Official title: Therapeutic Equivalence Study of Generic Brinzolamide 1% Ophthalmic suspension Compared to Reference Listed Drug Azopt® (Brinzolamide) Ophthalmic Suspension 1% in Subjects With Primary Open Angle Glaucoma or Ocular Hypertension.

Document: Clinical Study Protocol

NCT number: NCT05022004

Document date: 12-May-2021

PROTOCOL

A THERAPEUTIC EQUIVALENCE STUDY OF GENERIC BRINZOLAMIDE 1% OPHTHALMIC SUSPENSION COMPARED TO REFERENCE LISTED DRUG AZOPT® (BRINZOLAMIDE) OPHTHALMIC SUSPENSION 1% IN SUBJECTS WITH PRIMARY OPEN ANGLE GLAUCOMA OR OCULAR HYPERTENSION

Protocol No.:	BRIN-20-01
Initial protocol, date:	[redacted]
[redacted] Date:	[redacted] 12 May 2021 [redacted]
Investigational Product:	Brinzolamide 1%
Study Phase:	Therapeutic equivalence study
Sponsor:	Sun Pharmaceutical Industries Ltd. (SPIL), Sun house, CTS No. 201 B/1, Western Express Highway, Goregaon (E), Mumbai 400063

1.0 PROTOCOL SYNOPSIS

Name of Sponsor: Sun Pharmaceutical Industries Ltd. (SPIL).
Name of Investigational Product: Brinzolamide ophthalmic suspension USP 1%
Name of Active Ingredient: Brinzolamide ophthalmic suspension
Name of Reference Listed Drug: AZOPT®
Title of Trial: A Therapeutic equivalence Study of Generic Brinzolamide 1% Ophthalmic Suspension Compared to Reference Listed Drug Azopt® (Brinzolamide) Ophthalmic Suspension 1% in Subjects with Primary Open Angle Glaucoma or Ocular Hypertension.
Phase of Development: Therapeutic equivalence study
Trial Centers: Multicenter
Objectives: ***Primary Objective****:* To evaluate the efficacy of three times daily (TID) dosing of SPIL's Brinzolamide ophthalmic suspension USP 1% compared with Azopt® 1% in subjects with open-angle glaucoma or ocular hypertension. ***Secondary Objectives:*** To evaluate the safety of TID dosing of SPIL's Brinzolamide ophthalmic suspension USP 1% compared with Azopt® 1% in subjects with open-angle glaucoma or ocular hypertension.
Study Endpoints: ***Primary Efficacy Endpoint:*** Mean difference in IOP of both eyes between the 2 treatment groups at the following time points: approximately 8:00 AM. (hour 0; before the morning drop) and 10:00 AM. (hour 2) at Day 14 (Week 2) and Day 42 (Week 6) visits. ***Secondary Efficacy Endpoint:*** Change from baseline in IOP of both eyes between the 2 treatment groups at 4 time points, i.e., at approximately 8:00 AM. (hour 0; before the morning drop) and 10:00 AM. (hour 2) at the Day 14 (Week 2) and Day 42 (Week 6) visits. ***Safety:*** Incidence and severity of adverse events (AEs)
Study Design: This is a randomized, Investigator-masked, multi-center, parallel group, therapeutic equivalence study with clinical endpoint.
Duration of Treatment : 6 weeks Total duration: 6 weeks of Screening; 6 weeks of treatment period, and 1 week of telephonic follow-up

Study Population: Adult (≥ 18 years of age) subjects with open-angle glaucoma or ocular hypertension.

Number of Subjects Planned: Approximately 666 subjects will be randomized to have 532 (266 per treatment arm) evaluable subjects completing Day 42 (Week 6) of treatment.

Key Eligibility Criteria

Key Inclusion Criteria:

1. Male or nonpregnant female aged 18 years or older with chronic open angle glaucoma or ocular hypertension in both eyes.
2. Provide signed and dated informed consent in accordance with good clinical practice (GCP) and local legislation prior to any study procedure.
3. Be able and willing to follow study instructions and complete all required visits.
4. Subject requires treatment of both eyes and is able to discontinue use of all ocular hypotensive medication(s) or switch ocular hypotensive medications and undergo appropriate washout period.

[redacted]

Key Exclusion Criteria:

1. Subjects with angle closure glaucoma
2. Females who are pregnant, breast feeding, or planning a pregnancy.
3. Females of childbearing potential who do not agree to utilize an adequate form of contraception.

[redacted]

6. Current, or past history of, severe hepatic or renal impairment
7. Current, or history within 2 months prior to baseline of, significant ocular disease, [redacted]
8. Current corneal abnormalities [redacted]
9. Patients with severe central visual field loss in either eye; [redacted]

[redacted] Subjects currently in another clinical trial

Study Assessments:

Efficacy:

- Primary efficacy assessment is IOP measurement using Goldman Applanation Tonometer at 4 time points, i.e., at approximately 8:00AM. (hour 0; before the morning drop) and 10:00 AM. (hour: 2) at baseline, Day 14 (Week 2) and Day 42 (Week 6) visits.

Safety:

- Incidence and severity of AEs.

- Ocular safety assessments: BSCVA, slit lamp biomicroscopy, intraocular pressure, dilated ophthalmoscopy, including recording cup/disc ratio.

Sample size and statistical approach to primary analysis

An equivalence test of means using 2 one-sided tests on data from a parallel-group design with sample sizes of 266 in the SPIL's Brinzolamide ophthalmic suspension 1% and 266 in Azopt® 1% achieves 90% power at an $\alpha = 0.05$ significance level when the true difference between the means is 0, the standard deviation is 3.5, and the 95% equivalence limits are -1.0 and 1.0. Considering the possibility of 20% of subjects not being evaluable either due to dropping out of the study or having major protocol violations, approximately 333 subjects will be enrolled in each treatment group for a total of 666 subjects in the study.

Efficacy analyses: The primary analyses will be completed by constructing two-sided 95% confidence intervals of the treatment difference (test – reference) for mean IOP of both eyes (continuous variable) at all 4 follow-up points i.e., at approximately 8:00 AM. (hour 0; before the morning drop) and 10:00 AM. (hour 2) at the Day 14 (Week 2) and Day 42 (Week 6) visits. This mean IOP must be within ± 1.5 mm Hg using the per protocol (PP) population for all time points measured and within ± 1.0 mm Hg using the PP population for the majority of time points measured.

Safety analyses: The primary safety analysis will summarize ocular (in both eyes) and non-ocular AEs for all treated subjects using discrete summaries at the subject level by Medical Dictionary for Regulatory Activities (MedDRA®) system organ class (SOC) and preferred term (PT) for each treatment group. A treatment emergent adverse event (TEAE) will be defined as occurring after the first dose of study medication for the period. Treatment-related ocular and non-ocular TEAEs will be summarized similarly. Ocular and non-ocular TEAEs will also be summarized by severity.

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LIST OF ABBREVIATIONS

AE	Adverse Event
BSCVA	Best Spectacle Corrected Visual Acuity
CI	Confidence Interval
CRO	Contract Research Organization
eCRF	Electronic Case Report Form
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
HRT	Hormonal Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of technical requirements for pharmaceuticals for human use
IEC	Independent Ethics Committee
IMP / IP	Investigational Medicinal Product/Investigational Product
IOP	Intraocular Pressure
IRB	Institutional Review Board
ITT	Intent-To-Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
LOCF	Last Observation Carried Forward
logMAR	logarithm of the Minimum Angle of Resolution
MAO	Monoamine Oxidase Inhibitor
MedDRA	Medical Dictionary of Regulatory Affairs
MMRM	Mixed Model Of Repeated Measures
NCT	Non contact tonometer
OPD	(in-)office physician dispensing
OU	Both eyes
POC	Proof-of-concept
PP	Per Protocol
PT	Preferred Term
RLD	Reference Listed Drug
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	system organ class
[redacted]	[redacted]
SPIL	Sun Pharmaceutical Industries Ltd
SUSAR	Suspected Unexpected Serious Adverse Reaction

TOST	Two one-sided tests
TEAE	Treatment-Emergent Adverse Event
TID	Three Times Daily

2.0 KEY ROLES

Sponsor:

Name:	Sun Pharmaceutical Industries Ltd. (SPIL)
Address:	Sun house, CTS No. 201 B/1, Western Express Highway, Goregaon (E), Mumbai 400063

[redacted]

3.0 BACKGROUND INFORMATION

3.1 Introduction

Glaucoma is collection of disorders characterized by a slow and progressive degeneration of retinal ganglion cells and their axons, resulting in a distinct appearance of the optic disc and a concomitant pattern of visual field loss. (1) In 2010, 60.5 million people were estimated to be suffering from glaucoma worldwide, with a predicted increase to 79.6 million by 2020. It is a leading cause of blindness in the United States of America (USA), affecting 1% to 2% of individuals aged 60 and over. (2) In India, the estimated number of cases of glaucoma is 12 million, around one fifth of the global burden of glaucoma. (3, 4)

There are several recognized risk factors of glaucoma including an increased intraocular pressure (IOP), aging, family history, high myopia, systemic hypertension, cardiovascular disease, migraine headaches, peripheral vasospasm, and prior nerve damage. Elevated IOP is the only proven treatable risk factor in multiple forms of glaucoma. Increased IOP of greater than 21 mm Hg has traditionally been suspected to cause glaucoma, the higher the IOP, the greater the likelihood of optic nerve damage and visual field loss. With IOP > 30 mmHg, the potential risk for vision loss is 40 times greater compared to an IOP of 15 mm Hg. As IOP has been shown in several large-scale National Eye Institute-sponsored studies to be a major factor in the pathogenesis of the progression of glaucoma, pharmacologic reduction of IOP is today the mainstay of treatment for this condition. (5, 6, 7)

Carbonic anhydrase (CA) is an enzyme found in many tissues of the body including the eye. It catalyzes the reversible reaction involving the hydration of carbon dioxide and the dehydration of carbonic acid. In humans, carbonic anhydrase exists as a number of isoenzymes, the most active being carbonic anhydrase II (CA-II), found primarily in red blood cells (RBCs), but also in other tissues. Inhibition of CA in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. The result is a reduction in IOP.

Azopt® 1% (brinzolamide ophthalmic suspension) of Alcon Laboratories Inc, initially approved in 1998 is a carbonic anhydrase inhibitor indicated for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma. Sun Pharma Industries limited (SPIL) is developing a Q1/Q2 formulation to US reference listed drug (RLD) Azopt, and in 10mL and 15 mL packs. Sun Pharmaceutical Industries Ltd's Brinzolamide ophthalmic suspension USP 1% contains brinzolamide, an inhibitor of CA-II. Following topical ocular administration, brinzolamide inhibits aqueous humor formation and reduces elevated IOP.

3.2 Investigational Product

IMP: Brinzolamide ophthalmic suspension USP 1% w/v;

RLD: Azopt® 1% (brinzolamide ophthalmic suspension)

3.2.1 Name and Description

Sun Pharmaceutical Industries Ltd's Brinzolamide ophthalmic suspension USP 1% w/v contains [redacted] formulated for multidose topical ophthalmic use.

[redacted]

It is a white powder, which is insoluble in water, very soluble in methanol and soluble in ethanol. SPIL's Brinzolamide ophthalmic suspension USP 1% w/v is supplied as a sterile, suspension of brinzolamide USP which has been formulated to be readily suspended and slow settling, following shaking. It has a pH of approximately 7.5 and an osmolality of 300 mOsm/kg.

Each mL of SPIL's Brinzolamide ophthalmic suspension USP 1% w/v contains:

Active ingredient: brinzolamide USP 10 mg.

Preservative: benzalkonium chloride solution NF (50%) 0.02 mg

Inactive ingredients: mannitol USP, carbomer homopolymer type B NF, tyloxapol USP, edetate disodium dihydrate USP, sodium chloride USP, water for Injection USP, and hydrochloric acid NF and /or sodium hydroxide NF to adjust pH.

Full name of IMP: Brinzolamide ophthalmic suspension USP 1% w/v, 10 ml

Full name of RLD: Azopt® (brinzolamide) 1%, 10 ml

3.2.2 Non-clinical Data

No non-clinical studies have been conducted with SPIL's Brinzolamide ophthalmic suspension USP 1%.

3.2.3 Clinical Data

No clinical studies have been conducted with SPIL's Brinzolamide ophthalmic suspension USP 1%. All the following data here is from the studies done with RLD AZOPT brinzolamide ophthalmic suspension 1%. (7)

3.2.3.1 Pharmacokinetics:

Following topical ocular administration, brinzolamide is absorbed into the systemic circulation. Due to its affinity for CA-II, brinzolamide distributes extensively into the RBCs and exhibits a long half-life in whole blood (approximately 111 days). In humans, the metabolite N-desethyl brinzolamide is formed, which also binds to CA and accumulates in RBCs. This metabolite binds mainly to CA-I in the presence of brinzolamide. In plasma, both parent brinzolamide and

N-desethyl brinzolamide concentrations are low and generally below assay quantitation limits. An oral pharmacokinetic study was conducted in which healthy volunteers received 1 mg capsule of brinzolamide twice per day for up to 32 weeks. This regimen approximates the amount of drug delivered by topical ocular administration of Azopt® (brinzolamide ophthalmic suspension) 1% dosed to both eyes three times per day and simulates systemic drug and metabolite concentrations similar to those achieved with long-term topical dosing. Red blood cell CA activity was measured to assess the degree of systemic CA inhibition. Brinzolamide saturation of RBC CA-II was achieved within 4 weeks (RBC concentrations of approximately 20 mcM). N-desethyl brinzolamide accumulated in RBCs to steady-state within 20 to 28 weeks reaching concentrations ranging from 6 to30 mcM. The inhibition of CA-II activity at steady-state was approximately 70 to 75%, which is below the degree of inhibition expected to have a pharmacological effect on renal function or respiration in healthy subjects.

3.2.3.2 Pharmacodynamics:

In 2, 3-month clinical studies, Azopt® (brinzolamide ophthalmic suspension) 1% dosed three times daily (TID) in subjects with elevated IOP, produced significant reductions in IOPs (4 to 5 mmHg). These IOP reductions are equivalent to the reductions observed with TRUSOPT* (dorzolamide hydrochloride ophthalmic solution) 2% dosed TID in the same studies.

3.2.3.3 Safety:

In clinical studies of AZOPT (brinzolamide ophthalmic suspension) 1%, the most frequently reported adverse reactions reported in 5 to 10% of patients were blurred vision and bitter, sour or unusual taste. Adverse reactions occurring in 1 to 5% of patients were blepharitis, dermatitis, dry eye, foreign body sensation, headache, hyperemia, ocular discharge, ocular discomfort, ocular keratitis, ocular pain, ocular pruritus and rhinitis. The following adverse reactions were reported at an incidence below 1%: allergic reactions, alopecia, chest pain, conjunctivitis, diarrhea, diplopia, dizziness, dry mouth, dyspnea, dyspepsia, eye fatigue, hypertonia, keratoconjunctivitis, keratopathy, kidney pain, lid margin crusting or sticky sensation, nausea, pharyngitis, tearing, and urticaria.

3.3 Rationale

The Office of Generic Drugs (OGD) of the US Food and Drug Administration (FDA), recommends conducting a BE study with a clinical endpoint in the treatment of open angle glaucoma and ocular hypertension comparing the test product to the RLD, each applied as 1 drop in both eyes TID at approximately 8:00 AM, 4:00 PM, and 10:00 PM for 42 days (6 weeks)

3.3.1 Rationale for the Trial and Selected Subject Population:

The subjects population for the study are males and females with chronic open angle glaucoma or ocular hypertension in both eyes, this is in accordance with the OGD Draft Guidance on Brinzolamide (Recommended Apr 2014; Revised Dec 2014, Mar 2015). (9)

3.3.2 Rationale for Dose Selection

The dose of the study medication either SPIL's Brinzolamide ophthalmic suspension USP 1% or Azopt® is 1 drop in both eyes TID at approximately 8:00 AM., 4:00 PM., and 10:00 PM for 42 days (6 weeks). This is as per the dosing schedule of the RLD Azopt®.

3.3.3 Rationale for the Use of Comparator

The comparator chosen is the RLD Azopt® (brinzolamide ophthalmic suspension 1%), this is in accordance with the Office of Generic Drugs (OGD) Draft Guidance on Brinzolamide (Recommended Apr 2014; Revised Dec 2014, Mar 2015). (9)

3.3.4 Rationale for Study Endpoints

The primary efficacy endpoint is mean difference in IOP of both eyes between the 2 treatment groups at 4 time points, i.e., at approximately 8:00 AM. (hour 0; before the morning drop) and 10:00 AM (hour 2) at the Day 14 (Week 2) and Day 42 (Week 6) visits. This is in accordance with the OGD Draft Guidance on brinzolamide (Recommended Apr 2014; Revised Dec 2014, Mar 2015). (9)

3.4 Compliance Statement for Study Conduct in Accordance with Protocol, GCP and Applicable Regulatory Requirements

The study protocol, amendments to the protocol, Investigator's Brochure (IB), subject recruitment procedures (e.g., advertisements), the subjects' information and informed consent form (ICF) as well as consent form updates (if applicable), written information to be provided to the subjects, available safety information, information about payment and compensation available to subjects, the Investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents will be submitted to the Institutional Review Board (IRB)/Ethics Committee (EC), which is constituted according to local law to obtain approval before initiation of the study and as applicable thereafter.

The study will only be initiated after receipt of the approval from the IRB or EC and/or regulatory authority. The Investigator will report promptly to the IRB/EC new information that may adversely affect the safety of the subjects or the conduct of the study.

The PI (Principal Investigator) will follow the protocol in conformity with Good Clinical Practice (GCP) described in Guideline E6 of the ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) and applicable regulatory requirements before admission into the study, the written ICF must be signed and personally dated by the subject and by the PI or designee who conducted the informed consent discussion.

In obtaining and documenting informed consents, the PI must comply with the applicable regulatory requirement(s), and must adhere to GCP. The PI must inform the subject of all pertinent aspects of the study including the written information approved/favorably assessed by the IRB/EC.

4.0 STUDY OBJECTIVES

4.1 Primary Objective (s)

To evaluate the efficacy of TID dosing of SPIL's Brinzolamide ophthalmic suspension USP 1% w/v compared with Azopt® 1% in subjects with open-angle glaucoma or ocular hypertension.

4.2 Secondary Objective (s)

To evaluate the safety of TID dosing of SPIL's Brinzolamide ophthalmic suspension USP 1% w/v compared with Azopt® 1% in subjects with open-angle glaucoma or ocular hypertension.

5.0 SELECTION OF SUBJECTS

5.1 Description of the Study Population

Males and females with chronic open angle glaucoma or ocular hypertension in both eyes

5.2 Inclusion criteria

1. Male or nonpregnant females aged at least 18 years with chronic open angle glaucoma or ocular hypertension in both eyes.
2. Provide signed and dated informed consent in accordance with good clinical practice (GCP) and local legislation prior to any study procedure.
3. Be able and willing to follow study instructions and complete all required visits.
4. Subject requires treatment of both eyes and is able to discontinue use of all ocular hypotensive medication(s) or switch ocular hypotensive medications and undergo appropriate washout period.

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

5.3 Exclusion criteria

1. Subjects with angle closure glaucoma
2. Females who are pregnant, breast feeding, or planning a pregnancy.
3. Females of childbearing potential who do not agree to utilize an adequate form of contraception.

[redacted]

6. Current, or past history of, severe hepatic or renal impairment
7. Current, or history within 2 months prior to baseline of, significant ocular disease [redacted]
8. Current corneal abnormalities [redacted]
9. Patients with severe central visual field loss [redacted]

11. Contraindication to brinzolamide or sulfonamide therapy or known hypersensitivity to any component of brinzolamide or sulfonamide therapy

[redacted]

[redacted]

[redacted] Subjects currently in another clinical trial

6.0 STUDY DESIGN

This is a randomized, Investigator-masked, multi-center, parallel Group, therapeutic equivalence study with clinical endpoint.

6.1 Description of Type and Design of Study

Treatment period will consist of TID dosing for 6 weeks. Subjects who are chronically treated with ocular hypotensive medications are required to undergo appropriate washout periods prior to study entry to minimize any residual effects of other active ocular hypotensive medications.

6.2 General Instructions for Study Visits

The Schedules of Assessments (Table 1-1) provides an overview of the timing of each visit, with allowed time window for the visit, along with events to occur at each visit. Individual trial procedures are described below, though efficacy assessments are described in more detail in assessment section and safety assessments and AE reporting is described in more detail in safety assessment section. The Sponsor or Contract Research Organization (CRO) will be notified immediately of any critical deviation from study procedures. All protocol deviations will be routinely examined by the Sponsor and CRO.

6.3 Schedule of Assessments

6.3.1 Visit 1 Screening Visit (-42 days to Day -1)

Screening Assessments

Informed consent: Prior to any changes in a subject's medical treatment and/or study visit procedures, the study will be discussed with each subject, and subjects wishing to participate must give written informed consent. The informed consent process will be captured in the subject's source documentation.

Demographic data and medical/surgical/medication/ocular history: Collect and record demographic data (age/date of birth, gender, and iris colour), medical and surgical history, any medications and any underlying condition(s). Current underlying conditions, including those that began within the last 30 days, which may have been resolved before screening, must be recorded. Record any medications the subject is taking, as well as those the subject may have taken but discontinued within the thirty days prior to screening.

Urine pregnancy test (if applicable): Women of childbearing potential must have a negative urine pregnancy test to continue in the study and must agree to use an adequate method of contraception as per Investigator's discretion in order to be enrolled.

NOTE: If a female becomes pregnant during the study, then the Investigator will notify the CRO within 24 hours of knowledge of the pregnancy and the subject should be withdrawn from the study. The CRO will notify [redacted] within 1 business day of knowledge of the pregnancy. The Investigator shall request from the subject and/or the subject's physician copies of all related medical reports during the pregnancy and shall document the outcome of the pregnancy. The Investigator will retain these reports together with the subject's source documents and will provide a copy of all documentation to the CRO.

Examination procedures: The sequence of procedures will be in the following order: BSCVA, corneal pachymetry, slit lamp biomicroscopy, IOP measurement by Goldmann Tonometer and Gonioscopy. After this, pupil dilation is performed followed by fundus ophthalmoscopy.

The following tests may be performed at any time during the visits: Heart rate and blood pressure, urine pregnancy test, and automated perimetry

BSCVA: Subjects must have a score of 0.8 logMAR or better in each eye in order to qualify (see Appendix 1).

Heart rate: Heart rate will be measured and recorded after the subject has been sitting for at least 5 minutes.

Blood pressure: Blood pressure will be measured and recorded after the subject has been sitting for at least 5 minutes.

Automated perimetry (if applicable: required only if there is no data within the past 6 months): Automated perimetry procedures are outlined in Appendix 1.

Slit lamp biomicroscopy: A slit lamp exam will be performed to exclude subjects with disallowed ocular conditions (see Appendix 1).

Intraocular pressure (Goldmann applanation tonometry): IOP measurements will be taken using a Goldmann applanation tonometer. IOP will be measured at least twice in each eye with the right eye measured first. If the difference of the first 2 measurements is ≤ 1 mm Hg, the average of these 2 measurements will be used as the IOP data for this eye. If the difference is > 1 mm Hg, a third measurement will be taken, and the median of these 3 measurements will be used as the IOP data for this eye (see Appendix 1).

Corneal pachymetry for central corneal thickness: (If applicable: required only if there is no data in subject's file within past 30 days). Corneal thickness will be measured using an ultrasound pachymeter. Subjects will be excluded in corneal thickness is > 600 µm (see Appendix 1**)**.

Gonioscopy: To examine iridocorneal angles (open, closed, or partially closed); the procedure will be conducted per the investigator's standard of practice with grading based on the Shaffer scale (see Appendix 1).

Dilated ophthalmoscopy including C/D ratio: A dilated ophthalmoscopy will be performed by the investigator to evaluate the presence or absence of clinically significant fundus abnormalities, vitreous pathology (see Appendix 1).

Discontinuation of current IOP lowering medications, if any

Evaluation of inclusion and exclusion criteria

AE assessment (reported, elicited, observed)

- *Telephonic follow up:* to be scheduled during screening period at 2 weeks from date of signing consent form for subjects if both of the following conditions are met:Screening period is > 3 weeks, and
- ocular hypotensive medication(s) were changed specifically for study purpose

The Investigator will assess if the subject has any features of raised IOP. Accordingly, an unscheduled site visit may be required as per PI discretion, if the subject is having clinical suspicion of raised IOP. If the IOP is found to be significantly raised (e.g. > 34 mm Hg in either eye), then the subject will be considered a screen failure and the appropriate medical management performed as per PI discretion.

Schedule for Visit 2

6.3.2 Visit 2 (Day 0) Baseline/Randomization

- Confirmation of subject eligibility and reassessment of inclusion/exclusion after washout
- Randomization
- Concomitant medications (systemic and ophthalmic)
- Adverse event assessment (reported, elicited, observed)
- Urine pregnancy test (if applicable)
- Heart rate and blood pressure
- BSCVA
- Slit lamp biomicroscopy
- Intraocular pressure 8:00 AM ± 30 min: by Goldmann applanation tonometer (this will be the qualifying IOP for enrollment)
- Dispensation of study medication and study medication compliance diary after IOP reading.
- Intraocular pressure at 10:00 AM ± 30 min: by Goldmann applanation tonometer
- Subjects will be instructed to use their assigned study medication at home starting the next day. Subjects will be instructed to shake the bottle well and then instill study medication into the inferior cul-de-sac of both eyes (OU) at 8.00 AM. (±60 minutes), 4.00 PM. (±60 minutes) and 10.00 PM. (±60 minutes).
- Schedule next visit - subjects will be instructed to come for the next visit without instilling the morning dose on the visit date

6.3.3 Visit 3 -Week 2 ± 4 days

- Concomitant medications (systemic and ophthalmic)
- Adverse event assessment (reported, elicited, observed)
- Heart rate, Blood pressure
- BSCVA
- Slit lamp biomicroscopy
- Intraocular pressure at 8:00 AM ± 30 min and at 10:00 AM ± 30 min by Goldmann applanation tonometer.
- In house study medication instillation (8:00 AM ± 30 min dose) after IOP reading.Review compliance diary
- Dispensation of study medication and study medication compliance diary after IOP reading.
- Subjects will be instructed to continue their assigned medication as per the dosage
- Schedule next visit -subjects will be instructed to come for the next visit without instilling the morning dose on the visit date

6.3.4 End of treatment/Visit 4 (Week 6 ± 4 days)

- Concomitant medications
- AE assessment (reported, elicited, observed)
- Urine pregnancy test (if applicable)
- Review study medication compliance diary
- Collect the study medication and medication dairy
- Heart rate and blood pressure
- BSCVA
- Slit lamp biomicroscopy
- Intraocular pressure at 08:00 AM ± 30 min and at 10:00 AM ± 30 min by Goldmann applanation
- In house study medication instillation (8:00 AM ± 30 min dose) after IOP reading
- Dilated ophthalmoscopy
- Study exit

6.3.5 End of Study Visit 5: Telephonic Visit (Week 7 ± 4 days)

A telephonic call will be done from the study site personnel to the subject after at least 1 week ± 2 days of end of treatment visit 4 (Week 6 ± 2 days). This is to ensure the overall well being of the subject.

6.3.6 Early Discontinuation (ED) Visit

An Early Discontinuation (ED) Visit will occur if a subject requests to withdraw from the study or is asked to withdraw by an Investigator (withdrawal rules). Document reason of subject's termination from study participation, record timing subject took dose of study drug prior day and on day of visit and perform all procedures that are applicable for Visit 4 /End of Treatment Visit (Week 6±2 days).

Subjects whose condition worsens (e.g., IOP ≥ 36 mm Hg in either eye) and require alternate or supplemental therapy for the treatment of their chronic open angle glaucoma or ocular hypertension during the study should be discontinued, excluded from the per protocol (PP) population analysis, and provided with effective treatment.

6.3.7 Unscheduled Visits

An unscheduled visit is defined as any visit to the Investigator site outside of the protocol-specified time points due to safety reasons or when a repeated measurement is required (e.g., obvious measurement errors, confirmation of out-of-range results), or if a test is missed at a visit and needs to be performed, or for dispensing study drug to the subject, where the subject is seen by study personnel.

All unscheduled visits and assessments performed during the visits will be recorded in the subject's source documents and electronic Case Report Form (eCRF). During any unscheduled visits the Investigator will record any AEs and concomitant medications as well as performing any assessments or collecting samples deemed necessary at the discretion of the Investigator.

6.3.8 COVID 19 restrictions

Wherever possible, subjects will visit the site for their routine visit. However if this is not possible due to COVID19 restrictions, the best possible efforts shall be made to capture the safety data virtually. Considering the study design, it is difficult to capture the efficacy data virtually. If necessary, site will also consider if visits can be rescheduled and postponed without impact after discussion with the CRO and Sponsor.

Access to clinical trial medication (study medication): Sponsor through sites will try to make provision for study medication to be delivered to subject's residence after obtaining a verbal consent from subject wherever feasible.

Patient assessments: Necessary subject assessments will be collected as per protocol, except if not possible due to restrictions. In this case, AEs can be collected virtually. If necessary, the Sponsor will also approve the nurse/ site staff visiting the subject's residence for collecting other assessments if feasible and necessary.

In the situation where none of the above can be done, the subject visit shall be recorded as missed and protocol deviation shall be captured.

Clinical trial monitoring: Sponsor shall encourage the monitoring of clinical trial data remotely either through webex or video call. The source data verification of the data reviewed remotely shall be completed onsite, when the situation normalize. All above changes shall be documented in the Study Monitoring Plan.

6.4 Measures Taken to Avoid Bias

6.4.1 Subject Number

Subjects will be allotted a unique subject number at time of consent. The subject number will appear on all study documents relating to that subject and will be cross-referenced by the subject's year of birth.

6.4.2 Randomization

A computer generated randomization scheme will be produced by the CRO. Randomization will be 1:1 to each group. Approximately 666 subjects (333 per treatment arm) will be randomized in this study. Since the study will be conducted in Russia and India, 466 subjects will be recruited in Russia and 200 subjects will be recruited in India.

Masking: This is an evaluator-masked study. The Investigator, masked to treatment assignment, will perform all ophthalmic examinations. An unmasked study coordinator may perform study procedures other than ophthalmic/clinical examination, or treatment of the subjects. The Investigator will be responsible for deciding the type of medical care a subject will get; identifying the kinds of work a subject can safely perform while in the study, and assessment of safety. In order to maintain masking, the unmasked site personnel will dispense IP on Visit 2, 3, and 4 in a room separate from the evaluating Investigator and the subjects will be asked not to discuss the treatment received with the Investigator in order to maintain Investigator-masking. The blinding code will be stored in the Interactive Web Response System (IWRS) system, available only to parties independent of study conduct.

To minimize bias, test and reference bottles will be packed in an identical box with similar label. An unmasked site personnel will instill the in-office physician dispensing (OPD) doses in a room separate from the evaluating Investigator in order to maintain Investigator-masking. In order to maintain masking, the Investigator will not personally retrieve/review the study medication diary; only designated study personnel will collect and review the diary at each visit to ensure treatment compliance.

The code will be broken when the database is cleaned and locked. Prior to the final unblinding, a review to identify the per-protocol population will be undertaken. After database lock, unblinding will be performed by matching the randomization codes to the data in the database and the results will be analyzed.

The treatment code may be revealed on an individual basis in the case of SAE or a safety emergency for which the Investigator must know the identity of the study medication to initiate appropriate treatment. The Investigator will use the IWRS to unblind the subject. Only PI or appropriately delegated sub-Investigator will be given necessary access to open the blind for an individual subject. If the blind is broken, the site must inform the medical monitor or designee and report the reason for unblinding. Date, time, and reason for unblinding, with Investigator's signature, must be recorded. All serious SAEs will be evaluated for causality by the Investigator or designee. A designated member of the Sponsor's safety team will be un-blinded for any SAE that needs unblinding for regulatory reporting purpose or for the subjects safety.

6.5 Withdrawal and Replacement Rules

The Investigator will make every effort to keep each subject in the study. However a subject may withdraw from the study at any time without giving any reason; and should a subject be removed from the study or elect to decline further study participation, the Sponsor will be notified and the reason(s) for discontinuing the study will be recorded in the source documents and eCRF. If a subject withdraws or is removed from the study, they should perform all examinations scheduled for the ED Visit.

The following are justifiable reasons for removing a subject from the study:

- Occurrence of AE or SAE that do not justify continuation of the study
- Protocol deviation (to be defined in the Statistical Analysis Plan [SAP]) which jeopardizes safety of the subject or puts threat to scientific validity of the study.
- Subject becomes pregnant during the study
- Withdrawal of consent by the subject
- If, in the Investigator's opinion, continuation in the study would be detrimental to the subject's well-being

Subjects who are withdrawn from the study due to AE will be treated according to established acceptable medical practice and followed for outcome. All pertinent information concerning the outcome of such treatment will be entered in the source document and eCRF.

6.5.1 Lost to Follow-Up

Randomized subjects who have received at least 1 dose of the study medication but not evaluated for subsequent visits will be considered as lost to follow-up. The Investigator will make every effort to contact subjects lost to follow-up and ask them to return for an ED Visit. Subjects lost to follow up will not be replaced.

6.5.2 Discontinued due to Adverse Event

Subjects who are discontinued on the study medication due to the occurrence of an AE will be recorded as dropouts. The AE will be recorded and all subjects irrespective of time of dropout (after getting randomized and having taken 1 study dose) will be considered for safety analysis.

6.5.3 Replacement of Subjects

Subjects who drop out after randomization will not be replaced.

6.5.4 Premature Discontinuation of the Complete Study

If the trial is prematurely terminated or suspended for any reason, the Investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority (ies). Additionally:

1. If the Investigator terminates or suspends a trial without prior agreement of the Sponsor, the Investigator should inform the institution where applicable, and the Investigator/institution should promptly inform the sponsor and the IRB/EC, and should provide the Sponsor and the IRB/EC a detailed written explanation of the termination or suspension.
2. The Sponsor may discontinue entire study at any time, for business, ethical or scientific reasons. If the Sponsor terminates or suspends the trial, the Investigator should promptly inform the institution where applicable and the Investigator/institution should promptly inform the IRB/EC and provide the IRB/EC a detailed written explanation of the termination or suspension.
3. If the IRB/EC terminates or suspends its approval/favorable opinion of a trial, the Investigator should inform the institution where applicable and the Investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

6.6 The Identification of Any Data to be Recorded Directly in the eCRF

No data will be directly recorded in eCRF. Subjects' information will be documented on source documents and then transferred to the individual eCRFs. The original reports, e.g., laboratory reports, will be kept at the study site. The date and time of report will be transcribed to specific sections in the eCRFs. Electronically generated data like laboratory results, etc could be directly integrated with or transferred to the clinical database.

7.0 TREATMENT OF SUBJECTS

7.1 Investigational Medicinal Products

7.1.1 Study Medication

SPIL's Brinzolamide ophthalmic suspension USP 1% w/v, 10mL

Azopt® 1% brinzolamide ophthalmic suspension (Alcon Laboratories, Inc), 10mL

7.1.2 Handling Requirements of the Investigational Product

The Sponsor will be permitted upon request to audit the supplies, storage, dispensing procedures and records provided that the blind of the study is not compromised.

Subjects will be instructed to store study medication/IP at room temperature 20° to 25°C, not to freeze and to protect from light (direct light, sunlight). Study medications will be permitted with temperature excursion of 15° to 30° C. Subjects will be dispensed their assigned study medication at Visit 2 and Visit 3.

7.1.3 Dispensing (Labeling and Packaging) and Compliance

The study drug will be supplied to the study centers by a CRO appointed by the Sponsor. The IWRS supports drug supply process. Individual subject treatments will be dispensed by the study center pharmacist/appropriately qualified designee in bottles. All clinical study material will be packaged and labelled to comply with applicable regulations. The study drug will be clearly labelled according to local requirements regarding use for clinical study investigation only. For further details see the IP Manual.

The following information will be given on the label statement:

- Sponsor name, address, and manufactured by
- Protocol number
- Study medication/IP name
- Study medication/IP number
- Volume of content
- Batch number
- Manufacturing/expiry date (as per local regulatory requirement)
- Storage conditions
- Re-test date
- Do not use after
- Subject number
- Investigator's name
- Investigator's contact number
- Study site number
- For ophthalmic topical use only

Any additional information required as per the local regulatory requirements

7.1.4 Investigational Product Numbering

Each study medication container will be uniquely numbered. The study medication number(s) will be recorded in the source documents.

7.1.5 Accountability Procedures for the Investigational Product

The Sponsor will supply sufficient quantities of the study drug to allow completion of this study, in an appropriate package deemed to maintain the integrity of the products. In accordance with GCP, the study site will account for all supplies of study medication. The supplies will be stored

as per label instructions until dispensed, in a pharmacy accessible only to pharmacist or authorized person. Details of receipt, storage, assembly, dispensing, and return will be recorded. All unused supplies of study drug will either be destroyed by a designated vendor or will be returned to the study Sponsor at the end of the study in accordance with instructions by the Sponsor.

7.2 Dosage and Dosage Regimen

7.2.1 General Dosing Instructions

Subjects will be instructed to shake the study medication bottle well before use and to instill 1 drop of study medication into the inferior cul-de-sac of each eye TID at 8.00 AM. (±60 minutes), 4.00 PM. (±60 minutes) and 10.00 PM. (±60 minutes). Subjects will be instructed not to dose at home prior to their study visits on Week 2 and Week 6.

7.3 Medication(s)/Treatment(s) Permitted and Not Permitted Before and/or During the Study

Concomitant medications are any medications taken by the subject other than the assigned study drug, these will be recorded in the source document as concomitant medications.

Any medications (other than those excluded by the inclusion/exclusion criteria) that are considered mandatory for the subjects' welfare and that are not anticipated by the Investigator to be likely to interfere with the efficacy assessments, may be given at the discretion of the Investigator.

Medications other than those specifically excluded in this study may be administered for management of concomitant illness, AEs, or symptoms associated with study medications may be administered.

7.3.1 Prohibited medications include the following:

a. Ocular hypotensive drug product other than a study treatment, e.g., acetazolamide (Diamox®), betaxolol (Betoptic®, Betopic-S®), betaxolol and pilocarpine (Betoptic® Pilo), bimatoprost (Lumigan®), brimonidine tartrate (Alphagan®, Alphagan® P), brimonidine tartrate and brinzolamide (Simbrinza®), brimonidine tartrate and timolol maleate (Combigan®), carbachol (Miostat®), carteolol (Ocupress®), dorzolamide hydrochloride (Trusopt®), dorzolamide hydrochloride and timolol maleate (Cosopt®), epinephrine (Epifrin®), latanoprost (Xalatan®), levobetaxolol (Betaxon®), levobunolol (Akbeta®, Betagan®), mannitol (Osmitrol®), metipranolol (OptiPranolol®), pilocarpine (Isopto® Carpine, Pilopine HS®), tafluprost (Zioptan™), timolol (Betimol®, Istalol®, Timoptic®, Timoptic XE®), travoprost (Travatan®, Travatan Z®)
b. Ophthalmic over-the-counter or prescription product, other than study treatment and the occasional use of artificial tears
c. Oral carbonic anhydrase inhibitor
d. High-dose salicylate therapy

e. Topical or systemic corticosteroid
f. Topical ophthalmic corticosteroid
g. Intraocular corticosteroid implant
h. Intravitreal or subtenon injection of ophthalmic corticosteroid
i. Systemic beta-adrenergic blocking drug product
j. Change in concurrent treatment or initiation of treatment with agents potentially affecting IOP, e.g., antihypertensive medication
k. Contact lenses

All concomitant medications must be appropriately recorded in the source documents and described in the eCRF.

7.4 Procedure(s) for Monitoring Subject Compliance

Study medication will be dispensed by the site personnel. Dispensation will be documented in the drug accountability log or equivalent document. Subjects will be instructed to bring their dosing diary and used and unused medication bottle at the time of visit, they will be instructed to record in a dosing diary the date and time at which they took the study drug.

Compliance to study medication will be determined by subject self-report as recorded in subject diaries. Missing diary data may be collected by subject questioning. At Week 4 ± 2 days, the site personnel shall call the subject to remind them to continue dosing. This is simply a measure to enhance compliance to the study medication.

8.0 ASSESSMENT OF EFFICACY

As per the OGD guidance, primary efficacy endpoint is the mean difference in IOP of both eyes between the 2 treatment groups at 4 time points, i.e., at approximately 8:00 a.m. (hour 0; before the morning drop) and 10:00 a.m. (hour 2) at the Day 14 (Week 2) and Day 42 (Week 6) visits

This will be done by measuring IOP at 08:00 AM ± 30 min and at 10:00 AM ± 30 min using Goldmann applanation tonometer at the baseline visit (Visit 2) and at the Day 14 (Week 2) and Day 42 (Week 6) visits.

The secondary efficacy endpoint is change from baseline in IOP of both eyes between the 2 treatment groups at 4 time points, i.e., at approximately 8:00 AM (hour 0; before the morning drop) and 10:00 AM (hour 2) at the Day 14 (Week 2) and Day 42 (Week 6) visits.

9.0 ASSESSMENT OF SAFETY

9.1 Description of Safety Parameters

The following ocular safety assessments will be done during the study as per the Schedule of Assessments

The order of assessment will be the following:

1. BSCVA
2. Slit lamp biomicroscopy
3. Goldmann tonometry
4. Dilated ophthalmoscopy, including recording cup/disc ratio

9.2 Definitions of Adverse Events

9.2.1 Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a drug and does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study medication (investigational), whether or not related to the study medication (investigational).

Untoward medical experience occurring during medication-free pre-treatment periods does not meet the above-mentioned definition of an AE. Nevertheless, they have to be documented in the same way as AE. Each subject will be queried generally for the occurrence of adverse experiences prior to study medication administration and throughout the subject's participation in the study. During and following a subject's participation in this study, the Investigator has to ensure that adequate medical care is provided to a subject for any AE, including clinically significant laboratory values. The subject will be treated and/or followed up until the symptom(s) return to normal, as judged by the Investigator.

9.2.2 Serious Adverse Event

A SAE is any untoward medical occurrence that, at any dose

- Results in death
- Is life-threatening
- Requires in-subject hospitalization or prolongation of existing hospitalization*
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Important medical event: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion, etc.), convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event, which, hypothetically, might have caused death if it were more severe.

*A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health or if the hospitalization is clearly not associated with an AE (e.g., hospitalization due to social / logistic reason) are not to be considered as SAEs.

9.3 Pregnancy

Women of childbearing potential must agree to the use of a reliable method of contraception (e.g., total abstinence, intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], oral, transdermal, injected or implanted non- or hormonal contraceptive), throughout the study. A sterile sexual partner is not considered an adequate form of birth control. Subjects on hormonal contraceptives must have been on the same hormonal contraceptive for at least 1 month before the Screening and continue throughout the duration of the study.

A female is considered of childbearing potential if she has had her first menses and she is either:

a. not postmenopausal for at least 12 consecutive months prior to enrollment; or
b. not surgically sterilized by bilateral tubal ligation, or bilateral oophorectomy, or hysterectomy
c. Male subjects with partners of childbearing potential who are not using birth control as described above must use a barrier method of contraception (e.g., condom) if not surgically sterile (i.e., vasectomy).

Male subjects enrolled in the study will be instructed to avoid passage of semen to their partner by using an acceptable contraceptive method to avoid fathering a child. If a female subject becomes pregnant during the study, the pregnancy will be recorded as a significant medical event and reported per SAE reporting procedures and the subject will be withdrawn from the study immediately. If a female partner of a male subject becomes pregnant during the study, the medical event will be recorded appropriately with the 'Pregnancy Reporting Form' and submitted to the Sponsor's safety physician/CRO. All pregnancies shall be followed every 3-months until outcome and up to one month post delivery to assess the functional status of the child. If any SAE occurs during pregnancy then it will be reported using SAE forms. Any congenital abnormalities or birth defects in the newborn will be followed 3-months post delivery.

9.4 Eliciting, Documentation and Reporting of Adverse Events

Information on AEs will be derived by questioning the subjects in general terms (e.g., "How do you feel?" or "How have you been feeling since the last questioning?" respectively), by subjects' spontaneous reports, or by observation.

Adverse events will be documented on the source document. Trained monitors will check the entries on the source document. The AE will be transcribed to the AE eCRF-sections. The following information will be given for each AE: description of the AE, start date, stop date, severity, pattern, action taken, outcome, seriousness, dose of study drug, and relationship to the study medications. The dose of study medication assigned to an AE will be the dose the subject was assigned to take on the date the subject reported the AE first began.

The AE/SAE collection period for safety surveillance begins when the subject signs the ICF and continues until the end of treatment visit or until the last dose of study medication for subjects with early discontinuation. Adverse events with an onset before the subject receives first dose of the study medication will be categorized as non-treatment emergent AEs (non-TEAEs). Adverse events with an onset after at least 1 dose of study medication is received will be reported as TEAEs.

Safety reporting is inline with the local regulatory requirements in which the study will be conducted.

9.5 Causality of Adverse Events

The relationship of AEs to study medication will be assessed by the Investigator, and will be a clinical decision based on all available information. Following definitions shall be used for assessment of causality.

Category	Definition
Unrelated	Those adverse events (AEs) which, after thorough assessment, are clearly due to extraneous causes (disease, environment, etc.)
Related	The causal relation between the study medication and event cannot be excluded

The Investigator should consider the following, for causality assessment:

- Time relationship between study medication intake and event's onset

- Dechallenge
- Rechallenge
- Medical history
- Study treatment
- Mechanism of action of study medication
- Concomitant medications in use
- Lack of efficacy/worsening of existing condition
- Erroneous treatment with study medication or concomitant medication
- Protocol-related procedure.

9.6 Assessment of severity, outcome and expectedness of Adverse Events

The severity of an AE will be characterized as:

- Mild: AE which is easily tolerated
- Moderate: AE sufficiently discomforting to interfere with daily activity.
- Severe: AE, which prevents normal daily activities.
- Life-threatening: The subject is at risk of death due to the AE as it occurred. This does not refer to an event that hypothetically might have caused death if it were more severe.
- Death: Death related to AE

Event outcome or time last follow-up is recorded is categorized as “fatal”, “resolved”, “resolved with sequelae”, “resolving”, “not resolved”, or “unknown”.

Action taken with respect to study drug is categorized as “none”, “study medication discontinued / withdrawn”, “study medication discontinued and restarted”, “required concomitant medication”, “required procedure”, or “other”.

Assessment of Expectedness will be determined by the version of the IB effective at the time of onset of the adverse event.

9.7 Documentation and Reporting of Immediately Reportable Adverse Events

All SAEs must be reported according to ICH GCP or local regulations, applying the regulation with the stricter requirements. The report will contain as much available information concerning the SAE to enable the Sponsor’s safety physician/CRO to file a report, which satisfies regulatory reporting requirements. The SAE report will be notified by Investigator within 24 hours of his / her awareness to the Sponsor’s safety physician/CRO. These timelines apply to initial reports of SAEs and to all follow-up reports.

All AEs/SAEs will be recorded on the AE/SAE Report Form in the eCRF and source documents. As much information as possible should be supplied at the time of the initial report with at least the following information using SAE Report Form:

- Name, address, and telephone number of the reporting Investigator
- Investigational product(s) (study medication)

- Protocol number
- Subject identification number, initials, sex and date of birth
- Description of the AE, reason considered serious, measures taken and outcome (if resolved)
- Likelihood of drug causation of the AE assessed by the Investigator.
- Additional follow-up information should be completed on an SAE follow-up form with a copy sent to the Sponsor's safety physician/CRO.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone. In these cases, a written report must be sent immediately thereafter by email to the Sponsor's safety physician/CRO.

Relevant pages from the source document and eCRF may be provided in parallel (e.g., medical history, and concomitant drugs). Additional documents may be provided by the Investigator, if available (e.g., laboratory results, hospital report, and autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the eCRF.

The Investigator must respond to any request for follow-up information (e.g., additional information, outcome, final evaluation, and other records where needed) or to any question the Sponsor's safety physician/CRO may have on the SAE. This is necessary to ensure prompt assessment of the event by the Sponsor's safety physician to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the Sponsor's safety physician/CRO.

9.7.1 Serious Adverse Events/Suspected Unexpected Serious Adverse Reactions (SUSARs) Reporting to Regulatory Authorities/EC/IRBs/Participating Investigators

The applicable Regulatory Authorities shall be notified by Sponsor Safety Physician/CRO of any SAE/SUSAR, as per local Regulatory Authorities guidelines and timeframe specified as per local regulation.

All participating Investigators, EC/IRB and other stakeholders shall be notified of any SAE/SUSAR by CRO as per local regulatory requirement.

For any SAE, the Investigator must notify the contact person listed below immediately:

[redacted]	
[redacted]	

The Investigator is obligated to pursue and provide information to Sponsor and the responsible CRO on all SAEs in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by Sponsor and the responsible CRO to obtain specific additional

follow-up information in an expedited fashion. This information may be more detailed than that captured on eCRF. In general, this will include a description of the SAE, which should be provided in sufficient detail so as to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Sponsor or its designated representative.

The initial reports should be followed promptly by detailed written reports. The initial and follow-up reports should identify patients by unique code numbers assigned to the trial patients rather than by the patients' names, personal identification numbers, and/or addresses.

Exposure In Utero During Clinical Studies

If a patient becomes pregnant during the treatment period or within 7 days after the last dose of study treatment, she must not receive additional study drug or treatment and must be promptly discontinued from the study. The patient must be followed up until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, additional follow-up information may be requested.

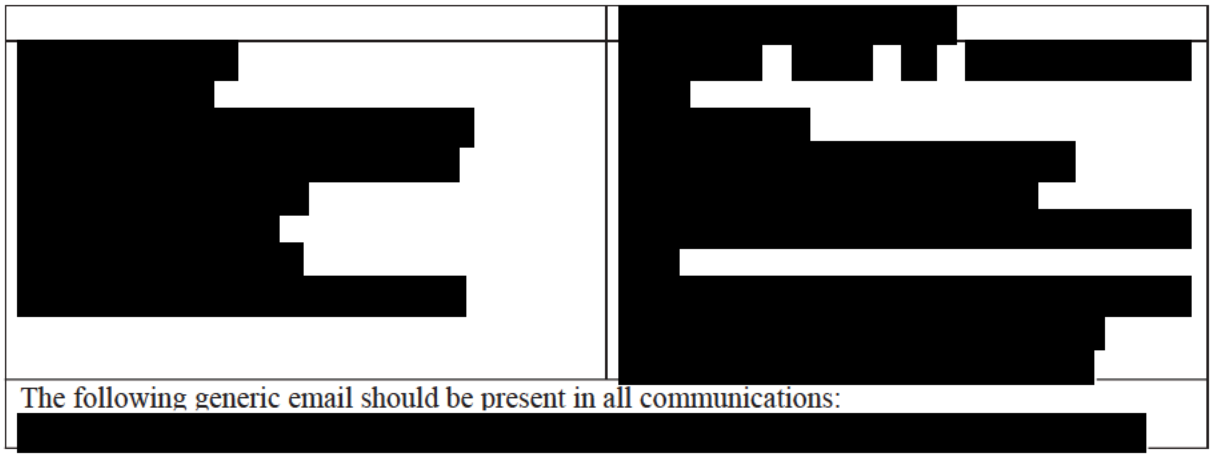
The Investigator must notify the responsible CRO (at the below mentioned e-mail address) within 24 hours of first learning of the occurrence of pregnancy using the Pregnancy Notification Form providing as much information as possible. The Investigator must notify the responsible CRO about reported complications within 24 hours using the same procedure. Outcome of pregnancy, once known by the Investigator, must also be reported to the responsible CRO within 24 hours using the Pregnancy Outcome Form. Pregnancy communications will be directed to:

Pregnancy Reporting Contact Details Email
[redacted]

Contract Research Organization who will relay pregnancy notifications to Sponsor. Please note that pregnancy in and of itself is not an AE or SAE. Pregnancy should not be entered into the CRF as an AE unless the Investigator suspects an interaction between the study treatment and contraceptive method. Pregnancy will be documented as the reason for study discontinuation.

CRO will direct the pregnancy communication to Sponsor (Pharmacovigilance Responsible Person) as soon as it is received.

[redacted]



Progress reports: Where required by applicable regulatory requirements, the investigator should submit written summaries of the trial's status to the institution. The investigator/institution should submit written summaries of the status of the trial to the IRB/EC annually, or more frequently, as requested. The Investigator should promptly provide written reports to the Sponsor, the IRB or EC, and, where required by the applicable regulatory requirements, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to the subjects.

9.8 Follow-Up of Subjects after Adverse Events (Serious and Non-Serious)

9.8.1 Unresolved Events

If an AE/SAE is continuing when the subject has completed the study, the event must be followed and reported until resolution/stabilization as per medical judgment of the Investigator.

9.8.2 Post-study Events

Any AE/SAE which occurs past the end of the treatment visit will be reported if it is considered related to study drug by the Investigator.

10.0 STATISTICS

Summary statistics will be presented by treatment group. For continuous variables, unless otherwise stated, the number of available observations (n), mean, standard deviation (SD), median, and range will be provided. For categorical variables, the number and percentage in each category will be displayed. Unless otherwise specified, missing or dropout data will not be imputed for the purpose of data analysis. Complete details of the approaches to handling missing data will be provided in the SAP. Exposure and compliance with IMP will be summarized descriptively. Incidence of prior and concomitant medication use will be summarized by World Health Organization (WHO) Drug dictionary coded terms - Anatomic Therapeutic Chemical (ATC) classification and preferred term.

A more detailed description of study analyses will be presented in the SAP.

10.1 Study Population

10.1.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population consists of all subjects who are randomized into the study. All data will be included and no subjects will be excluded because of protocol violations. The ITT population will summarize subjects as randomized and will be used for confirmatory analyses.

10.1.2 Per Protocol Population

The PP population includes all randomized subjects who meet all inclusion/exclusion criteria, and complete evaluations at week 2, week 6 (with compliance between 75 to 125%) with no protocol violations that would affect the treatment evaluation. The PP population will be considered the primary analysis population for the study and will summarize subjects as treated.

10.1.3 Safety Population

The safety population includes all subjects who receive at least 1 dose of study medication. The safety population will be used to summarize safety variables and will summarize subjects as treated.

10.2 Study Endpoints

10.2.1 Primary Efficacy End point:

Mean difference in IOP of both eyes between the two treatment groups at four time points, i.e., at approximately 8:00 a.m. (hour 0; before the morning drop) and 10:00 a.m. (2 hours) at the Day 14 (Week 2) and Day 42 (Week 6) visits.

10.2.2 Secondary Efficacy endpoint:

Change from baseline in IOP of both eyes between the 2 treatment groups at 4 time points, i.e., at approximately 8:00 a.m. (hour 0; before the morning drop) and 10:00 a.m. (hour 2) at the Day 14 (Week 2) and Day 42 (Week 6) visits.

10.2.3 Safety:

- Incidence and severity of AEs
- BSCVA
- Slit lamp Biomicroscopy
- Tonometry
- Dilated fundus exam, including Cup/Disc ratio

10.3 Efficacy Analysis

The accepted PP population used for BE evaluation includes all randomized subjects who meet all inclusion/exclusion criteria, instill a pre-specified proportion of the scheduled doses (i.e., compliance between 75 to 125%) of the assigned product for the specified duration of the study,

and complete evaluations at Day 14 (Week 2) and Day 42 (Week 6) with no protocol violations that would affect the treatment evaluation.

Subjects whose condition worsens (e.g., IOP ≥ 36 mm Hg in either eye) and require alternate or supplemental therapy for the treatment of their chronic open angle glaucoma or ocular hypertension during the study should be discontinued, excluded from the PP population analysis, and provided with effective treatment.

Analysis will be done in both eyes. The primary analyses will be completed by constructing two-sided 95% confidence intervals of the treatment difference (test – reference) for mean IOP of both eyes (continuous variable) at all four follow-up points (i.e., at approximately 8:00 a.m. [hour 0; before the morning drop] and 10:00 a.m. [hour 2] at the Day 14 [Week 2] and Day 42 [Week 6]) visits. This mean IOP must be within ± 1.5 mm Hg using the PP population for all time points measured and within ± 1.0 mm Hg using the PP population for the majority of time points measured. Additional details of the statistical approach considering country wise analysis will be provided in the SAP.

For change from baseline IOP, baseline will refer to the time-matched measure at Visit 2. For all other variables, baseline is defined as the last measurement prior to the first dose of study medication. Change from baseline will be calculated as visit – baseline. The p-values for testing equivalence of these time-matched means between treatment groups will be generated using the TOST (two one-sided tests) procedure at each of the equivalence limits (-1.0, 1.0) and (-1.5, 1.5).

In addition to these individual confidence intervals, a mixed effects repeated measures model, with random effect for subject, covariate for baseline IOP, and fixed effects for treatment and day/time (within subject repeated measures) will be fitted to the data. Appropriate covariance structure will be used to model the within subject, between time point variances. Individual and simultaneous confidence intervals will then be constructed based on this MMRM model at each of the time points. The 95% simultaneous confidence intervals will use the Tukey-Kramer method to adjust for multiple comparisons across all 4 time points.

The analyses of the efficacy variable will be completed on observed data only (without imputation). To check robustness of results, sensitivity analyses of the primary efficacy data will include using: a multiple imputation technique to impute missing data.

For the multiple imputation approach, the multiple imputation technique proposed by Rubin (1987) replaces each missing value with a set of plausible values and these imputed data sets are then analyzed by using standard procedures for complete data and combining the results from these analyses. A Markov chain Monte Carlo (MCMC) method, which can be implemented within SAS software that assumes multivariate normality, will be used for imputation.

10.4 Safety Analysis

The safety population includes all randomized subjects who receive study product.

The primary safety analysis will summarize ocular (in both the eyes) and non-ocular AEs for all treated subjects using discrete summaries at the subject level by Medical Dictionary for Regulatory Activities (MedDRA®), SOC, and PT for each treatment group. A TEAE will be defined as occurring after the first dose of study medication for the period. Treatment-related ocular and non-ocular TEAEs will be summarized similarly. Ocular and non-ocular TEAEs will also be summarized by severity. For safety summaries the unit of analyses will be both eyes for ocular measures and will be the subject for non-ocular safety measures as well as all AEs.
Ocular safety assessments include:

a. Biomicroscopy: Slit lamp biomicroscopy will be performed at every visit during the study to observe the overall health of the eye, including the lid/lashes, conjunctiva, cornea anterior chamber, iris and lens. Any observations at the screening visit should be recorded as ocular medical history, and any new or worsened observations may be recorded as AEs

b. Dilated ophthalmoscopy (Visits 1 and Visit 4) items to be observed are retina, macula, choroids, optic nerve, and optic disc pallor examination measures will be summarized at each visit using discrete summary statistics.

c. Visual acuity: Data will be summarized at each visit, using continuous and discrete summaries, including change from baseline in the number of lines and the proportion of subjects with a worsening of ≥ 3 lines from baseline.

Heart rate and blood pressure: Data will be summarized using continuous summary statistics (mean, standard deviation, minimum, median, and maximum) by visit including change from baseline summaries.

Deaths, other SAEs, and other significant AEs, including those leading to discontinuation of study drugs, will be listed. Adverse events will also be summarized by actual dose at time of onset of the AE to account for possible dose reductions over the course of the study.

10.5 Sample Size

An equivalence test of means using two one-sided tests on data from a parallel-group design with sample sizes of 266 in the SPIL's Brinzolamide ophthalmic suspension 1% and 266 in Azopt® 1% achieves 90% power at an $\alpha = 0.05$ significance level when the true difference between the means is 0, the standard deviation is 3.5, and the 95% equivalence limits are -1.0 and 1.0.
Considering the possibility of 20% of subjects not being evaluable either due to dropping out of the study or having major protocol violations, approximately 333 subjects will be enrolled in each treatment group for a total of 666 subjects in the study.

11.0 STUDY MANAGEMENT

11.1 Monitoring

Onsite monitoring will be performed during the study. The monitor will ensure that the study is conducted, recorded and reported in accordance with the protocol, standard operating procedure

(SOP), GCP, and the applicable regulatory requirements. The monitor will check the accuracy and completeness of the eCRF entries, source documents, and other study-related records against each other. The monitor will follow written SOPs as well as those procedures that are specified by CRO for monitoring a specific study. The monitor will record the date of each visit together with a summary of the status and progress of the study. Proposed actions will be confirmed with the Investigator in writing.

The Investigator will provide direct access to source data/documents for study related monitoring. It is important that the Investigator and/or other staff are available at these visits. The Investigator should maintain source documents such as laboratory reports, history and physical examination reports, etc., for possible review.

11.2 Documentation at the Study Site

Data relating to the study will be documented in the source documents and eCRFs. The Investigator will ensure the accuracy, completeness, legibility, and timeliness of the data recorded in the source documents and eCRFs. Any change or correction to a source document or eCRF will be dated, initialed, and explained (if necessary) and will not obscure the original entry.

At the beginning of the study, a site master file will be established at the investigational site. The Investigator will maintain the study documents as specified in the ICH Guideline of GCP and as required by the applicable regulatory requirements. The Investigator will take measures to prevent accidental or premature destruction of these documents. The Investigator will permit study-related monitoring, audits, and IRB/EC or regulatory inspection, providing direct access to source data or documents.

Prior to the start of the study, a signature and delegation log will be completed showing the signatures and hand-written initials of all study staff. This log allows the PI to delegate study tasks to individual members of his/her team, identifies site staff participating in the study and the start/stop times of their participation, and provides a handwriting sample for all site staff participating in the study.

11.3 Retention Samples

The clinical investigator or designee should randomly select sufficient test article and reference standard to conduct the study from the supplies received from the sponsor and/or drug manufacturer, and retain the remaining study samples as study reserves.

The testing facility or the pharmacy of the testing facility should retain the reserve samples.
If the testing facility does not have adequate storage, or goes out of business, the reserve samples can be transferred to an independent third party with an adequate facility for storage under conditions consistent with product labeling.

11.4 Subject Data and Data Protection

To protect the subject's identity, a subject number will be assigned by the Investigator to each study subject and used in lieu of the subject's name when the Investigator reports AEs and/or other study-related data. Personal information will be treated as confidential but may need to be reviewed by authorized representatives of CRO/Sponsor (if applicable) (monitor and auditor), IRB/EC and regulatory authorities. The subject's consent for direct access to his/her original medical records for data verification purposes has to be obtained prior to a subject's participation in the study.

The Investigator must maintain a list of names and identifying information (e.g. initials, date of birth, subject identification code and date of study randomization) of all subjects enrolled in the study. The Investigator will keep the subject identification code list in the site master file.

11.5 Data Management

A Code of Federal Regulations (CFR) Title 21 Part 11-compliance Electronic Data Capture (EDC) system will be used for this study. The eCRFs will be produced for each subject. The majority of study data collected on the source documents will be entered by the study center staff or directly captured from devices and submitted to the database. Data will be available for Sponsor review via predefined reports extracted from the database at agreed intervals. The eCRFs must be kept in order and up-to-date so that they reflect the latest observations on the enrolled subjects.

All source documents will be retained. Photocopies of completed source documents will be provided only if essential (i.e., for regulatory purposes) at the request of the Sponsor.

Safety laboratory data are managed and stored within the appropriate system and the date and time of sampling will be recorded in the eCRF. Safety laboratory data will be integrated or transferred with the consolidated clinical data before database lock.

The informed consent will be kept with a copy of the completed source documents in the appropriate file folder provided, or a note to indicate where the records can be located. All records should be kept in conformance to applicable national laws and regulations.

Validity and consistency of data will be checked by employing pre-programmed data validation rules that will be applied to the data extracted from the EDC system during the course of the study. The data management team will raise queries in the EDC system to resolve discrepancies. The Investigator must verify that all data entries in the eCRFs are accurate and correct per the source document. After completion of the study and when all collected data is validated, the database will be locked, pursuant to the prior approval by the Sponsor. Final data will be extracted from the EDC system and delivered to the Sponsor in form of SAS® datasets. A portable document format copy of the eCRF will be produced for each study subject and included in the final delivery.

All eCRF entries, corrections, and alterations must be made by the Investigator or other, authorized, study center staff and only by individuals who have received training on the EDC

system. Study center staff may be allowed access to the system only after the relevant training is completed. Training must be documented and a log of all EDC users and their rights within the system be maintained.

Adverse events will be coded using the current MedDRA thesaurus and concomitant medications will be coded using World Health Organization's Drug Dictionary.

The EDC system will keep track of all data entry, alterations and query resolution in an audit trail. The audit trail will form an integral part of the database and will be archived alongside with the data.

Details of the data management process including the data to be entered of the screening failure subjects will included in the data management plan.

11.6 Compliance with Protocol

The investigator or institution should conduct the trial in compliance with the protocol agreed to by the Sponsor and, if required, by the regulatory authority(ies) and which was given approval/favorable opinion by the IRB/EC.

The Investigator will not implement any deviation from, or changes to the protocol without agreement by Sponsor and prior review and documented approval/favorable opinion from the IRB/EC of an amendment, except where necessary to eliminate immediate hazards to study subject or when the changes involve only logistical or administrative aspects of the study (e.g., change in monitor(s), change in telephone numbers).

11.7 Amendments to the Protocol

All changes or deviations of the trial must be confirmed in writing. The amendments to protocol will be made jointly between the CRO (if applicable), the Sponsor and Investigator(s). Protocol amendment(s) will be signed off in the same way as the protocol.

11.8 Investigator Responsibilities

11.8.1 Protocol Compliance

The Investigator will conduct the study in compliance with the protocol provided by the Sponsor or designee, and given approval/favorable opinion by the IRB and the appropriate regulatory authorities. The Investigator will sign this protocol to confirm agreement (see PI Signature Page).

11.8.2 Protocol Deviations

The Investigator should not implement any deviation from, or change to the protocol without prior agreement with the Sponsor or designee. When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact Sponsor or designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol

must be fully documented and submitted to the IRB in accordance with the IRB's reporting requirements.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

Quality assurance and quality control systems are implemented and maintained using written SOPs to ensure that the study is conducted and data are generated, documented (recorded) and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s). Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

12.1 Audit

Sponsor or designee may conduct an internal or external audit. In such an instance, the auditor will be allowed direct access to the source medical records, the pharmacy, the eCRFs, and the Site's master file for the study. In addition, the regulatory authorities may also request an audit.

13.0 ETHICS

Before initiation of the study, Sponsor will seek permission from the regulatory authorities and EC for conducting the study. All documents required by the appropriate authorities will be submitted. Any notification/submission will be dated and contain sufficient information to identify the protocol.

13.1 Ethics Committee (EC) or Institutional Review Board (IRB)

This study will be initiated after the protocol is reviewed and approved by the concerned IRB or EC. All documents required by the appropriate authorities will be submitted. Any notifications/submission will be dated and contain sufficient information to identify the protocol.

13.2 Ethical Conduct of the Study

This study will be carried out in conformity with GCP described in Guideline E6 of the ICH. This study will also be carried out in conformity with the laws, rules, and regulations prevailing in the state and country of the study site.

13.3 Subject Information and Consent

Subject will be screened and included in the study only after giving them adequate and appropriate information, and obtaining a written informed consent. The subject will be given sufficient time to consider the study's implications before deciding to participate. The subject will be provided with a copy of the signed ICF. The confidentiality of the subject's records will be maintained. If there is any major amendment in the protocol affecting the subject's participation in the study e.g., a change in any procedure, the ICF will be amended to incorporate this modification and previously consented subjects will sign an amended consent form (when relevant). The Investigator is responsible for obtaining the subject's freely given written consent.

14.0 DATA HANDLING AND RECORD KEEPING

The Investigator must maintain all documentation relating to this study. Essential documents (as defined in the ICH Guideline of GCP) must be retained until at least 2-years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region or at least 2-years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents must be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by Sponsor.

In any case, all study records such as but not limited to CRFs, regulatory documents, the subject identification code list, subject files and other source data that support CRFs must be retained for at least 15-years after the completion or discontinuation of the study. If the Investigator retires, relocates or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred and Sponsor notified in writing. Sponsor will notify the Investigator in writing when the study-related records are no longer needed.

15.0 FINANCING AND INSURANCE

The Sponsor is covered by a liability insurance that also covers liability towards subjects in clinical trials. Sponsor is covered by a General and Products liability insurance that includes clinical trials.

16.0 PUBLICATION POLICY

The CRO and Investigator agree to keep strictly confidential all unpublished information and results concerning this study. Any publication or disclosure by the investigator contrary to the provisions of this section or without prior written consent of Sponsor shall be void-ab-initio. Sponsor reserves all the rights to declare any of its data confidential or of business importance and will provide it only to the regulatory authorities of concern on request/demand.

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18.0 APPENDICES

Appendix 1: Examination Procedures, Tests, Equipment and Techniques

Urine Pregnancy Tests (If applicable)

Standard dipstick-based urine pregnancy tests will be administered to subjects that are of child bearing potential to assess pregnancy status. Child bearing potential is defined as any female who has had her first menses, not had a hysterectomy or bilateral tubal ligation, and has not been post-menopausal for at least 12 consecutive months. Pregnancy is not to be considered an AE, but it is an important medical event that must be followed up as described in Section 9.3.

Best Spectacle Corrected Visual Acuity (BSCVA) Procedures (Each Eye)

LogMAR Visual Acuity must be assessed using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart and as indicated in the study flowchart in Appendix 1. The procedure used will be consistent with the recommendations provided for using the ETDRS eye chart. Visual acuity should be evaluated at the beginning of each visit in the study (ie, prior to slit lamp examination). Visual acuity testing should be done with best (most recent) correction.

Equipment

The visual acuity chart to be used is the ETDRS chart. If smaller reproduction (18" by 18", e.g., from Prevent Blindness) wall charts are used, the subject viewing distance should be exactly 10 feet (or as specified by the manufacturer). In all cases, for purposes of standardizing the testing conditions during the study, all sites must use only the 'R' charts, and the right eye should be tested first. For reflectance (wall) charts, the chart should be placed frontally and well-illuminated.

Measurement Technique

The chart should be at a comfortable viewing angle. The right eye should be tested first. The subject should attempt to read each letter, line-by-line, left to right, beginning with line 1 at the top of the chart. The subject should be told that the chart has letters only, no numbers. If the subject reads a number, he or she should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number. The subject should be asked to read slowly, so as to achieve the best identification of each letter. He/she is not to proceed to the next letter until he/she has given a definite response.

If the subject changes a response (e.g., 'that was a "C" not an "O"') before he has read aloud the next letter, then the change must be accepted. If the subject changes a response having read the next letter, then the change is not to be accepted. The examiner should never point to the chart or to specific letters on the chart during the test.

A maximum effort should be made to identify each letter on the chart. When the subject says he or she cannot read a letter, he or she should be encouraged to guess. If the subject identifies a letter as one of two letters, he or she should be asked to choose one letter and, if necessary, to guess. When it becomes evident that no further meaningful readings can be made, despite encouragement to read or guess, the examiner should stop the test for that eye. However, all letters on the last line

should be attempted as letter difficulties vary and the last may be the only one read correctly. The number of letters missed or read incorrectly should be noted.

LogMAR Visual Acuity Calculations

The last line in which a letter is read correctly will be taken as the base logMAR reading. To this value will be added the number "N × 0.02" where 'N' represents the total number of letters missed up to and included in the last line read. This total sum represents the logMAR visual acuity for that eye.

For example: Subject correctly reads 4 of 5 letters on the 0.2 line, and 2 of 5 letters on the 0.1 line.

Base logMAR	= 0.1
N (total number of letters incorrect on line 0.2 as well as 0.1)	= 4
N × T (T=0.02)	= 0.08
Base logMAR + (N × T)	= 0.1 + 0.08
logMAR VA	**= 0.18**

Repeat the procedure for the left eye.

In order to provide standardized and well-controlled assessments of visual acuity during the study, all visual acuity assessments at a single site must be consistently done using the same lighting conditions and same correction if possible during the entire study. If the same correction cannot be used (ie, a subject forgets his glasses), the reason for the change in correction should be documented.

Gonioscopy (Both eyes)

Gonioscopy will be graded with the Shaffer scale:

Shaffer Scale		
Classification	**Finding**	**Angle width (degree)**
Grade 4	Ciliary body is visible	35-45
Grade 3	Scleral spur is visible	20-35
Grade 2	Only trabecular meshwork is visible	20
Grade 1	Only Schwalbe's line is visible	≤10
Grade 0	Angle is closed	0

Automated Perimetry

(Each Eye, if applicable: required only if there is no data within the past 6 months)

Automated perimetry will be performed as indicated in the study flowchart in Appendix 1. If the brow is heavy or the upper lid is drooping, tape accordingly. Visual field results must be reliable (i.e., ≤ 33% fixation losses, false positive or false negative errors) or the field should be repeated within two weeks. Visual field examinations will be performed using an automated perimetry test preferably Humphrey automated perimeter (full threshold 24-2 program or SITA standard). Preferred equipment is the Humphrey 700 HFA-2 series machines (eg, 740 or 750). Visual fields will be reported as normal or abnormal and the mean deviation will also be recorded in decibels.

Begin by testing the right eye. Adjust the chin rest and the table height as needed to achieve proper alignment as well as to maintain the subject in a comfortable seated position throughout the test. It is permissible to encourage the subject occasionally if the subject seems to be fatigued or losing concentration, and to allow the subject to pause and rest if necessary. The subject should also be informed that a good time to blink is when the response button is pushed so as not to affect the results of the test.

Slit Lamp Biomicroscopy (Each Eye)

Biomicroscopy will be performed using a slit lamp. Magnification will be consistent with standard clinical practice at every visit. The subject will be seated.

This will be done to observe the overall health of the eye, including the lid/lashes, conjunctiva, cornea anterior chamber, iris, and lens. Any observations at the screening visit will be recorded as ocular medical history, and any new or worsened observations may be recorded as AEs. Observations will be graded as Normal or Abnormal. Abnormal findings which are clinically significant will be described.

Goldmann Applanation Tonometry (Each Eye)

The time of tonometry will be recorded on the source document for all visits. Measurements will be taken by two qualified independent study site personnel using a Goldmann applanation tonometer affixed to a slit lamp with the subject seated. One person will adjust the dial in masked fashion and a second person will read and record the value. The subject and slit lamp should be adjusted so that the subject's head is firmly positioned on the chin rest and against the forehead rest without leaning forward or straining. Both eyes will be tested, with the right eye preceding the left eye. Each IOP measurement is to be recorded.

One person ("the measurer") looks through the binocular viewer of the slit lamp at low power. The tension knob is pre-set at a low pressure value (4 to 6 mmHg). The measurer follows the image of the fluorescein-stained semicircles while he/she slowly rotates the tension knob until the inner borders of the fluorescein rings touch each other at the midpoint of their pulsation in response to

the cardiac cycle. When this image is reached, the measurer takes his/her fingers off the tension knob and the second person ("the reader") records the IOP reading along with the date and time of day in the source document, thus maintaining a masked IOP reading.

At least two, and if necessary, three consecutive measurements will be taken to determine IOP in the manner described above. After first measurement remove applanator (prism) from the corneal surface, reset the dial to low number, reapply applanator and re-measure.

If the first two measurements differ by 1 mmHg or less, a third measurement is not required, the two measurements will be recorded and the mean IOP of the two measurements will be recorded and used in the analysis. If the first 2 measurements differ by more than 1 mmHg, a third measurement should be made, all 3 measurements will be recorded and the median IOP of the three measurements will be recorded and used in the analysis.

Corneal Pachymetry

(Each Eye, if applicable: required only if there is no data in the subject's file within past 30 days)

Central corneal thickness measurements of each eye will be performed using an ultrasonic pachymeter and as indicated in the study flowchart in Appendix 1. Measurements will be made before IOP is taken. For ultrasound probes, the Probe Quality Factor must be greater than or equal to 85%. With the subject seated and visualizing a consistent fixation target, position the probe tip on the cornea, perpendicular to the corneal surface, on the visual axis (ie, centered on the pupil). Once the probe tip is positioned properly, take a measurement. A total of 3 acceptable measurements, as described above, should be made for each eye, and the 3 measurements will be recorded in microns.

Dilated Ophthalmoscopy (Each Eye)

Dilated exam will be performed after tonometry. The examination will not be performed until the subject's eyes are deemed sufficiently dilated in the opinion of the investigator. The investigator will note any findings present and whether or not the findings are clinically significant or not clinically significant. Findings which are clinically significant will be described. The following will be examined:

- Vitreous
- Retina
- Macula
- Choroid
- Optic Nerve
- Cup-to-Disc Ratio (may be assessed using slit lamp following dilation)

Additional Study Supplies:

- Urine pregnancy test
- Study medication dosing diary
- Fluorescein and anesthetic for IOP measurement
- Dilating drop(s) for ophthalmoscopy exam
- Anesthetic for gonioscopy
- Lubricating gel for gonioscopy (if applicable)

Appendix 2 Contraceptive Guidance

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   a) Documented hysterectomy.
   b) Documented bilateral salpingectomy.
   c) Documented bilateral oophorectomy.
   Note: Documentation can come from the study center personnel's: review of the subject's medical records, medical examination, or medical history interview.
3. Postmenopausal female:
   a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   b) Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male subjects

- Male subjects with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the Clinical Investigational Plan-defined time frame in Section 5.3
    - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
    - Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described below when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

- Male subjects with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during study period (until Visit 5).

Female subjects

Female subjects of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below.

Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation Oral. Intravaginal. Transdermal.
Progestogen only hormonal contraception associated with inhibition of ovulation Oral. Injectable.
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation Intrauterine device (IUD). Intrauterine hormone-releasing system (IUS). Bilateral tubal occlusion.
Vasectomized partner *A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*
NOTES: [a]Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

Pregnancy Testing:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test at screening and at Visit 2 and Visit 4.