) in both eyes (OAG in one eye and OHT in the fellow eye is acceptable)

3. Unmedicated (post-washout) IOP > 20 mmHg and < 36 mmHg in both eyes at 2 qualification visits at 08:00 hour, 2-7 days apart. At the second qualification visit, have IOP > 17 mmHg and < 36 mmHg in both eyes at 10:00 and 16:00 hours. Both eyes must qualify at all qualification visit time points. **Note: For purposes of determining eligibility of subjects to be enrolled, any non-integral mean IOP number should not be rounded.**

4. Best corrected visual acuity +1.0 logMAR or better by ETDRS in each eye (equivalent to 20/200 or better Snellen visual acuity in each eye)

5. Be able and willing to give signed informed consent and follow study instructions

4.3 Exclusion Criteria

Individuals with the following characteristics will be excluded from the study:

Ophthalmic:

1. Clinically significant ocular disease (eg corneal edema, uveitis, severe keratoconjunctivitis sicca) which might interfere with interpretation of the study efficacy endpoints or with safety assessments, including subjects with glaucomatous damage so severe that washout of ocular hypotensive medications (if needed) for up to 1 month is not judged safe as it would put the subject at risk for further vision loss

2. Pseudoexfoliation or pigment dispersion component glaucoma, history of angle closure glaucoma, or narrow angles (i.e., Grade 2 or less [Shaffer scale]; extreme narrow angle with complete or partial closure). Note: Previous laser peripheral iridotomy is NOT acceptable

3. Intraocular pressure ≥ 36 mmHg (unmedicated) in either eyes at any time point (individuals who are excluded for this criterion are not allowed to attempt requalification), or use of more than two ocular hypotensive medications within 30 days of screening. Note: fixed dose combination medications, for the purpose of this exclusion criterion, count as one medication

4. Known hypersensitivity to any component of the formulation, to latanoprost, or to topical anesthetic

5. Previous glaucoma intraocular surgery, including SLT or ALT in either eye

6. Refractive surgery in either eye (eg, radial keratotomy, PRK, LASIK, corneal cross-linking, etc.)

7. Ocular trauma in either eye within the six months prior to screening, or ocular surgery or non-refractive laser treatment within the three months prior to screening

8. Recent or current evidence of ocular infection or inflammation in either eye. Current evidence of clinically significant blepharitis, keratitis or conjunctivitis. Additionally, current evidence or **history** of herpes simplex or zoster keratitis in either eye at screening is excluded.

9. Used ocular medication in either eye of any kind within 30 days of screening and throughout the study, with the exception of a) ocular hypotensive medications (which must be washed out according to the provided schedule), b) lid scrubs (which may be used prior to, but not after screening), c) lubricating drops for dry eye (which may be used throughout the study), or d) non-corticosteroid or non-vasoconstrictor-containing allergy drops and allergy drops that do not have a redness reliever effect as prescribed by the Investigator

10. Mean central corneal thickness greater than 620 μm in either eye at screening

11. Any abnormality preventing reliable applanation tonometry of either eye (eg, keratoconus, etc.)

Systemic:

12. Clinically significant abnormalities in laboratory tests at screening

13. Clinically significant systemic disease (eg, uncontrolled diabetes, myasthenia gravis, hepatic, renal, endocrine or cardiovascular disorders) which might interfere with the study

14. Participation in any investigational study within 60 days prior to screening

15. Systemic medication that could have a substantial effect on IOP within 30 days prior to screening, or anticipated during the study, including any corticosteroid-containing drug regardless of route of administration.

16. Women of childbearing potential who are pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. An adult woman is considered to be of childbearing potential unless she is one year post-menopausal or three months post-surgical sterilization. All females of childbearing potential must have a negative urine pregnancy test result at the screening examination and must not intend to become pregnant during the study.

4.4 Subject Enrollment

Enrollment numbers are higher in this study (230 subjects per arm) than statistically required for demonstrating efficacy at 90% power, accounting for an estimated 15% discontinuation rate over the course of the first 3 months of the study.

5. STUDY TREATMENTS

5.1 Description of Treatments

5.1.1 Investigational Product

- PG324 Ophthalmic Solution is a sterile, isotonic, buffered aqueous solution containing AR-13324 (0.02%), latanoprost (0.005%), boric acid, mannitol, water for injection, and preserved with benzalkonium chloride (0.02%). The product formulation is adjusted to approximately pH 5.

5.1.2 Comparator Products

- Latanoprost Ophthalmic Solution, 0.005% is a sterile, isotonic, buffered aqueous solution of latanoprost with a pH of approximately 6.7 and an osmolality of approximately 267 mOsmol/kg. Each mL of Latanoprost Ophthalmic Solution, 0.005% contains 50 micrograms of latanoprost. Benzalkonium chloride, 0.02% is added as a preservative. The inactive ingredients are sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous, and water for injection.

- AR-13324 Ophthalmic Solution is a sterile, isotonic, buffered aqueous solution containing AR-13324 (0.02%), boric acid, mannitol, water for injection, and preserved with benzalkonium chloride (0.015%). The product formulation is adjusted to approximately pH 5.

5.2 Treatments Administered

There will be 3 treatments in this study:

- PG324 (AR-13324, 0.02% and latanoprost, 0.005%) Ophthalmic Solution
- AR-13324 Ophthalmic Solution, 0.02%
- Latanoprost Ophthalmic Solution, 0.005%

Subjects will be assigned according to a computer-generated randomization list in a 1:1:1 ratio to PG324 Ophthalmic Solution, AR-13324 Ophthalmic Solution, 0.02%, or Latanoprost Ophthalmic Solution, 0.005% (stratified by investigative site and by maximum baseline IOP [< 25 mmHg vs ≥ 25 mmHg]). Subjects will instill 1 drop of study drug into each eye, one time per day in the evening, at approximately 24 hour intervals; all treatments will be OU. Doses will be self-administered by the study subjects. For subjects deemed unable to

self-administer the doses, a caregiver will be asked to administer the medication. All subjects will administer study treatment for approximately 365 days.

5.3 Selection and Timing of Dose for Each Subject

The dose of PG324 selected for this study is based upon the positive outcomes seen for PG324 in the PG324-CS201 clinical study. Each investigational product is being dosed QD OU (in the evening between 20:00 and 22:00 hours) in this study to allow for estimated peak and trough levels of both AR-13324 and latanoprost to be present in ocular tissue at the observation times selected in the clinic for the following morning and the subsequent afternoon. The treatment period is selected on the basis of nonclinical safety studies and regulatory requirements for pivotal studies of ophthalmic glaucoma medications.

5.4 Method of Assigning Subjects to Treatment Groups

A randomization code for allocating the treatments will be prepared by an independent biostatistician who is not involved in the day-to-day conduct of the study. Subjects will be randomized using an IWRS in a 1:1:1 ratio to receive PG324 Ophthalmic Solution, AR-13324 Ophthalmic Solution, 0.02%, or Latanoprost Ophthalmic Solution, 0.005%.

5.5 Masking

An independent person at the site not responsible for performing any of the study procedures is assigned to dispense, collect, and store investigational product while maintaining the masking of the study.

Study related site personnel will be cautioned that any used or unused subject kits are not to be opened at the clinical site by the site staff involved in efficacy or safety measurements.

Treatment assignments will be masked to the Investigator, the clinical study team (Sponsor, personnel involved in day to day study management, Data Managers, and Statisticians), and the subjects prior to all subjects completing 3 months of treatment. Treatment assignment(s) will be unmasked and made available to the Investigator and the Sponsor's Medical Monitor during this period only in case of medical emergency or occurrence of adverse events that in the opinion of the investigator warrant unmasking. In the absence of medical need, the randomization code/treatment assignment(s) will not be available to the above study personnel until after the study is completed and the database is locked.

If the Investigator feels it is necessary to unmask a subject's treatment assignment after an emergency situation, the Investigator should promptly contact the Sponsor's Medical Monitor or designee. A decision will be made as to whether or not the treatment for the subject should be unmasked, preferably after consultation with the Sponsor's Medical Monitor or designee. The treatment assignment will be revealed on a subject-by-subject basis, thus leaving the masking on remaining subjects intact.

In an emergency situation in which treatment of an adverse event requires immediate unmasking, and the Investigator is unable to promptly contact the Sponsor's Medical Monitor, the Investigator may unmask the treatment. The masked portion of the kit label may be revealed for the treatment assignment. In the case of such unmasking in an emergency situation, the Investigator should contact the Sponsor immediately thereafter and document the unmasking in writing, recording the date, time, and reason for unmasking the study drug treatment in the source documentation. Individual unmasking by the Investigator will normally result in withdrawal of the subject from the study and should only be performed for the specific subject requiring unmasking in their treatment group.

5.6 Concomitant Therapy

Intermittent use of over-the-counter (OTC) artificial tear lubricant products is acceptable, with a minimum of 10 minutes between use of OTC products and study medication. However, concurrent therapy with any form of ocular hypotensive medications (prescription or over-the-counter) is not allowed during the study. Subjects who are not taking any concomitant disallowed ocular medication or who do not require washout of ocular hypotensive medication can return as soon as clinical chemistry and hematology results are received for Qualification Visit #1 (see Section 7.1.2 of this protocol for more details).

Disallowed concomitant ocular medications for enrolled subjects include:

- Miotics
- Epinephrine-related compounds
- Carbonic anhydrase inhibitors (ocular or systemic)
- α-adrenoceptor agonists
- β- adrenoceptor antagonists
- Muscarinic agonists (eg, pilocarpine)
- Prostaglandin analogues other than that contained in the provided investigational product

Systemic therapy with agents that could have an effect on IOP is to be consistent in dose, regimen and agent within the 30 days prior to screening and throughout the study, except for corticosteroid-containing drugs. For example, a subject can be treated with a systemic β-adrenoceptor antagonist as long as the particular agent and its dose and regimen had been consistent for the 30 days prior to screening, and there is no reason to believe that alteration would be necessary at some point later during the study. Subjects should be cautioned to avoid use of alcohol or the use of drugs such as marijuana during the study visit days.

Any corticosteroid-containing systemic drug is disallowed during the study regardless of route of administration.

Contact lens wear during the study is acceptable. However, subjects must remove their contact lenses at least 30 minutes before instillation of study medication, and not place them in their eye(s) until 30 minutes after instillation.

Use of all medications should be documented on the appropriate CRF. Investigators are encouraged to contact the Sponsor for any questions regarding allowed medications. Judgment of continued study participation by the subject, and inclusion of this subject's subsequent visits in the safety and efficacy analysis will be made by the Sponsor.

All medications which the subject has taken within 30 days prior to screening and during the study will be recorded in the CRF. The name of the drug, dose, route of administration, duration of treatment and indication will be recorded for each medication. For combination products (eg, Contac®), the brand name is required. For non-combination products, the generic name is desired. The use of routine ophthalmic diagnostic pharmaceutical agents (eg, fluorescein and local anesthetic) will be allowed, and individual documentation not required. Any change in dosing parameters should also be recorded in the CRF.

5.7 Restrictions

5.7.1 Prior Therapy

Individuals currently using ocular hypotensive medications must undergo a minimum washout period as specified in Table 1. If washout is to be extended beyond 6 weeks (42 days) for logistical or other reasons, the Sponsor should be contacted. If subjects need to washout of a hypotensive medication, they are not allowed to use a washout medication of shorter required washout time (including Azopt) than for the original hypotensive medication.

Table 1 Ocular Hypotensive Medication Washout Period

Medication class	Minimum washout period
Prostaglandins	4 weeks
β-adrenoceptor antagonists	4 weeks
Adrenergic agonists (including α-agonists such as brimonidine and apraclonidine)	2 weeks
Muscarinic agonists (eg, pilocarpine), Carbonic anhydrase inhibitors (topical or oral)	5 days

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5.7.2 Fluid and Food Intake

There are no general restrictions on fluid or food intake for subjects participating in this study.

5.7.3 Subject Activity Restrictions

On days during which diurnal IOP measurements are made, subjects may not engage in strenuous activity. Otherwise, there are no restrictions on subject activities during their participation in this study.

5.8 Treatment Compliance

All subjects will be instructed on the importance of following the once daily dosing regimen. Dosing should occur in the evening between 20:00 and 22:00 hours. [redacted]
Subjects should be reminded at all visits to dose every evening. Subjects may optionally use a Dosing Reminder worksheet that will be provided.

5.9 Packaging and Labeling

The container-closure systems for the investigational products are similar; the container-closure system has been chosen to be similar to the Latanoprost Ophthalmic Solution, 0.005% commercial product presentation. All clinical trial material packers (containing subject kits) and subject kits containing the bottles will be identical in appearance. Clinical supplies of PG324 Ophthalmic Solution and AR-13324 Ophthalmic Solution, 0.02% will each be filled in a dropper-dose bottle to a volume of not less than 2.5 mL. A clinical trial material packer, which contains multiple subject kits sufficient for a 3 month supply, will be packaged and provided to the site for distribution to each subject. Subject packers therefore contain all kits for an individual subject that will be distributed during this study.

Each packaged unit will be labeled with an investigational label with the following minimal information: the study number, kit number, and storage statement, including a statement "Caution – New Drug – Limited by Federal (US) Law to Investigational Use" or equivalent.

A commercially available and approved generic formulation of Latanoprost Ophthalmic Solution, 0.005% will be used for this study, with the label removed for masking purposes. All investigational product bottles will then be labeled with identical investigational labels containing the study salient information:

- Study number
- Kit number
- Storage statement
- The statement "Caution – New Drug – Limited by Federal (US) Law to Investigational Use" or its equivalent

The cartons used to package individual dropper bottles for both investigational products will be identical to ensure adequate masking. Similarly, the labels applied to the clinical trial material packers and kit cartons will be similar for all 3 investigational products, with the key difference being the unique kit number. The label from the commercial bottle of Latanoprost

Ophthalmic Solution, 0.005% will be removed and replaced with an investigational label which will be similar in appearance for all treatment groups.

Upon dispensing of a clinical trial material packer or kit to a subject, a portion of the kit label will be affixed to the designated study drug kit label log which will be part of the study files at the individual study site for this study.

5.10 Storage and Accountability

The investigational products should be stored refrigerated (2°C to 8°C/36°F to 46°F) until provided to the subject. The subject should be instructed that, once an investigational product bottle is opened, the product may be kept refrigerated or at room temperature (up to 25°C/77°F) while continuing to store the bottle in the carton. Do not freeze the product and protect from light. Prior to dispensing to the subject, all investigational material must be stored in a secure location at the recommended long-term storage condition (2°C to 8°C) with strictly limited access documented by signature of authorized persons who may dispense investigational product. Temporary temperature excursions up to 30°C are permissible.

5.11 Investigational Product Accountability at Study Site

5.11.1 Receipt and Disposition of Study Medication

Investigational product will be shipped to the Investigator's site from a central depot. A study staff member at the Investigator's site who is not involved in conducting any efficacy or safety procedures will verify study medication shipment records by comparing the shipping documentation accompanying the study medication to the study medication actually received at the Investigator's site. If a discrepancy is noted, the appropriate individual at the Sponsor or designee must be notified immediately. The responsible person for dispensing study medication at the Investigator's institution is the only site staff member that can distribute investigational product and also has sole responsibility to account for all returned used, partially used and unused bottles and kits of investigational products. The investigational product(s) must not be used outside this protocol. A Drug Accountability Log will be kept at the clinical site.

5.11.2 Return of Study Medication

When the study is completed or is terminated by the Sponsor, all study material including used and unused study medication kits will be returned to the Sponsor or their designee. All study medication accounting procedures must be completed before the study is considered to be concluded. The responsible person at the Investigator's institution has the sole responsibility to account for all used, partially used and unused bottles of investigational products. This site staff member at the Investigator's institution will complete a study drug returns form or equivalent that will be signed by the Investigator or designee prior to returning the used and unused study medication kits and bottles to the Sponsor or their designee.

6. STUDY PROCEDURES

Please see Appendix 1 for Schedule of Visits and Examinations and Appendix 2 for detailed description of study procedures.

6.1 Informed Consent

Prior to any study procedures in the treatment period (Screening through Visit 9 [Day 365]), the study will be discussed with each subject and subjects wishing to participate must give written informed consent. The verbal explanation of the study will cover all the elements specified in the written information provided for the subject. The Investigator will inform the subject of the aims, methods, anticipated benefits and potential hazards of the study, including any discomfort it may entail. The subject must be given every opportunity to clarify any points he/she does not understand and, if necessary, may ask for more information. At the end of the interview, the subject should be given time to reflect. Subjects and/or legally authorized representative then will be required to sign and date the informed consent form.

[redacted]

The informed consent form must have received approval/favorable review by a properly constituted IRB/IEC prior to use. A copy of the signed and dated consent document will be given to each subject. The original signed and dated informed consent document must be maintained in the study files at the Investigator's site.

The Investigator or staff is responsible for ensuring that no subject is subject to any study-related examination or activity before the subject has given written informed consent in the treatment period and again in the observation period (extension visits). It should be emphasized that the subject is at liberty to withdraw consent to participate at any time, without penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give, or withdraw, written informed consent may not be included or continued in this study, and should be notified that discontinuation from the study will not impact on their subsequent care.

6.2 Demographics and Medical History

Demographic data and any ongoing medication use will be collected and recorded.
Any medications the subject took but discontinued within the 30 days prior to screening also will be recorded. Significant medical history will be collected and any current underlying medical conditions, including those that began within the last 30 days and which may have resolved before screening, additionally must be recorded.

6.3 Dispensing Investigational Product

Study related site personnel will be cautioned that any used or unused subject kits are not to be opened at the clinical site by the site staff involved in efficacy or safety measurements.

Study staff responsible for dispensing investigational product will be listed on the Delegation of Responsibilities log. When a subject meets all criteria for selection and has completed all screening assessments, the subject will be assigned to a treatment according to the interactive web-based response system (IWRS). The responsible study staff will account for all used and unused investigation product packers and their kit contents by maintaining an investigational product accountability log.

6.4 Appropriateness of Measurements

The ophthalmic and systemic measures used in this study are consistent with standard of care. In particular, intraocular pressure (IOP) as measured by Goldmann applanation tonometry, the primary efficacy assessment in this study, is accepted worldwide as a standard for testing of pharmacologically active agents intended to reduce IOP.

6.5 Efficacy Assessments

6.5.1 Specification of the Efficacy Parameters

The primary efficacy outcome will be the comparison of PG324 Ophthalmic Solution relative to each of its active components, AR-13324, 0.02% and latanoprost, 0.005%, for the mean IOP within a treatment group at 08:00, 10:00, and 16:00 hrs at the Week 2, Week 6, and Month 3 study visits. A description of the method for measuring IOP to be used in this study is contained in Appendix 2. Study visits at Month 6, Month 9, and Month 12 will focus primarily on safety and will include measurement of IOP at 08:00, 10:00 and 16:00 hrs.

Secondary efficacy outcomes will include a summary of the following comparisons of PG324 Ophthalmic Solution relative to each of its active components (AR-13324, 0.02% and latanoprost, 0.005%) for:

- Mean IOP within a treatment group at each post-treatment time point
- Mean diurnal IOP within a treatment group at each post-treatment visit
- Mean change from diurnally adjusted baseline IOP at each post-treatment time point
- Mean change from baseline in diurnal IOP at each post-treatment visit
- Mean percent change from diurnally adjusted baseline IOP at each post-treatment time point
- Mean percent change from baseline in diurnal IOP at each post-treatment visit
- Percentages of subjects achieving pre-specified mean, mean change, and percent mean change diurnal IOP levels

Other secondary efficacy analyses will be carried out as described in the study Statistical Analysis Plan.

[redacted]

6.5.2 Method and Timing for Assessing Efficacy Parameters

As detailed in the following sections and in the Schedule of Visits and Examinations in Appendix 1 describing each study visit, IOP will be measured at a screening visit, at 2 qualification visits after washout (if needed) of any ocular hypotensive medications as required, and frequently throughout the study.

6.6 Assessment of Safety

The assessment of systemic and ocular safety is a primary objective of this study.

Systemic safety will be assessed for subjects by:

- Measurements of heart rate, blood pressure, and collection of clinical laboratory findings (including hematology and clinical chemistry) (see Sections 6.7.1, 6.7.2, and 6.8.1)
- Pregnancy testing (see Section 6.8.2)

The primary ocular safety assessments in both eyes of enrolled subjects will be:

- Ocular symptoms/adverse events
- Ocular comfort test
- ETDRS best corrected visual acuity
- Pupil size
- Objective findings of biomicroscopic examinations (ie, anterior segment examinations including evaluation of cornea, conjunctiva, and lens)
- Pachymetry
- Gonioscopy
- Visual field and cup-disc ratio measurements
- Dilated ophthalmoscopy

[redacted]

[redacted]

6.7 Vital Signs

6.7.1 Heart Rate

Subject heart rate will be measured at screening, and at 08:00 hours (±30 minutes) during each subsequent study visit attended by the subject. Heart rate will be determined only once during each study visit by the method described in Appendix 2.

6.7.2 Blood Pressure

Blood pressure will be measured once for each subject after the subject heart rate has been determined. Blood pressure will be determined only once during each study visit by the method described in Appendix 2.

6.8 Clinical Laboratory Tests

6.8.1 Laboratory Parameters

Clinical laboratory tests will include a panel of clinical chemistry assessments and a complete blood count (hematology and differentials) as described in Appendix 2.

6.8.2 Pregnancy Testing

A urine hCG (human chorionic gonadotropin) pregnancy test (only for females who are not diagnosed as postmenopausal or surgically sterile) will be used in this study and performed at the screening visit to immediately confirm non-pregnancy eligibility for females of child-bearing potential.

The Sponsor will provide urine pregnancy test to the sites. Expiration dates on the pregnancy tests will be reviewed and confirmed by the site prior to use.

If a female becomes pregnant during the study, the Investigator should notify the Sponsor immediately after the pregnancy is confirmed and the subject will be exited from the study. The Investigator should follow the progress of the pregnancy until the fetus is carried to term.

6.9 Adverse Event Assessments and Ocular Safety

6.9.1 Performing Adverse Events Assessments

Qualified study staff responsible for assessing adverse events (AEs) will be listed on the Site Signature/Delegation of Responsibilities Log. This includes assessment of AE severity and relationship to investigational product. AE information may be volunteered by the subject or solicited by study personnel through non-leading questions.

All treatment-emergent adverse events occurring during the study, regardless of the assumption of causal relationship, must be documented on the respective CRF.
Adverse events should be documented from the time the subject receives the first dose of Investigational Product until the subject's participation in the study has been completed.
If a subject has an ongoing adverse event at the time of study completion, the ongoing adverse event must be followed-up and provided appropriate medical care until the event has resolved or stabilized.

Documentation of adverse events/adverse reactions includes start date and stop date, severity, action(s) taken, seriousness and outcome.

6.9.2 Adverse Event Definitions

The following definitions of terms apply to this section:

- Adverse event: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

- Life-threatening adverse event or life-threatening suspected adverse reaction: an adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- Serious adverse event (SAE) or serious suspected adverse reaction (SSAR): an adverse event or suspected adverse reaction is considered ''serious'' if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: Death, a life-threatening or sight-threatening adverse event, in subject hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse.

- Suspected adverse reaction: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, ''reasonable possibility'' means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

- Unexpected adverse event or unexpected suspected adverse reaction: an adverse event or suspected adverse reaction is considered ‘‘unexpected’’ if it is not listed in the Investigator’s Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator’s Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator’s Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator’s Brochure listed only cerebral vascular accidents. “Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the Investigator’s Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Note: Any medical condition present prior to administration of the masked study medication which remains unchanged or improved should not be recorded as an adverse event at subsequent visits.

Note: If an event occurs during the washout period, prior to subject enrollment and the commencement of study medication, it should be recorded as part of the Medical History and not as an adverse event. As noted in Section 7.1.2, any change in their Visit 1 (screening) health status should be recorded on the Medical History page of the CRF (eg, the subject has been diagnosed with cancer).

Note: In the present study, Investigators are asked to use the verbatim term “conjunctival hyperemia” on the study AE form to describe observations of conjunctival redness if the ocular redness observation is increased from Visit 1 (Screening) observations. Investigators are also asked to note all observations of conjunctival hyperemia on the biomicroscopy CRF as well as on the study AE form.

6.9.3 Timing for Reporting of Adverse Events

The AEs occurring during the study must be documented, regardless of the assumption of a causal relationship. AEs should be documented from the time the subject receives the first dose of investigational product until subject participation in the study has been completed. If a subject has one or more ongoing AEs at the time of study completion, the subject must be followed and provided appropriate medical care until the sign(s) and/or symptoms(s) of the AE have remitted or stabilized in the opinion of the Investigator.

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

1. Action Taken with Study Drug:

   - None

- Investigational Product Discontinued
- Investigational Product Interrupted

2. Other Action Taken:

- None
- Non-Drug Therapy
- New OTC or Rx Drug Added
- Hospitalized less than 24 hours
- Hospitalized greater than or equal to 24 hours

3. Outcome of an adverse event is to be coded as:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with sequelae
- Recovering/Resolving
- Unknown/Lost to follow-up

6.9.4 Severity

Severity of an adverse event is defined as a qualitative assessment of the level of discomfort or the degree of intensity of an adverse event as determined by the Investigator or reported to him/her 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:

- 1 = Mild: present and noticeable, but not distressing, and no disruption of normal daily activities
- 2 = Moderate: bothersome, discomfort sufficient to possibly reduce or affect normal daily activity
- 3 = Severe: incapacitating, with inability to work or perform normal daily activity

A change in 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 severe, or from severe to moderate. In either case, the start and stop dates should be recorded.

Please 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 6.9.9 for further information on serious AEs [SAEs]).

6.9.5 Relationship

The study medication relationship for each adverse event/adverse reaction should be determined by the Investigator using these explanations:

- N**ot 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, or improves on stopping the study medication, or reappears on repeat exposure, or there is a positive reaction at the application site.

6.9.6 Expectedness

For AR-13324, the most frequently reported AE in 3 Phase 2 studies (AR-13324-CS201, AR-13324-CS202, and PG324-CS201) has been conjunctival hyperemia. Other AEs seen in greater frequency with AR-13324 than in active control treatment arms in these studies include instillation site erythema or pain, conjunctival hemorrhage, blurred vision, eye irritation, increased lacrimation, and foreign body sensation.

The most common AEs seen with Latanoprost Ophthalmic Solution, 0.005% in clinical trials as reported in the latanoprost prescribing information (Appendix 3) include conjunctival hyperemia, eyelash changes, increased iris pigmentation, eyelid skin darkening, macular edema (including cystoid macular edema), and intraocular inflammation (iritis/uveitis).

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with this class of drugs or as anticipated from the pharmacological properties of AR-13324 or latanoprost, and are not specifically mentioned as occurring with the investigational product. The AEs that are both unexpected and serious should be reported in an expedited fashion to the Sponsor (see Section 6.9.10 for further details).

6.9.7 Clinical Significance

Determination of whether a finding is clinically significant will be made by the Principal Investigator or the Sub-Investigator and will be documented on the CRF.

6.9.8 Clinical Laboratory Adverse Events

Clinical laboratory values (other than pregnancy tests results) that are noted as abnormal and clinically significant at study exit and that are changes from Visit 1 (screening) values will be documented as AEs.

6.9.9 Serious Adverse Events (SAEs) or Serious Suspected Adverse Reactions

6.9.9.1 Reporting Serious Adverse Events

An investigator must immediately report any SAE or SSAR (see Section 6.9.2 for definitions) to the Sponsor or Rho Product Safety, the Sponsor CRO representative, whether or not the SAE or SSAR is considered drug-related, including those listed in the protocol or Investigator's Brochure. The investigator report must include an assessment of whether there is a reasonable possibility that the drug caused the event. The Investigator must report any SAE or SSAR that occurs during the study for a subject or any SAE or SSAR that occurs within 4 weeks (ie, 30 days) after the last administration of IP. Study endpoints that are serious adverse events (eg, all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (eg, death from anaphylaxis). In that case, the Investigator must immediately report the event to the Sponsor. The investigator must record non-serious adverse events and report them to the Sponsor according to the timetable for reporting specified in the protocol. In case of incomplete information, the Investigator must provide follow-up information as soon as possible, again using the SAE report form.

In addition, in the case of immediately life-threatening AEs or AEs with fatal outcome, or adverse events that are serious, unexpected (ie, not in the Investigator's Brochure) and

judged related to the investigational product, the Investigator must inform the Sponsor or Sponsor representative by phone within 24 hours of observation or occurrence of the SAE.

Pregnancies occurring in subjects enrolled in the study or in their partners must be reported and followed to outcome. While pregnancy itself is not considered to be an AE or SAE, pregnancy reports are tracked by Rho Product Safety. Premature terminations including miscarriage, spontaneous abortion, or elective termination of a pregnancy for medical reasons will be reported as an SAE. Other pregnancy complications should be reported as SAEs, if they meet serious criteria. Should the pregnancy result in a congenital anomaly or birth defect, a separate SAE report must be submitted. Furthermore, all neonatal deaths that occur within 30 days of the birth should be reported as SAEs, without regard to causality.

The Investigator must complete the pregnancy report form and fax or email the form to Rho Product Safety within one business day of knowledge of the pregnancy. Following delivery or termination of pregnancy, the pregnancy report form is to be completed and submitted by fax or email to Rho Product Safety.

SAEs must be reported to the IRB/IEC according to the IRB/EC requirements.

Important: The Investigator must report an SAE or SSAR occurring at his/her site to the Sponsor and IRB/IEC, regardless of causality.

Safety Hotline: [redacted]
Safety Email: [redacted]
Safety Fax: [redacted]

6.9.10 Serious Unexpected Suspected Adverse Reactions (SUSARs)

6.9.10.1 Reporting Serious Unexpected Suspected Adverse Reactions

The Investigator must immediately report serious unexpected suspected adverse reactions (SUSARs) that occur or are observed during the course of the study or within 4 weeks (ie, 30 days) of the last administration of investigational product to a subject. In the event of a SUSAR, the site must notify the Sponsor and/or the Sponsor Medical Monitor by telephone within 24 hours of knowledge of the event:

Sponsor Contact Telephone Number: [redacted]

Sponsor Medical Monitor Telephone Number: [redacted]

In addition, an SAE report form must be completed and sent by FAX to Rho Product Safety within 24 hours of notification, observation, or occurrence of the SUSAR, whether or not complete information is available. In case of incomplete information, the Investigator must provide follow-up information as soon as possible, using the SAE report form.

Reports will be evaluated by the Medical Monitor/Sponsor. The IRB/IEC and Investigators at other study sites will be informed as required.

6.9.11 Follow-up of Subjects after Adverse Events

If an adverse event/adverse reaction occurs, the Investigator will institute support and/or treatment as deemed appropriate. If a non-serious adverse event/adverse reaction is unresolved at the time of the last visit, efforts will be made to follow up until the adverse event/adverse reaction is resolved or stabilized, the subject is lost to follow-up, or there is other resolution to the event.

6.10 Comfort Test

Individuals will be asked "Did you experience any discomfort when placing the drops in your eyes?" This will refer to the study medication use the previous evening. The response will be scored as None, Mild, Moderate or Severe.

6.11 Best Corrected Visual Acuity (BCVA)

Best corrected visual acuity (BCVA) will be taken at visits as a measure of ocular function and will be measured at screening and frequently throughout the study. Visual acuity will be measured using ETDRS charts or their equivalents. Accepted charts are those designed according to the principles described by Ferris and coworkers (Ferris 1982) and supported by the guidelines from the Eye Care Technology Forum (Ferris 1996).

See Appendix 2 for details of the procedures to be followed when determining BCVA.

6.12 Pupil Size

Pupil size will be measured prior to dilation with a ruler to the nearest 0.5 mm in ambient room light.

6.13 Biomicroscopy

Biomicroscopic examination of the eyelids, conjunctiva, cornea, anterior chamber, lens, iris, and pupil of both lenses will be carried out at every study visit for both eyes of subjects. Normal or abnormal status of these ocular tissues will be graded as described in Appendix 2.

6.14 Gonioscopy/Pachymetry

Gonioscopy will be used to confirm the iridocorneal angle is open and to what extent. Eligible subjects must have an angle grading of 3 or 4 (Shaffer grading scale: Kolker 1976) for participation in the study. Pachymetry will be used to measure the thickness of the central cornea. Both of these assessments will be done in order to determine the eligibility of a subject to be enrolled in this study. Further information on these procedures is found in Appendix 2.

6.15 Visual Field Testing

Visual fields must be performed prior to randomization and at selected subsequent visit(s). Visual fields must be determined as automated threshold visual fields (eg, 30-2 or 24-2 Humphrey). SITA Standard is preferred, SITA fast also is allowed. Visual fields must be reliable, defined as those with a) fixation losses less than or equal to 33%, b) false positives less than or equal to 33%, and c) false negatives less than or equal to 33%.

For the visual field test required at study entry:

- In order for an individual to enter the study, unreliable entry visual fields (excessive fixation losses, false negatives or false positives) must be repeated until they meet the above criteria
- They may have been performed within three months prior to randomization, given that they meet the above requirements

See Appendix 2 for further information.

6.16 Dilated Ophthalmoscopy

A dilated funduscopic examination including evaluation of the retina, vitreous, macula, choroid, optic nerve, and cup/disc ratio will be performed. See Appendix 2 for further information on scoring. Evaluation of cup-disc ratio will be performed when ophthalmoscopy is performed.

6.17 Removal of Subjects from the Study or Investigational Product

6.17.1 Completed subject

A completed subject is defined as one who completes all 12 months (365 days) of planned participation in the treatment period of the study [redacted]

6.17.2 Non-completing subject

A non-completing subject is defined as one who exits the study by their own volition or at the discretion of the Investigator, the Medical Monitor, and/or the Sponsor Safety Officer. Any subject may decide to voluntarily withdraw from the study at any time without prejudice. In the event that discontinuation of treatment is necessary, the Investigator will make every attempt to complete all subsequent safety assessments listed for Visit 9.0 (Day 365) as well as a dilated ophthalmoscopy examination.

The subject may be discontinued from the study for any of the following reasons:

- **Adverse Events** (adverse events including, in the opinion of the investigator, clinically relevant laboratory abnormalities and intercurrent diseases reported by the subject or observed by the investigator with documentation on the CRF)
- **Withdrawal of consent**
- **Non-compliance** (eg, use of disallowed medication and/or non-adherence to scheduled follow-up visits)
- **Lost to follow-up**
- **Lack of efficacy** (as demonstrated by IOP measurements and investigator decision that there is a risk of additional glaucomatous damage if the subject continues in the study)
- **Disallowed concurrent medication**
- **Investigator decision**
- **Protocol violation**
- **Death**
- **Other**

6.17.3 Actions after Discontinuation

All subjects who discontinue Investigational Product due to a report of an AE must be followed-up and provided appropriate medical care until their signs and symptoms have remitted or stabilized or until clinically significant abnormal laboratory findings have returned to acceptable or pre-study limits.

For the subject who chooses to withdraw consent or who is discontinued for non-compliance, every possible effort should be made by the Investigator to assure there is an exit visit that includes all examinations listed for Visit 9.0 (Day 365) and dilated ophthalmoscopy.

6.17.4 Discontinuation of the Entire Study

The entire study may be discontinued at a given site (by the Investigator or the Sponsor) or for all sites (by the Sponsor). Prompt, written notice of reasonable cause to all other relevant parties (Sponsor or Investigator) is required. Prompt notice to the IRB/IEC and to regulatory authorities is also required.

6.17.5 Completed study

The study is completed when the planned enrollment has been completed, and all enrolled subjects have completed the study. The Sponsor or their designated representative(s) will be

in communication with investigational sites regarding completion of enrollment and the in-life portion of the study.

7. STUDY ACTIVITIES

The schedule of study visits and procedures is shown in Appendix 1.

7.1 Study Visits

7.1.1 Visit 1 (Screening Visit)

This visit may occur at any time of the day. Individuals who are potential subjects will arrive at the Investigator's office at any time point during the day.

A member of the Investigator's staff will interview the individual as to their qualifications for participation in the study. Individuals will be asked to review the informed consent, discuss issues as needed, and to sign the form. Significant medical and ophthalmic history including systemic and ocular medication use will be taken, and demographic measures recorded (see Section 6.2). An examination will be conducted, including measurement of heart rate and blood pressure, a urine pregnancy test (for females of childbearing potential), collection of a blood sample for clinical laboratory assessments, and an ophthalmic examination to include symptoms, best corrected visual acuity (BCVA), intraocular pressure (before pupil dilation), biomicroscopy, gonioscopy, central corneal thickness by ultrasound pachymetry, visual field testing, and dilated ophthalmoscopy. Gonioscopy and visual fields may be taken up to three months (ie, within 90 days) prior to randomization. If assessment of visual fields requires dilation due to subject small pupils, visual field testing should not take place within 48 hours of Visit 2 (Qualification Visit #1).

Pachymetry must be taken at screening Visit 1 or within one week of Visit 1. The results of blood work should be reviewed after this study visit in order to determine eligibility of the subject prior to undertaking the examination at Visit 2 (Qualification Visit #1). For subjects who are unable or unwilling to have blood drawn for clinical labs at Visit 1 (screening), the blood sample may be drawn at Visit 2 (Qualification Visit #1) so long as the results of the clinical labs are available for that subject prior to Visit 3 (Qualification Visit #2).

All females of childbearing potential must have a negative urine pregnancy test result at the screening examination and must not intend to become pregnant during the study.

The Investigator will evaluate the results of these examinations for possible enrollment of the individual into the study. All individuals who are qualified for enrollment at this study visit should undergo a washout period (if needed) as noted in Section 5.7.1 and will be asked to return for Visit 2 (Qualification Visit #1).

7.1.1.1 Evaluation of eye-drop instillation performance

Subjects (or a legally authorized representative for subjects deemed unable to self-administer) will be provided a bottle of commercially available, multi-dose,

non-medicated artificial tears in a room with access to water and soap. Medication instiller will be asked to instill a drop of the artificial tear in each eye under the observation of a member of the investigator's staff. The staff will observe the subject or representative to assure that they instill one drop of the artificial tear into each eye, without touching the tip of the bottle to their eye or face (Stone 2009). The staff member may work with the individual to improve their delivery technique to meet this standard. If the instiller (or representative) cannot demonstrate proper delivery of the eye drop, or if staff member feels that the individual will be unable to do so consistently, then the subject will be excluded from further study participation.

7.1.1.2 Washout

As noted in Section 5.7.1., a washout period is required for individuals currently using ocular hypotensive medications. The Investigator is encouraged to have interim visits during the washout period for intraocular pressure measurement for individuals to whom the washout period may be a risk for further glaucomatous progression.

7.1.2 Visit 2 (Qualifying Visit #1, for 08:00 hours IOP measurement)

After the washout, if required, individuals will return to the Investigator's office in the early morning. For individuals not requiring washout of ocular hypotensive medication, this visit should take place at least one day and no later than approximately 28 days subsequent to the screening visit. The subject will be questioned regarding any changes in their health or concomitant medication use. Any change in the individual's Visit 1 health status or use of concomitant medications should be recorded on the Medical History page of the CRF (eg, the subject has been diagnosed with cancer). Inclusion/exclusion criteria will be reviewed again for the qualified individual, and the subject's heart rate and blood pressure will be measured. Results of the clinical laboratory tests from Visit 1 need to be available, and reviewed by the Investigator. For subjects who were unable or unwilling to have blood drawn for clinical labs at Visit 1, the blood sample may be drawn at Visit 2 (Qualification Visit #1) so long as the results of the clinical labs are available for that subject prior to Visit 3 (Qualification Visit #2).

The following procedures then will be performed:

- Symptomatology: Individuals will be asked "How are you feeling?"
- Best corrected visual acuity
- A non-dilated eye examination will be performed, including IOP and biomicroscopy
    - IOP must be measured within 30 minutes of the nominal time (ie, 07:30 to 08:30 hours)
    - IOP measurements: Unmedicated (post-washout) IOP > 20 mmHg and < 36 mmHg in both eyes at this qualification visit at 08:00 hour is required. **This is the first of four qualifying IOPs for randomization**. Individuals who do

NOT meet this requirement may return for up to 2 additional (unscheduled) qualification visits within 1 week of failing this qualification visit. Individuals returning at an unscheduled visit within 1 week are required to only re-measure IOP in both eyes. Individuals who screen fail due to IOP being ≥ 36 mmHg in either eye at this study visit or at an unscheduled visit within 1 week of the original visit MAY NOT return for additional qualification visits and are to be exited from the study.

Qualified individuals who have met all criteria at this study visit will be scheduled to return 2-7 days later for the second qualification visit.

7.1.3 Visit 3.0 (Qualifying Visit #2 [Day 1] for IOP measurement at 08:00 hours)

Within 2 to 7 days after Visit 2, individuals will return to the Investigator's office for the next 08:00 hour IOP measurement. The results of the clinical laboratory tests from Visit 1 or Visit 2 need to be available, and reviewed by the Investigator. In order for the individual to be enrolled at a subsequent visit, the tests CANNOT be indicative of any clinically significant disease in the opinion of the Investigator. The subject will be questioned regarding any changes in their health or concomitant medication use. Any change in the individual's health relative to their Visit 1 (screening) or Visit 2 health status and concomitant medication use should be recorded on the Medical History page of the CRF (eg, the subject has been diagnosed with cancer). Inclusion/exclusion criteria will be reviewed *again* for the qualified individual.

The following procedures will be performed:

- Symptomatology: Individuals will be asked "How are you feeling?"
- Heart rate and blood pressure
- Best corrected visual acuity
- A non-dilated eye examination will be performed, including pupil size, IOP and biomicroscopy
    - IOP must be measured within 30 minutes of the nominal time (ie, 07:30 to 08:30 hours)
    - IOP measurements: Unmedicated (post-washout) IOP > 20 mmHg and < 36 mmHg in both eyes at this study visit at 08:00 hour is required. **This is the second of four qualifying IOPs for randomization**.

Qualified individuals will continue with the measurements of IOP at 10:00 hours and 16:00 hours on the day of this study visit. Individuals who do NOT meet the above IOP requirement may return for up to 2 additional (unscheduled) qualification visits within 1 week of failing this qualification visit. Individuals returning at an unscheduled visit within 1 week are required to only re-measure IOP in both eyes. Upon return for an unscheduled

qualification visit, such individuals' IOP measurements would need to qualify at each of 08:00, 10:00 and 16:00 hours. Individuals who screen fail due to IOP being ≥ 36 mmHg in either eye (exclusion criterion) at any of these time points at this study visit or at an unscheduled visit within 1 week of the original visit MAY NOT return for additional qualification visits and are to be exited from the study.

Individuals are allowed to leave the Investigator's office on the day of this study visit between assessments, and eat and drink with no restrictions. However, individuals are not to consume alcohol or engage in strenuous exercise.

7.1.4 Visit 3.1 (Day 1, for IOP measurement at 10:00 hours)

Inclusion/exclusion criteria will be reviewed *again* for the qualified individual. Qualified individuals will be examined. Each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"
- A non-dilated eye examination will be performed, including IOP and biomicroscopy
    - IOP must be measured within 30 minutes of the nominal time (ie, 09:30 to 10:30 hours)

At this and any other in-office visit, any subject complaining of visual function issues will have visual function assessed as judged appropriate by the Investigator.

For further participation in the study, unmedicated IOP at this time (10:00 hours, Day 1) must be > 17 mmHg and < 36 mmHg in both eyes. **This is the third of four qualifying IOPs for randomization.**

Qualified individuals will continue with the qualification visit. Individuals who do NOT meet this requirement may return for up to 2 additional unscheduled qualification visits within 1 week of failing this qualification visit. Individuals returning at an unscheduled visit within 1 week are required to only re-measure IOP in both eyes. Upon return, such individuals would need to qualify at 08:00, 10:00 and 16:00 hours. Individuals who screen fail due to IOP being ≥ 36 mmHg in either eye (exclusion criterion) at any of these time points at this study visit or at an unscheduled visit within 1 week of the original visit MAY NOT return for additional qualification visits and are to be exited from the study.

Individuals are allowed to leave the Investigator's office on the day of this study visit between assessments, and eat and drink without restrictions. However, individuals are not to consume alcohol or engage in strenuous exercise.

7.1.5 Visit 3.2 (Day 1, for IOP measurement at 16:00 hours)

Inclusion/exclusion criteria will be reviewed again for the qualified individual.

Qualified individuals will be examined. Each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"
- A non-dilated eye examination will be performed, including IOP and biomicroscopy
    - IOP must be measured within 30 minutes of the nominal time (ie, 15:30 to 16:30 hours)

For further participation in the study, unmedicated IOP for a subject must be > 17 mmHg and < 36 mmHg in both eyes at this time (16:00 hours, Day 1). **This is the fourth of four qualifying IOPs for randomization**.

Individuals who do NOT meet this requirement may return for up to 2 additional unscheduled qualification visits within 1 week of failing the first qualification visit. Individuals returning at an unscheduled visit within 1 week are required to only re-measure IOP in both eyes. Upon return, such individuals would need to qualify at 08:00, 10:00 and 16:00 hours. Individuals who screen fail due to IOP being ≥ 36 mmHg in either eye (exclusion criterion) at any of these time points at this study visit or at an unscheduled visit within 1 week of the original visit MAY NOT return for additional qualification visits and are to be exited from the study.

As noted in Section 4.2, subjects must qualify in both eyes based upon IOP and ocular history. For a subject who qualifies, the study eye will be the eye with the higher IOP at 08:00 hours on Visit 3. If both eyes have the same IOP at 08:00 hours on Visit 3, then the right eye will be the study eye. In each subject, BOTH eyes will be treated.

At this point, eligible subjects will be enrolled and assigned to an investigational product through an IWRS system according to a computer-generated randomization list. The first kit removed from an investigational product packer assigned through the IWRS system to the eligible subject will be dispensed unopened to the subject, along with written storage instructions.

Subjects will be:

- Instructed to self-administer their masked medication at home between 20:00-22:00 hours (8 PM and 10 PM) beginning with the evening dose on that day
- Instructed to return to the office with their study medication at Week 2 (Day 15)

7.1.6 Visit 4.0 (Week 2 [Day 15], for IOP measurement at 08:00 hours)

Subjects will return to the Investigator's office with their study medication. The subject will be questioned about any missed doses and any changes in their health or concomitant medication use.

Subjects will be examined and each examination will include:

- Heart rate and blood pressure

- Symptomatology: Individuals will be asked "How are you feeling"?
- Recording of any AEs
- Comfort Test: Individuals will be asked "Did you experience any discomfort when placing the drops in your eyes?"
- Best corrected visual acuity
- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy
    - IOP must be measured within 30 minutes of the nominal time (ie, 07:30 to 08:30 hours)
- Collect study medication from the subject.

After randomization, any new or worsening of symptoms beyond those collected at the baseline visit are to be entered as adverse events.

Subjects are allowed to leave the Investigator's office on the day of this study visit between assessments, and eat and drink without restrictions. However, individuals are not to consume alcohol or engage in strenuous exercise.

7.1.7 Visit 4.1 (Week 2 [Day 15], for IOP measurement at 10:00 hours)

Subjects will be examined and each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"
- A non-dilated eye examination will be performed, including IOP and biomicroscopy
    - IOP must be measured within 30 minutes of the nominal time (ie, 09:30 to 10:30 hours)

Subjects are allowed to leave the Investigator's office on the day of this study visit between assessments, and eat and drink without restrictions. However, individuals are not to consume alcohol or engage in strenuous exercise.

7.1.8 Visit 4.2 (Week 2 [Day 15], for IOP measurement at 16:00 hours)

Subjects will be examined and each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"
- A non-dilated eye examination will be performed, including IOP and biomicroscopy

- IOP must be measured within 30 minutes of the nominal time (ie, 15:30 to 16:30 hours)

Subjects will be:

- Instructed to continue to self-administer their masked medication at home between 20:00 - 22:00 hours (8 PM and 10 PM, beginning with the evening dose on that day).
- They also will be instructed to return to the office with their study medication at Week 6 (Day 43)

One subject kit from the originally assigned subject packer will be dispensed to the subject, along with storage instructions.

7.1.9 Visit 5.0 (Week 6 [Day 43], for IOP measurement at 08:00 hours)

Subjects will return to the Investigator's office with their study medication. The subject will be questioned about any missed doses and any changes in their health or concomitant medication use.

Subjects will be examined and each examination will include:

- Heart rate and blood pressure
- Symptomatology: Individuals will be asked "How are you feeling?"
- Recording of any AEs
- Comfort Test: Individuals will be asked "Did you experience any discomfort when placing the drops in your eyes?"
- Best corrected visual acuity
- A non-dilated eye examination will be performed, including IOP measurements and biomicroscopy
    - IOP must be measured within 30 minutes of the nominal time (ie, 07:30 to 08:30 hours)
- Collect study medication from the subject

After randomization, any new or worsening of symptoms beyond those collected at the baseline visit are to be entered as adverse events.

Subjects are allowed to leave the Investigator's office on the day of this study visit between assessments, and eat and drink without restrictions. However, individuals are not to consume alcohol or engage in strenuous exercise.

7.1.10 Visit 5.1 (Week 6 [Day 43], for IOP measurement at 10:00 hours)

Subjects will be examined and each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"
- A non-dilated eye examination will be performed, including IOP and biomicroscopy
    - IOP must be measured within 30 minutes of the nominal time (ie, 09:30 to 10:30 hours)

Subjects are allowed to leave the Investigator's office on the day of this study visit between assessments, and eat and drink without restrictions. However, individuals are not to consume alcohol or engage in strenuous exercise.

7.1.11 Visit 5.2 (Week 6 [Day 43], for IOP measurement at 16:00 hours)

Subjects will be examined and each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"
- A non-dilated eye examination will be performed, including IOP and biomicroscopy
    - IOP must be measured within 30 minutes of the nominal time (ie, 15:30 to 16:30 hours)

Subjects will be:

- Instructed to continue to self-administer their masked medication at home between 20:00 - 22:00 hours (8 PM and 10 PM, beginning with the evening dose on that day)
- Instructed to return to the office with their study medication on Month 3 (Day 90)
- Two subject kits from the originally assigned subject packer for this subject will be dispensed to the subject, along with storage instructions

7.1.12 Visit 6.0 (Month 3 [Day 90], for IOP measurement at 08:00 hours)

Subjects will return to the Investigator's office with their study medication. The subject will be questioned about any missed doses and any changes in their health or concomitant medication use.

Subjects will be examined and each examination will include:

- Heart rate and blood pressure
- Urine Pregnancy Test (female subjects of childbearing potential; as applicable)

- Blood samples will be taken for clinical chemistry and hematology (see Appendix 1). Note that these samples may be taken at any time of the day
- Symptomatology: Individuals will be asked "How are you feeling?"
- Recording of any AEs
- Comfort Test: Individuals will be asked "Did you experience any discomfort when placing the drops in your eyes?"
- Best corrected visual acuity
- A non-dilated eye examination will be performed, including pupil size, IOP measurements and biomicroscopy
    - IOP must be measured within 30 minutes of the nominal time (ie, 07:30 to 08:30 hours)
- Pachymetry at the study visit or within one week of the study visit
- Visual fields (Note: may be assessed up to one week prior to this visit, or later in the morning or afternoon of this series of Day 90 visits so long as it occurs after IOP measurement at that visit). See Appendix 2 for further details when dilation is required due to subject small pupils
- Collect study medication from the subject.

After randomization, any new or worsening of symptoms beyond those collected at baseline are to be entered as adverse events.

Subjects are allowed to leave the Investigator's office on the day of this study visit between assessments, and eat and drink without restrictions. However, individuals are not to consume alcohol or engage in strenuous exercise.

7.1.13 Visit 6.1 (Month 3 [Day 90], for IOP measurement at 10:00 hours)

Subjects will be examined and each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"
- A non-dilated eye examination will be performed, including IOP and biomicroscopy
    - IOP must be measured within 30 minutes of the nominal time (ie, 09:30 to 10:30 hours)

Subjects are allowed to leave the Investigator's office on the day of this study visit between assessments, and eat and drink without restrictions. However, individuals are not to consume alcohol or engage in strenuous exercise.

7.1.14 Visit 6.2 (Month 3 [Day 90], for IOP measurement at 16:00 hours)

Subjects will be examined and each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"
- A non-dilated eye examination will be performed, including IOP and biomicroscopy
    - IOP must be measured within 30 minutes of the nominal time (ie, 15:30 to 16:30 hours)
- A dilated ophthalmoscopy examination (including cup-disc ratio)

Subjects will be:

- Instructed to continue to self-administer their masked medication at home between 20:00 - 22:00 hours (8 PM and 10 PM, beginning with the evening dose on that day)
- Instructed to return to the office with their study medication on Month 6 (Day 180)
- A new packer containing 3 kits will be dispensed to the subject, along with storage instructions

7.1.15 Visit 7.0 (Month 6 [Day 180], for IOP and safety measurements at 08:00 hours)

Subjects will return to the Investigator's office with their study medication. The subject will be questioned about any missed doses and any changes in their health or concomitant medication use.

Subjects will be examined and each examination will include:

- Heart rate and blood pressure
- Urine Pregnancy Test (female subjects of childbearing potential; as applicable)
- Blood samples will be taken for clinical chemistry and hematology (see Appendix 1). Note that these samples may be taken at any time of the day
- Symptomatology: Individuals will be asked "How are you feeling?"
- Recording of any AEs

- Comfort Test: Individuals will be asked "Did you experience any discomfort when placing the drops in your eyes?"
- Best corrected visual acuity
- A non-dilated eye examination will be performed, including pupil size, IOP and biomicroscopy
    - IOP must be measured within 30 minutes of the nominal time (ie, 07:30 to 08:30 hours)
- Pachymetry at the study visit or within one week of the study visit
- Visual fields (Note: may be assessed up to one week prior to this visit, or later in the morning or afternoon of this series of Day 180 visits so long as it occurs after IOP measurement at that visit). See Appendix 2 for further details when dilation is required due to subject small pupils
- Collect study medication from the subject.

After randomization, any new or worsening of symptoms beyond those collected at baseline are to be entered as adverse events.

Subjects are allowed to leave the Investigator's office on the day of this study visit between assessments, and eat and drink without restrictions. However, individuals are not to consume alcohol or engage in strenuous exercise.

7.1.16 Visit 7.1 (Month 6 [Day 180], for IOP and safety measurements at 10:00 hours)

Subjects will be examined and each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"
- A non-dilated eye examination will be performed, including IOP and biomicroscopy
    - IOP must be measured within 30 minutes of the nominal time (ie, 09:30 to 10:30 hours)

Subjects are allowed to leave the Investigator's office on the day of this study visit between assessments, and eat and drink without restrictions. However, individuals are not to consume alcohol or engage in strenuous exercise.

7.1.17 Visit 7.2 (Month 6 [Day 180}, for IOP and safety measurements at 16:00 hours)

Subjects will be examined and each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"
- A non-dilated eye examination will be performed, including IOP and biomicroscopy
    - IOP must be measured within 30 minutes of the nominal time (ie, 15:30 to 16:30 hours)
- A dilated ophthalmoscopy examination (including cup-disc ratio)

Subjects will be:

- Instructed to continue to self-administer their masked medication at home between 20:00 - 22:00 hours (8 PM and 10 PM, beginning with the evening dose on that day)
- Instructed to return to the office with their study medication on Month 9 (Day 270)
- A new packer containing 3 kits will be dispensed to the subject, along with storage instructions

7.1.18 Visit 8.0 (Month 9 [Day 270], for IOP and safety measurements at 08:00 hours)

Subjects will return to the Investigator's office with their study medication. The subject will be questioned about any missed doses and any changes in their health or concomitant medication use.

Subjects will be examined and each examination will include:

- Heart rate and blood pressure
- Urine Pregnancy Test (female subjects of childbearing potential; as applicable)
- Symptomatology: Individuals will be asked "How are you feeling?"
- Recording of any AEs
- Comfort Test: Individuals will be asked "Did you experience any discomfort when placing the drops in your eyes?"
- Best corrected visual acuity
- A non-dilated eye examination will be performed, including IOP and biomicroscopy
    - IOP must be measured within 30 minutes of the nominal time (ie, 07:30 to 08:30 hours)
- Collect study medication from the subject.

After randomization, any new or worsening of symptoms beyond those collected at baseline are to be entered as adverse events.

Subjects are allowed to leave the Investigator's office on the day of this study visit between assessments, and eat and drink without restrictions. However, individuals are not to consume alcohol or engage in strenuous exercise.

7.1.19 Visit 8.1 (Month 9 [Day 270], for IOP and safety measurements at 10:00 hours)

Subjects will be examined and each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"
- IOP measurement
    - IOP must be measured within 30 minutes of the nominal time (ie, 09:30 to 10:30 hours)

Subjects are allowed to leave the Investigator's office on the day of this study visit between assessments, and eat and drink without restrictions. However, individuals are not to consume alcohol or engage in strenuous exercise.

7.1.20 Visit 8.2 (Month 9 [Day 270], for IOP and safety measurements at 16:00 hours)

- Symptomatology: Individuals will be asked "How are you feeling?"
- IOP measurement
    - IOP must be measured within 30 minutes of the nominal time (ie, 15:30 to 16:30 hours)

Subjects will be:

- Instructed to continue to self-administer their masked medication at home between 20:00 - 22:00 hours (8 PM and 10 PM, beginning with the evening dose on that day)
- Instructed to return to the office with their study medication on Month12 (Day 365)
- A new packer containing 3 kits will be dispensed to the subject, along with storage instructions

7.1.21 Visit 9.0 (Month 12 [Day 365], for IOP and safety measurements at 08:00 hours)

Subjects will return to the Investigator's office with their study medication. The subject will be questioned about any missed doses and any changes in their health or concomitant medication use.

Subjects will be examined and each examination will include:

- Heart rate and blood pressure
- Urine Pregnancy Test (female subjects of childbearing potential; as applicable)
- Blood samples will be taken for clinical chemistry and hematology (see Appendix 1). Note that these samples may be taken at any time of the day
- Symptomatology: Individuals will be asked "How are you feeling?"
- Recording of any AEs
- Comfort Test: Individuals will be asked "Did you experience any discomfort when placing the drops in your eyes?"
- Best corrected visual acuity
- A non-dilated eye examination will be performed, including pupil size, IOP and biomicroscopy
    - IOP must be measured within 30 minutes of the nominal time (ie, 07:30 to 08:30 hours)
- Visual fields (Note: may be assessed up to one week prior to this visit, or later in the morning or afternoon of this series of Day 365 visits so long as it occurs after IOP measurement at that visit). See Appendix 2 for further details when dilation is required due to subject small pupils
- Collect study medication from the subject.

After randomization, any new or worsening of symptoms beyond those collected at baseline are to be entered as adverse events.

Subjects are allowed to leave the Investigator's office on the day of this study visit between assessments, and eat and drink without restrictions. However, individuals are not to consume alcohol or engage in strenuous exercise.

7.1.22 Visit 9.1 (Month 12 [Day 365], for IOP and safety measurements at 10:00 hours)

Subjects will be examined and each examination will include:

- Symptomatology: Individuals will be asked "How are you feeling?"
- IOP measurement
    - IOP must be measured within 30 minutes of the nominal time (ie, 09:30 to 10:30 hours)

Subjects are allowed to leave the Investigator's office on the day of this study visit between assessments, and eat and drink without restrictions. However, individuals are not to consume alcohol or engage in strenuous exercise.

7.1.23 Visit 9.2 (Month 12 [Day 365], for IOP and safety measurements at 16:00 hours)

- Symptomatology: Individuals will be asked "How are you feeling?"
- IOP measurement
    - IOP must be measured within 30 minutes of the nominal time (ie, 15:30 to 16:30 hours)
- A dilated ophthalmoscopy examination (including cup-disc ratio)
- [redacted] Study medication is to be collected at 08:00 hours on this day (see section 7.1.21) and none dispensed. [redacted]

[redacted]

[redacted] The subject will exit the study, and will be released to the normal care of their ophthalmologist.

[redacted]

[redacted]

[redacted]

[redacted]

7.2 Unscheduled Visits

An unscheduled visit may be any visit to the Investigator other than the specific visits requested in the protocol as possibly required for the subject's ophthalmic condition. The Investigator will perform all procedures necessary to evaluate the study participant at these visits and record any adverse events in the case report form (CRF).

As noted in Section 6.17.3, every possible effort should be made by Investigators to assure that non-completing subjects have a final visit that includes all examinations listed for Visit 9.0 (Day 365) and dilated ophthalmoscopy.

8. QUALITY CONTROL AND ASSURANCE

The progress of the 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 consent forms
- Records of study medication receipt, storage, preparation, and disposition
- Regulatory files related to this study

9. STATISTICAL METHODS

9.1 Primary Hypotheses

- H_{01}: The difference between study eyes treated with PG324 Ophthalmic Solution and study eyes treated with latanoprost Ophthalmic Solution, 0.005% (PG324 - latanoprost), in mean IOP at the following time points: 08:00, 10:00, and 16:00 hours at the Week 2, Week 6, and Month 3 Visits, is ≥ 0 mmHg for at least one time point over all visits.

- H_{11}: The difference between study eyes treated with PG324 Ophthalmic Solution and study eyes treated with latanoprost Ophthalmic Solution, 0.005% (PG324 − latanoprost), in mean IOP at the following time points: 08:00, 10:00, and 16:00 hours at the Week 2, Week 6, and Month 3 Visits, is < 0 mmHg for all time points over all visits.

- H_{02}: The difference between study eyes treated with PG324 Ophthalmic Solution and study eyes treated with AR-13324 Ophthalmic Solution, 0.02% (PG324 − AR-13324), in mean IOP at the following time points: 08:00, 10:00, and 16:00 hours at the Week 2, Week 6, and Month 3 Visits, is ≥ 0 mmHg for at least one time point over all visits.

- H_{12}: The difference between study eyes treated with PG324 Ophthalmic Solution and study eyes treated with AR-13324 Ophthalmic Solution, 0.02% (PG324 − AR-13324), in mean IOP at the following time points: 08:00, 10:00, and 16:00 hours at the Week 2, Week 6, and Month 3 Visits, is < 0 mmHg for all time points over all visits.

The study will be considered a success if both H_{01} and H_{02} are rejected.

9.2 Sample Size Considerations

Efficacy:

One-hundred ninety six (196) subjects per arm completing 3 months of treatment yields at least 90% power to conclude statistical superiority of PG324 to latanoprost and >99% power to conclude statistical superiority of PG324 to AR-13324 at all nine time points assuming a two-sided alpha = 0.05, a true mean difference of 1.5 mmHg (to latanoprost) and 2.0 mmHg (to AR-13324), a common standard deviation of 3.5 mmHg at each time point, and independence among time points. Power increases as the correlation among time points increases. Therefore, 196 subjects per arm yield at least 90% power to conclude superiority to both controls over all nine time points.

9.3 Analysis Populations

Randomized Population: The randomized population will include all subjects who were randomized to treatment. Baseline variables and demographic characteristics will be summarized for this population.

Intent-to-Treat Population (ITT): The ITT population will include all randomized subjects who have received at least one dose of study medication. This population will be the primary population for efficacy analyses and will be used to summarize all efficacy variables and will summarize subjects as randomized.

Per-protocol population (PP): The PP population is a subset of the ITT population, which will include those subjects (and their visits) who do not have major protocol violations likely to seriously affect the primary outcome of the study as judged by a masked evaluation prior to the unmasking of the study treatment. This population will be the secondary population for efficacy analyses and will be used to summarize a subset of efficacy variables. If the PP and ITT populations are exactly the same, then additional efficacy analyses on the PP population will not be performed. The PP population will summarize subjects as treated.

Safety Population: The safety population will include all randomized subjects who have received at least one dose of study medication. This population will be used to summarize safety variables and will summarize subjects as treated.

9.4 Statistical Methods to be Employed

9.4.1 General Considerations

All continuous study assessments will be summarized by treatment and time point (as applicable) using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). All categorical study assessments will be summarized by treatment and time point (as applicable) using frequency counts and percentages.

Hypothesis testing, unless otherwise indicated, will be performed at a 2-sided 0.05 significance level. When applicable, two-sided 95% confidence intervals will be reported. All p-values will be displayed to four decimal places, with p-values less than 0.0001 presented as '<0.0001' and p-values greater than 0.9999 presented as '>0.9999'. Differences between PG324 and each comparator (latanoprost and AR-13324) will be calculated as PG324 – comparator.

All study data will be listed by treatment, subject and time point (as applicable).

For diurnally-adjusted IOP, baseline will refer to the time-relevant measure at Visit 3.0 through 3.2 (eg, IOP at 08:00 hours at Visit 3.0 will be the baseline for 08:00 hours at Visit 4.0, Visit 5.0, and Visit 6.0; IOP at 10:00 hours at Visit 3.1 will be the baseline for 10:00 hours at Visit 4.1, Visit 5.1, and Visit 6.1; etc.). For all other variables, baseline is defined as the last measurement prior to the first dose of study medication.

The unit of analysis for efficacy will be the study eye. For a subject who qualifies, the study eye will be the eye with the higher IOP at 08:00 hours on Visit 3. If both eyes have the same IOP at 08:00 hours on Visit 3, then the right eye will be the study eye.

Data collected during the observation extension visits may be summarized separately from the data collected during the main portion of the study.

Statistical methods will be more fully described in separate document(s) (ie, the Statistical Analysis Plan).

9.4.2 Interim Analyses

When all subjects have completed three months of treatment, the Sponsor will unmask the study to analyze the 3 month efficacy and safety data. This is the time for primary efficacy analysis of the study. Efforts will be made to keep the Investigators, site staff, and subjects masked as to individual subject assignments, as the subjects continue to be evaluated for safety for the following 9 months. The Sponsor will conduct an additional data base lock and unmask the study when all subjects have completed their 12 month visit. This is the time for primary analysis of the 12 month safety data. Interim analyses will be conducted so as to

maintain the study masking for subjects, Investigators, and site staff, while the Sponsor and data management CRO will be unmasked at both the 3-month interim analysis, and the 12-month interim analysis. [redacted]
The details of the means for maintaining the study masking during the interim analyses will be provided in the study Statistical Analysis Plan.

As the first interim analysis will be the formal primary efficacy analysis, completed on all subjects, no alpha adjustment is required. The second interim analysis will be the formal primary safety analysis, completed on all subjects. [redacted]

9.4.3 Analysis of Baseline Data

Demographic and baseline characteristics such as age, gender, or disease status will be summarized and listed. Medical history, history of ocular surgery and procedures, glaucoma history and washout period (if needed) will also be summarized and listed.

9.4.4 Subject Disposition

Subject enrollment, discontinuation of Investigational Product, and withdrawal from the study will be summarized and listed.

9.4.5 Analysis of Efficacy

The primary efficacy outcome will be the comparison of PG324 Ophthalmic Solution relative to each of its active components (AR-13324, 0.02% and latanoprost, 0.005%) for:

- Mean IOP within a treatment group at 08:00, 10:00, and 16:00 hrs at the Week 2, Week 6, and Month 3 study visits

Secondary efficacy endpoints will include comparison of PG324 Ophthalmic Solution relative to each of its active components (AR 13324, 0.02% and latanoprost, 0.005%) for:

- Mean IOP within a treatment group at each post-treatment time point
- Mean diurnal IOP within a treatment group at each post-treatment visit
- Mean change from diurnally adjusted baseline IOP at each post-treatment time point
- Mean change from baseline in diurnal IOP at each post-treatment visit
- Mean percent change from diurnally adjusted baseline IOP at each post-treatment time point
- Mean percent change from baseline in diurnal IOP at each post-treatment visit

- Percentages of subjects achieving pre-specified mean, mean change, and percent mean change diurnal IOP levels

Other secondary efficacy analyses will be conducted as described in the study Statistical Analysis Plan. Note that each subject will have one eye designated as the study eye. Only the study eyes will be evaluated for the primary efficacy measure or for selected secondary efficacy measures; however, both eyes will be treated. Qualifying fellow eyes will be evaluated separately for the primary analysis of the primary efficacy measure.

The primary analysis of the primary outcome will employ a linear model with mean IOP at the given visit (Week 2, Week 6, and Month 3) and time point (08:00, 10:00, and 16:00 hours) as the response, baseline IOP as a covariate, and treatment as a main effect factor, using the intent to treat population with multiple imputation techniques (eg, Monte Carlo Markov Chain) used to impute missing data. Each time point within each visit will be modeled separately. The least squares mean differences (test – control) between PG324 Ophthalmic Solution and each of Latanoprost Ophthalmic Solution, 0.005% and AR-13324 Ophthalmic Solution, 0.02% will be presented as well as 2-sided p-values and 95% confidence intervals. For a given comparator (latanoprost and AR-13324), if the p-value is $P < 0.05$ and the point estimate < 0 for all time points at the Week 2, Week 6, and Month 3 Visits, then the corresponding null hypothesis will be rejected in favor of the alternative hypothesis and PG324 will be considered to be superior to the comparator. Results will be presented in both tabular and graphical form.

Analyses will be performed primarily on the ITT population using multiple imputation techniques to impute missing data and secondarily using: observed data only, last observation carried forward (LOCF) where LOCF will be performed using time-relevant measures; and baseline observation carried forward (BOCF) using time-relevant measures to determine the robustness of results. Additionally, the above analyses will be repeated on the PP population to determine robustness of results. Additional imputation techniques may be designated in the formal statistical analysis plan. Sample SAS code to demonstrate the methodology that will be used for data imputation can be found in Appendix 7.

Secondary analyses of the primary endpoint will be completed using individual two-sample t-tests and 95% t-distribution confidence intervals for each comparison (PG324 vs latanoprost and AR-13324) at each time point (08:00, 10:00, and 16:00 at the Week 2, Week 6, and Month 3 Visits) using the ITT population. Similar analyses will be completed on the secondary endpoints: mean IOP measure at each time point and visit and mean diurnal IOP and change from baseline diurnal IOP measures. Models adjusting for baseline will only be performed on the mean IOP response variable as inference is identical between this response and the change from baseline IOP response variable in such a model.

Additionally, for the mean IOP values at each time point, mixed model repeated measures will be run with baseline as the covariate; treatment, visit, time point, treatment by visit, treatment by time point, visit by time point, and treatment by visit by time point as the fixed effect factors; and subject as the random effect, repeated measure. An unstructured covariance structure will be used to model the within subject, between visit and time point

variances. This allows for different variances and covariances within and between time points and visits. The treatment by visit, treatment by time point, visit by time point, and treatment by visit by time point interactions allow for a different rate of change in IOP in the different treatment arms among visits and time points. This model will be run including the Week 2, Week 6, and Month 3 visits.

Percent change from diurnally adjusted baseline IOP at each time point will be analyzed using two-sample t-tests, between PG324 and each comparator, at each time point and visit, including two-sample t-tests and 95% t-distribution confidence intervals on the difference (PG324 – comparator).

Mean diurnal IOP values will be constructed by averaging the three diurnal IOP measurements on each of Week 2, Week 6, and Month 3 visits. Mean diurnal baseline IOP will be constructed as the average of the three Day 1 IOP measurements. Mean change from mean baseline diurnal IOP will be created by taking the average of the three time points on each of Week 2, Week 6, and Month 3 visits and subtracting the single mean baseline diurnal IOP measurement.

Sub-group analyses based upon pre-study characteristics such as site, demographics, or pre-study ocular hypotensive medications may be completed to further investigate the efficacy measures.

Analyses of IOP will also include summarizing the number and percentage of study eyes achieving mean diurnal IOP reduction from baseline of ≥ 4 to ≥ 12 mmHg in 2 mmHg increments and percent reduction from baseline of $\geq 5\%$ to $\geq 40\%$ in 5% increments at Week 2, Week 6, and Month 3. Additionally, the number and percentage of study eyes attaining a mean diurnal IOP of ≤ 22 to ≤ 14 mmHg in 1 mmHg increments will be summarized at Week 2, Week 6, and Month 3. Fisher's exact test (2-sided p-values) will be used to test the pair wise differences between treatment groups for each category at each visit. These analyses will be presented for both the ITT and PP populations with observed data only.

[redacted]

[redacted]

9.4.6 Analysis of Safety

9.4.6.1 Ocular and Systemic Safety Assessments

Slit lamp biomicroscopy and dilated ophthalmoscopy measures will be summarized at each measured time point using discrete summary statistics.

Visual acuity data will be summarized at each time point using both continuous summaries (logMAR), including change from baseline, and discrete summaries, including change from baseline on an ETDRS chart in the number of lines and the proportion of subjects with a worsening of ≥ 3 lines from baseline.

Pupil size will be summarized at each visit and for change from baseline to each visit using continuous summary statistics by treatment group and visit.

Visual field mean deviation and cup-to-disc ratio will be summarized at each visit and for change from baseline to each visit using continuous summary statistics by treatment group and visit.

Vital signs will be summarized at each visit and for change from baseline to each visit using continuous summary statistics by treatment group and visit.

Clinical laboratory results will be summarized using both continuous summaries, including change from baseline, and discrete summaries, including frequency and percent of subjects with an abnormal value and shift tables from baseline. Additionally, laboratory data will be presented in data listings. A copy of the certification and a table of the normal ranges for the reference laboratory conducting any clinical laboratory tests required by this protocol must be provided.

[redacted]

[redacted]

9.4.6.2 Adverse Events

Verbatim descriptions of AEs will be mapped to MedDRA thesaurus terms and be presented in a data listing. Treatment emergent AEs, those that occur after the first dose of study medication, will be summarized by treatment group using frequency and percent for each system organ class (SOC) and preferred term (PT) within each SOC. Summaries will be

presented separately for ocular and non-ocular AEs. These summaries will also be presented for relation to Investigational Product and by severity. Fisher's exact test will be used to test the difference in proportions of subjects with each AE between treatment groups (SOC and PT).

9.5 Procedure for Accounting for Missing, Unused, or Spurious Data

Analyses will be performed primarily on observed data only (without imputation) and secondarily using: last observation carried forward (LOCF) where LOCF will be performed using time-relevant measures (ie, from the same time point of the most recent visit with a non-missing value); BOCF using time-relevant measures; and using multiple imputation methods to determine the robustness of results. Any missing, unused, or spurious data will be noted in the final statistical report.

9.6 Procedure for Reporting Deviations from the Statistical Plan

Any deviations from the statistical plan will be described and a justification given in the final statistical report.

9.7 Data Listings

Data listings will be prepared for all data on the database.

10. ADMINISTRATIVE CONSIDERATIONS

10.1 GCP compliance

The proposed study is subject to all applicable governmental rules and regulations concerning the conduct of clinical trials on human subjects. This includes, but is not necessarily limited to:

- Approval of properly constituted Institutional Review Boards
- Helsinki Declaration (See Appendix 6)
- U.S. FDA Law
- ICH GCP guidelines
- Obtaining prospective informed consent
- Monitoring of the conduct of the study
- Completeness of the Case Report Forms by the Sponsor or its designee(s)
- Appropriate record retention by the Investigator.

Protocol change or amendment procedures, applicable IRB requirements, Investigator/Sponsor obligations, and study monitoring procedures are detailed in Section 10.2 through Section 10.8 of this protocol.

10.2 Amendments to the Protocol

Modifications of the signed protocol are only possible by approved protocol amendments and with the agreement of all responsible persons. The procedure for approval of a protocol amendment is identical to that for approval of the protocol. The ethics committee must be informed of all protocol amendments and should be asked for its opinion as to whether a full re-evaluation of the ethical aspects of the study is necessary by the committee. This should be fully documented.

The investigator must not implement any deviation from or change to the protocol, without discussion with, and agreement by Aerie and prior review and documented approval/favorable opinion of the amendment from the relevant ethics committee, except where it is necessary to eliminate an immediate hazard to study subjects, or where the change(s) involves only logistical or administrative aspects of the study (eg, change in monitor(s), change of telephone number(s)).

Protocol amendments will be submitted to the appropriate authority(ies) as required by the applicable regulatory requirement(s).

10.3 Investigators and Study Administrative Structure

The principal investigator is responsible for all site medical-related decisions. The qualified Sponsor Medical Monitor is responsible for the safe conduct of this study. The contact information of the Sponsor Medical Monitor is as follows:

10.4 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

This study is to be conducted in accordance with IRB regulations (ie, US 21CFR Part 56.103) and GCPs. The protocol, protocol amendments, informed consent form, and all documents that will be provided to subjects (for example, subject diary, subject dosing instructions) will be submitted to the central and/or local IRB(s)/IEC(s) for review and approval. This protocol, materials used to recruit subjects, and materials used to document consent must be approved by the IRB prior to initiation of the study. Written IRB approval must adequately identify the protocol and informed consent. A copy of the letter from the IRB/IEC indicating approval of an Investigator must be received by the Sponsor prior to conducting any study-specific procedures. In addition to approving the protocol and an Investigator participating in the study, the IRB must also approve the Subject Information and Consent Form, as well as any advertising tools that will be used for the study. Written approval also must indicate whether approval was granted based on full committee review or expedited review. Copies of all approved materials, all correspondence with the

IRB, and written approval from the IRB must be made available to the Sponsor prior to the start of subject enrollment into the study.

When the study is completed, the Investigator will provide the governing IRB with a brief final review report.

10.5 Ethical Conduct of the Study

The study will be conducted according to this clinical protocol and will be governed by the following directives and guidelines:

- US Code of Federal Regulations, Title 21
- ICH – Consolidated Good Clinical Practices Guideline (E6)
- Standard Operating Procedures (SOPs) of the Sponsor and any vendors participating in the conduct of the study
- The ethical principles that have their origin in the Declaration of Helsinki (Appendix 6)

10.6 Subject Information and Consent

Informed consent must take place before any study specific procedures are initiated in the treatment period of the study (Screening through Visit 9 [Month 12, Day 365]) [redacted] Signed and dated written informed consent must be obtained from each subject and/or from the subject's legal guardian prior to enrollment into the treatment period of the study [redacted]

All informed consent forms must be approved for use by the Sponsor and receive approval/favorable opinion from an IRB/IEC prior to their use. If the consent form requires revision (eg, due to a protocol amendment or significant new safety information), it is the Investigator's responsibility to ensure that the amended informed consent is reviewed and approved by the Sponsor prior to submission to the governing IRB/IEC and that it is read, signed and dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study if directed by the IRB/IEC.

10.7 Subject Confidentiality

The Investigator and his/her staff will maintain all personal subject data collected and processed for the purposes of this study using adequate precautions to ensure confidentiality, in accordance with local, state and federal laws and regulations.

Monitors, auditors and other authorized representatives of Aerie, the IRB/IEC approving this study, and government regulatory authorities (eg, FDA and other foreign regulatory

agencies) may be granted direct access to the study subject's original medical and study records for verification of the data or clinical study procedures. Access to this information will be permitted to representatives of the aforementioned organizations to the extent permitted by law.

A report of this study's results may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but subject identities will not be disclosed in these documents.

10.8 Study Monitoring

Clinical research associates hired or contracted by the Sponsor will be responsible for monitoring the study sites and study activities. They will contact and visit the Investigator regularly. The actual frequency of monitoring visits depends on subject enrollment and on study site performance. Among others, the following items will be reviewed:

- Study progress
- Compliance with the protocol
- Completion of CRFs
- Dispensing, storage, and accountability of IP, including intentional or inadvertent unmasking of IP
- Source data verification
- AE and SAE reporting
- Essential documents contained within the regulatory binder

For source data verification (ie, comparison of CRF entries with subject records), data will be 100% source verified and will include as a minimum:

- Subject identification
- Informed consent (procedure, signature, and date)
- Selection criteria
- Primary efficacy and safety parameters (ie, AEs)

Member(s) of the Sponsor or their designee will meet with the Investigator prior to the initiation of the study in order to assess the adequacy of the Investigator's subject population, facilities, and equipment, and to familiarize the Investigator with the protocol.

A member of the Sponsor or their designee in the role of Study Monitor will subsequently meet with the Investigator after several of the subjects have initiated the study in order to ensure that the subjects are being properly selected, that adequate supplies for the study have been provided and that the assignment of medication is properly recorded. In addition, the Study Monitor will verify that the Investigator follows the approved protocol and all approved amendments, if any, by reviewing the Investigator's regulatory documents, source documents, Informed Consent Forms, and Case Report Forms of study subjects.

The Study Monitor will meet with the Investigator when all subjects have completed the Final Visit of the study, in order to collect the Case Report Forms, unused study medications, and unused supplies and materials.

Interim monitoring visits and telephone consultations will be done by the Study Monitor as necessary, to ensure the proper progression and documentation of the study.

10.9 Case Report Forms and Study Records

The initial point of entry of study data should be the subject source documentation. The location and nature of the source documentation for all data collected in the study will be identified in the study files at the investigator's site. In cases where no source documents will be used (ie, data will be recorded directly onto the case report form (CRF) without first being recorded on another document, such as a flowsheet, laboratory report, or other typical form of data reporting for later transcription to the CRF), the original data will be included in the CRF.

Source document information should be legible. Recorded data should only be corrected by drawing a single line through the incorrect entry and writing the revision next to the corrected data. The person who has made the correction should place his or her initials as well as the date of the correction next to the correction. Data may not be obliterated by erasure, redaction, or with correction fluid.

Study data will be transcribed and recorded via an electronic data capture (EDC) system as electronic CRFs (eCRFs). Security and authorization procedures consistent with the EDC system must be used. At each subject visit, the appropriate eCRFs must be completed. Whenever an eCRF is used, be sure to provide all information requested including subject identification number and initials, name or number of Investigator, date(s), etc.
All applicable questions should be answered and all data requested should be provided. Those areas that require a response but are not filled in correctly are considered incomplete or erroneous entries, and will have to be corrected.

Each authorized study staff member will receive a unique access account in order to use the EDC system. Access accounts will not be shared among study staff. Authorized users will make entries and/or changes to eCRFs via a secure internet access. Each completed set of eCRFs will be reviewed by the Investigator who will then electronically sign and date the eCRF confirming that data for the subjects are complete and accurate.

The study records must include a copy of each Investigator's CV and medical license, completed, FDA Form 1572 or statement of Investigator, each eCRF, subject charts/source documents, Investigator's Brochure, protocol, protocol amendments, correspondence with the Sponsor and the IRB/IEC, IP storage, receipts, returns and dispensing records, Delegation of Responsibilities Log, site training records, records of site monitoring, any unmasking documentation, AE and SAE reporting, IRB/IEC approvals, advertisements, written information provided to subjects, and subject completed ICFs. If the Investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person (eg, Sponsor, other Investigator) who will accept the responsibility. Notice of this transfer, including written acceptance, must be made to and agreed upon by the Sponsor.

10.10 Protocol Deviations

A protocol deviation occurs when there is non-adherence to study procedures or schedules which does not involve inclusion/exclusion criteria or the primary efficacy endpoint and which does not place the subject at any added risk or affect the data quality or study outcome. Examples of deviations include common out of window visits or timed procedures, a missed procedure, etc. Sites will record protocol deviations in the study records. To the extent possible, sites will make their best efforts to quickly remedy deviations.

The site will contact the Sponsor for clarification of inclusion/exclusion criteria as needed prior to enrollment of a study subject. The Sponsor will document clarification requests and responses. If a potential subject does not meet all inclusion and exclusion criteria during screening, that subject may not be enrolled in the study.

The site will notify the Sponsor or their representative and IRB/IEC within 10 days of becoming aware of any significant protocol deviation. Typically, significant protocol deviation include significant deviations from the inclusion and exclusion criteria that may impact interpretation or the quality of efficacy information or the safety of a subject, concomitant medication restrictions, or any other protocol requirement that results in a significant added risk to the subject or has an impact on the quality of the data collected or the outcome of the study.

The Sponsor will review, designate, and/or approve all protocol deviations prior to database lock.

10.11 Access to Source Documentation

Monitors, auditors, and other authorized representatives of the Sponsor, the governing IRB(s)/IEC(s), the FDA, the DHHS, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study subject's original medical and study records for verification of the data and/or clinical study procedures. Access to this information will be permitted to representatives of the aforementioned organizations to the extent permitted by law.

10.12 Data Generation and Analysis

After data have been entered into the study EDC system database, a system of computerized data validation checks will be implemented and applied to the database. Query reports pertaining to data omissions and discrepancies will be forwarded to the clinical Investigator and the Sponsor for resolution. Where required, the Investigator will be asked for supplementary information through a query. The study EDC system database will be updated by the clinical investigator or their staff, in accordance with the resolved query reports. All changes to the study database will be documented.

Once the eCRFs are monitored in the EDC system, the data management CRO and the Sponsor will further check the eCRFs for completeness and plausibility of the data. The data management CRO will use quality systems in order to verify accurate and complete data entry, including additional checks of the data once entered in a database (eg, range checks, cross checks and other edit checks).

All procedures for the handling and analysis of data will be conducted using good computing practices meeting ICH and US Food and Drug Administration (FDA) guidelines for the handling and analysis of data for clinical trials. Data will be checked per the data management CRO's SOPs. The database then will be locked and a biostatistician will complete the analyses of the data in accordance with the Statistical Analysis Plan.

10.13 Retention of Data

Archived versions of the EDC system database will be saved by the Sponsor consistent with ICH Good Clinical Practices Guidelines. The Sponsor will notify the investigator when documents should be returned.

The Investigator's site and the study clinical laboratory will retain all records related to the study in compliance with ICH Good Clinical Practices Guidelines and 21 CFR 312.57(c) (see Appendix 5 for additional investigator obligations).

10.14 Financial Disclosure

The Principal Investigator and Sub-investigators (as listed on Form FDA 1572) will provide financial disclosure information prior to participation in the study. The Principal Investigator and any Sub-investigators will notify the Sponsor promptly of any required revision to their financial disclosure status during the term of this study, annually, or at the end of the study (if applicable). The Principal Investigator and Sub-investigators will provide updated financial disclosure information upon the Sponsor's written request following completion of the study.

10.15 Publication and Disclosure Policy

Aerie Pharmaceuticals, as the Sponsor, has proprietary interest in the study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Aerie Pharmaceuticals personnel. As this study involves multiple centers, no

individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Aerie Pharmaceuticals.

11. REFERENCES

11.1 Published References

1. Chen J, Runyan SA, Robinson MR. Novel ocular antihypertensive compounds in clinical trials. Clin Ophthalmol 2011; 5:667-77.
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5. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol 2002; 120: 1268-79.
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15. Wang R-F, Williamson JE, Kopczynski C, et al. Effect of 0.04% AR-13324, a ROCK and Norepinephrine Transporter Inhibitor, on Aqueous Humor Dynamics in Normotensive Monkey Eyes. J Glaucoma, 2015; 24:51-4.

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11.2 Internal References

1. Aerie Pharmaceuticals, Inc., AR-13324 Investigator's Brochure, 2017.

2. AR-13324-CS101 Clinical Study Report: An Open-Label Study Assessing the Ocular and Systemic Safety and Systemic Absorption of AR-13324 Ophthalmic Solution, 0.02% in Healthy Volunteers (2014).

3. AR-13324-CS201 Clinical Study Report: A Phase 2, double-masked, randomized, placebo-controlled, dose-response study assessing the safety and ocular hypotensive efficacy of three doses of AR-13324 Ophthalmic Solution in patients with elevated intraocular pressure (2012).

4. AR-13324-CS202 Clinical Study Report: A phase 2, double-masked, randomized, multi-center, active-controlled, dose-response parallel-group study comparing the safety and ocular hypotensive efficacy of AR-13324 to latanoprost in patients with elevated intraocular pressure (2013).

5. PG324-CS201 Clinical Study Report: A double-masked, randomized, controlled study assessing the safety and ocular hypotensive efficacy of PG324 Ophthalmic Solution, 0.01% and PG324 Ophthalmic Solution, 0.02%, compared to AR-13324 Ophthalmic Solution, 0.02% and Latanoprost Ophthalmic Solution, 0.005% in patients with elevated intraocular pressure (2014).

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Appendix 1 Schedule of Visits and Examinations

Day/Week/Month	Screen	Qual #1	Qual. #2 D1			Post D1 Treatment Period Assessments															Observational Period	
						W2 (Day 15±3)			W6 (Day 43±3)			M3, M6 (Day 90±3, Day 180±7)			M9 (Day 270±7)			M12 (Day 365±7)			M13 (D395± 7)	M14 (D425± 7)
Visit	**1**	**2**	**3.0**	**3.1**	**3.2**	**4.0**	**4.1**	**4.2**	**5.0**	**5.1**	**5.2**	**6.0, 7.0**	**6.1, 7.1**	**6.2, 7.2**	**8.0**	**8.1**	**8.2**	**9.0**	**9.1**	**9.2**	**10**	**11**
Hour (XY = XY:00)		**08**	**08**	**10**	**16**	**08**	**10**	**16**	**08**	**10**	**16**	**08**	**10**	**16**	**08**	**10**	**16**	**08**	**10**	**16**	**08**	**08**
Informed Consent	X																			X[12]		
Inclusion/Exclusion	X	X	X	X	X																	
Washout[1]	X																					
Demography	X																					
Medical/Ophthalmic Hist.	X	X	X																			
Concomitant Medications	X	X	X			X			X			X			X			X			X	X
HR/BP	X	X	X			X			X			X			X			X				
Urine Pregnancy Test[2]	X											X			X			X				
Clinical Labs (Chem/Hem)	X[3]											X						X				
Symptoms/AEs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comfort Test[5]						X			X			X			X			X				
Visual Acuity (ETDRS)	X	X	X			X			X			X			X			X			X	X
Pupil size			X									X						X				
IOP	X	X[6]	X[6]	X[6]	X[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biomicroscopy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X			X	X
Gonioscopy[7]/ Pachymetry[8]	G/P											P										
Visual Field[9]	X											X						X				X
Ophthalmoscopy (dilated)	X													X				X[11]		X		X
Eye-Drop Instillation Eval.	X																					
Study Meds Dispensed					X			X			X			X			X					
Collect Study Meds						X[10]			X[10]			X[10]			X[10]			X[10]				
Study Completed																		X[13]				X[13]

Abbreviations: D, day; W, week; M, month; Med/Ophthalmic Hist, Medical/Ophthalmic History; HR/BP, heart rate/blood pressure; Clin Labs, Clinical Labs (Chemistry/Hematology); G, gonioscopy; P, pachymetry; AE, adverse event; ETDRS, early treatment diabetic retinopathy study; IOP, intraocular pressure

Appendix 1 Schedule of Visits and Examinations (cont'd)

[1] Subjects currently using ocular hypotensive medications must undergo a minimum washout period (Table 1 for details).
[2] Urine pregnancy test for women of childbearing potential is required.
[3] For subjects who are unable or unwilling to have blood drawn for clinical labs at Visit 1 (screening), the blood sample may be drawn at Visit 2 (Qualification Visit #1) so long as the results of the clinical labs are available for that subject prior to Visit 3 (Qualification Visit #2).
[4] Ocular symptoms: Subjects will be queried at each visit "How are you feeling?" and treatment emergent AEs beginning at Visit 3 (Qualification Visit #2) will be documented on the AE form. Additional symptoms reported after screening and before randomization will be documented on the medical history form.
[5] Comfort test: At 08:00 hour for study drug visits, subjects will be queried "Did you experience any discomfort when placing the drops in your eyes?"
[6] Individuals returning at an unscheduled visit within 1 week are required to only remeasure IOP in both eyes (Section 7.1.2 to Section 7.1.5).
[7] Gonioscopy evaluation up to 3 months prior to randomization is acceptable.
[8] Pachymetry within one week of study visit is acceptable.
[9] Entry visual field evaluation up to 3 months prior to randomization is acceptable. Visual field collection must meet the requirement for automated threshold visual field assessment (eg, 30-2 or 24-2 Humphrey) and reliability.
[10] Collect used kit(s) dispensed during the previous visit.
[11] Ophthalmoscopy (dilated) at Visit 9.0 at 08:00: this assessment should be performed for all non-completing subjects during the exit visit.
[12] Informed consent must be completed by the subjects before entering the extension visits.
[13] Month 12 visit completed for the treatment period. Month 14 visit completed for the subjects entering the extension visits of the study.

Appendix 3 Marketed Product Information: Latanoprost Ophthalmic Solution, 0.005%

The following is taken from the most recent package insert as of the date of this protocol for latanoprost ophthalmic solution 0.005% as marketed by Bausch & Lomb.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LATANOPROST safely and effectively. See full prescribing information for LATANOPROST.
LATANOPROST (latanoprost ophthalmic solution) 0.005%
Initial U.S. Approval: 1996

----------INDICATIONS AND USAGE----------
Latanoprost is a prostaglandin F2α analogue indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. **(1)**

----------DOSAGE AND ADMINISTRATION----------
One drop in the affected eye(s) once daily in the evening. **(2)**

---------- DOSAGE FORMS AND STRENGTHS----------
Ophthalmic solution containing 50 mcg/mL latanoprost (0.005%). **(3)**

----------CONTRAINDICATIONS----------
Known hypersensitivity to latanoprost, benzalkonium chloride, or any other ingredients in this product. **(4)**
----------WARNINGS AND PRECAUTIONS----------
• Pigmentation: pigmentation of the iris, periorbital tissue (eyelid) and eyelashes can occur. Iris pigmentation likely to be permanent. **(5.1)**
• Eyelash Changes: gradual change to eyelashes including increased length, thickness and number of lashes. Usually reversible. **(5.2)**

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥4%) from clinical trials are blurred vision, burning and stinging, conjunctival hyperemia, foreign body sensation, itching, increased pigmentation of the iris, punctate epithelial keratopathy, and upper respiratory tract infection/cold/flu. **(6).**

To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb at 1-800-323-0000 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
In vitro studies have shown that precipitation occurs when eye drops containing thimerosal are mixed with Latanoprost. If such drugs are used, they should be administered at least 5 minutes apart. **(7)**

See 17 for PATIENT COUNSELING INFORMATION

Revised: 02/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*****_Sections or subsections omitted from the full prescribing information are not listed._

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
Latanoprost Sterile Ophthalmic Solution is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

2 DOSAGE AND ADMINISTRATION
The recommended dosage is one drop in the affected eye(s) once daily in the evening. If one dose is missed, treatment should continue with the next dose as normal.

The dosage of latanoprost ophthalmic solution should not exceed once daily; the combined use of two or more prostaglandins, or prostaglandin analogs including latanoprost is not recommended. It has been shown that administration of these prostaglandin drug products more than once daily may decrease the intraocular pressure (IOP) lowering effect or cause paradoxical elevations in IOP.

Reduction of the IOP starts approximately 3 to 4 hours after administration and the maximum effect is reached after 8 to 12 hours.

Latanoprost ophthalmic solution may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart. Contact lenses should be removed prior to the administration of latanoprost ophthalmic solution, and may be reinserted 15 minutes after administration.

3 DOSAGE FORMS AND STRENGTHS
Sterile ophthalmic solution containing 50 mcg/mL latanoprost.

4 CONTRAINDICATIONS
Known hypersensitivity to latanoprost, benzalkonium chloride, or any other ingredients in this product.

5 WARNINGS AND PRECAUTIONS

5.1 Pigmentation
Latanoprost has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as latanoprost is administered.

The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of latanoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. Beyond 5 years the effects of increased pigmentation are not known [see Clinical Studies (14.2)].

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and

the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with latanoprost can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly [see Patient Counseling Information (17.1)].

5.2 Eyelash Changes
Latanoprost may gradually change eyelashes and vellus hair in the treated eye; these changes include increased length, thickness, pigmentation, the number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are usually reversible upon discontinuation of treatment [see Patient Counseling Information (17.2)].

5.3 Intraocular Inflammation
Latanoprost should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation because inflammation may be exacerbated.

5.4 Macular Edema
Macular edema, including cystoid macular edema, has been reported during treatment with latanoprost. Latanoprost ophthalmic solution should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

5.5 Herpetic Keratitis
Reactivation of Herpes Simplex keratitis has been reported during treatment with latanoprost ophthalmic solution. Latanoprost should be used with caution in patients with a history of herpetic keratitis. Latanoprost should be avoided in cases of active herpes simplex keratitis because inflammation may be exacerbated.

5.6 Bacterial Keratitis
There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface [see Patient Counseling Information (17.3)].

5.7 Use with Contact Lenses
Contact lenses should be removed prior to the administration of latanoprost ophthalmic solution, and may be reinserted 15 minutes after administration.

6 ADVERSE REACTIONS
The following adverse reactions were reported in postmarketing experience and are discussed in greater detail in other sections of the label:

• Iris pigmentation changes [see Warnings and Precautions (5.1)]
• Eyelid skin darkening [see Warnings and Precautions (5.1)]
• Eyelash changes (increased length, thickness, pigmentation, and number of lashes) [see Warnings and Precautions (5.2)]
• Intraocular inflammation (iritis/uveitis) [see Warnings and Precautions (5.3)]

• Macular edema, including cystoid macular edema [see Warnings and Precautions (5.4)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Latanoprost was studied in three multicenter, randomized, controlled clinical trials. Patients received 50 mcg/mL latanoprost once daily or 5 mg/mL active-comparator (timolol) twice daily. The patient population studied had a mean age of 65±10 years. Seven percent of patients withdrew before the 6-month endpoint.

Table 1: Ocular Adverse Reactions and ocular signs/symptoms reported by 5–15% of patients receiving Latanoprost

Symptom/Finding	Adverse Reactions (incidence (%)	
	Latanoprost (n = 460)	**Timolol (n = 369)**
Foreign body sensation	**13**	**8**
Punctate epithelial keratopathy	**10**	**9**
Stinging	**9**	**12**
Conjunctival hyperemia	**8**	**3**
Blurred vision	**8**	**8**
Itching	**8**	**8**
Burning	**7**	**8**
Increased pigmentation of the iris	**7**	**0**

Less than 1% of the patients treated with latanoprost required discontinuation of therapy because of intolerance to conjunctival hyperemia.

6.2 Postmarketing Experience

The following reactions have been identified during postmarketing use of latanoprost in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to latanoprost, or a combination of these factors, include:

Nervous System Disorders: dizziness, headache, and toxic epidermal necrolysis

Eye Disorders: eyelash and vellus hair changes (increased length, thickness, pigmentation, and number); keratitis; corneal edema and erosions; intraocular inflammation (iritis/uveitis); macular edema, including cystoid macular edema; misdirected eyelashes sometimes resulting in eye irritation; periorbital and lid changes resulting in deepening of the eyelid sulcus.

Respiratory, Thoracic and Mediastinal Disorders: asthma and exacerbation of asthma; dyspnea

Skin and Subcutaneous Tissue Disorders: eyelid skin darkening Infections and Infestations: Herpes keratitis

Table 2: Adverse Reactions that were reported in 1–5% of patients receiving Latanoprost

	Adverse Reactions (incidence (%))	
	Latanoprost (n = 460)	**Timolol (n = 369)**
Ocular Events/Signs and Symptoms		
Excessive tearing	**4**	**6**
Lid discomfort/pain	**4**	**2**
Dry eye	**3**	**3**
Eye pain	**3**	**3**
Lid crusting	**3**	**3**
Lid erythema	**3**	**2**
Photophobia	**2**	**1**
Lid edema	**1**	**3**
Systemic Events		
Upper respiratory tract infection/cold/flu	**3**	**3**
Muscle/joint/back pain	**1**	**0.5**
Rash/allergic skin reaction	**1**	**0.3**

7 DRUG INTERACTIONS

In vitro studies have shown that precipitation occurs when eye drops containing thimerosal are mixed with latanoprost. If such drugs are used, they should be administered at least five (5) minutes apart.

The combined use of two or more prostaglandins, or prostaglandin analogs including latanoprost is not recommended. It has been shown that administration of these prostaglandin drug products more than once daily may decrease the IOP lowering effect or cause paradoxical elevations in IOP.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.

Reproduction studies have been performed in rats and rabbits. In rabbits, an incidence of 4 of 16 dams had no viable fetuses at a dose that was approximately 80 times the maximum human dose, and the highest nonembryocidal dose in rabbits was approximately 15 times the maximum human dose.

There are no adequate and well-controlled studies in pregnant women. Latanoprost should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when latanoprost is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

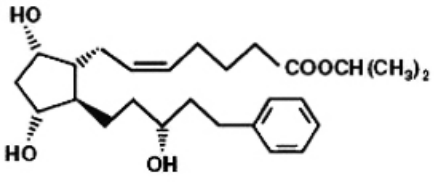
10 OVERDOSAGE

Intravenous infusion of up to 3 mcg/kg in healthy volunteers produced mean plasma concentrations 200 times higher than during clinical treatment and no adverse reactions were observed. Intravenous dosages of 5.5 to 10 mcg/kg caused abdominal pain, dizziness, fatigue, hot flushes, nausea, and sweating. If overdosage with latanoprost occurs, treatment should be symptomatic.

11 DESCRIPTION

Latanoprost is a prostaglandin F2α analogue. Its chemical name is isopropyl-(Z)-7[(1R,2R,3R,5S)3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate. Its molecular formula is C26H40O5 and its chemical structure is:

M.W. 432.58



Latanoprost is a colorless to slightly yellow oil that is very soluble in acetonitrile and freely soluble in acetone, ethanol, ethyl acetate, isopropanol, methanol, and octanol. It is practically insoluble in water.

Latanoprost ophthalmic solution 0.005% is supplied as a sterile, isotonic, buffered aqueous solution of latanoprost with a pH of approximately 6.7 and an osmolality of approximately

267 mOsmol/kg. Each mL of Latanoprost ophthalmic solution contains 50 micrograms of latanoprost. Benzalkonium chloride, 0.02% is added as a preservative. The inactive ingredients are: sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous, and water for injection. One drop contains approximately 1.5 mcg of latanoprost.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Latanoprost is a prostanoid selective FP receptor agonist that is believed to reduce the intraocular pressure (IOP) by increasing the outflow of aqueous humor. Studies in animals and man suggest that the main mechanism of action is increased uveoscleral outflow. Elevated IOP represents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.

12.2 Pharmacodynamics

Reduction of the IOP in man starts about 3–4 hours after administration and maximum effect is reached after 8–12 hours. IOP reduction is present for at least 24 hours.

12.3 Pharmacokinetics

Absorption

Latanoprost is absorbed through the cornea where the isopropyl ester prodrug is hydrolyzed to the acid form to become biologically active.

Distribution

The distribution volume in humans is 0.16 ± 0.02 L/kg. The acid of latanoprost can be measured in aqueous humor during the first 4 hours, and in plasma only during the first hour after local administration. Studies in man indicate that the peak concentration in the aqueous humor is reached about two hours after topical administration.

Metabolism

Latanoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to the biologically active acid. The active acid of latanoprost reaching the systemic circulation is primarily metabolized by the liver to the 1,2-dinor and 1,2,3,4-tetranor metabolites via fatty acid β-oxidation.

Excretion

The elimination of the acid of latanoprost from human plasma is rapid (t1/2 = 17 min) after both intravenous and topical administration. Systemic clearance is approximately 7 mL/min/kg. Following hepatic β-oxidation, the metabolites are mainly eliminated via the kidneys. Approximately 88% and 98% of the administered dose are recovered in the urine after topical and intravenous dosing, respectively.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Latanoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 170 mcg/kg/day (approximately 2800 times the recommended maximum human dose) for up to 20 and 24 months, respectively.

Latanoprost was not mutagenic in bacteria, in mouse lymphoma, or in mouse micronucleus tests. Chromosome aberrations were observed in vitro with human lymphocytes. Additional in vitro and in vivo studies on unscheduled DNA synthesis in rats were negative.

Latanoprost has not been found to have any effect on male or female fertility in animal studies.

14 CLINICAL STUDIES

14.1 Elevated Baseline IOP

Patients with mean baseline IOP of 24 – 25 mmHg who were treated for 6 months in multi-center, randomized, controlled trials demonstrated 6 – 8 mmHg reductions in IOP. This IOP reduction with latanoprost 0.005% dosed once daily was equivalent to the effect of timolol 0.5% dosed twice daily.

14.2 Progression of Increased Iris Pigmentation

A 3-year open-label, prospective safety study with a 2-year extension phase was conducted to evaluate the progression of increased iris pigmentation with continuous use of latanoprost once-daily as adjunctive therapy in 519 patients with open-angle glaucoma. The analysis was based on observed-cases population of the 380 patients who continued in the extension phase. Results showed that the onset of noticeable increased iris pigmentation occurred within the first year of treatment for the majority of the patients who developed noticeable increased iris pigmentation. Patients continued to show signs of increasing iris pigmentation throughout the five years of the study. Observation of increased iris pigmentation did not affect the incidence, nature, or severity of adverse events (other than increased iris pigmentation) recorded in the study. IOP reduction was similar regardless of the development of increased iris pigmentation during the study.

16 HOW SUPPLIED/STORAGE AND HANDLING

Latanoprost ophthalmic solution is a clear, isotonic, buffered, preserved colorless solution of latanoprost 0.005% (50 mcg/mL). It is supplied as a 2.5 mL solution in a 4 mL clear low density polyethylene bottle with a low density polyethylene dropper tip, and a turquoise high density polypropylene screw cap, and a clear PVC film with a single perforation.

2.5 mL fill, 0.005% (50 mcg/mL): Package of 1 bottle:

NDC 24208-463-25

Storage: Protect from light. Store unopened bottle(s) under refrigeration at 2° to 8°C (36° to 46°F). During shipment to the patient, the bottle may be maintained at temperatures up to 40°C (104°F) for a period not exceeding 8 days. Once a bottle is opened for use, it may be stored at room temperature up to 25°C (77°F) for 6 weeks.

17 PATIENT COUNSELING INFORMATION

17.1 Potential for Pigmentation
Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent. Inform patients about the possibility of eyelid skin darkening, which may be reversible after discontinuation of Latanoprost ophthalmic solution [see Warnings and Precautions (5.1)].

17.2 Potential for Eyelash Changes
Inform patients of the possibility of eyelash and vellus hair changes in the treated eye during treatment with Latanoprost ophthalmic solution. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

17.3 Handling the Container
Instruct patients to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions [see Warnings and Precautions (5.6)].

17.4 When to Seek Physician Advice
Advise patients that if they develop an intercurrent ocular condition (e.g., trauma or infection) or have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of the multiple-dose container.

17.5 Use with Contact Lenses
Advise patients that Latanoprost ophthalmic solution contains benzalkonium chloride, which may be absorbed by contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of Latanoprost ophthalmic solution.

17.6 Use with Other Ophthalmic Drugs
If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

Manufactured By:
Bausch & Lomb Incorporated
Tampa, Florida 33637
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Revised: February 2015

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Appendix 4 Sponsor's Obligations

Aerie Pharmaceuticals, Inc. is committed to:

1. Complying with the local health authority regulations for the conduct of clinical research studies.

2. Informing the Investigator of any new information about the investigational product that may affect the subject's welfare or may influence the subject's decision to continue participation in the study.

3. In the event of a serious adverse experience, whether related to the use of the study medication or device or not, or the death of a subject, the Sponsor is responsible for notifying the regulatory authority(ies) immediately (see Section 6.9, Adverse events).

4. When the study is terminated the Sponsor should promptly inform the regulatory authority(ies) of the termination and the reason(s) for it. The IRB should also be informed promptly and provide the reason(s) for the termination by the Sponsor as specified by the applicable regulatory requirement(s).

5. Providing to the Investigator the most up-to-date editions of the Clinical Investigator's Brochure (for the investigational product), the protocol, Serious Adverse Experience forms, and a full set of Case Report Forms for each subject entered into the study to document the study evaluation parameters.

6. Providing study medications suitably masked/blinded, coded and packaged for use with subjects entered into the study.

7. Providing statistical and report writing resources to complete appropriate reporting of study results.

8. Ensuring equity considerations among all Investigators in multicenter studies, including all matters of publications and meeting presentations, etc. (where applicable).

9. Prepare an FDA Form No. 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) or 3455 (Disclosure: Financial Interests and Arrangements of Clinical Investigators) or Sponsor's equivalent.

Appendix 5 Investigator's Obligations

The Investigator is obligated to:

1. In the event of a serious adverse experience, whether related to the use of the study medication or device or not, or the death of a subject, the Investigator is responsible for notifying the Sponsor Safety Officer immediately (see Section 6.9, Adverse events). The Investigator must also notify the Sponsor Representative and the Institutional Review Board (IRB) to which he/she is responsible.

2. Prior to initiating the study, sign and return to the Sponsor Representative, the relevant form (Statement of Investigator form provided by the Sponsor for studies involving non-significant risk devices, or OTC drugs; or an FDA No. 1572 is required for IND Phase I, II, III and IV studies). Each sub-Investigator who will assist in the study is to be identified in the required form. The current curriculum vitae (signed and dated) of the principal Investigator and of each sub-Investigator named in the Statement of Investigator form or 1572 form is to accompany the form.

3. Cooperate with the Sponsor on the preparation of an FDA Form No. 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) or 3455 (Disclosure: Financial Interests and Arrangements of Clinical Investigators).

4. Obtain and submit to the Sponsor a copy of his/her IRB approval of the protocol prior to initiating the study.

5. Obtain signed informed consent from each subject or his/her legal guardian prior to acceptance of the subject into the study.

6. Read, and agree to adhere to the study protocol prior to the initiation of the study. Deviations from the study protocol are not to be implemented without the prior written approval of the Sponsor and IRB, unless protection of the safety and welfare of study subjects requires prompt action. During the study, if the Investigator feels that in his/her clinical judgment, it is necessary to promptly terminate one or more subjects from the study, or to promptly implement reasonable alternatives to, or deviations from the protocol in consideration of the safety of study subjects, the Sponsor is to be notified of these terminations, alternatives, and deviations, and the reasons for such changes are to be documented in the study records. The Investigator is to also notify his/her IRB of any such changes.

7. Accurately record, at the Investigator's site, all required data on each subject's electronic Case Report Form.

8. Replace subjects consistent with the directions in Section 4.4.

9. Keep accurate records of the number of study medication or device units received from the Sponsor and dispensed or administered to each subject during the study, and return any unused study medication or devices to the Sponsor at the completion of the study. Before returning the study medications or devices to the Sponsor, a detailed inventory should be recorded and placed in the Investigator's file.

10. Assure that Investigational Products will be dispensed or administered only to subjects under his/her personal supervision, or under the supervision of authorized sub-Investigators responsible to him/her.

11. Allow a representative of the Sponsor and/or representatives of health regulatory agencies to inspect all Case Report Forms and corresponding portions of each study subject's source documentation (ie, original office, hospital, and laboratory records) at mutually convenient times at regular intervals during the study, and upon request after the study has been completed. The purpose of these on-site monitoring visits is to provide the Sponsor the opportunity to evaluate the progress of the study, document compliance with the protocol and with regulatory requirements, verify the accuracy and completeness of subject electronic Case Report Forms, resolve any apparent discrepancies or inconsistencies in the study records, and account for all investigational supplies.

12. Provide the governing IRB with a brief (ie, one to three pages) Investigator's summary within 90 working days of the study completion.

13. Complete the study within the time limits agreed upon with the Sponsor prior to the initiation of the study.

14. Maintenance of records

    a. Disposition of drug. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the Sponsor, or otherwise provide for disposition of the unused supplies of the drug under 21 CFR 312.59.

    b. Case histories. An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

    c. Record retention. An investigator shall retain records required to be maintained under this part for a period of 2 years following the date a

marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor.

If for any reason the Investigator withdraws from the responsibility of maintaining the study records for the required period of time, custody of the records may be transferred to any other person who will accept responsibility for the records. The Sponsor is to be notified in writing of any such transfer.

Appendix 6 Declaration of Helsinki

Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest with the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Doctors should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Doctors should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the doctor is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to

abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The doctor should then obtain the subject's given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the doctor should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case, the informed consent should be obtained by a doctor who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (CLINICAL RESEARCH)

13. In the treatment of the sick person, the doctor must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

14. The potential benefits, hazards and discomforts of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

15. In any medical study, all subjects - including those of a control group, if any, should be assured of the best proven diagnostic and therapeutic methods.

16. The refusal of the subject to participate in a study must never interfere with the doctor-subject relationship.

17. If the doctor considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee.

18. The doctor can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the subject.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECT (NONCLINICAL BIOMEDICAL RESEARCH)

19. In the purely scientific application of medical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom biomedical research is being carried out.

20. The subjects should be volunteers - either healthy person or subjects for whom the experimental design is not related to the subject's illness.

21. The Investigator or the team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

22. In research on man, the interest of science and society should never take precedence over consideration related to the well-being of the subject.

Appendix 7 Sample SAS Code

The following SAS code will be used for multiple imputations using the Monte-Carlo Markov Chain method, where a separate model will be fit for each time point at each visit.

```
proc mi data = indata seed = 48669 out = outdata1;
    mcmc initial = em;
    var trt01pn baseline IOP;
run;
```

where

- *indata* is the name of the input dataset
- *outdata1* is the name of the output dataset
- *trt01pn* is the name of the treatment group variable in numeric format
- *baseline* captures the baseline IOP for the given time point
- *IOP* is the name of the IOP measure.

Five complete data sets will be generated from the above code. Each complete data set will be used to analyze this primary efficacy endpoint separately using analysis of variance. Then, the SAS procedure MIANALYZE will be used to analyze the results from the 5 complete data sets to generate a combined inference. The following SAS code will be used:

```
ods output diffs = outdata2;
proc mixed data= outdata1;
    by _IMPUTATION_;
    class trt01pn;
    model IOP = trt01pn baseline;
    lsmeans trt01pn / cl pdiff;
run;

proc sort data= outdata2;
    by trt01pn _trt01pn;
run;

ods output ParameterEstimates = outdata3;
proc mianalyze data= outdata2 alpha = 0.05;
    by trt01pn _trt01pn;
    class trt01pn _trt01pn;
    modeleffects estimate;
    stderr;
```

run;

where

- *outdata1* is the name of the input dataset from Proc MI
- *_IMPUTATION_* is the imputation number
- *trt01pn* is the name of the treatment group variable in numeric format
- *IOP* is the name of the IOP measure
- *baseline* captures the baseline IOP for the given time point
- *outdata2* is the name of the output dataset that contains the statistical results of the difference between treatment groups
- *outdata3* is the name of the output dataset that contains summary and inferential statistics.