16.0 APPENDICES

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

The original protocol (Version 0, dated 25-Feb-2020) was amended twice. Amendment #1 (Version 1.0, dated 28-Apr-2020) and Amendment #2 of the protocol (Version 2.0, dated 17-May-2020) were implemented before any subjects were screened for the study.

The latest protocol (Amendment 2, Version 2.0, dated 17-May-2020) is provided in this Appendix.

A summary of the changes in Amendment #1 and #2 follows:

Amendment	Summary of Changes

Amendment #1
version 1.0
28-April-2020
	• The following modifications are made to the protocol. The synopsis and study schedule of events are updated to align with the changes described below. Additionally, minor text changes and clarifications are made throughout the document.
	• The changes are made to optimize the protocol design. The changes are not considered to impact the safety of subjects in the study or the scientific integrity of the study.
	• Section 5.3 Efficacy Endpoints
	  • Primary and secondary efficacy endpoints are clarified.
	  • Mean diurnal IOP on Days 14 and 28 in both eyes is added as a secondary endpoint.
	• Section 5.4 Safety Measures
	  • Safety measures are clarified.
	  • Gonioscopy, visual field and cup disc ratio measurements are removed from safety endpoints.
	• Section 6.1 Overall Study Design and Plan
	  • Timing of visits is clarified
	  • Study design is modified to require that subjects must be on stable dose of topical prostaglandin eyedrops for at least 2 weeks prior to screening (Visit 1).
	  • A minimum four-week washout is now required following completion of Visit 1.
	  • Clarification is added that stratification will occur based on IOP mean diurnal IOP in the study eye.
	  • An interim analysis for futility when 50% of subjects have completed 28 days of treatment is now added
	  • Blood sampling for exploratory genetic analyses is removed
	• Section 7.2 Subject Eligibility and Study Eye Determination
	  • This section is added to provide clarity on selection of study eye.
	• Section 7.3 Inclusion Criteria
	  • Inclusion criterion is added to state that subjects must be on stable regimen of topical prostaglandins for a minimum of 2 weeks prior to the Screening Visit
	  • Screening visit IOP criterion is modified to require IOP of ≥18 mmHg and ≤27 mm Hg in one eye (study eye) or both eyes at screening.

	• Ability to properly self-administer eye drops (or have a caregiver that can suitably administer eye drops) is added as an inclusion criterion. • Section 7.4 Exclusion Criteria • Additional examples of clinically significant ocular disease that should be excluded are added to Exclusion Criterion #1. • Evidence of peripheral anterior synechiae ≥ 180 degrees by gonioscopy within 6 months prior to Screening is added to exclusion criterion # 3. • Exclusion Criterion #4 is clarified to state that IOP ≥ 36 mmHg at Screening, Qualification Visit #1 or at any assessment on Qualification Visit # 2 is exclusionary. • Exclusion Criterion #7 is modified to state that known hypersensitivity to any topical prostaglandin eyedrop is exclusionary. • Exclusion Criterion # 8 is modified to state that that SLT within the past 6 months is exclusionary and additional minimally invasive glaucoma surgery is added as exclusionary. • Exclusion Criterion # 9 is modified to add that limbal relaxing incision in either eye within 12 months prior to screening is exclusionary. • Exclusion Criterion # 10 is added to state any intravitreal injection within 30 days prior to screening or anticipated intravitreal injection during the course of the study is exclusionary. • Exclusion Criterion # 13 is modified to state that bulbar conjunctival hyperemia scores of ≥ 3 on the hyperemia scale is exclusionary at any visit during Screening, Qual # 1 and Qual #2 visits. • Exclusion Criterion #15 is modified to clarify prohibited ocular medications. • Exclusion Criterion #16 is modified to state that corneal thickness of less than 480um in either eye is exclusionary. • Exclusion Criterion # 19 is modified to state that tubal ligation is not considered surgical sterilization. • Section 8.2 Dispensing Procedures • Text describing kit dispensation is simplified and clarified. • Section 8.6 Study Medication and Latanoprost Administration. • Eye drop instillation technique assessment is removed from Screen Visit #1 and a statement is added that on the days of study visits, subjects should not wear contacts until the visit is completed. • Section 8.7 Concomitant Mediations • Text is clarified to state preservative artificial tears are allowed, latanoprost is provided by the Sponsor, and Rho kinase inhibitors are added as prohibited medications. • Section 8.8.1 Prior Therapy and Washout • Text is modified to state that eligible subjects must be on a stable dose of topical prostaglandin eye drops (for at least 2 weeks) prior to Screening and that after completion of the screening visits subjects must undergo a minimum 4 week washout period. • Section 9.2.2 Ophthalmic Assessments • Assessments are now listed in suggested order of conduct, the conjunctival grading scale is updated to the Efron scale and hyperemia AE reporting guidance is updated to state an increase of 2 or more grades on the hyperemia scale when compared to the lowest score recorded at any previous time point should be recorded as an AE in addition to if a

	subject complains of an AE regardless of grade on the hyperemia scale.
	• Section 9.2.3 Laboratory Evaluations.
	  • Pregnancy guidance is clarified and blood sampling for genetic analysis is removed.
	• Section 10. 0 Schedule of Activities
	  • This section is modified to provide clarification on timing and conduct of assessments.
	• Section 10.1 Visit Windows and Study Days
	  • This section is modified to provide clarity that IOP and hyperemia assessments at 8:00, 10:00, 12:00 and 16:00 hours must be conducted at a minimum of the protocol prescribed 2- or 4- hour interval.
	  • A section is added to state that study days will be numbered relative to the first day of dosing and to define the start of study.
	• Section 10.2 Visit 1 (Screening Visit)
	  • This section is updated to remove the eye drop instillation technique evaluation, update the order of assessments to reflect conduct of assessments, IOP eligibility criteria at this visit is clarified and the washout period is updated from optional to required.
	• (Former) Section 10.2.1 Evaluation of Eye Drop Instillation Performance
	  • This section is removed; a formal assessment of eye drop instillation technique is deemed not necessary as eligible subjects will have prior experience with dosing topical eye drops via the requirement to have a history of stable treatment with prostaglandin eyedrops. Per Investigator discretion, an instillation assessment can be conducted but is no longer required per protocol.
	• Section 10.2.2 Visit 2
	  • Text describing the optional washout period is removed as the washout is now required. Timing of the visit is corrected to state that the visit will occur no later than 42 days after the screening visit.
	  • IOP eligibility criteria at this visit is clarified
	• Sections 10.2.3 -10.2.15
	  • These sections are updated to include statements that that IOP and hyperemia assessments at 8:00, 10:00, 12:00 and 16:00 hours must be conducted at a minimum of the protocol prescribed 2- or 4- hour interval.
	  • Study medication dispensing instructions are clarified.
	• Section 11.1.1 Adverse Events
	  • Guidance for reporting hyperemia is updated to align with changes to Section 9.2.2 Ophthalmic Assessments.
	  • Guidance for reporting abnormal labs as adverse events (AEs) is removed as no clinical laboratory assessments are conducted in this study.
	• Section 12.5.2. Interim Analysis
	  • This section is updated to describe the planned interim analysis for futility.
	• Section 12.5.5 Analysis of Efficacy
	  • Primary and secondary efficacy endpoints are clarified.
	  • Mean diurnal IOP on Days 14 and 28 in both eyes is added as a secondary endpoint.
	• Section 12.6 Procedure for Accounting for Missing, Unused or Spurious data.

AKB-9778-CI-OS-2001

Phase 2 Multi-Center, Double-Masked, Randomized, 28-Day Study to Assess the Efficacy, Safety and Tolerability of Single or Twice Daily Doses of AKB-9778 Ophthalmic Solution as an Adjunct to Latanoprost in Patients with Ocular Hypertension (OHT) or Open Angle Glaucoma (OAG)

Original Protocol (Version 0) February 25, 2020

Amendment #1 (Version 1.0) April 28, 2020

Amendment #2 (Version 2.0) May 17, 2020

1.0 STUDY CONTACTS

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1.1 Protocol Approval

17 may 2020
Date

Kevin Peters, MD
Chief Scientific Officer, Chief Medical Officer and Senior Vice President, Research and Development
Aerpio Pharmaceuticals, Inc.

17 MAY 2020
Date

Mitchell Brigell, PhD
Vice President, Clinical Development
Aerpio Pharmaceuticals, Inc.

May 17, 2020
Date

Barbara Withers, PhD
Vice President, Clinical Operations
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17 MAY 2020
Date

Christopher Ernst
Vice President of CMC and Quality Assurance
Aerpio Pharmaceuticals, Inc.

May 17, 2020
Date

Akshay Buch, PhD
Senior Director, Clinical Pharmacokinetics
Aerpio Pharmaceuticals, Inc.

1.2 Investigator Agreement

I confirm that I have read and that I understand this protocol, and other product information provided by the Sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation Guidance for Industry, Good Clinical Practice E6R(2).
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in this protocol.
- Terms outlined in the Clinical Trial Agreement.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Name of Facility

_____

Location of Facility (City, State)

2.0 SYNOPSIS

Sponsor: **Aerpio Pharmaceuticals, Inc.**	**Investigational Product: AKB-9778 Ophthalmic Solution**
Protocol Number: AKB-9778-CI-OS-2001	
Study Title: Phase 2 Multi-Center, Double-Masked, Randomized, 28-Day Study to Assess the Efficacy, Safety and Tolerability of Single or Twice Daily Doses of AKB-9778 Ophthalmic Solution as an Adjunct to Latanoprost in Patients with Ocular Hypertension (OHT) or Open Angle Glaucoma (OAG)	
Phase of Development: 2	
Objectives: Primary: • To evaluate the ocular hypotensive effects of AKB-9778 Ophthalmic Solution 4.0% administered once or twice daily for 28 days when used as an adjunctive therapy to latanoprost ophthalmic solution 0.005% in subjects with OAG or OHT Secondary: • To evaluate the safety and tolerability of AKB-9778 Ophthalmic Solution 4.0% administered once or twice daily for 28 days when used as an adjunctive therapy to latanoprost ophthalmic solution 0.005% in subjects with OAG or OHT	
Endpoints: **All efficacy analyses will be conducted in study eye and both eyes (average of study eye and eligible fellow eye)** Primary Efficacy Endpoint: • Mean change from baseline in diurnal intraocular pressure (IOP) on Day 28 (study eye) Secondary Efficacy Measures: • Mean change from baseline in diurnal IOP on Day 14 (study eye) • Mean change from baseline in diurnal IOP on Days 14 and 28 (both eyes) • Mean diurnal IOP on Days 14 and 28 (both eyes) • Mean observed IOP at each time point on Days 14 and 28 • Mean change from diurnally adjusted baseline IOP at each time point on Days 14 and 28 • Mean percent change from diurnally adjusted baseline IOP at each time point on Days 14 and 28 • Mean percent change from baseline in diurnal IOP on Days 14 and 28 • Percentages of subjects achieving pre-specified mean, mean change, and percent mean change in diurnal IOP levels Safety Measures: • AEs • Hyperemia assessments (study eye and worse eye) • Pachymetry • Visual acuity • Biomicroscopic examinations (*i.e.*, lids, conjunctiva, cornea, anterior chamber, iris and lens)	

- Dilated ophthalmoscopy

Study Design:

This is a phase 2, double masked, randomized, multi-center, parallel-group, 28-day study assessing the safety, tolerability and ocular hypotensive efficacy of AKB-9778 Ophthalmic Solution 4.0% administered once (AM) or twice (AM & PM) daily when used as an adjunctive therapy to latanoprost ophthalmic solution 0.005% once daily (PM) in subjects with elevated IOP due to OAG or OHT. Eligible subjects are required to have a diagnosis of either OAG or OHT in each eye and are on stable dose of topical prostaglandin eye drops (for at least 2 weeks prior to screening). Subjects eligible to be enrolled in this study must meet all inclusion criteria and none of the exclusion criteria. Subjects who agree to participate in this study and are randomized in the study will attend a total of 6 study visits: a Screening Visit, Qualification Visit #1, Qualification Visit #2/Day -1 (Baseline), and visits on Days 7, 14 and 28. After completion of the Screening Visit, subjects will undergo a minimum 4-week washout period from IOP lowering treatment prior to attending Qualification Visit #1. Subjects will receive an eye examination including IOP measurements at Qualification Visits #1 and #2/Day -1. If deemed eligible, subjects will be enrolled at Qualification Visit #2/Day -1 and assigned to 1 of 3 treatment arms (AKB-9778 QD + Latanoprost; AKB-9778 BID + Latanoprost; or Latanoprost monotherapy) in a 1:1:1 ratio according to a computer-generated randomization list. Subject randomization will be stratified by mean diurnal IOP on Day -1 (< 26 mmHg vs ≥ 26 mmHg) in the study eye. During the treatment period, randomized subjects will self-administer study medication (AKB-9778 4.0% or placebo for AKB-9778) daily in the AM and PM and will also administer 0.005% latanoprost ophthalmic solution daily in the PM. Daily AM dose administration of study medication should occur between 7:00 and 10:00 hours and PM dose administration should occur between 19:00 and 22:00 hours. Latanoprost PM dose administration will occur at least 5 minutes before administration of the PM dose of study medication. Subjects will begin dosing with the AM dose of study medication on the morning of Day 1 and conclude dosing after administration of the AM dose of study medication on Day 28 (there is no PM dose on Day 28). At visits conducted on Days 14 and 28, subjects will self-administer the AM dose of study medication at the site after the 8:00 hour ophthalmic assessments have been completed. During the treatment period, subjects will be seen in the clinic on Days 7, 14 and 28; safety assessments will be conducted on all days and efficacy measurements (IOP) will be conducted on Days 14 and 28 at the following time points: 08:00, 10:00, 12:00 and 16:00 hours. Following completion of the Day 28 study visit procedures, subjects will exit from the study. For subjects who discontinue early, every possible effort will be made to assure there is an exit visit that includes all required examinations for the Day 28 visit.

Number of Subjects Planned:

Approximately 195 subjects are planned to be randomized (approximately 65 per treatment group).

Number of Sites Planned:

Approximately 25 sites across the USA are planned.

Duration of Treatment: 28 days

Duration of Participation:

The Screening, Washout, Qualification Visits and Treatment periods will require subject participation for up to approximately 11 weeks.

Eligibility Criteria:

Inclusion Criteria

Subjects must meet all of the following criteria at screening and qualification visits to enter into the study. **For a subject to be included in the study, at least one eye (the same eye) must meet ALL ophthalmic inclusion and no exclusion criteria through the screening period (Screening, Qualification #1 and Qualification #2 [Day -1] visits).**

1. Males and non-pregnant, non breast-feeding females
2. Aged ≥ 18 years
3. Diagnosis of OAG or OHT in each eye (OAG in one eye and OHT in the fellow eye is acceptable)
4. Must be receiving treatment with a stable regimen of topical prostaglandin eyedrop for a minimum of 2 weeks prior to the Screening Visit; may be taking one additional IOP lowering eyedrop (for the purposes of this inclusion criterion, a combination product is counted as a single eyedrop)
5. IOP of ≥ 18 mmHg and ≤ 27 mmHg in one eye (study eye) or both eyes at the Screening Visit
6. Unmedicated (post-washout) IOP at 2 qualification visits 2-7 days apart meeting the following criterion. At the first qualification visit, if tested at or before 10:00 hour, have IOP ≥ 24 mmHg in study eye or both eyes **and** < 36 mmHg in both eyes *or* if tested after 10:00 hour, have IOP ≥ 22 mmHg in study eye or both eyes **and** < 36 in both eyes. At the second qualification visit, IOP ≥ 24 mmHg in study eye or both eyes **and** < 36 mmHg in both eyes at 08:00 hour and IOP ≥ 22 mmHg in study eye or both eyes **and** < 36 mmHg in both eyes at 10:00, 12:00 and 16:00 hours.
7. Visual Acuity (VA) of +0.5 logMAR (20/63 Snellen) or better in each eye
8. Must be willing and able to communicate and participate for the duration of the study
9. Ability to properly self-administer eye drops (or have a caregiver that can suitably administer eye drops)
10. Must provide written informed consent

Exclusion Criteria

Subjects meeting any of the following criteria during screening or qualification evaluations will be excluded from entry into the study:

Ophthalmic:

1. Clinically significant ocular disease (*e.g.*, corneal edema, uveitis, severe keratoconjunctivitis sicca, diabetic macular edema, proliferative diabetic retinopathy, or neovascular age-related macular degeneration) which might interfere with interpretation of the study efficacy endpoints or with safety assessments
2. Pseudoexfoliation or pigment dispersion component glaucoma
3. History of angle closure glaucoma, or narrow angles (*i.e.*, Shaffer Grade 2 or less; extreme narrow angle with complete or partial closure), or with evidence of peripheral anterior synechiae (PAS) ≥ 180 degrees by gonioscopy within 6 months prior to Screening visit in either eye. Note: Previous laser peripheral iridotomy is NOT acceptable
4. Intraocular pressure ≥ 36 mmHg in either eye at the Screening Visit, Qualification Visit #1, or at any assessment on Qualification Visit #2/Day-1 (individuals who are excluded for this criterion are not allowed to attempt requalification)
5. Cup/disc ratio of > 0.8 in either eye
6. Severe visual field defect in either eye as assessed by the investigator, or significant defect (sensitivity of ≤ 10dB) within 10 degrees of fixation in either eye

7. Known hypersensitivity to any component of the investigational formulations or to any topical prostaglandin eyedrop
8. Selective laser trabeculoplasty (SLT) within the past 6 months or any history of argon laser trabeculoplasty (ALT) or minimally invasive glaucoma surgery (MIGS) in either eye
9. Any history of radial keratotomy, corneal cross linking, photorefractive keratectomy (PRK), Laser-assisted in-situ keratomileusis (LASIK), or limbal relaxing incision (LRI) in either eye within 12 months prior to screening
10. Any intravitreal injection within 30 days prior to screening or anticipated intravitreal injection during the course of the study
11. Ocular trauma in either eye within the 6 months prior to screening, or ocular surgery or non-refractive laser treatment within the 3 months prior to screening
12. Recent (within 90 days prior to screening) or current evidence of ocular infection or inflammation in either eye. Current evidence of clinically significant blepharitis, conjunctivitis, keratitis, or a history of herpes simplex or zoster keratitis in either eye at screening
13. Bulbar conjunctival hyperemia ≥3 (moderate) on the hyperemia scale (Section 9.2.2) in either eye at Screening, Qualification Visit #1, or at any assessment on Qualification Visit #2/Day -1
14. History of recurrent uveitis in either eye
15. Use of 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 or warm compresses (which may be used prior to, but not after, screening), c) preservative or preservative-free lubricating drops (excluding gels or ointments) for dry eye (which may be used throughout the study at maximum frequency of QID), or d) non-steroid allergy drops (note: must not contain a vasoconstrictor)
16. Mean central corneal thickness less than 480µm or greater than 600µm at screening in either eye
17. Any abnormality preventing reliable applanation tonometry of either eye (e.g., keratoconus, corneal scarring)

Systemic:

18. Women who are pregnant or breast-feeding or intending to become pregnant during the study
19. Women of child-bearing potential who are not on an acceptable method of birth control (*e.g.*, 1 highly effective method [less than 1% failure rate] of contraception, or a combination of 2 effective methods of contraception). An adult woman is considered to be of childbearing potential unless she is one year post-menopausal or three months post-surgical sterilization (excluding tubal ligation). All females of childbearing potential must have a negative urine pregnancy test result at the Screening Visit and Qualification Visit #2.
20. History of any clinically significant disease or disorder which, in the opinion of the Investigator, may put the subject at risk because of participation in the study, influence the subject's ability to participate in the study, or interfere with interpretation of the subject's study results. Subjects with stable baseline medical conditions on established medication may be included as per the judgement of the Investigator; e.g., well controlled hypertension, type 2 diabetes, or mild, stable asthma not requiring treatment with inhaled corticosteroids.
21. 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.
22. Use of an investigational medication or device within 30 days or 5-half-lives of the investigational medication, whichever is longer, preceding Day 1, or ongoing or scheduled participation in another investigational study during the present study through the last visit
23. Previous treatment with AKB-9778
24. Subjects who are study site employees, or immediate family members of a study site or sponsor employee

25. Failure to satisfy the Investigator of fitness to participate for any other reason

Investigational Products (IP), Dose and Treatment Regimens:

Study Medication

- AKB-9778: AKB-9778 Ophthalmic Solution 4.0%
- Placebo for AKB-9778 Ophthalmic Solution: placebo vehicle to match active formulation of AKB-9778

Latanoprost

- Latanoprost: latanoprost ophthalmic solution 0.005% (XALATAN® Pfizer)

AKB-9778 QD + Latanoprost

- AKB-9778 QD (AM) and placebo for AKB-9778 ophthalmic solution QD (PM) plus latanoprost QD (PM) for 28 days

AKB-9778 BID + Latanoprost

- AKB-9778 BID (AM & PM) plus latanoprost QD (PM) for 28 days

Latanoprost Monotherapy

- Placebo for AKB-9778 ophthalmic solution BID (AM & PM) plus latanoprost QD (PM) for 28 days

Subjects will self-administer study medication (AM & PM) and latanoprost (PM) to each eye by the topical ocular route using dropper bottle(s) to deliver eye drops. Daily AM dose administrations should occur between 7:00 and 10:00 hours and PM dose administrations should occur between 19:00 and 22:00 hours. Latanoprost PM dose administration will occur at least 5 minutes before administration of the PM dose of study medication.

Statistical Methods:

Primary Estimand

The primary comparisons in this trial will be between two doses of AKB-9778 (QD and BID) + Latanoprost vs Latanoprost monotherapy at the Day 28 Visit in the ITT population with intercurrent events handled as described in the following estimand.

- Population: subjects with Open-Angle Glaucoma or Ocular Hypertension defined through enrolment criteria
- Endpoint:
  - Mean diurnal (averaged over 08:00, 10:00, 12:00, and 16:00 hour time points) change from baseline IOP (mm Hg) at the Day 28 Visit in the study eye
- Intercurrent event:
  - Discontinuation of study medication and non-optimal compliance will be ignored [treatment policy strategy].
  - Withdrawal due to lack of efficacy or adverse event: missing data will be imputed employing Multiple Imputation (MI) assuming missing not at random using:
    - Control-based Markov Chain Monte Carlo (MCMC) methodology [hypothetical strategy].
  - Missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or adverse event: missing data will be imputed employing Multiple Imputation (MI) assuming missing at random

using randomized treatment-based Markov Chain Monte Carlo (MCMC) methodology [hypothetical strategy].

- Population-level summary:
  - The difference in the mean diurnal change from baseline IOP at the Day 28 Visit, between study eyes treated with each dose of AKB-9778 (QD and BID) + Latanoprost and study eyes treated with Latanoprost monotherapy

Sensitivity analyses will be performed on observed data only and where worst time consistent observation within a subject is carried forward for withdrawal due to lack of efficacy or adverse event and last time consistent observation within a subject is carried forward for other missing data.

The primary analysis of the primary efficacy outcome will employ a linear model with Day 28 mean diurnal change from baseline IOP as the response, baseline IOP (mean diurnal IOP on Day-1) as a covariate, and treatment as a main effect factor, using the intent to treat population with multiple imputation techniques used to impute missing data. The least squares mean differences (test – control) between AKB-9778 + Latanoprost and Latanoprost monotherapy will be presented as well as 2-sided p-values and 95% confidence intervals. Inference will be made on the p-value < 0.05.

Sixty-five (65) subjects per arm completing 28 days of treatment yields 80% power to conclude statistical superiority of AKB-9778 (QD or BID) + Latanoprost to Latanoprost monotherapy assuming a two-sided alpha = 0.05, a true difference in mean diurnal change from baseline IOP of 1.5 mmHg, a common standard deviation of 3.5 mmHg at each time point, and a correlation of 0.60 among time points within a subject's study eye (leading to an SD of the mean diurnal IOP of 3.0 mmHg).

An interim analysis for futility is planned to be performed when 50% of randomized subjects have completed 28 days of therapy.

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3.0 ABBREVIATIONS

Abbreviation	Definition
AEs	Adverse events
AH	Aqueous humor
ALT	Argon laser trabeculoplasty
Angpt	Angiopoietin
Angpt1 or 2	Angiopoietin1 or 2
AUC	Area under the curve
AUC_{last}	Area under the concentration-time curve from time 0 to last quantifiable concentration
BID	Twice daily
BLQ	Below limit of quantitation
BOCF	Baseline observation carried forward
C_{max}	Maximum plasma drug concentration
CO	Conventional outflow
CRF	Case report form
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EGF	Epidermal Growth Factor
eNOS	Endothelial nitric oxide synthase
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practices
HPTPβ	Human protein tyrosine phosphatase β
HPβCD	Hydroxypropyl-beta-cyclodextrin
ICH	International Council for Harmonisation
IP	Investigational product
IOP	Intraocular pressure
IRB	Institutional Review Board
ITT	Intent-to-Treat Population
IVT	Intravitreal injection
IWRS	Interactive Web-based response system
LASIK	Laser-assisted in-situ keratomileusis
LOCF	Last observation carried forward
logMAR	Logarithm of the minimum angle resolvable
MedDRA	Medical Dictionary for Regulatory Activities
MIGS	Minimally Invasive Glaucoma Surgery
MITT	Modified Intention-To-Treat
NOAEL	No observed adverse-effect level
OAG	Open angle glaucoma
OHT	Ocular hypertension

Abbreviation	Definition
OTC	Over-the-counter
OU	Both eyes
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per-protocol
PRK	Photorefractive keratectomy
PT	Preferred term
QA	Quality assurance
QC	Quality control
QD	Once daily
QID	Four times daily
Rac1	Ras-related C3 botulinum toxin substrate 1
Rap1	Ras-proximate 1
SAEs	Serious Adverse Events
SC	Subcutaneous
SITA	Swedish interactive threshold algorithm
SLT	Selective laser trabeculoplasty
SNPs	Single-nucleotide polymorphisms
SOC	System Organ Class
T½	Terminal half-life
TEAEs	Treatment-emergent adverse events
TID	Three times daily
Tie 2	Tyrosine kinase with immunoglobulin-like and EGF-like domains 2
TM	Trabecular meshwork
USP	United States Pharmacopeia
VA	Visual Acuity
VE-PTP	Vascular endothelial protein tyrosine phosphatase
w/v	Weight/volume

4.0 BACKGROUND INFORMATION

Open angle glaucoma (OAG) is a leading cause of blindness affecting approximately 44.7 million people worldwide with an estimated prevalence in the United States of 2.7 million in 2011, which is expected to increase to 7.3 million by 2050 (Tham et al., 2014; Vajaranant et al. 2012; Vajaranant et al., 2012b). OAG is characterized by optic nerve and neuroretina anomalies and progressive visual field defects. Elevated intraocular pressure (IOP)/Ocular hypertension (OHT) is the primary modifiable risk factor and reducing IOP is the only clinical approach shown to slow/prevent vision loss (Gordon et al., 2002; Heijl et al., 2002; Kass et al., 2002; Leske et al., 2007). Despite the availability of effective IOP lowering drugs, many patients require multiple agents to control IOP that together often fail to achieve a "target" IOP (Aptel et al., 2015).

Aerpio Pharmaceuticals, Inc. (Aerpio) is developing AKB-9778 Ophthalmic Solution as a treatment for OAG. AKB-9778 is a novel small molecule which selectively inhibits VE-PTP (vascular endothelial-protein tyrosine phosphatase), otherwise known as HPTPβ (human protein tyrosine phosphatase β), and enhances Tie2 (tyrosine kinase with immunoglobulin-like and Epidermal Growth Factor (EGF)-like domains 2) activation and signaling. Recent findings suggest that Angiopoietin (Angpt)/Tie2 pathway activation may have therapeutic benefit in patients with OAG and OHT by directly targeting the conventional outflow (CO) pathway.

The CO pathway, consisting of the trabecular meshwork (TM) and a specialized vessel called Schlemm's canal, controls IOP under normal physiology and has been identified as the site of increased resistance to aqueous humor (AH) outflow in OAG (Grant, 1951; Grant, 1963; Stamer and Acott, 2012). Importantly, a vast majority of topical ocular OAG therapies do not target CO, but rather reduce IOP by either decreasing the formation of AH or facilitating unconventional outflow pathways. The failure of current therapies to modify CO has been hypothesized to contribute to continued deterioration of the CO pathway and progressive increases in IOP over time (Braunger et al., 2015; Stamer, 2012). Relative to current therapies, developing agents that target CO pathology directly may have improved efficacy either alone or in combination with approved glaucoma agents, and may prevent progression of OAG that often occurs despite current therapy.

4.1 Rationale

Schlemm's canal develops postnatally from the intrascleral venous plexus but has a "hybrid" phenotype characterized by expression of lymphatic endothelial as well as blood endothelial markers (Aspelund et al., 2014; Hamanaka et al., 1992; Kizhatil et al., 2014; Park et al., 2014; Truong et al., 2014). Tie2, the receptor for the Angpt family of secreted proteins, is a receptor tyrosine kinase expressed on both blood and lymph endothelial cells and is required for development of both vascular systems (Augustin et al., 2009; Morisada et al., 2005; Peters et al., 2004; Saharinen et al., 2017; Tammela et al., 2005). Tie2 is constitutively expressed and activated in the normal adult blood vasculature, consistent with the established role of the Tie2 pathway in maintenance of endothelial function and vascular stability (Wong et al., 1997). Recently, two independent groups have shown that Tie2 is expressed and activated in Schlemm's canal endothelial cells during development and in the mature vessel (Bernier-Latmani and

Petrova, 2017; Kim et al., 2017; Thomson et al., 2014). Disruption of the Tie2 pathway in mice, by conditional knockout of Tie2 or both Tie2 ligands (Angpt1 and Angpt2) early in postnatal development (postnatal day 1), results in failure of the formation of Schlemm's canal, associated with increased IOP with retinal and optic nerve pathology resembling human congenital glaucoma (Kim et al., 2017; Thomson et al., 2014). Tie2 pathway disruption later in postnatal development (8 weeks) results in degeneration of Schlemm's canal with development of increased IOP and retinal and optic pathology reminiscent of OAG (Kim et al., 2017). Tie2 is most highly expressed in mature inner wall endothelium of Schlemm's canal and disruption of the Tie2 pathway results in increased apoptosis and reduced formation of giant vacuoles consistent with compromised CO. Supporting these preclinical findings, Tie2 loss of function variants were identified in 10 of 189 unrelated primary congenital glaucoma families, and single-nucleotide polymorphisms (SNPs) in Angpt1, the Tie2 activating ligand, were significantly associated with the risk of OAG (Bailey et al., 2017; Choquet et al., 2017; Kabra et al., 2017; Souma et al., 2016). The preclinical findings, along with human genetic evidence, suggest that activation of the Angpt/Tie2 pathway in Schlemm's canal could provide a novel CO-targeted OAG therapy.

VE-PTP is a receptor tyrosine phosphatase that is co-expressed with Tie2 in vascular endothelial cells that functions as a pivotal negative regulator of Tie2 activation (Shen et al., 2014). AKB-9778 is a potent and selective small molecule inhibitor of the catalytic activity of VE-PTP. Pharmacologic inhibition of VE-PTP with AKB-9778 restores Tie2 activation independent of the presence or absence of Tie2 ligands Angpt1 and Angpt2. Consistent with a role for VE-PTP in regulation of CO, subcutaneous (SC) administration of AKB-9778 reduced IOP in subjects with diabetic macular edema and nonproliferative diabetic retinopathy. Topical ocular administration of AKB-9778 reduced IOP more than subcutaneous AKB-9778 administration in rabbits and decreased IOP in mice in association with increased Tie2 activation in Schlemm's canal endothelium and increased outflow facility. Data in normotensive dogs indicate that topical ocular administration of AKB-9778 immediately following topical ocular dosing of 0.005% latanoprost is well tolerated and has an additive IOP-lowering effect relative to latanoprost alone. Moreover, in a recently completed Phase 1b study, topical ocular administration of AKB-9778 once a day for 7 days was well tolerated (minimal to mild conjunctival hyperemia only) and significantly reduced IOP in a cohort of OHT/OAG patients on standard of care prostaglandin therapy. Taken together, these data support development of AKB-9778 Ophthalmic Solution as a novel CO targeted treatment for OAG/OHT and provide strong rationale for the current study with AKB-9778 as an adjunct to latanoprost.

4.2 Summary of Non-Clinical Experience

Please see the AKB-9778 Ophthalmic Solution Investigator Brochure for additional discussion and information for the following section.

The nonclinical experience for AKB-9778 Ophthalmic Solution is supported by a comprehensive set of *in vitro* and systemic pharmacology and nonclinical studies completed during the development of the AKB-9778 SC Injection program, including evaluation in multiple retinopathy models, safety pharmacology studies, pharmacokinetic (PK) and metabolism studies, toxicology studies in rats, dogs, and monkeys, embryo-fetal development studies in rats and

rabbits, and genotoxicity studies. Some of these studies are briefly summarized in the sections below, as well as the nonclinical studies for topical ocular administration of AKB-9778.

4.2.1 Preclinical Pharmacology

AKB-9778 is a highly optimized small molecule inhibitor of the VE-PTP catalytic phosphatase domain that restores Tie2 activation and downstream signaling. Supporting a role in regulation of IOP, VE-PTP inhibition triggers signaling pathways downstream of Tie2 that have been implicated in modulation of CO facility including endothelial nitric oxide synthase (eNOS) activation and Rho pathway inhibition via Ras-related C3 botulinum toxin substrate 1 (Rac1)/ Ras-proximate 1 (Rap1) activation (Frye et al., 2015; Shen et al., 2014). In ocular normotensive mice, topical ocular administration of AKB-9778 activated Tie2 in Schlemm's canal endothelium after a single dose and reduced IOP via increased outflow facility after three days of once a day dosing.

In normotensive female New Zealand White rabbits (n = 5/group) administered bilateral topical ocular doses (30 µL to both eyes) of 1.5% weight/volume (w/v) AKB-9778 in 15% w/v hydroxypropyl-beta-cyclodextrin (HPβCD) + 2% w/v dextrose or 4.0% w/v AKB-9778 in 15% w/v HPβCD + 1% w/v dextrose either once daily (QD) or BID, or vehicle control (15% w/v HPβCD) twice daily (BID), or subcutaneous administration of 10 mg/kg AKB-9778 BID for seven consecutive days, IOP was measured daily at baseline prior to dosing, on each day of dosing, and 24 hours after the last dose. Results showed that AKB-9778 Ophthalmic Solution 4.0% w/v topically administered either QD or BID reduced IOP, whereas the 1.5% w/v BID topical dose and the 10 mg/kg SC dose were not as effective. IOP reductions persisted through the last assessment 24 hours after the end of dosing.

Preliminary data from a dog IOP-lowering efficacy study indicates that topical ocular administration of 4.0% w/v AKB-9778 in a 15% w/v HPβCD + 1% w/v mannitol formulation also lowers IOP in normotensive dogs. Further, administration of AKB-9778 immediately following topical ocular dosing of 0.005% latanoprost was well tolerated and had an additive IOP-lowering effect relative to latanoprost alone.

Safety Pharmacology

All *in vitro* and *in vivo* safety pharmacology assessments were conducted for AKB-9778 SC Injection program. *In vitro* assessments demonstrated very limited interactions with AKB-9778; and *in vivo* safety pharmacology assessments demonstrated no respiratory or neurobehavioral effects in rat and a minimal decrease in blood pressure in dog and no effects on QT interval following SC dosing.

4.2.2 Absorption, distribution, metabolism and excretion (ADME)

In a 3-day PK study conducted in New Zealand White rabbits, topical ocular instillation of 4.0% w/v AKB-9778 in 15% w/v HPβCD + 1% w/v mannitol three times daily (TID) to both eyes (7.2 mg total daily dose) resulted in dose normalized AKB-9778 concentrations in aqueous humor approximately 2-fold higher than achieved with SC BID doses (33 mg total daily dose). By contrast, relative to topical ocular administration, systemic exposure following subcutaneous

administration of the same AKB-9778 formulation had a ~44-fold greater maximum plasma drug concentration (C_{max}) and 29-fold greater area under the concentration-time curve from time 0 to last quantifiable concentration (AUC_{last}), based on dose normalized values. In dogs, following bilateral topical ocular instillation of 30µL of 4.0% w/v AKB-9778 in 15% w/v HPβCD + 1% w/v mannitol QD (2.4 mg/day), BID (4.8 mg/day), or four times daily (QID, 9.6 mg/day) for 3 days, plasma half-life (T½) was 0.5 hours and mean plasma C_{max} and AUC values were generally similar across groups, suggesting rapid elimination of AKB-9778 between the BID and QID inter-day dosing intervals. There was no evidence for accumulation between the QD, BID, and QID dosing regimens.

In the Good Laboratory Practices (GLP) 28-day rabbit and dog toxicity studies, quantifiable systemic exposure of AKB-9778 in plasma was observed following bilateral topical ocular administration of 30 µL of 4% w/v AKB-9778 in 15% w/v HPβCD + 1% w/v mannitol to each eye QD (2.4 mg/day), BID (4.8 mg/day), and QID (9.6 mg/day) in males and females on Day 1 and during the last week of dosing (Day 23 for rabbit; Day 26 for dog). There were no consistent sex-related differences in systemic exposure; however, the data exhibited a high degree of inter-animal variability. In most cases, an initial peak at ≤ 0.25 hours postdose was observed in the mean concentration-time profiles across all dosing regimens and days; however, a second peak in some cases constituted C_{max}. Systemic exposure to AKB-9778 was similar (C_{max} and AUC approximately within 2-fold) following BID and QID dosing regimens on Day 1 and Days 23 and 26 for rabbits and dogs, respectively. Exposure was generally similar across all three dosing regimens with no evidence of accumulation.

4.2.3 Toxicology

Topical Ocular (AKB-9778 Ophthalmic Solution)

The topical ocular instillation of 4.0% w/v AKB-9778 in 10% w/v to 15% w/v HPβCD-based solution formulations has been well tolerated in rabbits and dogs in non-GLP toleration and GLP toxicity studies.

In the 28-day GLP toxicity studies, New Zealand White rabbits and Beagle dogs were administered a 30 µL bilateral ocular instillation of 4.0% w/v AKB-9778 in 15% w/v HPβCD + 1% w/v mannitol (1.2 mg/eye) QD (2.4 mg/day), BID (4.8 mg/day), and QID (9.6 mg/day) for 28 days. In both species, there were no adverse vehicle- or test article-related effects on body weight, food consumption, clinical pathology, ophthalmologic or IOP parameters, electroretinography, or post-mortem organ weight or macroscopic histological findings. Test article-related clinical observations involved only the eyes and surrounding skin areas for both rabbit and dog.

In rabbit, AKB-9778-related effects were primarily limited to clinical observations that included red conjunctiva (palpebral conjunctiva), red skin of the periorbital region, and red eyeballs (bulbar conjunctiva). Palpebral conjunctiva and periorbital skin redness were observed in all drug-treated animals the last 2 weeks of dosing. Periorbital redness was also observed in saline and vehicle control animals the last week of dosing but at a lesser incidence. Red eyeballs (red bulbar conjunctiva) were observed only in the test article-treated rabbits at the end of the dosing period on Days 28 and 29. In dog, similar results were noted where AKB-9778-related effects

were also limited to clinical observations including clear discharge, red eyeballs (bulbar conjunctiva), and red conjunctiva (palpebral conjunctiva). Red eyeballs were observed in all but one drug-treated animal, in 2/10 vehicle control, and in 2/10 saline control animals beginning the second week of dosing. Palpebral conjunctiva redness was observed in all drug-treated dogs during most of the dosing phase, with the earliest onset in dogs treated at 9.6 mg/day. These non-adverse findings in dog and rabbit resolved quickly during the recovery phase. Dose-dependent clear ocular discharge was observed in dog at all dose levels, including the vehicle control, but with the greatest incidence following QID dosing, with persistence in the QID group throughout the recovery phase.

There were no microscopic histopathological findings in the 28-day dog toxicity study. In rabbit, marked diffuse unilateral corneal epithelial atrophy was observed in 1 male following QID dosing. While corneal epithelial atrophy is not a reported background finding in this rabbit strain, the single incidence and unilateral distribution suggest that this is unlikely to be a test article-related effect. It would be unexpected for a direct test article effect to result in marked severity in only a single eye when both eyes were treated identically. However, a test article-related effect could not be ruled out due to its occurrence in the high-dose group; therefore, this finding was considered to have an uncertain relationship to the administration of the test article.

The no observed adverse-effect level (NOAEL) in the 28-day rabbit and dog toxicity studies was considered to be the highest dose administered in each study at 9.6 mg/day (2.4 mg QID). In rabbits, this dose was associated with mean combined-sex C_{max} and estimated $AUC_{0\text{-}24}$ values of 20.7 ng/mL and 132 ng·hr/mL, respectively; and, in dogs, of 51.7 ng/mL and 243 ng·hr/mL, respectively. These exposures numerically describe the margin to human exposure since the measured human exposure following topical ocular administration of 40 mg/mL AKB-9778 QD and BID was below the limit of quantitation (BLQ = <1 ng/mL).

Systemic (AKB-9778 Injection)

In the in vivo GLP general, genetic, and reproductive toxicity studies for AKB-9778 Injection, AKB-9778 was formulated as a solution in 10% w/v HPβCD + 1.7% w/v dextrose and demonstrated an excellent safety profile and was well tolerated by SC administration in up to 6 months (182 days) dosing in rats and up to 9 months (273 days) dosing in dogs and monkeys. The primary target tissues for AKB-9778 were identified as injection site and liver in rat, dog and monkey; skin/subcutis (vascular) in dog and monkey; and gastrointestinal (GI; vascular) in dog. The NOAEL exposures measured in rat, dog, and monkey were, respectively, 4-, 25-, and 33-fold the AUC value associated with a human dose of 15 mg SC BID.

No liver findings or unusual or unexpected dermal findings have been observed in clinical studies with SC administration of AKB-9778.

AKB-9778 is not considered to be mutagenic or clastogenic based on the negative findings in the pivotal battery of genotoxicity studies.

Definitive systemic embryo-fetal development toxicity studies in rat and rabbit with SC administration showed no evidence of external fetal teratogenic effects or of skeletal or visceral

malformations; and a definitive systemic fertility study in male and female rats demonstrated no findings on fertility or reproductive outcome.

4.3 Summary of Clinical Experience

Please see the AKB-9778 Investigator Brochure for additional discussion and information for the following section.

A robust clinical program has been conducted with a subcutaneous formulation of AKB-9778 (AKB-9778 SC injection) and a phase 1 study evaluating topical ocular administration of AKB-9778 Ophthalmic Solution in healthy volunteers and subjects with OAG/OHT has recently been completed. Clinical experience is summarized below. IOP reduction effects observed in studies conducted with AKB-9778 are consistent with preclinical and genetic evidence for the importance of Tie2 function on the CO pathway and support evaluation of Tie2 activation by AKB-9778 as a potential approach for IOP reduction in subjects with OAG or OHT.

4.3.1 AKB-9778 SC Injection

AKB-9778 SC injection 20 mg/mL has been evaluated under an ongoing clinical development program in the United States for diabetic eye disease, including diabetic retinopathy and diabetic macular edema. A total of 478 human subjects have been randomized in completed clinical trials evaluating AKB-9778 SC administration (in the abdomen). Data from the two largest clinical trials conducted with this formulation are summarized as follows.

Study AKB-9778-CI-2003, was a Phase 2, double-masked, parallel-group trial in which 144 subjects with diabetic retinopathy complicated by center-involved diabetic macular edema were randomized to one of 3 treatment groups: AKB-9778 (15 mg) SC BID monotherapy; AKB-9778 SC BID plus monthly Lucentis® (0.3 mg) intravitreal injection (IVT); and monthly Lucentis® IVT monotherapy. Ophthalmic assessment at baseline, during and at the end of the 3-month treatment period, included IOP measurement by applanation tonometry in both the study eye and the fellow eye. Pretreatment baseline IOP assessment showed both the study eye and fellow eyes of each treatment group to be normotensive and well balanced between treatment groups. Both active AKB-9778 treatment arms achieved statistically significant reductions in IOP in both the study eye and the fellow eye compared to baseline. In the subgroup of subjects with baseline IOP > 16 mm Hg, a greater IOP reduction was achieved.

Study AKB-9778-CI-5001, was a Phase 2, double-masked, placebo-controlled, parallel-group trial in which 167 subjects with moderate to severe non-proliferative diabetic retinopathy were randomized to receive once or twice daily AKB-9778 SC (15 mg) for 12 months. Positive effects on IOP reduction were observed in this study and were similar to those observed in the AKB-9778-CI-2003 study.

AKB-9778 SC injection has shown no evidence of significant safety issues to date. A transient, generally asymptomatic reduction in blood pressure is observed reflecting the vasodilatory pharmacodynamic effect of Tie-2 activation. Vasovagal events (presyncope/syncope) have been observed following the first dose of AKB-9778 at doses >22 mg. A vasovagal event was observed after the first dose in 1/144 (0.7%) subjects in the Phase 2 AKB-9778-CI-2003 study.

This subject did not experience any such events during the subsequent 3 months of dosing. No other vasovagal events were observed in this study. In both studies there was a significant correlation between baseline blood pressure (BP) and change in BP. Specifically, subjects with higher BP had greater reductions in BP. To date there has been no evidence of adverse effects on clinical chemistry assessments, including liver function tests, and no evidence of unusual dermal findings.

4.3.2 AKB-9778 Ophthalmic Solution

A Phase 1b study evaluating AKB-9778 ophthalmic solution has been recently completed. Study AKB-9778-CI-OS-1001 was a randomized, double-masked study designed to assess increasing concentrations of AKB-9778 dosed topically as eye drops (5mg/mL QD, 15 mg/mL QD, 40 mg/mL QD and 40 mg/mL BID) conducted initially in 4 sequential cohorts of 12 healthy (ocular normotensive subjects), randomized 3:1 to receive AKB-9778 or placebo, for 7 days. The primary outcome of the study was ocular safety and tolerability with change in IOP as a pharmacodynamic outcome. Conjunctival hyperemia grade and IOP were assessed prior to dosing and at 2-, 4- and 8-hours post-dose on Day 1 and Day 7. Topical ocular administration of AKB-9778 was well tolerated over 7 days at all dose levels. Compared to placebo, there was a dose dependent increase in minimal to mild conjunctival hyperemia with AKB-9778, which was transient and generally considered non-adverse. There was also a time and dose dependent reduction in IOP that, in the highest QD dose cohort (40mg/mL) peaked at 4 hours post-dose (- 1.47 mmHg; $p = 0.041$)/-10.64%; $p = 0.027$) and was sustained through eight hours on day 7, returning to baseline levels at 24 hours post-dose. There was a trend towards larger IOP decreases with BID dosing in Cohort 4, but hyperemia was similar to Cohort 3 with QD dosing. The results of the bioanalysis of approximately 100 plasma samples from the subjects administered the highest dose (40 mg/mL) indicated almost no systemic exposure (all samples (except 1 sample) were reported as below limit of quantitation (BLQ) using a bioanalytical method with a lower limit of quantification of 1 ng/mL). As a result, no systemic AEs are anticipated for the topical ophthalmic dosing of AKB-9778.

No significant safety issues were identified in Cohorts 1-4. Overall, there was 1 AE in the 5 mg/mL (upper airway cough syndrome), 15 mg/mL (scratch), and placebo (blood pressure increased) treatment groups and 7 AEs in 3 subjects in the 40 mg/mL QD treatment group (2 events of dysgeusia in 2 subjects; 2 events of conjunctival hyperemia in 2 subjects; 2 events of headache in 1 subject and 1 event of upper airway cough syndrome in 1 subject). All AEs were mild and all resolved by the end of the study. There were no significant changes in vital signs, body system assessment, clinical labs or visual acuity. In the formal assessments of hyperemia score, minimal to mild conjunctival hyperemia was observed in subjects receiving AKB-9778. The hyperemia was transient and uniformly resolved to minimal or none by 4-8 hrs post-dose.

Based on favorable tolerability and pharmacodynamic findings in these ocular normotensive subjects, a fifth cohort of subjects with OHT/POAG on standard of care prostaglandin therapy was added to assess the safety, tolerability and pilot efficacy of once-daily AKB-9778 (40 mg/mL) as an adjunctive therapy. Briefly, 43 subjects were recruited with OHT/POAG and baseline IOP measurements ≥ 17 and ≤ 27 mmHg while treated with once-daily prostaglandin therapy. Subjects were randomized 3:1 to receive either AKB-9778 (32 subjects) or placebo (11

subjects), administered in the morning for 7 days, while continuing their evening prostaglandin therapy. Conjunctival hyperemia and IOP were assessed in the same manner as described for Cohorts 1-4 (see above). Subjects in Cohort 5 randomized to the active treatment group exhibited statistically significant decreases in IOP at all post-AKB-9778 administration time points on both Days 1 and 7 compared with Day -1 baseline values when they were being treated with prostaglandin alone (see Figure 1; Diurnal = mean IOP of 2, 4 and 8 hour time points; ** $p < 0.05$, *** $p < 0.001$). On Day 7, the diurnal mean reduction was -1.58 mmHg ($p < 0.001$) compared to 0.06 mmHg for placebo ($p = 0.462$).

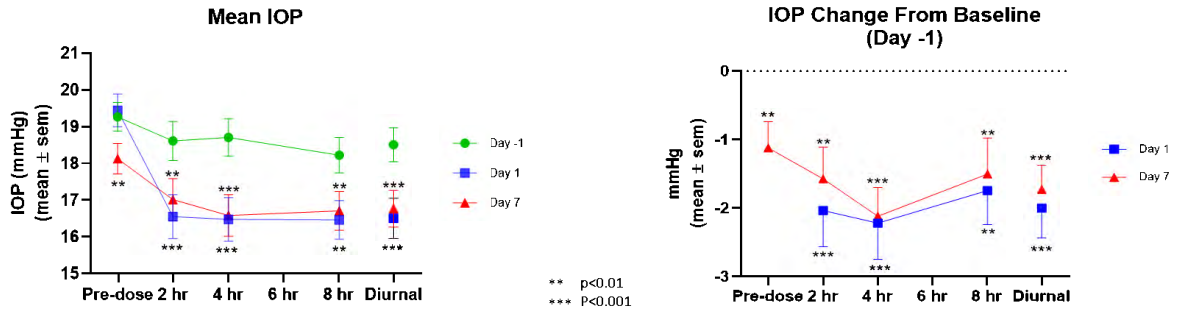


Figure 1: Mean IOP in the Cohort 5 AKB-9778 treated subjects (N = 32) at all time points with diurnal mean on Days -1, 1 and 7 (left panel) and mean change from baseline at all time points with diurnal mean change from baseline on Days 1 and 7 (right panel). Legend: green circle, Day-1; blue square, Day 1; red triangle, Day 7.

Topical ocular administration of AKB-9778 was well tolerated over seven days of dosing in Cohort 5. In the active treatment group treated with AKB-9778 plus prostaglandin, 21.9% of subjects experienced hyperemia compared with 9.1% of subjects in the prostaglandin monotherapy treatment group. In all cases, this hyperemia was minimal-to-mild in severity, transient in duration and generally considered non-adverse. There were no other ocular AEs and no systemic AEs reported during the seven days of dosing in Cohort 5.

4.4 Risks and Benefits to Human Subjects

4.4.1 Potential Benefits and Risks of AKB-9778

Please see the AKB-9778 Investigator Brochure for additional discussion and information for the following section.

Potential benefits: In this study, subjects are unlikely to benefit from the short-term administration of the AKB-9778 Ophthalmic Solution. However, the results of this study may lead to continued development of AKB-9778 Ophthalmic Solution as a novel CO-targeted treatment for OAG/OHT.

Potential risks: No serious risks have been identified in nonclinical toxicology studies of AKB-9778 Ophthalmic Solution of up to 28 days duration or in extensive nonclinical toxicology and clinical studies of AKB-9778 Subcutaneous Injection.

Potential risks based on the nonclinical topical ocular dosing of AKB-9778 include conjunctival hyperemia and local ocular irritation. Potential risks identified in AKB-9778 Subcutaneous Injection nonclinical studies include hemodynamic findings (blood pressure reduction), liver findings and dermal vascular findings. To date, similar findings relating to the liver and dermal vasculature have not been observed in clinical trials.

Based upon the observed clinical safety data from the subcutaneous program, the following risks have been identified: hemodynamic effects (transient reductions in blood pressure and compensatory increases in heart rate), adverse events related to local tolerability, and allergic reaction.

The identified non-ocular risks are mitigated by the expected much lower systemic exposure following administration of AKB-9778 Ophthalmic Solution compared to AKB-9778 Subcutaneous Injection and are not expected to represent significant risks for the topical ocular formulation.

To date, topical ocular dosing of AKB-9778 for up to 7 days has been very well tolerated. Mild transient hyperemia was observed, increasing in incidence with increasing dose of AKB-9778 and mild transient dysgeusia has been observed in some subjects at the highest dose tested (40 mg/mL). There were no clinically significant changes in vital signs including blood pressure and heart rate consistent with much lower systemic exposure of AKB-9778 Ophthalmic Solution compared to AKB-9778 Subcutaneous Injection.

There is no known antidote for AKB-9778. In cases of suspected overdose, subjects should be treated per standard medical practice based on the Investigator's judgment. Dose delays may be implemented as necessary. Subjects will be withdrawn from the study if persistent or unacceptable treatment-related toxicity is observed.

4.4.2 Latanoprost Safety Information

The following information is from the Highlights of Prescribing Information of the XALATAN® (latanoprost ophthalmic solution)0.005% Package Insert. For additional information, please refer to the full prescribing information [XALATAN Package Insert, 4/2017] (See Appendix 2).

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 keratitis, and upper respiratory tract infection/nasopharyngitis/influenza.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Primary Objectives

The primary objective of this study is:

- To evaluate the ocular hypotensive effects of AKB-9778 Ophthalmic Solution 4.0% administered once or twice daily for 28 days when used as an adjunctive therapy to latanoprost ophthalmic solution 0.005% in subjects with OAG or OHT

5.2 Secondary Objectives

The secondary objective of this study is:

- To evaluate the safety and tolerability of AKB-9778 Ophthalmic Solution 4.0% administered once or twice daily for 28 days when used as an adjunctive therapy to latanoprost ophthalmic solution 0.005% in subjects with OAG or OHT

5.3 Efficacy Endpoints

All efficacy analyses will be conducted in study eye and both eyes (average of study eye and fellow eye).

Primary Efficacy Endpoint:

- Mean change from baseline in diurnal IOP on Day 28 (study eye)

Secondary Efficacy Measures

- Mean change from baseline in diurnal IOP on Day 14 (study eye)
- Mean change from baseline in diurnal IOP on Days 14 and 28 (both eyes)
- Mean diurnal IOP on Days 14 and 28 (both eyes)
- Mean observed IOP at each time point on Days 14 and 28
- Mean change from diurnally adjusted baseline IOP at each time point on Days 14 and 28
- Mean percent change from diurnally adjusted baseline IOP at each time point on Days 14 and 28
- Mean percent change from baseline in diurnal IOP on Days 14 and 28
- Percentages of subjects achieving pre-specified mean, mean change, and percent mean change in diurnal IOP levels

5.4 Safety Measures

Safety measures include:

- Adverse events (AEs)
- Ophthalmic examination findings including:
  - Bulbar conjunctival hyperemia assessments (study eye and worse eye)
  - Pachymetry

- Visual acuity
- Biomicroscopic examinations (*i.e.*, lids, conjunctiva, cornea, anterior chamber, iris and lens)
- Dilated ophthalmoscopy

6.0 INVESTIGATIONAL PLAN

6.1 Overall Study Design and Plan

This is a phase 2, double masked, randomized, multi-center, parallel-group, 28-day study to evaluate the safety, tolerability and ocular hypotensive efficacy of AKB-9778 Ophthalmic Solution 4.0% administered once (AM) or twice (AM & PM) daily when used as an adjunctive therapy to latanoprost ophthalmic solution 0.005% once daily (PM) in subjects with elevated IOP due to OAG or OHT.

Subjects will participate in the study for up to approximately 11 weeks (Screening Visit, Washout period for 4-6 weeks, 2 Qualification Visits (2-7 days apart) and Treatment period for 28 days).

The study will be conducted at approximately 25 sites in the USA.

Approximately 195 subjects will be randomized in this study and will be assigned in a 1:1:1 ratio to one of the following treatment groups:

AKB-9778 QD + Latanoprost

- AKB-9778 ophthalmic solution 4.0% QD (AM) and placebo for AKB-9778 ophthalmic solution QD (PM) plus latanoprost ophthalmic solution 0.005% QD (PM) for 28 days

AKB-9778 BID + Latanoprost

- AKB-9778 ophthalmic solution 4.0% BID (AM & PM) plus latanoprost ophthalmic solution 0.005% QD (PM) for 28 days

Latanoprost Monotherapy

- Placebo for AKB-9778 ophthalmic solution BID (AM & PM) plus latanoprost ophthalmic solution 0.005% QD (PM) for 28 days

During the treatment period, subjects will self-administer study medication (AKB-9778 ophthalmic solution 4.0% or Placebo for AKB-9778) daily in the AM and PM and will also administer latanoprost daily in the PM. Subjects will dose into each eye by the topical ocular route using dropper bottles to deliver eye drops. Daily AM dose administration of study medication should occur between 7:00 and 10:00 hours and PM dose administration should occur between 19:00 and 22:00 hours. Latanoprost PM dose administration will occur at least 5 minutes before administration of the PM dose of study medication. Subjects will begin dosing

with the AM dose of study medication on the morning of Day 1 and conclude dosing after administration of the AM dose of study medication on Day 28; there is no PM dose administration on Day 28. At study visits conducted on Days 14 and 28, subjects will administer the AM dose of medication at the site after the 8:00 ophthalmic assessments have been completed. The Investigator, all study-site personnel, all Sponsor personnel (except for select personnel responsible for randomization scheme development and not involved with core study conduct), and subjects will be masked to treatment assignment during the entirety of the study.

Subjects who agree to participate in this study and are randomized in the study will attend a total of 6 study visits: a Screening Visit, Qualification Visit #1, Qualification Visit #2/Day -1 (Baseline), and visits on Days 7, 14 and 28. Eligible subjects must be on a stable dose of topical prostaglandin eye drops (eg, bimatoprost [Lumigan®], latanoprost [Xalatan®], tafluprost [Zioptan®] and travoprost [Travatan Z®]) for at least 2 weeks prior to screening. After completion of the Screening Visit, subjects will undergo a minimum 4-week washout period from IOP lowering treatment prior to attending Qualification Visit #1. Among multiple procedures, subjects will receive an eye examination including IOP measurements at Qualification Visits #1 and #2/Day -1 and, if deemed eligible, will be enrolled at Qualification Visit #2/Day -1 and assigned treatment group according to a computer-generated randomization list. Randomization will take place using IWRS methodology and will stratify subjects by mean diurnal IOP (IOP averaged over 08:00, 10:00, 12:00, and 16:00 hour time points) on Qualification Vist#2/Day -1 (< 26 mmHg vs ≥ 26 mmHg) in the study eye.

During the treatment period, subjects will be seen in the clinic on Days 7, 14 and 28; ocular safety assessments will be conducted on all days and efficacy measurements (IOP) will be conducted on Days 14 and 28 at the following time points: 08:00, 10:00, 12:00 and 16:00 hours. Following completion of the Day 28 study visit procedures, subjects will exit from the study. 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 the Day 28 visit. Following completion of the study, subjects will return to the care of their ophthalmologist.

At each study visit during the treatment period, multiple ocular safety assessments will be conducted including some or all of the following: adverse events, visual acuity, hyperemia assessment, objective findings of biomicroscopic examinations (i.e., lids, conjunctiva, cornea, anterior chamber, iris and lens), cup-disc ratio measurements, and dilated ophthalmoscopic examination.

An interim analysis for futility is planned to be performed when 50% of randomized subjects have completed 28 days of therapy.

6.2 Rationale for Study Design

This Phase 2 study is being conducted to assess the safety and ocular hypotensive efficacy of adding AKB-9778 QD or BID to latanoprost QD therapy for 28 days. In order to best evaluate the contributions of AKB-9778 to the ocular hypotensive efficacy of latanoprost, a parallel group, double-masked, three-arm study design was selected. The information to be gained from this study is considered critical in the development of AKB-9778 as an IOP lowering medication. Results from this study will assist in design of subsequent clinical studies.

6.3 Rationale for AKB-9778 Dose Selection and Frequency

The AKB-9778 dose selected for this study is based on the recently completed Phase 1b study, AKB-9778-CI-OS-1001. The treatment period and dosing frequency is selected on the basis of nonclinical safety studies with AKB-9778 and regulatory requirements for demonstration of ocular hypotensive efficacy.

In pre-clinical studies, a dose of 30 µL of a 40 mg/mL AKB-9778 formulation in 15% HPβCD in both eyes for 7 days demonstrated a consistent diurnal reduction in IOP in a normotensive rabbit model without exhibiting any systemic or significant local ophthalmic tolerability issues. In addition, no systemic or serious local ocular findings were observed in 28-day GLP repeat-dose toxicity studies in rabbit and dog following bilateral topical ocular administration of 30 µL of 40 mg/mL AKB-9778 in 15% HPβCD + 1% mannitol solution QD, BID, or QID for 28 consecutive days. Preliminary data in dog following a 35 µL topical ocular dose of a 40 mg/mL AKB-9778 formulation in 15% HPβCD in both eyes of normotensive dogs for 5 days also suggest diurnal reduction in IOP with only mild hyperemia. Further, administration of AKB-9778 immediately following topical ocular administration of latanoprost in dog appears to augment the IOP-lowering effect of latanoprost with a slight increase in the hyperemia observed with latanoprost alone and no other observed ocular changes. The 40 mg/mL AKB-9778 formulation used in the rabbit and dog studies represents the highest formulation strength of AKB-9778 Ophthalmic Solution to be used in the clinical trial and was assessed for safety in the 28-day toxicology studies at a high-dose QID dosing regimen, twice the highest daily dosing regimen (BID) to be used in clinical study. The dosing regimen in the clinical trial will be QD or BID at 4.0% w/v AKB–9778. The maximum total daily dose used in the repeat-dose toxicity study in rabbits and dogs (9.6 mg/day) is 2-fold the proposed highest dose in the clinical trial. The measured exposures in rabbit and dog at a total daily dose of 9.6 mg/day are estimated to be, respectively, at least 20- and 50-fold the measured human exposure (<1 ng/mL) following topical ocular administration of 4.8 mg/day (40 mg/mL AKB-9778 BID) in the Phase 1 study. The dose levels for the proposed study are selected to allow evaluation of tolerability and efficacy of AKB-9778 Ophthalmic Solution and are not expected to result in systemic adverse effects.

In the Phase 1b clinical trial, AKB-9778 Ophthalmic Solution (40 mg/mL) both QD and BID dosing were well tolerated in ocular normotensive volunteers with a dose dependent increase in IOP reduction. In OHT/OAG patients on standard of care prostaglandin therapy, QD dosing was well tolerated and resulted in significant IOP reduction. Thus, based on the available preclinical and clinical data, both QD and BID dosing of AKB-9778 Ophthalmic Solution (40 mg/mL [4.0%]) will be studied.

7.0 STUDY POPULATION SELECTION

7.1 General Criteria

Subjects will be recruited by the Investigative Sites.

To be eligible for this study, a subject must provide valid informed consent and must meet all of criteria outlined below. No study procedures (including Screening tests) may be performed until after the informed consent has been legally signed.

A Screening number will be allocated to each subject at the Screening visit. If the subject qualifies for participation in the study, (s)he will be assigned a subject number. If during the course of the screening tests and procedures, a subject does not meet the eligibility criteria or does not continue in the study, the subject will be considered a Screening failure (not a withdrawal).

7.2 Subject Eligibility and Study Eye Determination

For a subject to be included in the study, at least one eye (the same eye) must meet ALL ophthalmic inclusion and no exclusion criteria through the screening period (Screening, Qualification 1 and Qualification 2 [Day -1] visits). If both eyes are eligible at Screening, and Qualification Visits #1 and #2, then the study eye will be the eye with the higher diurnal IOP on Qualification Visit #2/Day -1. If both eyes have the same IOP at 08:00 hours on Qualification Visit #2, then the right eye will be the study eye.

7.3 Inclusion Criteria

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

1. Males and non-pregnant, non-breast feeding females
2. Aged ≥ 18 years
3. Diagnosis of OAG or OHT in each eye (OAG in one eye and OHT in the fellow eye is acceptable)
4. Must be treated with a stable regimen of topical prostaglandin eyedrop for a minimum of 2 weeks prior to the Screening visit; may be taking one additional IOP lowering eyedrop (for the purposes of this inclusion criterion, a combination product is counted as a single eyedrop)
5. IOP of ≥ 18 mmHg and ≤ 27 mmHg in one eye (study eye) or both eyes at the Screening Visit.
6. Unmedicated (post-washout) IOP at 2 qualification visits 2-7 days apart meeting the following criterion. At the first qualification visit, if tested at or before 10:00 hour, have IOP ≥ 24 mmHg in study eye or both eyes **and** < 36 mmHg in both eyes *or* if tested after 10:00 hour, have IOP ≥ 22 mmHg in study eye or both eyes **and** < 36 in both eyes. At the second qualification visit, IOP ≥ 24 mmHg in study eye or both eyes **and** < 36 mmHg in both eyes at 08:00 hour and IOP ≥ 22 mmHg in study eye or both eyes **and** < 36 mmHg in both eyes at 10:00, 12:00 and 16:00 hours.
7. Visual Acuity (VA) of +0.5 logarithm of the minimum angle resolvable (logMAR) (20/63 Snellen) or better in each eye
8. Must be willing and able to communicate and participate for the duration of the study

9. Ability to properly self-administer eye drops (or have a caregiver that can suitably administer eye drops)
10. Must provide written informed consent

7.4 Exclusion Criteria

Subjects meeting any of the following criteria during screening or qualification evaluations will be excluded from entry into the study:

Ophthalmic:

1. Clinically significant ocular disease (*e.g.*, corneal edema, uveitis, severe keratoconjunctivitis sicca, diabetic macular edema, proliferative diabetic retinopathy, or neovascular age-related macular degeneration) which might interfere with interpretation of the study efficacy endpoints or with safety assessments
2. Pseudoexfoliation or pigment dispersion component glaucoma
3. History of angle closure glaucoma, or narrow angles (*i.e.*, Shaffer Grade 2 or less; extreme narrow angle with complete or partial closure), or with evidence of peripheral anterior synechiae (PAS) ≥ 180 degrees by gonioscopy within 6 months prior to Screening visit in either eye. Note: Previous laser peripheral iridotomy is NOT acceptable
4. Intraocular pressure ≥ 36 mmHg in either eye at the Screening Visit, Qualification Visit #1, or at any assessment on Qualification Visit #2/Day-1 (individuals who are excluded for this criterion are not allowed to attempt requalification)
5. Cup/disc ratio of > 0.8 in either eye
6. Severe visual field defect in either eye as assessed by the investigator, or significant defect (sensitivity of ≤ 10dB) within 10 degrees of fixation in either eye
7. Known hypersensitivity to any component of the investigational formulations or to any topical prostaglandin eyedrop
8. Selective laser trabeculoplasty (SLT) within the past 6 months or any history of argon laser trabeculoplasty (ALT) or minimally invasive glaucoma surgery (MIGS) in either eye
9. Any history of radial keratotomy, corneal cross linking, photorefractive keratectomy (PRK), Laser-assisted in-situ keratomileusis (LASIK), or limbal relaxing incision (LRI) in either eye within 12 months prior to screening
10. Any intravitreal injection within 30 days prior to screening or anticipated intravitreal injection during the course of the study
11. Ocular trauma in either eye within the 6 months prior to screening, or ocular surgery or non-refractive laser treatment within the 3 months prior to screening
12. Recent (within 90 days prior to screening) or current evidence of ocular infection or inflammation in either eye. Current evidence of clinically significant blepharitis, conjunctivitis, keratitis, or a history of herpes simplex or zoster keratitis in either eye at screening

13. Bulbar conjunctival hyperemia ≥3 (moderate) on the hyperemia scale (Section 9.2.2) in either eye at Screening, Qualification Visit #1 or at any assessment on Qualification Visit #2 (Baseline Visit)
14. History of recurrent uveitis in either eye
15. Use of 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 or warm compresses (which may be used prior to, but not after, screening), c) preservative or preservative-free lubricating drops (excluding gels or ointments) for dry eye (which may be used throughout the study at maximum frequency of QID), or d) non-steroid allergy drops (note: must not contain a vasoconstrictor)
16. Mean central corneal thickness less than 480µm or greater than 600µm at screening in either eye
17. Any abnormality preventing reliable applanation tonometry of either eye (e.g., keratoconus, corneal scarring)

Systemic:

18. Women who are pregnant or breast-feeding or intending to become pregnant during the study
19. Women of child-bearing potential who are not on an acceptable method of birth control (e.g., 1 highly effective method [less than 1% failure rate] of contraception, or a combination of 2 effective methods of contraception). An adult woman is considered to be of childbearing potential unless she is one year post-menopausal or three months post-surgical sterilization (excluding tubal ligation). All females of childbearing potential must have a negative urine pregnancy test result at the Screening Visit and Qualification Visit #2.
20. History of any clinically significant disease or disorder which, in the opinion of the Investigator, may put the subject at risk because of participation in the study, influence the subject's ability to participate in the study, or interfere with interpretation of the subject's study results. Subjects with stable baseline medical conditions on established medication may be included as per the judgement of the Investigator; e.g., well controlled hypertension, type 2 diabetes, or mild, stable asthma not requiring treatment with inhaled corticosteroids.
21. 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
22. Use of an investigational medication or device within 30 days or 5-half-lives of the investigational medication, whichever is longer, preceding Day 1, or ongoing or scheduled participation in another investigational study during the present study through the last visit
23. Previous treatment with AKB-9778

24. Subjects who are study site employees, or immediate family members of a study site or sponsor employee
25. Failure to satisfy the Investigator of fitness to participate for any other reason

7.5 Withdrawal of Subjects

All subjects have the right to withdraw from this study at any time. In addition, it is the right of the Investigator to remove subjects from the study as a result of new symptoms, adverse reactions, protocol violation or for any other reason. Subjects will be discontinued from the study under any of the following circumstances:

- IOP in either eye ≥ 36 at any timepoint during the study
- Occurrence of intolerable AE, as assessed by the Investigator or designee
- Withdrawal of consent
- If, in the opinion of the Investigator, it is in the best interest of the subject
- Non-compliance with study requirements and restrictions
- Use of a concomitant medication that, in the opinion of the PI or designee, could interfere with the study procedures or data integrity or compromise the safety of the subject
- Termination of the study

Should a subject withdraw after administration of AKB-9778, or should the Investigator decide to withdraw the subject, all efforts will be made to complete and report the protocol-stipulated observations up to the time of withdrawal as thoroughly as possible. A final evaluation at the time of the subject's withdrawal should be made and an explanation given of why the subject is withdrawing or being withdrawn from the study.

Subjects who discontinue prior to completion of all planned study assessments, should undergo the Day 28 assessments at time of discontinuation.

The Investigator must document the primary reason for discontinuation of a study subject on the appropriate case report form (CRF). If the reason for withdrawal is a clinical AE, monitoring will continue until the AE resolves or the Investigator assesses the AE as chronic or stabilized.

7.6 Waivers

No waivers will be granted in the study.

7.7 Replacement of Subjects

No randomized subjects will be replaced.

8.0 STUDY PRODUCT AND TREATMENT OF SUBJECTS

8.1 Study Medication, Latanoprost, Supplies and Storage

The Investigator or designated study personnel will be responsible for study medication supply accountability and dispensing study medication to subjects.

8.1.1 Masked Study Medication: AKB-9778 Ophthalmic Solution and Matching Placebo

AKB-9778 Ophthalmic Solution and matching placebo will be provided as masked, sterile, pre-filled, single use dosing bottles packaged in kit boxes containing a one-week supply of study medication (seven "AM" dose bottles and seven "PM" dose bottles). Each dosing bottle is contained in a sealed foil pouch. Pouches contain a single dosing bottle to be used for binocular dose administration in the morning are labelled "AM" and pouches which contain a single dosing bottle to be used for binocular dose administration in the evening are labelled "PM". Kits will be shipped by the Sponsor or its designated supplier/distributors to the Investigative site.

AKB-9778

AKB-9778 Ophthalmic Solution will be supplied as a clear, colorless to slightly yellow, buffered, isotonic, sterile unpreserved solution, essentially free of particulates, of AKB-9778 (4.0% as the sodium salt) in a 5mM phosphate buffered vehicle (sodium phosphate, monobasic, monohydrate USP and sodium phosphate, dibasic anhydrous USP) containing 15% HPβCD, United States Pharmacopoeia (USP), and 1.2% mannitol, USP, and adjusted to a pH of 6.5 to 7.5 with 1N Hydrochloric Acid and/or 1N Sodium Hydroxide. The solution is filter sterilized and aseptically filled into single-use 1.0 mL LDPE sterile bottle suitable for ophthalmic delivery to which a sterile dropper tip is inserted (to deliver a ~30 uL drop), and then fitted with a sterile cap. The completed dropper assembly is placed into a foil pouch, sealed, and labelled with the appropriate "AM" or "PM" designation.

Placebo

The placebo to match AKB-9778 Ophthalmic Solution will be supplied as a clear, colorless to slightly yellow, buffered, isotonic, sterile unpreserved solution, essentially free of particulates, of a 5mM phosphate buffered vehicle (sodium phosphate, monobasic, monohydrate USP and sodium phosphate, dibasic anhydrous USP) containing 15% HPβCD, USP, and 2.5% mannitol, USP, adjusted to a pH of 6.5 to 7.5 with 1N Hydrochloric Acid and/or 1N Sodium Hydroxide. The solution is filter sterilized and is packaged in the same primary container/closure system as outlined for AKB-9778 Ophthalmic Solution.

8.1.2 Storage and Handling of AKB-9778 and Placebo for AKB-9778

At the investigational site, masked study medication kit boxes will be locked under controlled access and maintained at USP controlled room temperature, 20ºC - 25ºC (68ºF - 77ºF) with excursions between 15ºC to 30ºC (59ºF – 86ºF) permitted, which is documented by a suitable device.

The subject will be directed to store study medication in a secure location away from children at room temperature, 15ºC - 25ºC (59ºF - 77ºF).

8.1.3 Latanoprost

Commercially available XALATAN® (latanoprost ophthalmic solution) 0.005% multi-use bottles (2.5 mL) will be provided by the Sponsor or its designated supplier/distributors to the Investigative site.

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.

8.1.4 Storage and Handling of Latanoprost

At the investigational site, latanoprost ophthalmic solution (XALATAN) will be locked under controlled access and stored at refrigerated temperature (2°C to 8°C/36°F to 46°F) documented with a suitable device until provided to the subject.

The subject should be instructed that, once the latanoprost product bottle is opened, the product may be kept at room temperature (up to 25°C/77°F) while continuing to store the bottle in the carton for the duration of the study.

8.2 Dispensing Procedures

The Investigator will maintain drug accountability forms itemizing all latanoprost and masked study medication dispensed to and returned from each subject during the study.

Randomization to treatment group and assignment of study medication kits for dispensing will be made using an interactive web response system (IWRS).

On Day -1, all subjects will be dispensed a single carton of latanoprost ophthalmic solution sufficient for 28 days of dosing.

On the Day -1 and the Day 14 visits, subjects will be provided with study medication which is packaged in study medication kit boxes. Each study medication kit box contains a one-week supply of study medication. During the Day -1 and Day 14 visits, sufficient supply for 2 weeks of dosing plus one week of overage to allow for some flexibility in study visit scheduling are dispensed.

Subjects should discard used study medication bottles after each binocular dose administration into a zip lock bag provided by the site. At the Day 14 and Day 28 visits, subjects will return unused (unopened) study medication bottles and empty (or partial) kit boxes to the site for drug accountability. Latanoprost is provided in a multiuse format and is not discarded after dosing.

The subject will bring the latanoprost to the Day 14 and Day 28 site visits. The returned empty (or partial) study medication kit boxes and returned latanoprost should be available for the monitor to verify during an interim monitoring visit.

Subject dosing diaries should be returned at each study visit and subjects should be questioned regarding dosing compliance and whether they have questions or have experienced any problems related to the dosing of study medication or latanoprost.

All unused study medication should be retained at the investigative site and must be returned to the Sponsor or its designee for destruction at the end of the study. If an investigative site has SOPs for destruction of study medication on site; following review of the procedure, the Sponsor may authorize destruction of study medication at the investigative site once accountability procedures have been completed.

8.3 Treatment of Subjects

The Treatment period will last 28 days.

8.3.1 Treatment Group Assignments

Subjects meeting all eligibility criteria will be randomized 1:1:1 to one of the following 3 treatment groups:

AKB-9778 QD + Latanoprost

- AKB-9778 Ophthalmic Solution 4.0% QD (AM) and placebo for AKB-9778 ophthalmic solution QD (PM) plus latanoprost ophthalmic solution 0.005% QD (PM) for 28 days

AKB-9778 BID + Latanoprost

- AKB-9778 Ophthalmic Solution 4.0% BID (AM & PM) plus latanoprost ophthalmic solution 0.005% QD (PM) for 28 days

Latanoprost Monotherapy

- Placebo for AKB-9778 ophthalmic solution BID (AM & PM) plus latanoprost ophthalmic solution 0.005% QD (PM) for 28 days

8.3.2 Randomization and Allocation to Treatment Group

Approximately 195 subjects will be treated in the study.

A randomization code for treatment allocation will be prepared by an independent biostatistician, who is not involved in the day-to-day conduct of the study. Using a central IWRS randomization system, eligible subjects will be assigned in a 1:1:1 ratio to one of the 3 treatment groups. To maintain balance between treatment groups randomization will be stratified by mean diurnal IOP on Day -1 (< 26 mmHg vs ≥ 26 mmHg) in the study eye. Study medication kits will be allocated via the IWRS system.

8.4 Masking

This study will be conducted in a double-masked manner.

Study medication will be shipped as masked supplies.

Commercially available latanoprost will be provided in an unmasked manner to sites.

Treatment group assignment will be done through a central randomization system and completed using an IWRS.

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 treatment. Treatment assignment(s) will be unmasked and made available to the Investigator and the Sponsor's Medical Monitor 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.

8.5 Unmasking

Unmasking of the Investigator is restricted to emergency situations and should only be used under circumstances where knowledge of the treatment is necessary for the proper management of the subject. When possible, the Investigator should first discuss the unmasking request with the Sponsor and or Medical Monitor prior to unmasking. If treatment is unmasked, the subjects should be discontinued from the study, and the appropriate early termination visit procedures conducted per protocol requirements.

8.6 Study Medication and Latanoprost Administration

Subjects will be responsible for self-administering study medication and latanoprost. For subjects deemed unable to self-administer, a caregiver can administer the study medication and latanoprost provided the caregiver has received documented training from the investigative site. On the Qualification Visit #2/Day -1 visit, subjects will be trained on study medication kits and instructions for dosing and diary completion for study medication and latanoprost. If necessary, subjects can undergo additional eye drop training during their Day -1 visit.

During the treatment period, subjects will administer the study medication daily in the AM and PM to both eyes and will also administer latanoprost daily in the PM to both eyes. Daily AM dose administration of study medication should occur between 7:00 and 10:00 hours and PM dose administration of study medication should occur between 19:00 and 22:00 hours. Latanoprost PM dose administration will occur at least 5 minutes before administration of the PM dose of study medication. Subjects will begin dosing with the AM dose of study medication on the morning of Day 1 and conclude dosing after administration of the AM dose of study medication on Day 28; there is no PM dose administration on Day 28. At visits conducted on Days 14 and 28, subjects should not dose the AM dose of study medication at home and will

administer the AM dose of study medication at the site after the 8:00 hour assessments have been completed.

At completion of the study on Day 28, the subject will return to OAG/OHT treatment per the care of their ophthalmologist.

Subjects will dose study medication and latanoprost by instilling one drop of medication into each eye. Subjects will maintain a dosing diary noting date and time of study mediation and latanoprost dosing. If a subject forgets to administer a dose, that dose should be skipped, and noted along with the reason why in the dosing diary. If an administered dose misses the eye, that dose should not be repeated and the diary properly noted to indicate the surface of the eye was missed.

Contact lens wear during the study is acceptable. However, subjects must remove their contact lenses at least 15 minutes before instillation of masked study medication or latanoprost, and not place contact lenses in their eye(s) until a minimum of 15 minutes after instillation. On days of study visits, subjects should not wear contacts until the study visit is completed.

8.7 Concomitant Medication

Intermittent use of over-the-counter (OTC) artificial tear lubricant products is acceptable (including preservative and preservative-free), with a minimum of 10 minutes between use of OTC products and study medication and latanoprost.

All subjects will self-dose concomitant latanoprost QD (PM) provided by the Sponsor during the treatment period. The latanoprost evening dose will be administered at least 5 minutes before the evening dose of study medication.

With the exception of latanoprost dosing which begins on Day 1, concurrent therapy with any form of ocular hypotensive medications (prescription or OTC) is not allowed during the study.

Disallowed concomitant ocular medications for randomized subjects include:

- Miotics
- Epinephrine-related compounds
- Carbonic anhydrase inhibitors (ocular or systemic)
- β-adrenoceptor agonists
- β-adrenoceptor antagonists
- Muscarinic agonists (*e.g.*, pilocarpine)
- Rho kinase inhibitors

- Prostaglandin analogues other than that which may be contained in the provided investigational product

- Any corticosteroid-containing systemic drug regardless of route of administration

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. 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. PRN use of systemic or inhaled corticosteroid-containing therapies is not allowed. Subjects should be cautioned to avoid use of alcohol during the study visit days and use of drugs such as marijuana.

Use of all medications should be documented on the appropriate Electronic Case Report Form (eCRF). Investigators are encouraged to contact the Sponsor for any questions regarding allowed medications.

Judgment of continued study participation by any randomized 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 eCRF. The name of the drug, dose, route of administration, duration of treatment, and indication will be recorded for each medication. For combination products (*e.g.*, Contac®), the brand name is required. For non-combination products, the generic name is desired. Any change in dosing parameters should also be recorded in the eCRF.

The use of routine ophthalmic diagnostic pharmaceutical agents (*e.g.*, fluorescein and local anesthetic) will be allowed and individual documentation is not required.

8.8 Restrictions

8.8.1 Prior Therapy and Washout

Prior use of AKB-9778 or study participation in a prior Aerpio Pharmaceuticals Inc., study which studied the AKB-9778 investigational product is exclusionary.

Eligible subjects must be on a stable dose of topical prostaglandin eye drops (for at least 2 weeks prior to Screening). After completion of the Screening Visit, subjects must undergo a minimum 4-week washout period from IOP lowering treatment prior to attending Qualification Visit #1. If washout is to be extended beyond 6 weeks (42 days) for logistical or other reasons, the Sponsor should be contacted.

8.8.2 Fluid and Food Intake

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

8.8.3 Subject Activity Restrictions

On study visit 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.

8.9 Treatment Compliance

Subjects will be instructed on the importance of following their daily dosing regimen. Dosing of AM study medication should occur in the morning between 7:00 and 10:00 hours. Dosing of latanoprost and PM study medication should occur in the evening between 19:00 and 22:00 hours with the latanoprost dose administered at least 5 minutes prior to the dose of PM study medication.

Intermittent interruption of dosing is discouraged, whether initiated by the Investigator or the subject. Subjects should contact the Investigator before interrupting treatment, and Investigators should contact the Sponsor.

Subjects will complete a provided dosing diary worksheet to record dosing of study medication and latanoprost. Dosing diaries will be reviewed at each visit.

8.10 Product Accountability and Destruction

Product accountability should be an ongoing process throughout the study. All bulk study medication and latanoprost must be accounted for and any discrepancies explained.

Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry date or retest date is provided to the Investigator.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the master drug log is completed for all study medication and latanoprost received at the site and that all required fields are complete, accurate, and legible.
- Review of temperature log, and that the study medication and latanoprost is stored in locked access controlled conditions.
- Verifying the subject individual drug accountability log is completed for each subject and that all required fields (units dispensed, returned, used, compliance) etc., are complete accurate and legible.
- Verifying at each study visit, the subject has completed the dosing diary, and any doses missed or not administered are properly documented and explained if necessary. Compliance to the dosing regimen should be verified and documented by the site at each visit by review of the diary and returned study medication kits.

If any dispensing errors or discrepancies are discovered, the Sponsor must be notified immediately.

Prior to site close-out, a representative from the Sponsor will perform clinical study material accountability and reconciliation.

At the end of the study, the Investigator will retain all the original documentation regarding clinical study material accountability, return, and/or destruction, and copies will be sent to the Sponsor.

The Investigator or designated study personnel is responsible for keeping accurate records of the study medication and latanoprost received from the Sponsor or its designee, all supplies retained in inventory at the site, and study medication and latanoprost dispensed to and returned from each subject. This record will be maintained on a Drug Accountability Log that accurately reflects the accountability of the study medication and latanoprost at all times.

During the study, the Investigator will be notified of any expiry dates or retest date extensions of study medication or latanoprost. If an expiry date notification is received during the study, the site must complete all instructions outlined in the notification, including segregation of expired study material for return to the Sponsor or its designee for destruction.

At the end of the study, any unused study medication or latanoprost must be returned to the Sponsor or its designee for destruction. If an investigative site has SOPs for destruction of clinical trial material on site, the Sponsor may authorize destruction of at the investigative site following completion of accountability procedures.

9.0 STUDY PROCEDURES

Please see Appendix 1 for a detailed table of the Schedule of Activities.

9.1 Administrative Procedures

9.1.1 Informed Consent

Informed consent must be obtained prior to the subject entering into the study and before any protocol-directed procedures are performed (see Section 16.3).

9.1.2 Documentation of Screen Failures

The Investigator or designee must account for all subjects who sign informed consent and will maintain a log of subjects screened and indicate who was randomized or screen failed. If the subject is found to be ineligible prior to randomization, the reason(s) for ineligibility must be documented. Screening numbers assigned to subjects who fail screening will not be re-used.

9.1.3 Contraception and Pregnancy Avoidance Measures

Due to the unknown effects of AKB-9778 Ophthalmic Solution on sperm and the developing fetus, all subjects must agree to use adequate contraception throughout the study and for 3 months after administration of last dose of study medication.

Adequate contraception is defined as follows:

Male subjects must agree to use a reliable method of birth control and to not donate sperm during the study and for 3 months following the last dose of study medication.

- Examples of reliable methods of birth control are condoms with spermicide; effective, highly effective, or surgical contraceptive method by the female partner; and male sterilization such as bilateral orchiectomy or vasectomy.

Male subjects exclusively with women of non-childbearing potential partners are not required to use contraception.

Female subjects of child-bearing potential must agree to use 1 highly effective method (less than 1% failure rate) of contraception, or a combination of 2 effective methods of contraception for the entirety of the study and for 3 months following the last dose of study medication.

- Highly effective methods of contraception: Combination oral contraceptives, implanted/injectable contraceptives, intrauterine device, bilateral tubal ligation, or permanent tubal occlusion.

- Effective methods of contraception: Male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges. The subject may choose to use a double-barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide. It should be noted that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these methods are combined.

Female subjects not of child-bearing potential may participate and include those who are:

- Infertile due to a congenital anomaly such as mullerianagenesis.

- Surgical sterility such as hysterectomy, bilateral oophorectomy, or bilateral salpingectomy.

- Post-menopausal: defined as a woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had cessation of menses for at least 1 year.

9.2 Study Procedures and Evaluations

Please see the Schedule of Activities presented in Appendix 1 for designated time points for assessments.

9.2.1 Clinical Evaluations

The following section details clinical evaluations which will be conducted during the course of the study.

- Medical history and demographics: Medical history and demographic information will be collected at the Screening visit. Interim medical history will also be collected at Qualifying Visits #1 and #2. Relevant medical history (with particular emphasis on previous medical conditions that may lead to exclusion) and significant ongoing medical conditions or diseases should be documented.

- Adverse Event Assessments: From the time of informed consent through study completion Day 28, the Investigator and study personnel will review all ophthalmic and clinical findings and query the subject directly regarding AEs. Subjects must be followed for AEs until the final required protocol visit or until all drug-related toxicities and serious adverse events have resolved (or are considered chronic/stable), whichever is later.

- Concomitant Medication Recording: All medications, both prescription and non-prescription, and including vitamins, herbals, topicals, inhaled, and intranasal, taken within 30 days prior to screening and though Day 28, should be recorded on the appropriate eCRF. All medications and treatments, including vitamin supplements, OTC medications, and oral herbal preparations must be recorded in the eCRFs.

9.2.2 Ophthalmic Assessments (listed in order of assessment)

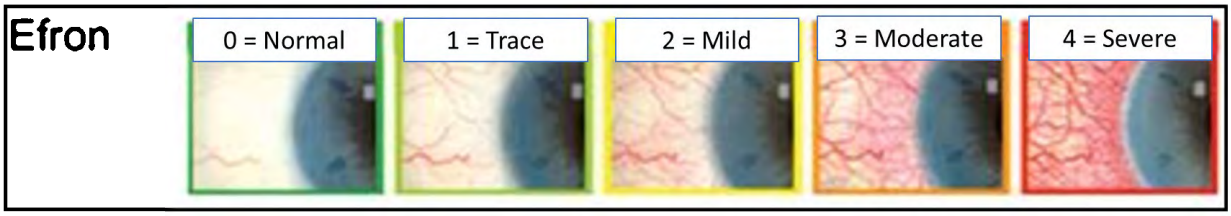
Further information on the conduct of the following procedures can be found in the study specific operations manual. Assessments are listed in suggested order of conduct when conducted on same visit.

- Visual Acuity: VA and pinhole visual acuity will be performed as a measure of ocular function and will be measured at Screening and frequently throughout the study.

- Visual Field Testing: Visual field testing must be performed within 3 months prior to randomization. Visual fields must be determined as automated threshold perimetry (*e.g.*, 30-2 or 24-2 Humphrey). Swedish interactive threshold algorithm (SITA) Standard is preferred, SITA fast also is allowed. Visual fields must be reliable, defined as those with a) fixation losses ≤ 33%, b) false positives ≤33%, and c) false negatives ≤33%.

- Biomicroscopy: A slit lamp biomicroscopy examination of the lids, conjunctiva, cornea, anterior chamber, iris and lens of both eyes will be conducted at Screening and selected subsequent visits.

- Bulbar Conjunctival Hyperemia Assessment & Grading: Bulbar conjunctival hyperemia will be assessed for both eyes at Screening, Qualification Visits #1 and #2, and frequently throughout the study. All hyperemia assessments coincide with a timed IOP evaluation. The hyperemia assessment and grading must be evaluated prior to the use of any ocular drops required for the IOP procedure. The Investigator will evaluate (grade) conjunctival hyperemia using the scale presented below. Note: An increase of 2 or more grades on the hyperemia scale when compared to the lowest score recorded at any previous timepoint for an individual eye should be reported as an adverse event. If a subject complains of hyperemia, an AE will be recorded regardless of grade on the hyperemia scale.



- Intraocular Pressure (IOP): IOP will be assessed by calibrated Goldmann applanation tonometry. IOP assessments are conducted as follows: measure twice, with 3rd measure if discordant (i.e. previous two readings >2mmHg different). The IOP used at each time point is the mean of 2 measurements or the median of 3 measurements. IOP will be measured at Screening, Qualification Visit #1 and #2 and frequently throughout the study. **Note: For purposes of determining eligibility, any non-integer (non-whole number) mean IOP should not be rounded (e.g. if the mean of 2 IOP readings is 23.5 do not round up to 24).**

- Pachymetry: Pachymetry (contact or non-contact method) will be performed at Screening and Day 28 and will be used to measure the thickness of the central cornea.

- Gonioscopy: Gonioscopy will conducted at Screening to confirm the iridocorneal angle is open and to what extent. Eligible subjects must have an angle of 3 or 4 (Shaffer grading scale; Kolker 1976) for participation in the study.

- Dilated Ophthalmoscopy: A dilated funduscopic examination including evaluation of the retina, vitreous, macula, choroid, optic nerve, and cup/disc ratio will be performed at Screening and Day 28. Evaluation of cup-disc ratio will be performed when ophthalmoscopy is performed.

9.2.3 Laboratory Evaluations

The following laboratory evaluations will be conducted during the course of the study:

Pregnancy test: A urine pregnancy test will be performed at Screening, Qualification Visit #2/Day -1 and Day 28 for females of childbearing potential.

The Sponsor will provide urine pregnancy tests 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 or within 3 months after administration of last dose of study medication, the Investigator should notify the Sponsor immediately after the pregnancy is confirmed (Section 11.4) and the subject will stop taking study medication and every possible effort will be made to assure there is an exit visit that includes all required examinations listed for the Day 28 visit. The Investigator should follow the progress of the pregnancy until the fetus is carried to term.

10.0 SCHEDULE OF ACTIVITIES

The Schedule of Activities is presented in Appendix 1 and shows the timing of planned study procedures to occur at the study site. Every effort should be made to adhere to the procedure schedule and all assessments should be completed at each study visit.

Subjects will be responsible for self-administration of study medication and latanoprost. As detailed in Section 8.6, subjects will self-dose study medication BID on a morning and evening schedule and latanoprost QD on an evening schedule. Subjects will begin dosing with the AM dose of study medication on the morning of Day 1 and conclude dosing after administration of the AM dose of study medication on Day 28; there is no PM dose administration on Day 28.

Subjects discontinuing study medication sooner than the planned 28 day dosing period or withdrawing from the study should complete the Day 28 assessments and return all unused study medication.

Detailed descriptions of procedures and activities to be followed during each site visit are presented in the following sections. For specific time points please refer to the Schedule of Activities in Appendix 1.

10.1 Visit Windows and Study Days

Clinical and ophthalmic evaluations performed during the Treatment period must be conducted within ± 30 minutes of the designated time. IOP and hyperemia assessments conducted at 8:00, 10:00, 12:00 and 16:00 hours must be conducted at a minimum of the protocol prescribed 2- or 4- hour interval (*e.g.* a minimum of at least 2 hours should occur between the 8:00 and 10:00 hour assessments and a minimum of at least 4 hours should occur between the 12:00 and 16:00 hour assessments).

Daily AM dose administration of study medication should occur between 7:00 and 10:00 hours and PM dose administration of study medication and latanoprost should occur between 19:00 and 22:00 hours. If a dose is missed, this dose should be skipped, and the subject should maintain the morning and evening dosing schedule.

At the site visits on Day 14 and 28, the subject will administer AM study medication at 08.00 (± 30 min) and will be administered after 8:00 hour ophthalmic assessments are conducted.

Site visits scheduled for Day 7, 14 and 28 should be conducted within ±3 days relative to the Day -1 Visit (*i.e.*, Day 7 visit window is 7 ±3 days from Day -1, Day 14 visit window is 14 ±3 days from Day -1 and Day 28 visit window is 28 ±3 days from Day -1).

Study days will be numbered relative to the first day of dosing. The start of study (Day 1) will be defined as the date on which a subject takes the first dose of any study medication, as recorded on the CRF. Relative to study start, days will be numbered …..-2, -1, 1, 2… with Day -1 being the day prior to the start of study medication.

10.2 Visit 1 (Screening Visit)

This visit may occur at any time of the day.

The Investigator or designee will maintain a log of subjects screened and indicate who was randomized or excluded and the reason for exclusion.

At Visit 1, the following activities/procedures will be performed:

- Informed consent
- Assignment of screening number
- Review of eligibility criteria
- Demographics
- Medical & Ophthalmic History
- Prior and concomitant medications
- Urine pregnancy test (for women of childbearing potential)
- AE monitoring
- Ophthalmic examination to include
    - Visual Acuity
    - Visual Field Testing
        - 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)
    - Biomicroscopy

- Bulbar Conjunctival Hyperemia Assessment
- IOP (before pupil dilation)
  - IOP ≥ 18mmHg and ≤ 27mmHg in one (study eye) or both eyes at this visit.
- Pachymetry
  - Pachymetry within one week of screening is acceptable.
- Gonioscopy
  - Gonioscopy and visual fields may be assessed up to three months (*i.e.*, within 90 days) prior to randomization.
- Dilated Ophthalmoscopy

- Begin Washout. All individuals who are qualified for enrollment at this study visit will undergo a washout period from IOP lowering treatment as noted in Section 8.8.1 and will be asked to return for Visit 2 (Qualification Visit #1).

10.2.1 Washout

As noted in Section 8.8.1, a washout period from IOP lowering treatment is required for all subjects. The Investigator is encouraged to have interim visits during the washout period for IOP measurements for individuals to whom a washout period may be a risk for further glaucomatous progression.

10.2.2 Visit 2 (Qualifying Visit #1, For IOP measurement at any hour)

This visit may occur at any time of the day. After washout of ocular hypotensive medication is completed subjects will return to the Investigator's office for the first IOP qualifying visit.

This visit should take place no later than 42 days after the screening visit.

The following activities/procedures will be performed:

- Review of eligibility criteria
- Medical & Ophthalmic History
- Prior and concomitant medications
- AE monitoring
- Visual Acuity
- Bulbar Conjunctival Hyperemia assessment
- IOP

  IOP measurements (Unmedicated (post-washout)):

- *if tested <u>at or before</u> 10:00 hour*: IOP ≥ 24 mmHg in study eye or both eyes

OR

- *if tested after 10:00 hour:* IOP ≥ 22 mmHg in study eye or both eyes

AND

- IOP <36 in both eyes at this qualification visit

This is the first of five qualifying IOPs for randomization.

Subjects who do NOT meet the IOP requirement may return for up to 2 additional (unscheduled) qualification visits within 1 week of failing this qualification visit. Subjects 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.

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

Two to 7 days after Visit 2, individuals will return to the Investigator's office in the morning for an 08:00 hour IOP measurement. Subjects 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 eCRF (*e.g.*, the subject has been diagnosed with cancer).

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

The following procedures will be performed:

- Review of eligibility criteria
- Medical & Ophthalmic History
- Urine pregnancy test (for women of childbearing potential). Maybe conducted at any time prior to randomization.
- Prior and concomitant medications
- AE monitoring
- Visual Acuity
- Biomicroscopy
- Bulbar Conjunctival Hyperemia assessment

- IOP
    - IOP must be measured within 30 minutes of the nominal time (*i.e.*, 07:30 to 08:30 hours).
    - For further participation in the study, unmedicated IOP at this time (8:00 hour, Day -1) must be ≥ 24 mmHg in study eye or both eyes and < 36 mmHg in both eyes.

This is the second of five qualifying IOPs for randomization.

Qualified individuals will continue with the measurements of IOP at 10:00 hours, 12:00 hours, and 16:00 hours on the day of this study visit. Individuals who do NOT meet the above IOP requirement in both eyes 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 in both eyes at each of 08:00, 10:00, 12:00 and 16:00 hours. Individuals who 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.

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.

10.2.4 Visit 3.1 (Qualifying Visit #2/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:

- AE Monitoring
- Bulbar Conjunctival Hyperemia assessment
- IOP
    - IOP must be measured within 30 minutes of the nominal time (*i.e.*, 09:30 to 10:30 hours)
        - IOP should be conducted at a minimum of the protocol prescribed 2-hour interval (*i.e.*, ≥ 2-hours)
    - For further participation in the study, unmedicated IOP at this time (10:00 hours, Day -1) must be ≥22 mmHg in the study eye or both eyes and < 36 mmHg in both eyes.

This is the third of five qualifying IOPs for randomization.

Qualified individuals will continue with the qualification visit. Individuals who do NOT meet this requirement in both eyes 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, 12:00 and 16:00 hours. Individuals who 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.

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.

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.

10.2.5 Visit 3.2 (Qualifying Visit #2/Day -1, for IOP measurement at 12:00 hours)

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

- AE Monitoring
- Bulbar Conjunctival Hyperemia Assessment
- IOP
    - IOP must be measured within 30 minutes of the nominal time (*i.e.*, 011:30 to 12:30 hours)
        - IOP measurement should be conducted at a minimum of the protocol prescribed 2-hour interval (*i.e.*, ≥ 2-hours)
    - For further participation in the study, unmedicated IOP at this time (12:00 hour, Day -1) must be ≥22 mmHg in the study eye or both eyes and < 36 mmHg in both eyes.

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.

This is the fourth of five qualifying IOPs for randomization.

Qualified individuals will continue with the qualification visit. Individuals who do NOT meet this requirement in both eyes 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 at 08:00, 10:00, 12:00 and 16:00 hours. Individuals who 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.

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.

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.

10.2.6 Visit 3.3 (Qualifying Visit #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:

- AE Monitoring
- Bulbar Conjunctival Hyperemia Assessment
- IOP
    - IOP must be measured within 30 minutes of the nominal time (*i.e.*, 15:30 to 16:30 hours)
        - IOP measurement should be conducted as at a minimum of the protocol prescribed 4-hour interval (ie, ≥ 4-hours)
    - For further participation in the study, unmedicated IOP at this time (16:00 hour, Day -1) must be ≥22 mmHg in the study eye or both eyes and < 36 mmHg in both eyes.

This is the fifth of five qualifying IOPs for randomization.

Individuals who do NOT meet this requirement in both eyes 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 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.

If both eyes qualify, the study eye will be the eye with the higher mean diurnal IOP on Visit 3 (Qualification Visit #2/Day -1). If both eyes have the same mean diurnal IOP 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. Study medication kits numbers will be assigned through the IWRS system and study medication and latanoprost will be dispensed to subjects.

Subjects will:

- Receive instructions for dosing study medication and latanoprost, review study medication kits and be trained on dosing diary completion.
- Be instructed to begin self-administration of study medication and latanoprost on the AM and PM schedule, starting with AM dosing of study medication on the next day (Day 1).
- Be instructed to return to the office with their dosing diary and study medication kits and latanoprost bottle at Day 7.

10.2.7 Visit 4 (Day 7, for IOP measurement at any hour)

This visit may occur at any hour. Subjects will return to the Investigator's office with their dosing diary. The subject will be questioned about any missed doses and any changes in their health or concomitant medication use.

The following assessments will be conducted:

- AE Monitoring
- Conmeds
- Visual Acuity
- Bulbar Conjunctival Hyperemia Assessments
- IOP
- Dosing diary review will be conducted. Used medication kits will be collected and retained by the site. The latanoprost bottle is retained/re-dispensed.

Subjects will be:

- Instructed to return to the office with their dosing diary and study medication kits and latanoprost bottle at Day 14.
- Instructed that they will dose their AM dose of study medication at the study site on Day 14.

10.2.8 Visit 5.0 (Day 14, for IOP measurement at 8:00 hours)

Subjects will return to the Investigator's office with study medication kits, latanoprost bottle and dosing diary. The subject will be questioned about any missed doses and any changes in their health or concomitant medication use. Subjects will dose the Day 14 AM dose of study medication following completion of the 8:00 hour ophthalmic assessments.

Subjects will be examined. Each examination will include:

- AE Monitoring
- Conmeds
- VA
- Biomicroscopy
- Bulbar conjunctival hyperemia Assessment
- IOP
    - IOP must be measured within 30 minutes of the nominal time (*i.e.*, 07:30 to 8:30 hours)
- After ophthalmic assessments are conducted, subjects will be dispensed study medication and retain their bottle of latanoprost provided by the sponsor and administer their Day 14 AM dose of study medication and record this dose in their dosing diary.
- Dosing diary review will be conducted. Used medication kits will be collected and retained by the site. The latanoprost bottle is retained/re-dispensed.

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.

10.2.9 Visit 5.1 (Day 14, for IOP measurement at 10:00 hours)

Subjects will be examined. Each examination will include:

- AE Monitoring
- Bulbar conjunctival hyperemia Assessment
- IOP
    - IOP must be measured within 30 minutes of the nominal time (*i.e.*, 09:30 to 10:30 hours)
        - IOP measurement should be conducted as at a minimum of the protocol prescribed 2-hour interval (*i.e.*, ≥ 2-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.

10.2.10 Visit 5.2 (Day 14, for IOP measurement at 12:00 hours)

Subjects will be examined. Each examination will include:

- AE Monitoring
- Bulbar conjunctival hyperemia Assessment
- IOP
    - IOP must be measured within 30 minutes of the nominal time (*i.e.*, 11:30 to 12:30 hours)
        - IOP measurement should be conducted as at a minimum of the protocol prescribed 2-hour interval (*i.e.*, ≥ 2-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.

10.2.11 Visit 5.3 (Day 14, for IOP measurement at 16:00 hours)

Subjects will be examined. Each examination will include:

- AE Monitoring
- Bulbar conjunctival hyperemia Assessment
- IOP
    - IOP must be measured within 30 minutes of the nominal time (*i.e.*, 15:30 to 16:30 hours)
        - IOP measurement should be conducted as at a minimum of the protocol prescribed 4-hour interval (*i.e.*, ≥ 4-hours)

Subjects subsequently will be:

- Instructed to continue to self-administer their study medication and latanoprost at home on the directed schedule and to record dosing in their dosing diary
- Instructed to return to the office with their dosing diary, study medication kits and latanoprost bottle at Day 28

10.2.12 Visit 6.0 (Day 28, for IOP measurement at 08:00 hours)

Subjects will return to the Investigator's office with study medication kits, latanoprost bottle and dosing diary. The subject will be questioned about any missed doses and any changes in their

health or concomitant medication use. Subjects will dose the Day 28 AM dose of study medication following completion of the 8:00 hour ophthalmic assessment.

Subjects will be examined. Each examination will include:

- Urine Pregnancy Test (female subjects of childbearing potential; as applicable)
- AE monitoring
- Conmeds
- VA
- Biomicroscopy
- Bulbar conjunctival hyperemia Assessment
- IOP
    - IOP must be measured within 30 minutes of the nominal time (*i.e.*, 07:30 to 08:30 hours)
- Collect study medication from the subject and review dosing diary at any time Day 28 visit. All remaining study medication kits and the latanoprost bottle are collected and retained by the site.
- Dose AM study medication from returned study medication kit or if necessary, a new kit is dispensed to complete the AM dose.

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.

10.2.13 Visit 6.1 (Day 28, for IOP measurement at 10:00 hours)

Subjects will be examined. Each examination will include:

- AE monitoring
- Bulbar conjunctival hyperemia assessment
- IOP
    - IOP must be measured within 30 minutes of the nominal time (*i.e.*, 09:30 to 10:30 hours)
        - IOP measurement should be conducted as at a minimum of the protocol prescribed 2-hour interval (*i.e.*, ≥ 2-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.

10.2.14 Visit 6.2 (Day 28, for IOP measurement at 12:00 hours)

Subjects will be examined. Each examination will include:

- AE Monitoring
- Bulbar conjunctival hyperemia assessment
- IOP
    - IOP must be measured within 30 minutes of the nominal time (*i.e.*, 11:30 to 12:30 hours)
        - IOP measurement should be conducted as at a minimum of the protocol prescribed 2-hour interval (*i.e.*, ≥ 2-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.

10.2.15 Visit 6.3 (Day 28, for IOP measurement at 16:00 hours)

- Subjects will be examined. Each examination will include:
- AE monitoring
- Bulbar conjunctival hyperemia Assessment
- IOP
    - IOP must be measured within 30 minutes of the nominal time (*i.e.*, 15:30 to 16:30 hours)
        - IOP measurement should be conducted as at a minimum of the protocol prescribed 4-hour interval (*i.e.*, ≥ 4-hours)
- Pachymetry
    - To be conducted after 16:00 IOP assessments are completed
- A dilated ophthalmoscopy examination (including cup-disc ratio)
    - To be conducted after 16:00 IOP and pachymetry assessments are completed.

Subjects will be thanked for their participation and released to care of their ophthalmologist.

10.3 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 CRF.

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 6.0 (Day 28) plus a dilated ophthalmoscopy examination.

10.4 Early Termination Visits

Should a subject withdraw after administration of AKB-9778, or should the Investigator decide to withdraw the subject, all efforts will be made to complete and report the protocol-stipulated observations up to the time of withdrawal as thoroughly as possible.

Subjects who discontinue prior to completion of all planned study assessments, should undergo the Day 28 assessments at time of discontinuation.

11.0 ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Events (AEs)

An AE is any untoward medical occurrence in a patient or trial subject administered a drug or biologic (medicinal product) or using a medical device; the event does not necessarily have a causal relationship with that treatment or usage.

AEs include the following:

- All suspected adverse medication reactions.
- All reactions from medication overdose, abuse, withdrawal, sensitivity, or toxicity.
- Apparently unrelated illnesses, including the worsening of a preexisting illness (see paragraph below on Preexisting Conditions).
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (*e.g.*, a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as two separate adverse events. The outcome of the accident (*e.g.*, hip fracture secondary to the fall) should be recorded under Comments.

- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).

- An increase of 2 or more grades on the hyperemia scale when compared to the lowest score recorded at any previous timepoint for an individual eye should be reported as an adverse event. If a subject complains of hyperemia, an AE will be recorded regardless of grade on the hyperemia scale (Section 9.2.2).

Procedures – Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event and the resulting appendectomy noted under Comments.

Preexisting Conditions – In this trial, a preexisting condition (*i.e.*, a disorder present before the adverse event reporting period started and noted on the pretreatment medical history/physical examination form) should not be reported as an adverse event unless the condition worsens, or episodes increase in frequency during the adverse event reporting period.

11.1.2 Serious Adverse Events (SAEs)

Each adverse event is to be classified by the Investigator as SERIOUS or NONSERIOUS. An adverse event that meets one or more of the following criteria/outcomes is classified as serious:

- Death

- Life-threatening (see paragraph below on Life-threatening)

- In-patient hospitalization or prolongation of existing hospitalization (see paragraph below on Hospitalization)

- Persistent or significant disability/incapacity (see paragraph below on Disability)

- Congenital anomaly/birth defect

Important adverse events that may not result in death, be life-threatening, or require hospitalization may be considered Serious Adverse Events (SAEs) when, based upon appropriate medical judgment, they may jeopardize the patient or subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

The term serious also includes any other event that the Investigator or Sponsor judges to be serious or which is defined as serious by the regulatory agency in the country in which the event occurred. If there is any doubt whether the information constitutes an AE or SAE, the information is to be treated as an SAE.

Life-threatening – Any AE that places the subject at immediate risk of death from the event as it occurred. A life-threatening event does not include an event that might have caused death had it occurred in a more severe form but that did not create an immediate risk of death as it actually occurred. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening, even though drug-induced hepatitis of a more severe nature can be fatal.

Hospitalization – Hospitalization is defined as an overnight admission with observation of a minimum of 24 hours. A hospitalization planned before the start of the study for a preexisting condition that has not worsened does not constitute an SAE (*e.g.*, elective hospitalization for a total knee replacement due to a preexisting condition of osteoarthritis of the knee that has not worsened during the course of the study).

Disability – Defined as a substantial disruption in a person's ability to conduct normal life functions.

11.1.3 Severity

If required on the adverse event CRF, the Investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:

MILD:	Does not interfere with subject's usual function
MODERATE:	Interferes to some extent with subject's usual function
SEVERE:	Interferes significantly with subject's usual function

Note the distinction between the gravity and the intensity of an adverse event. **Severe** is a measure of intensity; thus, a **severe** reaction is not necessarily a **serious** reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed above.

11.2 Eliciting Adverse Event Information

The Investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs at each visit following the initiation of treatment.

11.3 Reporting

Each AE is to be classified by the Investigator as SERIOUS or NONSERIOUS. This classification of the gravity of the event determines the reporting procedures to be followed. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

All AEs that occur in study subjects during the adverse event reporting period specified in the protocol must be reported, WHETHER OR NOT THE EVENT IS CONSIDERED MEDICATION RELATED.

11.3.1 Reporting Period

The AE reporting period for this study begins from the time of informed consent and ends at the final protocol required visit.

IN ADDITION, any known untoward event that occurs subsequent to the AE reporting period that the Investigator assesses as possibly or probably related to the study medication and meets criteria for serious should also be reported as an SAE.

11.3.2 Reporting AEs

NONSERIOUS AEs are to be reported on the adverse event case report forms.

11.3.3 Reporting SAEs

Serious adverse events should be reported on both the clinical trial adverse event CRF and the Serious Adverse Event Report Form.

Note: Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms.

Any SAE, regardless of causal relationship, must be reported to the clinical safety contact at the Sponsor within 24 hours after the Investigator becomes aware of the SAE by completing and sending an SAE report form. Compliance with this time requirement is essential so that the Sponsor may comply with its regulatory obligations.

The initial SAE report should be completed as fully as possible but should contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious
- Subject identification number
- Investigator's name
- Name of the suspected medicinal product (not applicable for double-masked studies)
- Causality assessment
- Onset date

Follow-Up information relating to an SAE must be reported to the clinical safety contact at the Sponsor within 24 hours of receipt by the Investigator by sending a completed SAE report form

with new information. The subject should be observed and monitored carefully until the condition resolves or stabilizes.

Any emergency event deemed related to study medication must be reported to the trial monitor or to the Sponsor's Medical Monitor immediately.

All deaths are to be thoroughly investigated and reported as SAEs. Autopsy reports are to be obtained, if possible.

The Sponsor and/or its designee are responsible for reporting SAEs to all applicable regulatory agencies and the central ethics committees within the required timeline.

The Investigator is responsible for submitting required safety information to their local IRB. This information includes but is not limited to any safety alert letter received from the Sponsor and any SAEs occurring at their site.

11.3.4 Relationship to Study Medication

The causal relationship of the AE to study medication will be assessed by both the Investigator and the Sponsor. The following definitions will be used in assessment.

Probably Related: The AE follows a reasonable temporal sequence from the time of drug administration. It follows a known response pattern to the study medication. The AE cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs.

Possibly Related: The AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by other factors such as the subject's clinical state, other therapeutic interventions, or concomitant drugs.

Unrelated: The AE does not follow a reasonable temporal sequence from administration of the product or the AE is clearly related to other factors such as the subject's clinical state, other therapeutic interventions, or concomitant drugs administered to the subject.

11.3.5 Follow-Up of Unresolved Events

All AEs should be followed until they are resolved or the PI assesses them as chronic or stable or the subject's participation in the trial ends (*i.e.*, until a final report is completed for that subject).

In addition, all serious adverse events and those nonserious events assessed by the Investigator as possibly or probably related to the study medication should continue to be followed even after the subject's participation in the trial is over. Such events should be followed until they resolve or until the Investigator assesses them as "chronic" or "stable." Resolution of such events is to be documented on the appropriate CRF.

11.4 Exposure *In Utero*

If any study subject becomes or is found to be pregnant while receiving a study medication or within 30 days of discontinuing the study medication, the Investigator submits this information on a Pregnancy Report Form which must be submitted within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of birth or pregnancy termination.

If the pregnancy is discovered during the study treatment period, the study medication should be discontinued.

The PI will follow the subject until completion of the pregnancy and will notify Aerpio Pharmaceuticals of the outcome within 5 days or as specified below.

If the outcome of the pregnancy meets the criteria for immediate classification as a serious adverse event (*i.e.*, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the Investigator should follow the procedures for reporting a serious adverse event.

Additional information about pregnancy outcomes that are classified as serious adverse events follows:

- Note that "spontaneous abortion" includes miscarriage and missed abortion.
- All neonatal deaths that occur within one month of birth should be reported, without regard to causality, as serious adverse events. In addition, any infant death after one month that the Investigator assesses as possibly or probably related to the *in utero* exposure to the study medication should also be reported.
- In the case of a live birth, the "normality" of the newborn can be assessed at time of birth.
- The "normality" of an aborted fetus can be assessed by gross visual inspection unless there are pre-abortion laboratory findings suggestive of a congenital anomaly.

12.0 STATISTICAL METHODS

12.1 Primary Hypotheses

- H_{01}: The difference between study eyes treated with AKB-9778 BID + Latanoprost and study eyes treated with Latanoprost monotherapy in Day 28 mean diurnal IOP (IOP averaged over the 08:00, 10:00, 12:00, and 16:00 hour time points) is ≥ 0 mmHg.
- H_{11}: The difference between study eyes treated with AKB-9778 BID + Latanoprost and study eyes treated with Latanoprost monotherapy in Day 28 mean diurnal IOP is < 0 mmHg

- H_{02}: The difference between study eyes treated with AKB-9778 QD + Latanoprost and study eyes treated with Latanoprost monotherapy in Day 28 mean diurnal IOP is ≥ 0 mmHg.

- H_{12}: The difference between study eyes treated with AKB-9778 QD + Latanoprost and study eyes treated with Latanoprost monotherapy in Day 28 mean diurnal IOP is < 0 mmHg.

The study will be considered a success if either H_{01} or H_{02} is rejected.

12.2 Multiplicity Adjustment

No multiplicity adjustment for the two sets of primary hypotheses will be made in this Phase 2 protocol, yielding an overall two-sided Type I Error of 0.10.

12.3 Sample Size Considerations

Efficacy:

Sixty-five (65) subjects per arm completing 28 days of treatment yields 80% power to conclude statistical superiority of AKB-9778 (QD or BID) + Latanoprost to Latanoprost monotherapy assuming a two-sided alpha = 0.05, a true difference in mean diurnal change from baseline IOP of 1.5 mmHg, a common standard deviation of 3.5 mmHg at each time point, and a correlation of 0.60 among time points within a subject's study eye (leading to an SD of the mean diurnal IOP of 3.0 mmHg)

12.4 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.

12.5 Statistical Methods to be Employed

12.5.1 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 AKB-9778 + Latanoprost and Latanoprost monotherapy will be calculated as AKB-9778 + Latanoprost minus Latanoprost monotherapy.

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 3.3 (*e.g.*, IOP at 08:00 hours at Visit 3.0 will be the baseline for 08:00 hours at Visits 5.0 and 6.0, IOP at 10:00 hours at Visit 3.1 will be the baseline for 10:00 hours at Visits 5.1 and 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. The study eye will be the eye with the higher mean diurnal IOP on Visit 3. If both eyes have the same mean diurnal IOP on Visit 3, then the right eye will be the study eye.

Statistical methods will be more fully described in a separate document (*i.e.*, the Statistical Analysis Plan).

12.5.2 Interim Analyses

An interim analysis for futility is planned to be performed when 50% of randomized subjects have completed 28 days of therapy. For this analysis the diurnal mean reduction of IOP in each AKB-9778 treatment group will be compared to that of the Latanoprost monotherapy treatment group. Futility will be declared if the conditional probability of achieving a 1.5 mmHg reduction in IOP compared to Latanoprost monotherapy in each AKB-9778 treatment group is < 30%.

Conditional probability of achieving a 1.5 mmHg reduction in IOP compared to Latanoprost monotherapy will be based on the observed data and projected data for the remaining subjects. Projections will be based on the initial assumptions of a true effect of AKB-9778 + Latanoprost over Latanoprost monotherapy of -1.5 mmHg with a SD of 3.0 mmHg.

12.5.3 Analysis of Baseline Data

Demographic and baseline characteristics such as age, gender, or disease status (*e.g.*, IOP, cup-disc ratio) will be summarized and listed. Medical history, history of ocular surgery and procedures, OAG/OHT history and washout period will also be summarized and listed.

12.5.4 Subject Disposition

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

12.5.5 Analysis of Efficacy

All efficacy analyses will be conducted in the study eye and both eyes (average of study eye and eligible fellow eye)

The primary efficacy outcome will be comparison of AKB-9778 + Latanoprost (QD or BID) relative to Latanoprost monotherapy for:

- Mean change from baseline in diurnal IOP on Day 28

Secondary efficacy outcomes will include comparison of AKB-9778 + Latanoprost (QD or BID) relative to Latanoprost monotherapy for:

- Mean change from baseline in diurnal IOP on Day 14 (study eye)
- Mean change from baseline in diurnal IOP on Days 14 and 28 (both eyes)
- Mean diurnal IOP on Days 14 and 28 (both eyes)
- Mean observed IOP at each time point on Days 14 and 28
- Mean change from diurnally adjusted baseline IOP at each time point on Days 14 and 28
- Mean percent change from diurnally adjusted baseline IOP at each time point on Days 14 and 28
- Mean percent change from baseline in diurnal IOP on Days 14 and 28
- Percentages of subjects achieving pre-specified mean, mean change, and percent mean change in diurnal IOP levels

Additional secondary efficacy analyses may 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. Fellow eyes will be evaluated separately for the primary analysis of the primary efficacy measure. In addition, analyses using the average IOP

between the Study and eligible Fellow eyes will be performed. If the Fellow eye of a given subject is ineligible, then the both eyes analysis will utilize only the Study eye for that subject

Primary Estimand

The primary comparisons in this trial will be between two doses of AKB-9778 (QD and BID) + Latanoprost vs Latanoprost monotherapy at the Day 28 Visit in the ITT population with intercurrent events handled as described in the following estimand.

- Population: subjects with Open-Angle Glaucoma or Ocular Hypertension defined through enrolment criteria
- Endpoint:
  - Mean diurnal (averaged over 08:00, 10:00, 12:00, and 16:00 hour time points) change from baseline IOP (mm Hg) at the Day 28 Visit in the study eye
- Intercurrent event:
  - Discontinuation of study medication and non-optimal compliance will be ignored [treatment policy strategy].
  - Withdrawal due to lack of efficacy or adverse event: missing data will be imputed employing Multiple Imputation (MI) assuming missing not at random using:
    - Control-based Markov Chain Monte Carlo (MCMC) methodology [hypothetical strategy].
  - Missing data without withdrawal or withdrawal due to reasons other than lack of efficacy or adverse event: missing data will be imputed employing Multiple Imputation (MI) assuming missing at random using randomized treatment-based Markov Chain Monte Carlo (MCMC) methodology [hypothetical strategy].
- Population-level summary:
  - The difference in the mean diurnal change from baseline IOP at the Day 28 Visit, between study eyes treated with each dose of AKB-9778 (QD and BID) + Latanoprost and study eyes treated with Latanoprost monotherapy.

Sensitivity analyses will be performed on observed data only and where worst time consistent observation within a subject is carried forward for withdrawal due to lack of efficacy or adverse event and last time consistent observation within a subject is carried forward for other missing data.

The primary analysis of the primary outcome will employ a linear model with Day 28 mean diurnal change from baseline IOP as the response, baseline mean diurnal IOP (mean diurnal IOP on Day -1) as a covariate, and treatment as a main effect factor, using the intent to treat population with multiple imputation techniques (*e.g.*, Monte Carlo Markov Chain) used to impute missing data. The least squares mean differences (test – control) between AKB-9778 + Latanoprost and Latanoprost monotherapy will be presented as well as 2-sided p-values and 95% confidence intervals. Inference will be made on the p-value < 0.05.

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.

Secondary analyses of the primary endpoint will be completed using individual two-sample t-tests and 95% t-distribution confidence intervals at each time point (08:00, 10:00, and 16:00 at the Day 14, and Day 28 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 Day 14, and Day 28 visits.

Percent change from diurnally adjusted baseline IOP at each time point will be analyzed using two-sample t-tests, between AKB-9778 and each comparator, at each time point and visit, including two-sample t-tests and 95% t-distribution confidence intervals on the difference (AKB-9778 – comparator).

Mean diurnal IOP values will be constructed by averaging the 4 diurnal IOP measurements on each of the Day 14, and Day 28 visits. Mean diurnal baseline IOP will be constructed as the average of the four Day -1 IOP measurements. Mean change from mean baseline diurnal IOP will be created by taking the average of the four time points on each of Day 14, and Day 28 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.

12.5.6 Analysis of Safety

12.5.6.1 Ocular and Systemic Safety Assessments

Slit lamp biomicroscopy, hyperemia 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.

12.5.6.2 Adverse Events

Verbatim descriptions of treatment-emergent adverse events (TEAEs) will be mapped to Medical Dictionary for Regulatory Activities (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 TEAEs. 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 TEAE between treatment groups (SOC and PT).

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

Analyses will be performed primarily on missing data imputed using multiple imputation techniques as defined in the primary estimand. Sensitivity analyses will be performed on observed data only and where worst time consistent observation within a subject is carried forward for withdrawal due to lack of efficacy or adverse event and last time consistent observation within a subject is carried forward for other missing data. Any missing, unused, or spurious data will be noted in the final statistical report.

12.7 Procedure for Reporting Deviations from the Statistical Plan

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

12.8 Data Listings

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

13.0 DATA HANDLING AND RECORD KEEPING

13.1 Case Report Forms (CRFs)

CRFs are required and should be completed for each included subject. The completed original CRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor. CRFs for this study will be electronic (eCRFs).

The PI has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms. The CRFs must be signed by the Investigator (for electronic CRFs, they can be signed electronically) or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs and source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are contained in the subject's chart at the hospital or the physician's office. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRFs, or part of the CRFs, may also serve as source documents. In these cases, a document should be available at both the Investigator's site and at the Sponsor or its designee that clearly identify those data that will be recorded in the CRFs, and for which the CRF will stand as the source document.

13.2 Record Retention

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, *e.g.*, CRFs and hospital records), all original signed Informed Consent Forms, copies of all CRFs, SAE forms, source documents, detailed records of drug disposition, and adequate documentation of relevant correspondence (*e.g.*, letters, meeting minutes, telephone calls reports). The records should be retained by the Investigator according to the International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Study Agreement, whichever time period is longer.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (*e.g.*, retirement, relocation), the Sponsor should be prospectively notified. The study records must be transferred to a designee acceptable to the Sponsor, such as another Investigator, another institution, or to the Sponsor. The Investigator must obtain Sponsor's written permission before disposing of any records, even if retention requirements have been met.

14.0 QUALITY CONTROL (QC) AND QUALITY ASSURANCE (QA)

14.1 Study Site Monitoring Visits

During study conduct, the Sponsor or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practice (GCP) are being followed. The monitors will review source documents to confirm that the data recorded on CRFs is accurate. The Investigator/institution will allow Sponsor monitors or designees and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may also be subject to Quality Assurance audits performed by the Sponsor or companies working with or on behalf of the Sponsor, and/or review by the independent review board (IRB), and/or to inspection by appropriate regulatory authorities

It is important that the PI and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The PI should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the Investigator should consult with the Sponsor or designee (and IRB, as required) to determine the appropriate course of action.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the Sponsor or its designee (and IRB, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessments.

15.0 TRIAL DISCONTINUATION/INVESTIGATIVE SITE TERMINATION

The Sponsor reserves the right to discontinue the trial prior to inclusion of the intended number of subjects but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigator must contact all participating subjects within a time period specified by the Sponsor to inform them of the decision to discontinue the trial.

15.1 Criteria for Premature Termination or Suspension of the Study

The following criteria may result in either temporary suspension or early termination of the study:

- New information regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.

- Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety.

The Sponsor reserves the right to discontinue the trial for other valid administrative reasons.

15.2 Criteria for Premature Termination or Suspension of Investigational Site

A study site may be terminated prematurely or suspended if the site (including the PI) is found to be in significant violation of GCP, protocol, contractual agreement, or is unable to ensure adequate performance of the study.

15.3 Procedures for Premature Termination or Suspension of the Study or Investigational Site(s)

In the event that the Sponsor elects to terminate or suspend the study or the participation of an Investigational site, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by applicable Investigational sites during the course of termination or study suspension.

16.0 ETHICS

16.1 Ethical Conduct of the Study

The study will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

16.2 Institutional Review Board (IRB)

It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, (*e.g.*, recruitment advertisements, if applicable) from the IRB. All correspondence with the IRB should be retained in the Investigator File. Copies of IRB approvals should be forwarded to the Sponsor.

The only circumstance in which an amendment may be initiated prior to IRB approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the Investigator must notify the IRB and the Sponsor in writing immediately after the implementation.

16.3 Subject Information and Consent

It is the responsibility of the Investigator to give each subject (or the subject's acceptable representative), prior to inclusion in the trial, full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. The subjects must be informed about their right to withdraw from the trial at any time.

Furthermore, it is the responsibility of the Investigator, or a person designated by the Investigator, to obtain signed informed consent from each subject or the subject's legally acceptable representative prior to inclusion in the trial. The Investigator will retain the original of each subject's signed consent form.

The informed consent form must be in compliance with International Conference on Harmonisation (ICH) GCP, local regulatory requirements, and legal requirements. The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB and the Sponsor before use.

16.4 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (*i.e.*, clinical hold) by an applicable Competent Authority, or if the Investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, the Sponsor should be informed immediately.

In addition, the Investigator will inform the Sponsor immediately of any urgent safety measures taken by the Investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that comes to the attention of the Investigator.

16.5 Subject Confidentiality

All parties will ensure protection of subject personal data and will not include subject names on any Sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, the Sponsor will maintain high standards of confidentiality and protection of subject personal data.

The Sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the Investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (*e.g.*, Food and Drug Administration [FDA]), the Sponsor's designated auditors, and the appropriate IRB to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports,

electrocardiogram (ECG) reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process.

Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed (*i.e.*, subject name, address, and other identifier fields not collected on the subject's CRF).

17.0 PUBLICATION OF STUDY RESULTS

No publication or disclosure of study results will be permitted, except under the terms and conditions of a separate, written agreement between Sponsor and the Investigator and/or the Investigator's institution. The Sponsor must have the opportunity to review and approve all proposed abstracts, manuscripts, or presentations regarding this study prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including: Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

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APPENDIX 1 SCHEDULE OF VISITS AND PROCEDURES

Day	**Screen**	**Qual. #1 [J]**	**Qual. #2 Day -1 (Baseline)**				**Day 1[H]**	**Day 7 (±3) [J]**	**Day 14 (±3)**				**Day 28 (±3)**			
Visit	**1**	**2**	**3.0**	**3.1**	**3.2**	**3.3**		**4.0**	**5.0**	**5.1**	**5.2**	**5.3**	**6.0**	**6.1**	**6.2**	**6.3**
Hour		**Any**	**08:00**	**10:00**	**12:00**	**16:00**	**8:00 & 20:00**	**Any**	**08:00**	**10:00**	**12:00**	**16:00**	**08:00**	**10:00**	**12:00**	**16:00**
Informed Consent	X															
Inclusion/Exclusion	X	X	X	X	X	X										
Washout [A]	X															
Demography	X															
Med/Ophthalmic Hist	X	X	X													
Concomitant Medications	X	X	X					X	X				X			
Urine Pregnancy Test[B]	X		X										X			
AEs	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
VA	X	X	X					X	X				X			
Visual Field[D]	X															
Biomicroscopy	X		X						X				X			
Bulbar Conjunctival Hyperemia Assessment [F]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
IOP	X	X	X[K]	X[K]	X[K]	X[K]		X	X	X	X	X	X	X	X	X
Pachymetry [C]	X															X[L]
Gonioscopy[E]	X															
Ophthalmoscopy (dilated)	X															X[L]
Study Med Dispensing[G]						X			X							
Study Med Return, Diary Review[H]								X	X				X			
Dosing[I]							X----------X									
Study Completed																X

Abbreviations: Qual, Qualification; Med/Ophthalmic Hist, Medical/Ophthalmic History; AE, adverse event; VA, visual acuity; IOP, intraocular pressure

[A] Subjects must undergo a minimum 4-week washout period.

[B] Urine pregnancy test for women of childbearing potential is required. May be taken anytime during Qual Visit # 2.

[C] Screening: Pachymetry within one week of Screening is acceptable; If conducted at Screening must not be conducted before IOP.

[D] 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 (*e.g.*, 30-2 or 24-2 Humphrey) and reliability.

[E] Gonioscopy evaluation up to 3 months prior to randomization is acceptable.

[F] All hyperemia assessments coincide with a timed IOP evaluation. The hyperemia assessment and grading must be evaluated prior to the use of any ocular drops required for the IOP procedure.

[G] Study Medication is dispensed on Day-1 after randomization and at anytime during the Day 14 Visit.

[H] Collect used study medication kit(s) and review dosing diary on Days 7, 14 and 28. Collection of used kit(s) and dosing diary may occur anytime during the visit. Subjects who fail to return their used study medication at Day 7 or 14 may return it at a subsequent visit.

[I] Subjects will begin dosing at home with the AM dose of study medication on the morning of Day 1 and conclude dosing after administration of the AM dose of study medication on Day 28; there is no PM dose administration on Day 28. At visits conducted on Days 14 and 28, subjects will self-administer the AM dose of study medication at the site after the 8:00 hour ophthalmic assessments have been completed.

[J] Subject visit can occur at anytime.

[K] Individuals returning at an unscheduled visit within 1 week are required to only remeasure IOP in both eyes (Section 10.2.3 to Section 10.2.6).

[L] Pachymetry and Ophthalmoscopy (dilated) at Visit 6.0 at 16:00 hours after 16:00 IOP assessments are completed. Pachymetry is conducted before dilated ophthalmoscopy.

APPENDIX 2 MARKETED PRODUCT: XALATAN® (LATANOPROST OPHTHALMIC SOLUTION) 0.005%

The following is taken from the most recent package insert (4/2017) as of the date of this protocol for latanoprost ophthalmic solution 0.005% as marketed by Pfizer.

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/nasopharyngitis/ingluenza. **(6).**

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer at 1-800-438-1985 or 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 XALATAN. If such drugs are used, they should be administered at least 5 minutes apart. **(7)**

Revised: 04/2017

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

XALATAN 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 XALATAN should not exceed once daily; the combined use of two or more prostaglandins, or prostaglandin analogs including XALATAN 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.

XALATAN 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 XALATAN, 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

XALATAN 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 XALATAN can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly [*see Patient Counseling Information (17)*].

5.2 Eyelash Changes

XALATAN 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)*].

5.3 Intraocular Inflammation

XALATAN 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 XALATAN. XALATAN 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 XALATAN. XALATAN should be used with caution in patients with a history of herpetic keratitis. XALATAN 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)*].

5.7 Use with Contact Lenses

Contact lenses should be removed prior to the administration of XALATAN, 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.

XALATAN was studied in three multicenter, randomized, controlled clinical trials. Patients received 50 mcg/mL XALATAN 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

	Adverse Reactions (incidence (%))	
Symptom/Finding	**Latanoprost (n=460)**	**Timolol (n=369)**
Foreign body sensation	13	8
Punctate keratitis	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 XALATAN required discontinuation of therapy because of intolerance to conjunctival hyperemia.

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
Eyelid discomfort/pain	4	2
Dry eye	3	3
Eye pain	3	3
Eyelid margin crusting	3	3
Erythema of the eyelid	3	2
Photophobia	2	1
Eyelid edema	1	3
Systemic Events		
Upper respiratory tract infection/nasopharyngitis/influenza	3	3
Myalgia/arthralgia/back pain	1	0.5
Rash/allergic skin reaction	1	0.3

The ocular event/signs and symptoms of blepharitis have been identified as “commonly observed” through analysis of clinical trial data.

6.2 Postmarketing Experience

The following reactions have been identified during postmarketing use of XALATAN in clinical practice. Because they are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to XALATAN, or a combination of these factors, include:

Nervous System disorders: Dizziness; headache; toxic epidermal necrolysis

Eye Disorders: Eyelash and vellus hair changes of the eyelid (increased length, thickness, pigmentation, and number of eyelashes); keratitis; corneal edema and erosions; intraocular inflammation (iritis/uveitis); macular edema, including cystoid macular edema; trichiasis; periorbital and lid changes resulting in deepening of the eyelid sulcus; iris cyst; eyelid skin darkening; localised skin reaction on the eyelids; conjunctivitis; pseudopemphigoid of the ocular conjunctiva

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

Skin and Subcutaneous Tissue Disorders: Pruritus

Infections and Infestations: Herpes; keratitis

Cardiac Disorders: Angina; palpitations; angina unstable

General Disorders and Administration Site Conditions: Chest pain

7 DRUG INTERACTIONS

In vitro studies have shown that precipitation occurs when eye drops containing thimerosal are mixed with XALATAN. 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 XALATAN 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. XALATAN 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 XALATAN 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.

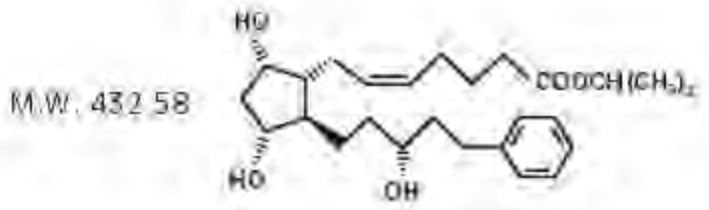
10 OVERDOSAGE

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 XALATAN occurs, treatment should be symptomatic.

11 DESCRIPTION

Latanoprost is a prostaglandin $F_{2\alpha}$ 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 $C_{26}H_{40}O_5$ and its chemical structure is:



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.

XALATAN® (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 XALATAN contains 50 mcg 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 ($t_{1/2}$ = 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 XALATAN 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 XALATAN 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

XALATAN 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 5 mL clear low density polyethylene bottle with a clear polyethylene dropper tip, a turquoise high density polyethylene screw cap, and a tamper-evident clear low density polyethylene overcap.

2.5 mL fill, 0.005% (50 mcg/mL): Package of 1 bottle: NDC 0013-8303-04

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

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 XALATAN [*see Warnings and Precautions (5.1)*].

Potential for Eyelash Changes

Inform patients of the possibility of eyelash and vellus hair changes in the treated eye during treatment with XALATAN. 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.

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)*].

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.

Use with Contact Lenses

Advise patients that XALATAN 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 XALATAN.

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.

Pfizer Manufacturing Belgium NV Puurs, Belgium

LAB-0135-13.0

	• This section is updated to state: Analyses will be performed primarily on missing data imputed using multiple imputation techniques as defined in the primary estimand. Sensitivity analyses will be performed on observed data only and where worst time consistent observation within a subject is carried forward for withdrawal due to lack of efficacy or adverse event and last time consistent observation within a subject is carried forward for other missing data
Amendment #2 version 2.0 17-May-2020	• Clarified that at the Day 7 Visit, subjects were to bring their dosing diary, study medication kits and latanoprost to the site • Moved the requirement to perform biomicroscopy from the Day 7 Visit to the Day 14 Visit 8:00 hours • Moved the requirement to perform pachymetry and dilated ophthalmoscopy from 12:00 hours to 16:00 hours