1 TITLE PAGE

Clinical Study Protocol

Brinzolamide 1% Ophthalmic Suspension

A RANDOMIZED, DOUBLE-MASKED, ACTIVE-CONTROLLED, PARALLEL GROUP, MULTI-CENTER BIOEQUIVALENCE STUDY OF THE 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 S0883

Developmental phase of study:	Bioequivalence, pivotal
Study design:	A multi-center, randomized, double-masked, active-controlled, parallel bioequivalence study of both eyes in subjects with primary open angle glaucoma or ocular hypertension
Date: Original	11 JAN 2018
Amendment 1	12 APR 2018
Sponsor representative	[redacted]
Sponsor	Valeant Pharmaceuticals North America LLC 400 Somerset Corporate Blvd, Bridgewater NJ 08807 Main office: (866) 246-8245

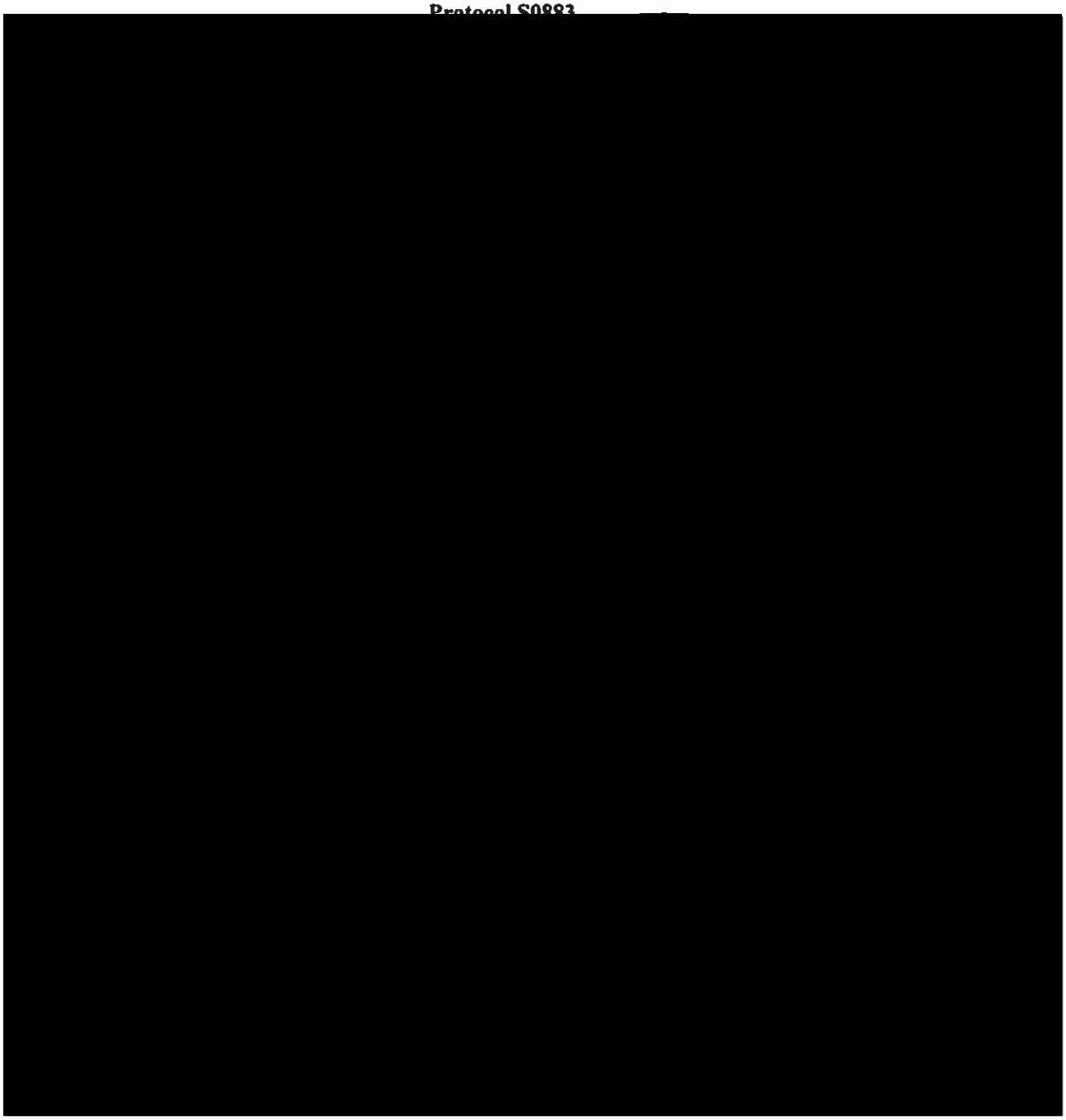
CONFIDENTIAL

Nothing herein is to be disclosed without prior approval of the sponsor.

Protocol Review and Approvals

A RANDOMIZED, DOUBLE-MASKED, ACTIVE-CONTROLLED, PARALLEL GROUP, MULTI-CENTER BIOEQUIVALENCE STUDY OF THE 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 S0883



Personnel Responsible for Conducting the Study

A RANDOMIZED, DOUBLE-MASKED, ACTIVE-CONTROLLED, PARALLEL GROUP, MULTI-CENTER BIOEQUIVALENCE STUDY OF THE 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 S0883

[redacted]

Contract Research Organization

[redacted]

Lexitas Pharma Services
313 Foster St
Durham, NC, 27701

Principal Investigator Protocol Agreement Page

I agree:

- To assume responsibility for the proper conduct of this clinical study at this site and to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by the sponsor.
- That I am aware of, and will comply with, the internationally recognized code of Good Clinical Practices (GCP) and all other applicable regulatory requirements to obtain written and dated approval from the Institutional or Central Review Board (IRB) or Independent Ethics Committee (IEC) for the study protocol, written informed consent, consent-form updates, subject-recruitment procedures (eg, advertisements), and any other written information to be provided to the subjects, before initiating this clinical study.
- Not to implement any changes to, or deviations from the protocol without prior agreement from the sponsor and review and documented approval from the IRB/IEC, except to eliminate an immediate hazard to the study subjects, or when change(s) involves only logistical or administrative aspects of the clinical study.
- To permit direct monitoring and auditing by the sponsor or sponsor's representatives and inspection by the appropriate regulatory authority (ies).
- That I am thoroughly familiar with the appropriate use of the investigational products(s), as described in this protocol, and any other information provided by the sponsor or designee, including, but not limited to, the current investigator Brochure or equivalent document and approved product label (if applicable).
- To provide sufficient time and adequate numbers of qualified staff and facilities for the foreseen duration of the clinical study to conduct the study properly, ethically, and safely.
- To ensure that all persons assisting in this study are adequately informed about the protocol, investigational product(s), and their clinical study-related duties and functions.

_____

Principal Investigator (print name)

_____ _____

Principal Investigator (signature) Date

2 Synopsis

Name of Sponsor/Company: Valeant Pharmaceuticals North America LLC
Name of Investigational Product (test product): Brinzolamide 1% Suspension
Name of Active Ingredient: Brinzolamide 1% Suspension
Title of Study: A randomized, double-masked, active-controlled, parallel group, multicenter bioequivalence study of the 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.
Number of clinical centers: Approximately 32 Sites, United States only
Objectives: **Primary:** • To establish that the generic brinzolamide 1% suspension is bioequivalent to brinzolamide 1% suspension (AZOPT®), the selected Reference Listed Drug. **Secondary:** • To compare the safety and tolerability of the generic brinzolamide 1% suspension to brinzolamide 1% suspension (AZOPT®).
Methodology: This repeat study will be prospective, randomized, double masked and will follow Food and Drug Administration (FDA) guidance, revised as of March 2015, for demonstrating bioequivalence of the generic brinzolamide 1% ophthalmic suspension compared to brinzolamide 1% Ophthalmic Suspension (AZOPT®) for the treatment of elevated intraocular pressure (IOP) in patients with Primary Open Angle Glaucoma (POAG) or Ocular Hypertension (OH).
Number of patients planned: Approximately 624 subjects will be randomized to ensure that 560 subjects complete the 42 days (6 weeks) of dosing.
Diagnosis and main criteria for inclusion: 1. Subjects must be of legal age (at least 18 years) on the date the Informed Consent Form (ICF) is signed. 2. Subjects must be able to read, understand, and provide written informed consent on the Institutional Review Board (IRB)/Ethics Committee (EC)-approved ICF and provide authorization as appropriate for local privacy regulations. 3. Subjects who are willing and able to comply with scheduled visits, treatment plan, and other study procedures. 4. Male subjects able to father children and female subjects of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for at least 28 days after last dose of assigned treatment. Acceptable contraceptive methods for female subjects (need at least one): a) Hormonal methods of contraception (including oral and transdermal contraceptives, injectable progesterone, progestin subdermal implants, progesterone-releasing intrauterine devices [IUDs]) initiated at least 14 days prior to the first dose of study drug b) True abstinence: when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception c) Placement of a copper-containing IUD d) Condom with spermicidal foam/gel/film/cream/suppository e) Postmenopausal at least 12 months (365 days) prior to the first dose of study drug or permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy) f) Male partner who has had a vasectomy for at least 3 months (90 days) prior to the first dose

of study drug or is surgically sterile

Acceptable contraceptive methods for male subjects with partners of childbearing potential (need at least one):

a) True abstinence: when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
b) Vasectomy for at least 3 months (90 days) prior to the first dose of study drug or surgically sterile
c) Without a vasectomy, must use a condom with spermicidal foam/gel/film/cream/suppository

5. Female subjects who are not of childbearing potential must meet at least one of the following criteria:
   a) Have undergone a documented hysterectomy and/or bilateral oophorectomy, and/or tubal ligation
   b) Have a medically confirmed ovarian failure, or;
   c) Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological causes
6. Diagnosis of primary-open angle glaucoma (including pigmentary or pseudoexfoliative) or ocular hypertension and requires treatment in both eyes.
7. Adequate wash-out period prior to baseline of any ocular hypotensive medication (see Table 1). In order to minimize potential risk to patients due to intraocular pressure (IOP) elevations during the washout period, the investigator may choose to substitute a parasympathomimetic or carbonic anhydrase inhibitor in place of a sympathomimetic, alpha-agonist, beta-adrenergic blocking agent, or prostaglandin; however, all patients must have discontinued all ocular hypotensive medication for the minimum washout period provided in Table 1.
8. Baseline (Day 1/hour 0) IOP $\geq$22 mmHg and $\leq$34 mmHg in both eyes and $\leq$5 mmHg IOP difference between eyes.
9. Screening and Baseline/Visit 1 BCVA equivalent to 20/200 or better in each eye.
10. Negative urine pregnancy test at screening and baseline for women of childbearing potential.

Key exclusion criteria:

1. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, subjects who are Sponsor employees directly involved in the conduct of the study, or household members of current subjects in the study.
2. Subjects participating in any clinical investigation within 30 days prior to Screening.
3. Any severe, acute, or chronic medical or psychiatric condition that may increase the risk associated with the study participation or investigational product administration or could interfere with the interpretation of study results and, in the judgment of the investigator, could make the patient inappropriate for entry in to this study.
4. Pregnant female subjects; breastfeeding female subjects; male subjects with partners currently pregnant; male subjects able to father children and female subject of childbearing potential who are unwilling or unable to use highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product.
5. Current or past history of severe hepatic or renal impairment.

6. Current or history within two months prior to baseline of significant ocular disease (eg, macular degeneration, hypertensive retinopathy, diabetic retinopathy, corneal edema, uveitis, ocular infection, or ocular trauma in either eye) that may increase the risk associated with the study participation or investigational product administration or could interfere with the interpretation of study results and, in the judgment of the investigator, could make the patient inappropriate for entry in to this study.
7. Current corneal abnormalities or any condition that would prevent accurate IOP readings with the Goldmann applanation tonometer.
8. Functionally significant visual field loss in either eye, measured within 6 months prior to screening.
9. At screening advanced glaucoma defined by horizontal and vertical cup/disc ratio >0.8 in either eye.
10. Contraindication of brinzolamide or sulfonamide therapy known hypersensitivity to any component of brinzolamide or sulfonamide therapy.
11. Use at any time prior to baseline of an intraocular corticosteroid implant.
12. Use within one week prior to baseline of contact lenses.
13. Use within two weeks prior to baseline of: 1) topical ophthalmic corticosteroid; 2) topical corticosteroid; 3) systemic corticosteroid, or 4) high dose salicylate therapy (defined as stable daily doses exceeding 325 mg aspirin or equivalent)
14. Use within six months prior to baseline intravitreal or subtenon injection of ophthalmic corticosteroid.
15. Intraocular or refractive surgery (eg, cataract surgery, LASIK, etc.) within six months prior to Screening.
16. IOP lowering surgery (eg, Trabeculectomy, Laser trabeculoplasty, tube shunts, etc.) within 12 months prior to baseline.
17. History of severe dry eye in either eye.
18. Persons with Central Corneal Thickness (CCT) >600um in either eye.
19. Anticipate the need to initiate or modify medication (systemic or topical) that is known to affect IOP or blood pressure (eg, β–adrenergic antagonists, α-adrenergic agonists, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers) during the study period.
20. Subjects with very narrow angles (3 quadrants with less than Grade 2 according to Shaffer's anterior chamber angle grading system) and subjects with angle closure, congenital, and secondary glaucoma, and subjects with history of angle closure in either eye.
21. Subjects with known or suspected drug or alcohol abuse.

Investigational product, dosage and mode of administration: Subjects who meet all include/exclusion criteria will be randomized to receive the generic brinzolamide 1% suspension or brinzolamide 1% suspension (AZOPT®) using computer generated, blocked treatment assignments in a 1:1 ratio stratified by investigational site.

Arm 1: One eye drop of the generic brinzolamide 1% suspension in each eye at approximately 8:00 AM, 4:00 PM and 10:00 PM Daily

Arm 2: One eye drop of brinzolamide 1% suspension (AZOPT®) in each eye at approximately 8:00 AM, 4:00 PM and 10:00 PM Daily

Note: the test article must be manufactured compliant to cGMP and meet the proposed ANDA specifications.
Duration of treatment: 42 days (6 weeks) after start of administration of study drug
Reference therapy, dosage and mode of administration: Brinzolamide (AZOPT®) 1% Ophthalmic Suspension
Criteria for evaluation: **Efficacy:** The primary endpoint is the mean difference in IOP of both eyes between the two treatment groups at four time points, eg, 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. **Safety:** The safety and tolerability of the generic brinzolamide 1% suspension and brinzolamide 1% suspension (AZOPT®) will be evaluated by monitoring of blood pressure and pulse, ophthalmic exams (BCVA, refraction, biomicroscopy, and ophthalmoscopy), and monitoring of treatment related adverse events.
Statistical methods: A comprehensive Statistical Analysis Plan (SAP) will be finalized and approved prior to the unmasking of the trial. The primary endpoint is the mean difference in IOP of both eyes between the two treatment groups at four time points, eg, 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. The endpoint will be analyzed using the per-protocol population, which will include all randomized subjects who meet all inclusion/exclusion criteria, instilled 75% to 125% of the planned doses for the entire duration of the study, as verified by patient diaries, and who did not miss the scheduled applications for more than 3 consecutive days, and completed evaluations at Day 14 and Day 42 within the designated visit window (± 4 days) with no protocol deviations that would affect the treatment evaluation. In order to establish equivalence of the two treatments: 1. The limits of each two-sided 95% CI of the treatment difference (test – reference) for mean IOP of both eyes (continuous variable) at all four follow-up points (eg, 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 must be within ± 1.5 mm Hg; and 2. For the majority of the time points [3 out of 4 follow-up time points; eg, 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) measured], the limits of each two-sided 95% CI of the differences in the mean IOP of both eyes between the two treatment groups is within ± 1.0 mmHg The point estimates of the difference between the two treatment groups and the two-sided 95% CIs will be presented. Since both of the above conditions have to be satisfied to establish equivalence, the type I error (α), will not be adjusted to account for multiple comparisons. The safety and tolerability of the generic brinzolamide 1% suspension and brinzolamide 1% suspension (AZOPT®) will be evaluated by monitoring of blood pressure and pulse, ophthalmic exams (BCVA, refraction, biomicroscopy, and ophthalmoscopy), and monitoring of adverse events.
Sample size calculations: A mean treatment difference of 0 mmHg, a standard deviation of 3.3 mmHg, and a correlation coefficient of 0.565 between any 2 different follow-up time points was assumed for the sample size calculation. To confirm the lower and the upper bounds of the two-sided 95% confidence interval (CI) of the treatment difference is within the range of ± 1.0 mmHg for at least 3 (out of 4) follow-up time points (at approximately 8:00 AM and 10:00 AM on days 14 and 42), and to confirm that the lower and the upper bounds of the two-sided 95% CI of the treatment difference at all 4 follow-up time points are within ±1.5 mmHg, a minimum number of 280 evaluable patients for each treatment group will be needed to achieve 90% power. To account for 10% attrition, a total of 624 subjects (312 subjects per group) will need to be randomized.

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4 List of Abbreviations and Definitions of Terms

Abbreviation or specialist term	Definition or Explanation
AE	Adverse event
ACE	Angiotensin-converting enzyme
BCVA	Best corrected visual acuity
BP	Blood Pressure
CA II	Carbonic anhydrase II
CAI	Carbonic anhydrous inhibitors
CCT	Central Corneal Thickness
CI	Confidence interval
CRF	Case report form
CSR	Clinical study report
DU	Dispensable unit
EC	Ethics committee
EDP	Exposure during pregnancy
ETDRS	Early treatment of diabetic retinopathy study
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
ID	Identification
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
ORS	Oracle Randomization and Supply Management System
IUD	Intrauterine device
IRB	Institutional Review Board
IWR	Interactive web response
LSLV	Last subject last visit
mmHG	Millimeters of mercury
OAG	Open angle glaucoma
POAG	Primary open angle glaucoma
SAE	Serious adverse event
SAP	Statistical analysis plan
SRSD	Single reference safety document
TEAE	Treatment emergent adverse event
US	United States
USPI	United States package insert

In this protocol, “sponsor duties” refer to responsibilities that will be performed by the Sponsor, the sponsor’s designee, or the sponsor’s designated contract research organization. In this protocol, “investigator” refers to the principal investigator or his/her designee, who is responsible for performing the study procedures and assessments.

5 Introduction

Mechanism of Action

Brinzolamide is a carbonic anhydrous inhibitor indicated for the reduction of intraocular pressure (IOP) in patients with primary open angle glaucoma (POAG) and ocular hypertension (OH).

Background and Rationale

Brinzolamide belongs to a class of heterocyclic sulfonamide carbonic anhydrous inhibitors (CAIs) that is topically active for reducing IOP. It has high affinity and inhibitory potency against human CA II, an isoenzyme of carbonic anhydrase found in the ciliary epithelia, which are involved with aqueous humor secretion. Branded brinzolamide is formulated as an ophthalmic 1% aqueous suspension with a physiologic pH (AZOPT®). AZOPT® is well tolerated and does not produce many of the side effects associated with the CAIs that are given systemically, making it an attractive treatment for patients with glaucoma, in whom compliance with therapy can be an issue. It reduces IOP from baseline in a statistically significant and clinically relevant manner in the majority of patients when used for primary or adjunctive therapy (Sall K. 2000) (Shin D. 2000).

Complete information for this compound may be found in the single reference safety document (SRSD), which for this study is the (AZOPT®) United States Package Insert (USPI, version date 07/2015).

Clinical Studies

The safety and efficacy of brinzolamide 1% ophthalmic suspension have been evaluated in several previous clinical studies (reference to Section 20).

In two, three-month clinical studies, brinzolamide 1% ophthalmic suspension in subjects with elevated IOP, produced significant reductions in IOP (4-5 mmHg) (Sall K. 2000) (Silver LH. 1998). These IOP reductions were statistically equivalent (confidence limit less than 1.5 mmHg) to the reductions observed with dorzolamide 2% hydrochloride ophthalmic solution (Sall K. 2000) (March WF, Ochsner KI 2000). The studies also demonstrated that

brinzolamide was associated with significantly less ocular discomfort (burning and stinging) than dorzolamide (Sall K. 2000) (Silver LH. 1998).

In a double masked, randomized, adjunctive study, 108 patients received brinzolamide 1% or placebo in addition to ocular timolol 0.5% for primary open-angle glaucoma (POAG) or ocular hypertension (OH). Adding topical ocular brinzolamide to timolol therapy further reduced IOP. Over the 3-month study, IOP changes ranged from -3.3 mmHg to -4.1 mmHg in the brinzolamide group compared to -0.9 mmHg to -2.5 mmHg in the placebo group ($p < 0.03$, brinzolamide vs. placebo) (Shin D. 2000).

In a long-term study, brinzolamide 1% ophthalmic suspension induced significant IOP reductions and caused less ocular discomfort than topical timolol 0.5%, in patients with open-angle glaucoma (OAG) or OH (March WF, Ochsner KI 2000). Patients treated with timolol attained a significantly greater mean reduction of 5.2 mmHg in IOP compared with patients receiving brinzolamide ($p < 0.0002$). There were no significant adverse events (March WF, Ochsner KI 2000).

In a 12 week InnoPharma/Pfizer (previous sponsor) bioequivalence study of the generic brinzolamide 1% suspension and brinzolamide 1% suspension (AZOPT®) in 256 patients with POAG or OH, the 95% confidence limits on the mean difference in IOP between treatment groups were within 1.5 mmHg at each time point with comparable safety and tolerance (InnoPharma Inc. 2012).

This repeat study will be prospective, randomized, double masked and will follow Food and Drug Administration (FDA) guidance for demonstrating bioequivalence of the generic brinzolamide 1% ophthalmic suspension (test article) compared to brinzolamide 1% ophthalmic suspension (AZOPT®; reference listed drug, reference article) to treat elevated IOP in patients with POAG or OH.

6 Study Objectives and Endpoints

6.1 Primary objective

- To establish that the generic brinzolamide 1% suspension is bioequivalent to brinzolamide 1% suspension (AZOPT®).

6.2 Secondary objectives

- To compare the safety and tolerability of the generic brinzolamide 1% suspension to brinzolamide 1% suspension (AZOPT®).

6.3 Primary Endpoint

- The mean difference in intraocular pressure (IOP) of both eyes between the two treatment groups at four time points, eg, 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.

6.4 Safety Endpoints

- The safety and tolerability of the generic brinzolamide 1% suspension and brinzolamide 1% suspension (AZOPT®) will be evaluated by monitoring of blood pressure and pulse, ophthalmic exams (BCVA, refraction, biomicroscopy, and ophthalmoscopy), and monitoring of treatment related adverse events.

7 Investigational plan

7.1 Overall Study Design and Plan: Description

Study S0883 is a 42 day, multi-center, randomized, double-masked, active-controlled, parallel bioequivalence study of both eyes in subjects with primary open angle glaucoma or ocular hypertension who, following a washout of 4 to 28 days (depending on pre-study treatment) have an IOP ≥22 mmHg and ≤34 mmHg, ≤5 mmHg IOP difference between eyes and best corrected visual acuity (BCVA) better than or equal to 20/200 in each eye.

The screening visit will be conducted 4 to 42 days before the baseline visit (Day 1). All subjects must be washed out of topical or systemic ocular hypotensive medications prior to the baseline visit.

Table 1 Minimum Washout Periods for Ocular Hypotensive Medications

Medication	Minimum Washout Periods
Parasympathomimetics [eg, pilocarpine (Isopto® Carpine), carbachol (Isopto® Carbachol)]	4 days
Carbonic anhydrase inhibitors (systemic or topical) [eg, acetazolamide (Diamox®), dorzolamide hydrochloride (Trusopt®), brinzolamide (AZOPT®)]	4 days
Sympathomimetics [eg, dipivefron (Propine®), epinephrine (Epifrin®)]	2 weeks
Alpha-agonists [eg, apraclonidine (Iopidine®) brimonidine tartarate (Alphagan®, Alphagan® P), brimonidine and brinzolamide (Simbrinza®)]	2 weeks
Beta-adrenergic blocking agents [eg, timolol (Timoptic®, Betimol®, Timoptic XE®, Isatol®), timolol maleate and dorzolamide hydrochloride (Cosopt®), timolol maleate and brimonidine tartrate (Combigan®), levobunolol (Akbeta®, Betagan®), betaxolol (Betoptioc®, Betoptic-S®), metipranolol (Opti-Pranolol®), careteolol (Ocupress®)]	4 weeks
Prostaglandin analogs [eg, latanoprost (Xalatan®), travoprost (Travatan®), bimatoprost (Lumigan®), tafluprost (Zioptan™)]	4 weeks

To account for 10% attrition, approximately 624 subjects will be randomized in order to ensure that 560 subjects complete the 42 days (6 weeks) of dosing. Subjects who meet all inclusion/exclusion criteria will be randomized to receive the generic brinzolamide 1% suspension or brinzolamide 1% suspension (AZOPT®) using computer generated, blocked treatment assignments in a 1:1 ratio stratified by investigational site. Investigational product will be administered at approximately 8:00 AM, 4:00 PM and 10:00 PM in both eyes for 42 days, with exception of Visit 1 (Day 1) dose administered at only 4:00PM and 10:00PM. IOP assessments will be performed at approximately 8:00 AM and 10:00 AM on days 1 (baseline), 14, 21, and 42. IOP will be performed a second time (at approximately 10:00AM) on Days 1 (baseline), 14, 21, and 42. For subjects who discontinue the study before the end

of the treatment period, an Early Termination visit will be conducted within approximately one week after last study dose.

Figure 1 Study Design

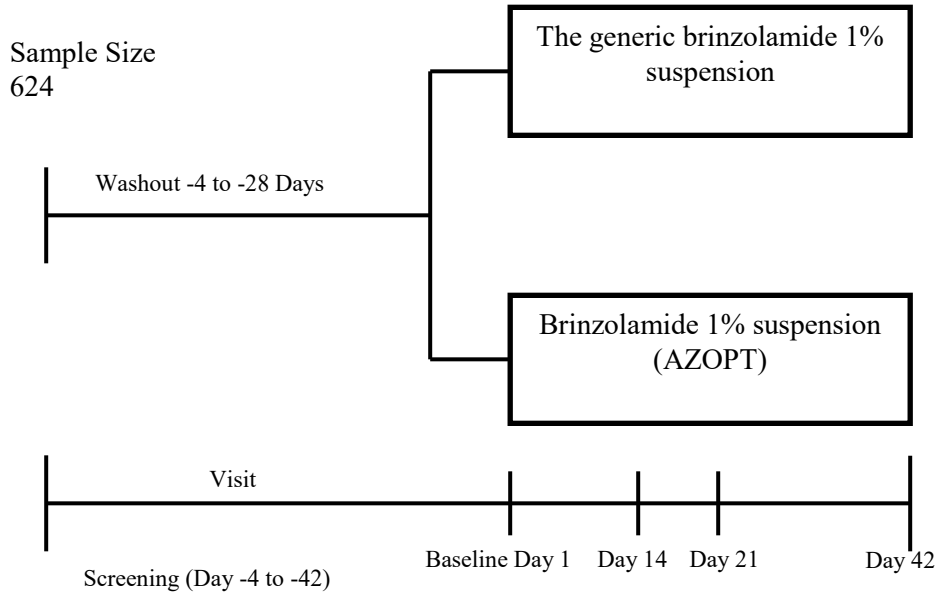

Table 2 Study Design and Schedule of Assessments

Visit identifier	Screening	Visit 1	Visit 2	Visit 3	Visit 4	Early Termination
Visit Window	Day -42 to -4	Day 1	Day 14 ±4 days	Day 21 ±4 days	Day 42 ±4 days	Approximately within 7 days after last dose
Informed Consent	X					
Obtain Subject ID	X					
Randomization		X				
Inclusion/Exclusion criteria	X	X				
Demographics	X					
Medical History	X					
Prior and Concomitant medications	X	X	X	X	X	X
AE Monitoring	X	X	X	X	X	X
Check dosing diary			X	X	X	X
Collect unused investigational product				X	X	X
Collect dosing diary				X	X	X
BP and Pulse (sitting)	X	X	X	X	X	X
Visual Field Testing	X[c]					
Refraction	X	X*	X*	X*	X*	X*
BCVA	X	X	X	X	X	X
Biomicroscopy	X	X	X	X	X	X
Intraocular Pressure	X	X[B]	X[B]	X[B]	X[B]	X
Gonioscopy	X[D]					
Pachymetry	X					
Ophthalmoscopy	X	X	X	X	X	X
Urine Pregnancy Test	X	X			X	X
Dispense Investigational Product		X		X		
Dispense Dosing Diary		X		X		
Self-Administer Investigational Drug [A]			X[A]	X[A]	X[A]	

[A]: indicates dosing will be self-administered at the site on visits 2, visit 3, and visit 4 after 8:00AM IOP measurement
[B]: IOP measurement will occur twice (within ± 30 minutes of) 8:00AM and 10:00AM) at visit 1, visit 2, visit 3, and visit 4
[c]: Visual Field testing to be conducted if no documentation within 6 months prior to screening
[D]: Gonioscopy testing to be conducted if no documentation within 6 months prior to screening
*: Refraction to be performed if there was a two line decrease in BCVA from the previous assessment
Table 2 above, should be followed in order as schedule of assessments

8 Subject Selection

The following eligibility criteria are designed to select subjects for whom participation in the study in considered appropriate. All relevant medical and nonmedical conditions should be

taken into consideration when deciding whether a particular subject is suitable for this protocol.

8.1 Subject Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment in to the study:

1. Subjects must be of legal age (at least 18 years) on the date the Informed Consent Form (ICF) is signed.
2. Subjects must be able to read, understand, and provide written informed consent on the Institutional Review Board (IRB)/Ethics Committee (EC)-approved ICF and provide authorization as appropriate for local privacy regulations.
3. Subjects who are willing and able to comply with scheduled visits, treatment plan, and other study procedures.
4. Male subjects able to father children and female subjects of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for at least 28 days after last dose of assigned treatment.

   Acceptable contraceptive methods for female subjects (need at least one):
   a) Hormonal methods of contraception (including oral and transdermal contraceptives, injectable progesterone, progestin subdermal implants, progesterone-releasing intrauterine devices [IUDs]) initiated at least 14 days prior to the first dose of study drug
   b) True abstinence: when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
   c) Placement of a copper-containing IUD
   d) Condom with spermicidal foam/gel/film/cream/suppository

e) Postmenopausal at least 12 months (365 days) prior to the first dose of study drug or permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy)
f) Male partner who has had a vasectomy for at least 3 months (90 days) prior to the first dose of study drug or is surgically sterile

Acceptable contraceptive methods for male subjects with partners of childbearing potential (need at least one):

a) True abstinence: when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
b) Vasectomy for at least 3 months (90 days) prior to the first dose of study drug or surgically sterile
c) Without a vasectomy, must use a condom with spermicidal foam/gel/film/cream/suppository

5. Female subjects who are not of childbearing potential must meet at least 1 of the following criteria:
    a. Have undergone a documented hysterectomy and/or bilateral oophorectomy, and/or tubal ligation;
    b. Have medically confirmed ovarian failure; or
    c. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause
6. Diagnosis of primary-open angle glaucoma (including pigmentary or pseudoexfoliative) or ocular hypertension and requires treatment in both eyes.
7. Adequate wash-out period prior to baseline of any ocular hypotensive medication (see Table 1). In order to minimize potential risk to patients due to intraocular pressure (IOP) elevations during the washout period, the investigator may choose to substitute a parasympathomimetic or carbonic anhydrase inhibitor in place of a

sympathomimetic, alpha-agonist, beta-adrenergic blocking agent, or prostaglandin; however, all patients must have discontinued all ocular hypotensive medication for the minimum washout period provided in Table 1.

8. Baseline (Day 1/hour 0) IOP ≥22 mmHg and ≤34 mmHg in both eyes and ≤5 mmHg IOP difference between eyes.
9. Screening and Baseline/Visit 1 BCVA equivalent to 20/200 or better in each eye.
10. Negative urine pregnancy test at screening and baseline for women of childbearing potential.

8.2 Subject Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, subjects who are Sponsor employees directly involved in the conduct of the study, or household members of current subjects in the study.
2. Subjects participating in any clinical investigation within 30 days prior to Screening.
3. Any severe, acute, or chronic medical or psychiatric condition that may increase the risk associated with the study participation or investigational product administration or could interfere with the interpretation of study results and, in the judgment of the investigator, could make the patient inappropriate for entry in to this study.
4. Pregnant female subjects; breastfeeding female subjects; male subjects with partners currently pregnant; male subjects able to father children and female subject of childbearing potential who are unwilling or unable to use highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product.
5. Current or past history of severe hepatic or renal impairment.

6. Current or history within two months prior to baseline of significant ocular disease (eg, macular degeneration, hypertensive retinopathy, diabetic retinopathy, corneal edema, uveitis, ocular infection, or ocular trauma in either eye) that may increase the risk associated with the study participation or investigational product administration or could interfere with the interpretation of study results and, in the judgment of the investigator, could make the patient inappropriate for entry in to this study.
7. Current corneal abnormalities or any condition that would prevent accurate IOP readings with the Goldmann applanation tonometer.
8. Functionally significant visual field loss in either eye, measured within 6 months prior to screening.
9. At the screening visit, advanced glaucoma defined by both a horizontal and vertical cup/disc ratio >0.8 in either eye.
10. Contraindiction to brinzolamide or sulfonamide therapy or known hypersensitivity to any component of brinzolamide or sulfonamide therapy.
11. Use at any time prior to baseline of an intraocular corticosteroid implant.
12. Use within one week prior to baseline of contact lenses.
13. Use within two weeks prior to baseline of: 1) topical ophthalmic corticosteroid; 2) topical corticosteroid; 3) systemic corticosteroid, or 4) high dose salicylate therapy (defined as stable daily doses exceeding 325 mg aspirin or equivalent)
14. Use within six months prior to baseline intravitreal or subtenon injection of ophthalmic corticosteroid.
15. Intraocular or refractive surgery (eg, cataract surgery, LASIK, etc.) within six months prior to Screening.
16. IOP lowering surgery (eg, Trabeculectomy, Laser trabeculoplasty, tube shunts, etc.) within 12 months prior to baseline.
17. History of severe dry eye in either eye.
18. Persons with Central Corneal Thickness (CCT) >600um in either eye.

19. Anticipate the need to initiate or modify medication (systemic or topical) that is known to affect IOP or blood pressure (eg, β−adrenergic antagonists, α-adrenergic agonists, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers) during the study period.
20. Subjects with very narrow angles (3 quadrants with less than Grade 2 according to Shaffer's anterior chamber angle grading system) and subjects with angle closure, congenital, and secondary glaucoma, and subjects with history of angle closure in either eye.
21. Subjects with known or suspected drug or alcohol abuse.

8.3 Subject Withdrawal Criteria

Withdrawal of consent: Subjects who wish to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when the subject specifically withdraws consent for any further contact with him or her or any persons previously authorized by the subject to provide information. Subjects are completely free to refuse to enter the study or to withdraw at any time, without giving a reason. The withdrawal of consent should be explained in detail in the medical records of the investigator, as to whether the withdrawal is only from further treatment of investigational product or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

For subjects that are lost to follow-up, all reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Prior to discontinuing a subject, every effort should be made to contact the subject, schedule a final study visit, obtain as much follow-up data as possible, and to retrieve all study materials. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible

local methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site.

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

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs. Where possible, the same assessments as Day 42 (Section (11.1.5), should be completed if the subject withdraws from the study early. If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

9 Treatment Plan

9.1 Study Treatments

For the purpose of this study, and per International Conference on harmonization (ICH) guidelines investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used to gain further information about an approved use (ICH E6 1.33).

9.1.1 Methods of Assigning Subjects to Treatment Groups

Subjects who meet all inclusive/exclusive criteria will be randomized to receive the generic brinzolamide 1% suspension or brinzolamide 1% suspension (AZOPT®) using computer generated, block treatment assignments in a 1:1 ratio stratified by investigational site.

Arm 1: One eye drop of the generic brinzolamide 1% ophthalmic suspension in each eye at approximately 8:00 AM, 4:00 PM and 10:00 PM Daily

Arm 2: One eye drop of brinzolamide 1% ophthalmic suspension (AZOPT®) in each eye at approximately 8:00 AM, 4:00 PM and 10:00 PM Daily

Allocation of subjects to treatment groups will proceed through the use of a randomization and supply management system (Oracle Randomization and Supply Management System [ORS]) (interactive Web-based response [IWR]). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, the subject number and the date of birth of the subject. The site personnel will then be provided with a treatment assignment and Kit Number or container number when drug is being supplied via the ORS system. The ORS system will provide a confirmation report containing the subject number or container number assigned. The confirmation report must be stored in the site files.

There is a 24-hour-a-day, 365-days-a-year ORS helpdesk available for any questions or issues. The study specified ORS reference manual will provide the contact information and further details on the use of the ORS system.

> Note: The ORS is the source of the subject number. The ORS system will provide the subject number at the end of the first ORS subject transaction.

9.1.2 Treatment Replacement

In the event that a subject's original container is lost, damaged, or consumed prior to the end of treatment, the Investigator will use the ORS, which will specify a new Kit Number to be dispensed to that subject from the supplies already available at the site.

9.2 Masking

The study subject, investigational staff, investigator, and sponsor personnel will be masked with respect to treatment group. The investigational site will employ procedures to avoid accidental unmasking of the masked staff. A sealed copy of the randomization scheme will be retained at the investigational site and will be available at the time of the site inspection to allow for verification of the treatment identity of each subject.

Masking codes should be broken only in emergency situations for reasons of subject safety. Whenever possible, the investigator or sub-investigator will consult with a member of the study team prior to breaking the mask. When the masking code is broken, the reason must be fully documented. At the initiation of the study, the study site will be instructed on the method for breaking the masking. The method will either be a manual or an electronic process.

9.3 Concomitant Medications

Subjects must abstain from the concomitant medications prohibited in the Exclusion Criteria (Section 8.2) of this protocol.

All medications taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant medications at each clinic visit.

Subjects who anticipate the need to initiate or modify medication (systemic or topical) that is known to affect IOP or blood pressure (BP) (eg, ß-adrenergic antagonists, α-adrenergic agonists, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers) during the study period should not be enrolled.

The following prescription and over-the-counter drug products, procedures, and activities are prohibited during the study:

- Ocular hypotensive drug product other than study treatment, eg, acetazolamide (Diamox®), betaxolol (Betoptic®, Betopic-S®), betaxolol and pilocarpine (Betoptic® Pilo), bimatoprost (Lumigan®), brimonidine tartrate (Alphagan®, Alphagan® P), brimonidine tartrate and brinzolamide (Simbrinza®), brimodidine 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®);
- Ophthalmic over-the-counter or prescription product, other than study treatment and the occasional use of artificial tears;
- Oral carbonic anhydrase inhibitor;
- High-dose salicylate therapy; defined as stable daily doses exceeding 325 mg aspirin or equivalent
- Topical Corticosteroid
- Systemic corticosteroid;
- Topical ophthalmic corticosteroid;
- Intraocular corticosteroid implant;
- Intravitreal or subtenon injection of ophthalmic corticosteroid;

- Marijuana (any form)
- Change in concurrent treatment or initiation of treatment with agents potentially affecting IOP, eg, antihypertensive medication;
- Ocular surgery during the study.

Administration of all medications used up to 30 days prior to study entry (date ICF signed) through study exit must be recorded in the source documentation and in the Concomitant Medications eCRF. Indications for these medications should be recorded in the subject's Medical History eCRF, as applicable.

9.4 Treatment Compliance

Subjects should be instructed that if they miss a dose, this should be recorded in their dosing diary and discussed with the investigational site personnel at the next contact or visit.

Subject's knowledge and understanding of the dosing diary completion must be verified before the subject leaves the investigator site at each visit.

Compliance of outpatient dosing will be assessed by site personnel at Day 14, Day 21, and Day 42 by review of the subject's dosing diary.

The dosing diary along with the investigational product, in its masked external packaging, will be collected from the subject at Visit 3 and also at the end of the subject's participation in the study.

9.5 Protocol Deviations

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. Deviations usually have an impact on individual patients or a small group of patients and do not involve inclusion/exclusion or primary endpoint criteria.

The investigator or designee must document and explain in the patients' source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study patients without prior IRB/IEC approval. As soon as possible after such an occurrence, the

implemented deviation or change, the reasons for it, and any proposed protocol amendment(s) should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

10 Study Drug Materials and Management

All study medication will be dispensed by the pharmacy or an appropriately qualified member of the study staff assigned by the investigator to this task.

10.1 Brinzolamide 1% Suspension

10.1.1 Packaging and Labeling

The generic brinzolamide 1% suspension and brinzolamide 1% suspension (AZOPT®) will be provided by the Sponsor as 10 mL topical ophthalmic solutions. Each mL of the generic brinzolamide 1% suspension and Brinzolamide 1% suspension (AZOPT®) contains 10 mg of brinzolamide (1% w/v) and one drop of each medication (approximately 0.03 ml) contains approximately 0.3 mg of brinzolamide. The generic brinzolamide 1% suspension and brinzolamide 1% suspension (AZOPT®) will be supplied in eyedropper bottles that are in masked external packaging. Investigational product will be dispensed on Day 1 and on Day 21. Investigational product will be labeled according to local regulatory requirements with appropriate dosing and storage information as well as a unique container number that will be used to assign the medication to the subject according to their treatment assignment. Investigational product will be supplied in sufficient quantities to allow unopened containers to be kept as bioequivalence retains. Bioequivalence retains should be stored in accordance with protocol-specified requirements for at least 5 years following the date on which the application or supplemental application is approved, or, if such application or supplemental application is not approved, at least 5 years following the date of completion of a bioavailability or bioequivalence study. The quantity and storage of bioequivalence retains will be outlined in separate instructions to the site.

10.1.1.1 Retention of Study Drug Samples

At the time of receipt of the investigational product by the investigator, the sponsor will specify the appropriate number of containers or units to select for retention by the investigator. The total amounts of reserve samples will, at a minimum, be equivalent to five times the quantity of investigational product (test product and reference product) required for release testing. The total amount of reserve samples will be divided among all study sites participating in this study. The number of retain samples per site is subject to change, if the total number of sites change.

The sponsor will also specify the conditions of sample storage, the required duration of sample retention and the provisions for returning the investigational product. When retention samples are selected, containers or units should be placed in packaging with a tamper evident seal. The packaging should be clearly identified as to its content (that it contains retention samples) and the investigational product should be stored in a restricted area with limited access.

10.1.2 Storage, Handling, and Disposal of Study Drug

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products, including any comparator and/or marketed products, are stored in a secured area with controlled access under required storage conditions in accordance with applicable regulatory requirements.

All investigational product must be stored at 4º to 30ºC (39-86 ºF) in accordance with the conditions specified on the study label. The storage location at the clinical site must have limited access, available to study site personnel only. Subjects must be instructed regarding proper storage. Investigational product should be stored in its original container and in accordance with the label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products) for business days only. This should be captured from the time of investigational product receipt

throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the investigational product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the investigational product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product.

Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the investigational product is briefly out of the temperature range described in the labeling are not considered excursions. More specific details will be provided to the sites separately in an investigational product manual or equivalent, including storage conditions and actions to be taken when conditions are outside the specified range.

Investigational site staff will instruct subjects on the proper storage requirements for take home investigational products.

Retention samples of investigational product will be stored in accordance with Sponsor procedures and FDA regulations.

10.1.3 Study Drug Preparation and Dispensing

Investigational product should not be used more than 28 days after opening. It will be dispensed using ORS on Day 1 and Day 21 to ensure the subject has a sufficient amount of investigational product for the duration of treatment. A qualified and experienced member of the investigational site staff will dispense the investigational product in masked external packaging provided throughout the course of dosing. Investigational site staff must not be in

the room whenever the treatment is taken out of the masked external packaging. The bottle that is dispensed on Day 1 will be returned to the site in the masked external packaging on Day 21(Visit 3), at which time a second bottle (again, in masked external packaging) will be dispensed to the subject; unused investigational product that was dispensed on Day 21 must be returned in the masked external packaging at the end of the Day 42 (Visit 4)(eg, after all assessments are performed). Note: The subject should also bring their bottle to Visit 2 for purposes of the in-office dose.

10.1.4 Administration

Administration instructions should be followed, which are on the investigational product label.

Each dose of investigational product (one eye drop) will contain 0.3 mg brinzolamide in either the generic brinzolamide 1% suspension or brinzolamide 1% suspension (AZOPT®).

One drop of investigational product should be instilled in each eye at approximately 8:00 AM, 4:00PM, and 10:00PM daily.On Day 1, the first day of dosing, only the 4pm and 10:00PM should be administered. On Day 42, the last day of dosing, only the 8:00AM dose is administered.

Subjects will self-administer investigational product daily on an outpatient basis; however, on Day 14, Day 21, and Day 42 the 8:00AM dose will be self-administered at the investigational site, following the 8:00AM IOP. The dose must be self-administered in a secluded room without any investigational site staff present within 30 minutes of 8:00 AM. Investigational site staff must not be in the room whenever the treatment is taken out of the masked external packaging or the subject is dosed with investigational product.

Subject knowledge and understanding of the dosing requirements must be verified before the subject leaves the investigator site at each visit.

10.2 Study Drug Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies, Unused investigational product that was dispensed on Day 1 must be returned in the masked external packaging to the

investigator at the Day 21 visit at which time another bottle (again, in masked external packaging) will be dispensed to the subject; unused investigational product that was dispensed on Day 21 must be returned in the masked external packaging at the end of the Day 42 visit (eg, after all assessments are performed and 8:00AM dose is instilled). The investigational site will employ procedures to avoid accidental unmasking of the masked staff. Investigational product accountability will be discussed in the study monitoring plan.

At various time points throughout the study and/or upon completion of the study, Valeant or representative of Valeant will review and verify the Investigator's accountability records. Following verification, and as directed by Valeant, all used and unused product must be returned to Valeant at the addresses below, or with Valeant's permission, disposed of at the site in an appropriate manner.

10.3 Destruction of Investigational Product Supplies

Following verification of investigational product accountability, and as directed by Sponsor, all used and unused product must be returned to [redacted], or with the Sponsor's permission, disposed of at the site in an appropriate manner.

11 Study Procedures and Evaluations

11.1 Schedule of Evaluations and Procedures

11.1.1 Screening Visit

Subjects will be screened from 4 to 42 days prior to administration of investigational product to confirm that they meet the subject selection criteria for the study. If the time between screening and dosing exceeds 6 weeks as a result of unexpected operational delays (eg, delayed drug shipment), then subjects do not require re-screening if at the baseline visit (Day 1) the patient meets the eligibility criteria.

The following procedures will be completed:

- Obtain informed consent;

- Obtain Subject Specific Identification
- Review inclusion/exclusion criteria;
- Collect demography;
- Complete medical history;
- Complete history of all prescription or nonprescription drugs, and dietary supplements taken within 30 days prior to signing the ICF;
- Blood pressure/pulse rate (sitting for 5 minutes);
- Visual field testing; if performed within 6 months (183 days) prior to screening and was documented in subject's records, no additional visual field testing is necessary
- Refraction
- Best corrected visual acuity;
- Collect Iris color: blue, brown, gray, green, hazel, or specify other;
- Biomicroscopy
- IOP
- Ophthalmoscopy
- Pachymetry
- Gonioscopy: (must use anesthesia): if performed within 6 months (183 days) prior to screening and was documented in subject's records, no additional screening gonioscopy examination is necessary
- Urine hCG for all females of childbearing potential;

If the subject meets the inclusion criteria:

- Discontinue topical and/or systemic ocular antihypertensives;

- Schedule the subject to return in 4 to 42 days (depending on washout time necessary for previous ocular hypotensive medication(s), Table 1, for the eligibility visit, Baseline (Day 1).
- Record any AEs that occur from the time the subject signs the ICF

To prepare for study participation, subjects will be instructed on use of Concomitant Medications (Section 9.3).

11.1.2 Visit 1 (Day 1)

Subjects must continue to satisfy all inclusion/exclusion criteria in order to be eligible for randomization.

The following procedures will be completed:

- Re-check inclusion/exclusion criteria (only those eligibility criteria that apply at Day 1);
- Review prior/concomitant treatments;
- Blood pressure/pulse rate (sitting);
- Best corrected visual acuity;

NOTE: Refraction must be performed if a decrease in VA of two or more lines from the previous assessment occurs.

- Biomicroscopy
- IOP at 8:00 AM ± 30 minutes and 10:00 AM ± 30 minutes;
- Ophthalmoscopy
- Assess and record adverse events (AEs);
- Urine hCG for all females of childbearing potential;
- Randomize the subject to a treatment group;

- To prepare for study participation, subjects will be instructed on the use of Concomitant Medications (Section 9.3);
- Dispense dosing diary and instruct subject on completion;
- Dispense investigational product in masked external packaging and instruct subject on self-administration, storage, and return.
- First dose will be self-administered at 4pm, then followed by 10pm dose.

11.1.3 Visit 2 (Day 14)

The following procedures will be completed on Day 14 ±4 days:

- Review concomitant treatments;
- Check dosing diary;
- Blood pressure/pulse rate (sitting for 5 minutes);
- Best corrected visual acuity;

NOTE: Refraction must be performed if a decrease in VA of two or more lines from the previous assessment occurs.

- Biomicroscopy;
- IOP at ±30 minutes of 8:00 AM (prior to 8:00 AM dose of investigational product) and 10:00 AM. The 8:00 AM dose must be self-administered within 30 minutes of 8:00 AM in a secluded room without any investigational site staff present. Investigational site staff must not be in the room whenever the treatment is taken out of the masked external packaging or the subject is dosed with investigational product. Subject knowledge and understanding of the dosing requirements must be verified before the subject leaves the investigator site at each visit
- Ophthalmoscopy
- Assess and record AEs.

11.1.4 Visit 3 (Day 21)

The following procedures will be completed on Day 21 ±4 days:

- Review concomitant treatments;
- Collect dosing diary, and dispense new dosing diary;
- Blood pressure/pulse rate (sitting for 5 minutes);
- Best corrected visual acuity;

NOTE: Refraction must be performed if a decrease in VA of two or more lines from the previous assessment occurs.

- Biomicroscopy;
- IOP at ±30 minutes 8:00 AM (prior to 8:00 AM dose of investigational product) and 10:00 AM. The 8:00 AM dose must be self-administered within 30 minutes of 8:00 AM in a secluded room without any investigational site staff present. Investigational site staff must not be in the room whenever the treatment is taken out of the masked external packaging or the subject is dosed with investigational product. Subject knowledge and understanding of the dosing requirements must be verified before the subject leaves the investigator site at each visit;
- Ophthalmoscopy
- Assess and record AEs;
- Collect the unused investigational product in the first bottle;
- Dispense investigational product in masked external packaging and instruct subject on the self-administration, storage, and return of product at visit 4.

11.1.5 Visit 4 (Day 42)

The subject has completed the study when Visit 4 (Day 42) has been completed and the subject has been exited. Subjects who require further follow-up for an AE will be followed according to Section 11.1.6.

The following procedures will be completed on Day 42 ±4 days:

- Review concomitant treatments;
- Check dosing diary;
- Collect dosing diary;
- Blood pressure/pulse rate (sitting for 5 minutes);
- Best corrected visual acuity;

NOTE: Refraction must be performed if a decrease in VA of two or more lines from the previous assessment occurs.

- Biomicroscopy;
- IOP at ±30 minutes 8:00 AM (prior to 8:00 AM dose of investigational product) and 10:00 AM. The 8:00 AM dose must be self-administered within 30 minutes of 8:00 AM in a secluded room without any investigational site staff present. Investigational site staff must not be in the room whenever the treatment is taken out of the masked external packaging or the subject is dosed with investigational product. Subject knowledge and understanding of the dosing requirements must be verified before the subject leaves the investigator site at each visit;
- Ophthalmoscopy
- Assess and record AEs;
- Urine hCG for all females of childbearing potential;
- Collect the unused investigational product in the second bottle;

11.1.6 Post Study Follow-up Visit

A post study follow-up telephone call (conducted by the study coordinator or other delegated site staff) will occur approximately 28 days ±4 days after the last dose of investigational product was taken. All outstanding unresolved adverse events and serious adverse events will be followed-up at this time. Concomitant treatments will also be recorded. The follow-up telephone call should be noted and documented in the subject's primary source records. If the subject had no new or ongoing adverse events, serious adverse events, or concomitant

treatments during this time, this should also be noted and added to the subject's primary source records. Any serious adverse event should be reported to Sponsor within 24 hours.

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform a test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

11.2 Blood Pressure and Pulse

Blood pressure measurements will be taken using a mercury sphygmomanometer, a recently calibrated aneroid manometer, or a validated electronic device. Both systolic and diastolic blood pressure should be recorded. The first appearance of sound (phase 1) should be used to define systolic blood pressure and the disappearance of sound (phase 5) should be used to define diastolic blood pressure. Preferably, the same device should be used throughout the study and the same individual should record blood pressure throughout the study. An appropriate cuff size with a bladder encircling at least 80 percent of the arm should be used to ensure accurate measurement. Blood pressure should be measured in the sitting position after the patient has remained seated for at least 5 minutes, using the same arm at each visit.

Pulse measurements will be recorded using a full 60-second count while the patient is in the seated position.

Any clinically significant change in blood pressure or pulse measurements, in the investigator's judgment, compared to the screening values should be reported as an adverse event.

11.3 Visual Fields

Perform visual fields assessments following the study site's standard practices. If a visual field assessment was performed within 6 months (183 days) prior to screening and is documented in subject's records, no additional screening visual field examination is necessary.

11.4 Best Corrected Visual Acuity

Preferably, the same visual acuity examiner should perform each best corrected visual acuity measurement for a given subject. Best corrected visual acuity (BCVA) will be assessed using an Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart (placed at 13 feet or 4 meters) or equivalent eye chart. BCVA should be performed prior to any exam requiring contact with the eye or drops to dilate or anesthetize the eye. If most of the letters are read on a line, then that line will be counted. For example, if the patient reads 20/25 +3, 20/20 will be recorded. Only the nearest Snellen line will be reported without plus and minus letters.

A decrease in BCVA of 3 lines or more from the screening visit will be reported as an adverse event. If visual acuity at screening is better than 20/20, any decrease in visual acuity will be calculated from 20/20.

The BCVA will be assessed at all visits as indicated in the Schedule of Activities.

11.5 Refraction

At the screening visit, the manifest refraction will be measured and recorded. The sphere will be noted, cylinder and axis of the refraction will be recorded. Plano will be recorded as 0.00 as it applies to the sphere and/or cylinder. Refraction must be performed at subsequent visits (1, 2, 3 and/or 4) only if a decrease in visual acuity (VA) of two or more lines from the previous assessment occurs. If refraction must be re-measured due to a decrease in BCVA from the previous assessment, the BCVA should also be repeated using the updated refraction values.

11.6 Iris Color

At screening, report iris color as blue, brown, gray, green, hazel, or other (with specification). All iris colors are desired to be enrolled, and the investigator's will not randomize, include or exclude subjects based on iris color.

11.7 Biomicroscopy

Biomicroscopic examination of the lids, conjunctiva, sclera, cornea, anterior chamber, iris and lens will be performed. Anterior chamber inflammation will be graded as follows:

Grade	0	1	2	3	4
Flare	Completely Absent	Barely Detectable	Moderate (iris and lens details clear)	Marked (iris and lens details hazy)	Intense (formed fibrin in aqueous)
Cells	No cells	1 to 5 cells	6 to 10 cells	11 to 20 cells	>20 cells

Examination of the anterior chamber for cells must be performed before either dilation or applanation tonometry. The light intensity of the slit lamp is to be turned to the maximum tolerated by the patient.

11.8 Intraocular Pressure

IOP will be measured by an MD or DO only, using a Goldmann applanation tonometer. Both eyes will be tested, with the right eye preceding the left eye. The operator will initially set the dial at 10 mmHg, then look through the slit lamp and adjust the dial to take the reading, and then record the results. The procedure will be repeated on the same eye twice consecutively. If the measurements are within 2 mmHg or less of each other, the mean of the 2 readings will be reported as the IOP at that time point. If the 2 readings are more than 2 mmHg apart from each other, a third (consecutive) reading will be taken and the median (middle) IOP will be reported as the IOP at that time point. Preferably, the same operator will measure IOP and the same tonometer will be used at each visit for a given patient.

11.9 Ophthalmoscopy

Ophthalmoscopy will be performed at the time points indicated in Table 2, to examine the vitreous body, retina, and optic nerve head. Ophthalmoscopic assessments will be recorded

as normal or abnormal. Any abnormalities and pathologic findings will be graded as mild, moderate, or severe. The cup /disc ratio will be recorded horizontally and vertically for each examination, and reported in 0.1 increments.

Vitreous, Retina, Macula, Choroid: Assess for abnormalities in the retina, macula and choroid.

0 = Normal

1 = Abnormal

Optic Nerve: Assess for abnormalities in the optic nerve.

0 = Normal

1 = Abnormal

Cup/Disc Ratio: Assess the cup/disc vertical and horizontal ratio.

Optic Disc Hemorrhage:

0 = Absent

1 = Present

Rim Loss:

0 = Absent

1 = Present

Retinal Nerve Fiber Layer (RNFL) Defect:

0 = Absent

1 = Present

11.10 Gonioscopy

Gonioscopy should be performed after application of a topical anesthetic with a low level of illumination throughout that is consistent with standard clinical practice. If performed within 6 months (183 days) prior to screening and was documented in subject's records, no additional screening gonioscopy examination is necessary. Any observation of peripheral anterior synechiae should be noted. All four quadrants of the angle (superior, inferior, nasal, and temporal) should be evaluated using Shaffer's anterior chamber angle grading system:

Grade 4 (35°-45°): Ciliary body can be visualized.

Grade 3 (20°-35°): At least scleral spur can be identified.

Grade 2 (20°): Moderately narrow angle in which only the trabeculum can be identified.
Grade 1 (10°): Very narrow angle in which only the Schwalbe's line, and perhaps also the top of the trabeculum, can be identified.
Grade 0 (0°): Closed angle resulting from iridocorneal contact.

11.11 Pachymetry

Measurements of central corneal thickness will be performed for each participating subject, by using a calibrated ultrasonic pachymeter. It should be done after VA, refraction, and slit-lamp examination. Three measurements should be taken per eye with the subject in the sitting position and fixating on a target straight ahead. The probe should be removed from the cornea between measurements. All measurements from the right eye should be completed before taking any measurements from the left eye. The mean of the 3 recorded central corneal thickness measurements should be used to assess subject eligibility, as the mean will most likely reflect perpendicular placement of the pachymeter probe.

12 Methods and timing for assessing, recording, and analyzing safety parameters.

12.1 Adverse Event Reporting

12.1.1 Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to Sponsor or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Sponsor concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

12.1.2 Reporting Period

For SAEs, the active reporting period to Sponsor or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subjects participation in the study, eg, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 30 calendar days after the last administration of the investigational product. SAEs occurring to a subject after the active reporting period has ended should be reported to the Designee/Sponsor if the investigator becomes aware of them; but will not be entered on a case report form; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the Designee/Sponsor.

12.1.3 Definition of an Adverse Event

Adverse Event is defined as any untoward medical occurrence in a subject participating in a clinical study which does not necessarily have a causal relationship with the study protocol or with the study treatment.

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease with onset following the signing of informed consent through study exit, whether or not considered related to the study.
- An AE can also include a progression/worsening of underlying disease and hypersensitivity.
- Events occurring from drug overdose, whether accidental or intentional, events occurring from drug abuse, drug misuse, drug interactions, drug dependency, events occurring from drug withdrawal, and medication errors.

A Treatment Emergent Adverse Event (TEAE) will be defined as an AE with a start date on or after the first dose of study drug, or that worsened following first administration of study drug.

12.2 Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject, or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

A serious injury that can cause a serious deterioration in state of health can include:

- a life-threatening illness, even if temporary in nature;
- a permanent impairment of a body function or permanent damage to a body structure;
- a condition necessitating medical or surgical intervention to prevent the above 2 bulleted items

  - Examples: clinically relevant increase in the duration of a surgical procedure; a condition that requires hospitalization or significant prolongation of existing hospitalization;
- any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic device test results when used within the manufacturer's instructions for use;
- fetal distress, fetal death, or any congenital abnormality or birth defects.

All SAEs, whether related or unrelated to study drug, must be immediately reported to the designee within 24 hours of the investigator's awareness of the event. All SAEs must be reported via confirmed email/facsimile transmission and must be submitted on a written SAE report form signed by the investigator within 24 hours of the investigator's awareness of the event.

- The fax number for reporting an SAE is:

Investigators should not wait to receive additional information to fully document the event before notifying Medical Monitor of an SAE. If only limited information is initially available, follow-up reports are required. Additional relevant information such as hospital records and autopsy reports should be provided to designee as soon as they are available. Should the investigator become aware of an SAE (regardless of its relationship to investigational product) that occurs within 30 days after stopping the study drug, the SAE must be reported in accordance with procedures specified in this protocol.
The investigator should take all appropriate measures to ensure the safety of the subjects, notably he/she should follow a subject with an SAE until the event has resolved or the condition has stabilized. This may imply that follow-up will continue after the subject has left the study, and that additional investigations may be requested by the sponsor.

The Designee will review forms and documents for completeness and forward to Sponsor within 24hrs of receipt via email: [redacted]

12.2.1 Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see the section on Serious Adverse Event Reporting Requirements).

12.2.2 Hospitalization

Hospitalization is a criterion for assessment of seriousness. If a subject is retained in the emergency room greater than 24 hours, but not admitted for medical care, these cases should not be considered as “hospital admissions,” but evaluated individually, as criteria such as “medically significant” may also apply.

Hospitalization without a medical AE should not be considered either serious, or an AE. Examples include:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with worsening of the pre-existing condition (eg, for work-up of persistent pre-treatment lab abnormality)
- Hospitalization for a purpose unrelated to the study (eg, "planned" or elective surgery scheduled prior to study participation) would not ordinarily need to be reported, unless a complication occurred that otherwise caused prolongation of this hospitalization
- Protocol-specified admission or procedure (eg, cataract surgery required by a study protocol)
- Social admission (eg, social hospitalization for purposes of respite care)

12.2.3 Severity Assessment

If required on the AE CRFs, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

12.3 Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious) Related or Not Related to the study drug; the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. The following should be taken into account when assessing SAE causality:

- Positive temporal relationship to study drug, such as if the study drug was withdrawn and the SAE resolved or the event recurred after re introduction.
- If there is a reasonable possibility that the AE is associated with an underlying or concomitant illness.
- Possible association with previous or concomitant therapy.
- No temporal relationship to the study drug and/or a more likely alternative etiology exists.
- If the AE is directly related to study procedures or there is a lack of efficacy.

If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see the section on Reporting Requirements).

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

12.4 Exposure during Pregnancy

In the event that a study subject or a study subject's partner becomes pregnant, the study site should notify the study Medical Monitor and the Global Safety and Vigilance contact within 24 hours of the time the event was reported to the Investigator, regardless of whether an AE/SAE was reported. The study site should also notify the Valeant Study Manager listed in the Personnel and Facilities section and the IRB of pregnancy, in accordance with IRB requirements. All pregnancies will be followed to term (in the event that a study subject's partner becomes pregnant, permission to follow the pregnancy needs to be granted by the partner). Every effort will be made to obtain the health status of the mother and infant or the fetus (including cases of miscarriage or therapeutic abortion).

12.5 Withdrawal Due to Adverse Events

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

12.6 Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

12.6.1 Serious Adverse Event Reporting Requirements

Any SAE must be reported to Valeant Global Safety and Vigilance, independent of the circumstance or suspected cause, within 24 hours from the time the event was reported to the Investigator. All SAEs experienced from the date of consent through approximately 30 days after the last dose of study drug or discontinuation from the study must be reported to Valeant regardless of the relationship to the study drug. Following the approximately 30-day period after the last dose of study drug or discontinuation from the study, or for any timeframe afterward deemed medically significant, only SAEs considered related to study drug should be reported promptly to Valeant Global Safety and Vigilance.
Within 24 hours of notification the Investigator will fax a completed Serious Adverse Event Report to the Valeant contact noted below. For SAEs with fatal outcomes, a summary of available autopsy findings should be submitted as soon as possible.

12.6.2 Non-serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

12.6.3 Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions will be carried out in accordance with applicable local regulations.

13 Statistics

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the

sponsor. The SAP may modify the plans outlined in the protocol; however, any major modifications of planned analyses will be reflected in a protocol amendment if it is modified before data unmasking.

13.1 Sample Size Determination

The sample size was determined to assess the bioequivalence of the generic brinzolamide 1% suspension compared to brinzolamide 1% suspension (AZOPT®) in patients with primary open angle glaucoma or ocular hypertension. Based on the IOP lowering effect of the generic brinzolamide 1% suspension and brinzolamide 1% suspension (AZOPT®) observed in the previous study performed by InnoPharma,[6] a mean treatment difference of 0 mmHg, a standard deviation of 3.3 mmHg and a correlation coefficient of 0.565 between any 2 different follow-up time points was assumed for the sample size calculation. To confirm the lower and the upper bounds of the two-sided 95% confidence interval (CI) of the treatment difference are within the range of ±1.0 mmHg for at least 3 (out of 4) follow-up time points (at approximately 8:00 AM and 10:00 AM on days 14 and 42), and to confirm that the lower and the upper bounds of the two-sided 95% CI of the treatment difference at all 4 follow-up time points are within ±1.5 mmHg, a minimum number of 280 evaluable subjects for each treatment group will be needed to achieve 90% power. To account for 10% attrition, a total of 624 subjects (312 per group) will need to be randomized.

13.2 Efficacy Analysis

13.2.1 Analysis of the Primary Endpoint

The primary endpoint is the mean difference in IOP of both eyes between the two treatment groups at four time points, eg, 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. The endpoint will be analyzed using the per-protocol population, which will include all randomized subjects who meet all inclusion/exclusion criteria, instilled 75% to 125% of the planned doses for the entire duration of the study, as verified by patient diaries, and who did not miss the scheduled applications for more than 3 consecutive days, and completed evaluations at Day 14 and Day

42 within the designated visit window (± 4 days) with no protocol deviations that would affect the treatment evaluation.

In addition to the deviations described in the previous paragraph, the following protocol deviations will be considered important and will result in exclusion from the per-protocol population.

- Use of the wrong treatment (eg, misrandomization)
- Use of prohibited prescription and over-the-counter drug products, procedures, and activities as outlined in Section 9.3
- Raised IOP requiring treatment, defined as subjects whose condition worsens (eg, IOP ≥36 mmHg in either eye) and who require alternate or supplemental therapy for the treatment of their primary open angle glaucoma or ocular hypertension during the study
- Additional criteria may be added prior to unmasking of the treatment assignments

In order to establish equivalence of the two treatments:

1. The limits of each two-sided 95% CI of the treatment difference (test – reference) for mean IOP of both eyes (continuous variable) at all four follow-up points [(eg, 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] must be within ± 1.5 mm Hg; and

2. For the majority of the time points [3 out of 4 follow-up time points; eg, 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)] measured, the limits of each two-sided 95% CI of the difference in the mean IOP of both eyes between the two treatment groups must be within ± 1.0 mmHg

The point estimates of the differences between the two treatment groups and the two-sided 95% CIs will be presented. Since both of the above conditions have to be satisfied to

establish equivalence, the type I error (α), will not be adjusted to account for multiple comparisons.

13.3 Safety Analysis

The safety and tolerability of the generic brinzolamide 1% suspension and brinzolamide 1% suspension (AZOPT®) will be evaluated by monitoring of blood pressure and pulse, ophthalmic exams (BCVA, refraction, biomicroscopy, and ophthalmoscopy), and monitoring of adverse events.

The "Safety Analysis Set" will include all subjects who receive at least 1 dose of study medication. Safety data will be summarized and presented in tabular and/or graphical format.

In addition to standard safety displays, a 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. Subjects in the Safety Analysis Set will have their safety data included in the tiered analysis below. There are no Tier-1 events for this study; only Tier-2 and Tier-3 events will be reported.

- Tier-2 events: These are events that are not tier-1 but are "common". A MedDRA Preferred Term (PT) is defined as a tier-2 event if there at least ≥ 5% of patients in any treatment group reporting an event.

- Tier-3 events: These are events that are neither tier-1 nor tier-2 events.

Tier-2 events will be reported using risk difference and 95% CI; tier-3 events will be reported using frequency tables.

For all other safety endpoints, continuous variables will be summarized using means, standard deviations, median, minimum, and maximum. Categorical variables will be summarized using frequencies and percentages.

13.4 Data Monitoring Committee

This study will not use a data monitoring committee.

14 Quality Control and Quality Assurance

Sponsor or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Sponsor monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Sponsor, or companies working with or on behalf of Sponsor, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Sponsor or its agents to prepare the study site for the inspection and will allow Sponsor or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide Sponsor or its agents with an opportunity to review and comment on responses to any such findings.

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

14.1 Study Monitoring

An Investigator Meeting or an initiation visit will be conducted with the principal investigator and study coordinators by sponsor and/or its designee. During this meeting, an extensive review and discussion of the protocol, the role of the study technician, all study procedures, source documents, and eCRFs will be conducted.

The study monitors/clinical research associates will be trained prior to study initiation. Following this training, an overview of the study disease and study material background will be understood. Specific monitoring guidelines and procedures to be followed during monitoring visits will also be utilized. During the course of the study, all data will be 100% source document verified by the monitors. All subject source records must be made available to the monitors.

The conduct of the study will be closely monitored by the sponsor following GCP guidelines. The reports of these verifications will also be archived with the study report. In addition, inspections or on site audits may be carried out by local authorities or by the sponsor's Quality Assurance Department. The investigators will allow the sponsor's representatives and any regulatory agency to examine all study records, corresponding subject medical records, clinical dispensing records and storage area, and any other documents considered source documentation. The investigators agree to assist the representative, if required.

14.2 Audits and Inspections

Audits of clinical research activities in accordance with the Valeant’s internal Standard Operating Procedures (SOPs) to evaluate compliance with the principles of GCP may take place. A regulatory authority may also wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority and/or IRB/EC, the Investigator must inform the Sponsor immediately that this request has been made.

14.3 Data Quality Assurance

All assessments performed will be accurately documented in the subject’s source documents and eCRFs. The investigator or designee will enter the information required by the protocol

into the source documents and eCRFs provided by the sponsor or designee. Subjects will be identified in the eCRFs by their assigned subject number and initials only.

The investigators must read the protocol thoroughly and must follow the instructions exactly. Any deviations should be agreed to by prior discussion between the sponsor and the investigator, with appropriate written protocol amendments made prior to implementing the agreed changes. Any amendment containing major modifications (particularly if it may involve an increased risk to the subjects) will be approved by the IRB before it may be implemented. No change in the conduct of the study can be instituted without written approval from the sponsor.

15 Data Handling and Record Keeping

15.1 Inspection of Records

Investigators must maintain detailed records on all study subjects who are enrolled in the study or undergo screening. Data will be recorded in the subject's source documents and in applicable study logs provided by the sponsor. Source documents include subject medical records, hospital charts, clinic charts, investigator subject study files, as well as the results of diagnostic tests (eg, laboratory tests). All required data should be recorded in the study documentation completely for prompt data review. Upon study completion or at any other time specified by the sponsor or designee, the appropriate study documents must be submitted.

The investigator must keep accurate separate records (source documentation) of all subject visits, being sure to include all pertinent study related information. At a minimum, this includes the following information:

- A statement indicating that the subject has been enrolled in the study and the subject number
- Date that informed consent was obtained
- Evidence that the subject meets study eligibility requirements (eg, medical history, screening evaluations)

- Dates of all study related visits and results of any evaluations/procedures performed, including who performed each assessment at each visit
- Use of any concurrent medications during the study
- Documentation of study drug accountability
- Any and all side effects and AEs must be thoroughly documented to conclusion
- Results of any diagnostic tests conducted during the study
- The date the subject exited the study and a statement indicating that the subject completed the study or was discontinued early, including the reason for discontinuation

Notes describing telephone conversations and all electronic mail with the subject or the sponsor (sponsor's designee) concerning the study must be recorded or kept on file. All source documents must be made available to the sponsor and the sponsor's designated monitor upon request.

15.2 Record Retention

Subject data recorded on eCRFs during the study will be documented in a coded fashion. The subject will only be identified by the subject initials, subject number, and year of birth. Confidentiality of subject records must be maintained to ensure adherence to applicable local privacy regulations.

The Investigator must retain essential documents indefinitely after the completion of the study, unless otherwise notified by Valeant. The Investigator agrees to adhere to the document retention procedures when signing the protocol Investigator Statement of Approval.

Essential documents include but are not limited to the following:

- IRB/EC approvals for the study protocol, all amendments, ICF(s), and advertisements
- IRB/EC annual study review, if applicable
- IRB/EC correspondence and reports (eg, SAE reports, protocol deviations, and safety updates)

- Regulatory documents (eg, financial disclosure and delegation of authority forms)
- All source documents
- Archive of eCRFs
- Subject's signed ICF
- FDA Form 1572 (or equivalent forms)
- Accountability records for the study drugs
- Correspondence from and to Valeant
- Any other documents relevant to the conduct of the study

In the event that the Investigator withdraws from the study (eg, retirement, relocation), study records will be transferred to a mutually agreed upon designee (eg, another Investigator, site IRB/EC). The Investigator will provide notice of such transfer in writing to Valeant Global Clinical Operations.

16 Ethics

16.1 Institution Review Board/Ethics Committee

In the US, the Investigator, or in the EU, Valeant or legal representative, should ensure that participation in the study, in addition to the protocol, subject recruitment materials (written information or materials including web pages, radio advertisements, television spots or written text developed to encourage subject enrollment) and the ICF to be used in this study are approved by their institution IRB/EC, or if not using their institution's IRB/EC, approved by the reviewing central IRB/EC prior to entering any subjects in the study. Documentation of IRB/EC approval of the study protocol and informed consent must be provided to Valeant prior to initiation of the study. In addition, in the US, the Investigator, or in the EU, Valeant or legal representative, must ensure that the reviewing IRB/EC has provided approval for any protocol amendments prior to implementation. If the amendment necessitates a revision to the ICF, the Investigator should ensure the revised form is also submitted to and approved by Valeant and the IRB/EC prior to implementation.

16.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki, ICH guidelines, GCP, and in compliance with local regulatory requirements. The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP. In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

16.3 Written Informed Consent

Written informed consent, in accordance with local clinical investigation regulations, must be obtained prior to participation in the study. The investigator or designee will discuss the purpose of the study with each subject, and provide a description of the study drug (including any potential and possible side effects) and the study procedures. Information must be given both in oral and written form. Subject information will be provided in a language understandable to the subject and may not include any language that appears to waive any of the subject‘s legal rights or appears to release the investigator, the sponsor or the institution from liability or negligence.

The investigator will provide the prospective subject sufficient time to consider whether or not to participate, minimizing the possibility of coercion or undue influence and will discuss any questions the subject may have. The investigator will explain to the subject that participation in the study is voluntary and that withdrawal from the study is possible at any time without detriment to care. The consent must include acknowledgment that medical records and medical data derived from the study may be forwarded to the sponsor or to responsible local or federal authorities.

No subject can enter the study or have any study related procedures performed before his/her written informed consent has been obtained. The original signed and dated informed consent form will be retained with the study records, and a copy of the signed form will be given to the subject.

An informed consent template will be supplied by the sponsor. Any changes to the informed consent form must be agreed to by the sponsor or designee prior to submission to the IRB/IEC, and a copy of the approved version must be provided to the sponsor or designee after IRB/IEC approval.

16.4 Subject Data Protection

Subject data will be protected by ensuring that no captured data contain subject names, addresses, telephone numbers, email addresses, or other direct personally identifying information. It is acknowledged that subject initials, demographics (including birthdates), medical histories, and prior concomitant medication uses, along with the name and address of the enrolling investigator may allow for personal identification of study participants. Other than where necessary to meet regulatory requirements, all data collected in this study will be presented in tabulated (eg, aggregate) form and listings containing information that could be used to identify an individual subject will not be included in any public disclosures of the study data or the study results.

16.5 Reporting of Safety Issues and Serious Breaches of the Protocol ICH GCP

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Sponsor should be informed immediately.

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

16.6 Confidentiality/Publication of the Study

All study data generated as a result of this study will be regarded as confidential, until appropriate analysis and review by Valeant or its designee and the Investigator(s) are completed. The results of the study may be published or presented by the Investigator(s) after

the review by, and in consultation and agreement with the Valeant, and such that confidential or proprietary information is not disclosed.

Prior to publication or presentation, a copy of the final text should be forwarded by the Investigator(s) to the Valeant or its designee, for comment. Such comments shall aim to ensure the scientific integrity of the proposed publications and/or presentations and ensure that the data and material referring to Valeant Incorporated products and activities receive fair, accurate, and reasonable presentation. Financial disclosures will be obtained from all investigators in order to document any potential conflicts of interest.

16.7 Investigator Obligations

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice (GCP).

16.8 Changes to the Protocol

The investigators must read the protocol thoroughly and must follow the instructions exactly. Whenever possible, any planned deviations should be agreed to by prior discussion between the sponsor and the investigator, with appropriate documentation of sponsor approval prior to effecting the changes agreed upon. Any amendment to the protocol containing major modifications (particularly if it may involve an increased risk to the subjects) will be approved by the IRB before it may be implemented. No change in the conduct of the study can be instituted without written approval from the sponsor.

17 Definition of End of Trial

17.1 End of Trial in All Participating Countries

This study will only be performed in the USA. The end of the trial is defined as last subject last visit (LSLV).

18 Sponsor Discontinuation Criteria

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Sponsor. In addition, Sponsor retains the right to discontinue development of brinzolamide 1% suspension at any time.

If a study is prematurely terminated or discontinued, Sponsor will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 48 hours. As directed by Sponsor, all study materials must be collected and all CRFs completed to the greatest extent possible.

19 References

AZOPT®. United States Product Insert (USPI). NDA 20-816/S-009

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[redacted]

20 Appendices

21.1 Appendix A. Current Full Prescribing Information of AZOPT®

*On following page

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AZOPT† safely and effectively. See full prescribing information for AZOPT.

AZOPT (brinzolamide ophthalmic suspension) 1%
Sterile topical ophthalmic drops
Initial U.S. Approval: 1998

----------INDICATIONS AND USAGE----------

AZOPT is a carbonic anhydrase inhibitor indicated for in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma (1).

----------DOSAGE AND ADMINISTRATION----------

- Instill one drop in the affected eye(s) three times daily (2).
- If more than one topical ophthalmic drug is being used, the drugs should be administered at least (10) minutes apart (2).

----------DOSAGE FORMS AND STRENGTHS----------

Solution containing 10 mg/mL brinzolamide (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to any component of this product. (4)

----------WARNINGS AND PRECAUTIONS----------

- Sulfonamide hypersensitivity reactions (5.1).
- Corneal edema may occur in patients with low endothelial cell counts (5.2).

----------ADVERSE REACTIONS----------

Most common adverse reactions are blurred vision and bitter, sour or unusual taste (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Alcon Laboratories, Inc. at 1-800-757-9195 or www.alconlabs.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- There is a potential additive effect of the known systemic effects of carbonic anhydrase inhibition in patients receiving both oral and topical carbonic anhydrase inhibitors (7.1).
- Rare instance of acid-base alterations have occurred with high-dose salicylate therapy (7.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 7/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

AZOPT† (brinzolamide ophthalmic suspension) 1% is a carbonic anhydrase inhibitor indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

2 DOSAGE AND ADMINISTRATION

The recommended dose is one drop of AZOPT (brinzolamide ophthalmic suspension) 1% in the affected eye(s) three times daily. AZOPT (brinzolamide ophthalmic suspension) 1% may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is used, the drugs should be administered at least ten (10) minutes apart.

3 DOSAGE FORMS AND STRENGTHS

Solution containing 10 mg/mL brinzolamide.

4 CONTRAINDICATIONS

AZOPT (brinzolamide ophthalmic suspension) 1% is contraindicated in patients who are hypersensitive to any component of this product.

5 WARNINGS AND PRECAUTIONS

5.1 Sulfonamide Hypersensitivity Reactions

AZOPT (brinzolamide ophthalmic suspension) 1% is a sulfonamide and although administered topically it is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration of AZOPT (brinzolamide ophthalmic suspension) 1%. Fatalities have occurred, although rarely, due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitization may recur when a sulfonamide is re-administered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

5.2 Corneal Endothelium

Carbonic anhydrase activity has been observed in both the cytoplasm and around the plasma membranes of the corneal endothelium. There is an increased potential for developing corneal edema in patients with low endothelial cell counts. Caution should be used when prescribing AZOPT (brinzolamide ophthalmic suspension) 1% to this group of patients.

5.3 Severe Renal Impairment

AZOPT (brinzolamide ophthalmic suspension) 1% has not been studied in patients with severe renal impairment (CrCl < 30 mL/min). Because AZOPT (brinzolamide ophthalmic suspension) 1% and its metabolite are excreted predominantly by the kidney, AZOPT (brinzolamide ophthalmic suspension) 1% is not recommended in such patients.

5.4 Acute Angle-Closure Glaucoma

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. AZOPT (brinzolamide ophthalmic suspension) 1% has not been studied in patients with acute angle-closure glaucoma.

5.5 Contact Lens Wear

The preservative in AZOPT (brinzolamide ophthalmic suspension) 1%, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of AZOPT (brinzolamide ophthalmic suspension) 1%, but may be reinserted 15 minutes after instillation.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

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

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.

7 DRUG INTERACTIONS

7.1 Oral Carbonic Anhydrase Inhibitors

There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and AZOPT (brinzolamide ophthalmic suspension) 1%. The concomitant administration of AZOPT (brinzolamide ophthalmic suspension) 1% and oral carbonic anhydrase inhibitors is not recommended.

7.2 High-Dose Salicylate Therapy

Carbonic anhydrase inhibitors may produce acid-base and electrolyte alterations. These alterations were not reported in the clinical trials with brinzolamide. However, in patients treated with oral carbonic anhydrase inhibitors, rare instances of acid-base alterations have occurred with high-dose salicylate therapy. Therefore, the potential for such drug interactions should be considered in patients receiving AZOPT (brinzolamide ophthalmic suspension) 1%.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Developmental toxicity studies with brinzolamide in rabbits at oral doses of 1, 3, and 6 mg/kg/day (20, 62, and 125 times the recommended human ophthalmic dose) produced maternal toxicity at 6 mg/kg/day and a significant increase in the number of fetal variations, such as accessory skull bones, which was only slightly higher than the historic value at 1 and 6 mg/kg. In rats, statistically decreased body weights of fetuses from dams receiving oral doses of 18 mg/kg/day (375 times the recommended human ophthalmic dose) during gestation were proportional to the reduced maternal weight gain, with no statistically significant effects on organ or tissue development. Increases in unossified sternebrae, reduced ossification of the skull, and unossified hyoid that occurred at 6 and 18 mg/kg were not statistically

significant. No treatment-related malformations were seen. Following oral administration of 14C-brinzolamide to pregnant rats, radioactivity was found to cross the placenta and was present in the fetal tissues and blood.

There are no adequate and well-controlled studies in pregnant women. AZOPT (brinzolamide ophthalmic suspension) 1% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

In a study of brinzolamide in lactating rats, decreases in body weight gain in offspring at an oral dose of 15 mg/kg/day (312 times the recommended human ophthalmic dose) were seen during lactation. No other effects were observed. However, following oral administration of 14C-brinzolamide to lactating rats, radioactivity was found in milk at concentrations below those in the blood and plasma.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from AZOPT (brinzolamide ophthalmic suspension) 1%, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

A three-month controlled clinical study was conducted in which AZOPT (brinzolamide ophthalmic suspension) 1% was dosed only twice a day in pediatric patients 4 weeks to 5 years of age. Patients were not required to discontinue their IOP-lowering medication(s) until initiation of monotherapy with AZOPT. IOP-lowering efficacy was not demonstrated in this study in which the mean decrease in elevated IOP was between 0 and 2 mmHg. Five out of 32 patients demonstrated an increase in corneal diameter of one millimeter.

8.5 Geriatric Use

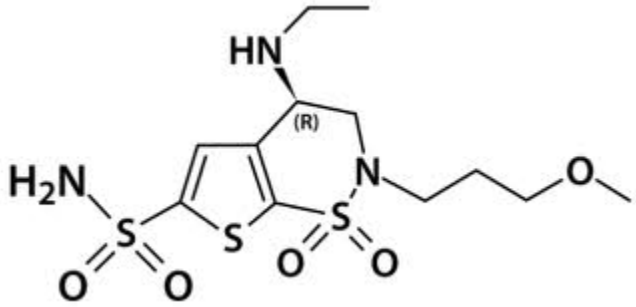
No overall differences in safety or effectiveness have been observed between elderly and younger patients.

10 OVERDOSAGE

Although no human data are available, electrolyte imbalance, development of an acidotic state, and possible nervous system effects may occur following oral administration of an overdose. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

11 DESCRIPTION

AZOPT (brinzolamide ophthalmic suspension) 1% contains a carbonic anhydrase inhibitor formulated for multidose topical ophthalmic use. Brinzolamide is described chemically as: (R)-(+)-4-Ethylamino-2-(3-methoxypropyl)-3,4-dihydro-2H-thieno [3,2-e]-1,2-thiazine-6-sulfonamide-1,1- dioxide. Its empirical formula is $C_{12}H_{21}N_3O_5S_3$, and its structural formula is:



Brinzolamide has a molecular weight of 383.5 and a melting point of about 131°C. It is a white powder, which is insoluble in water, very soluble in methanol and soluble in ethanol.

AZOPT (brinzolamide ophthalmic suspension) 1% is supplied as a sterile, aqueous suspension of brinzolamide 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 AZOPT (brinzolamide ophthalmic suspension) 1% contains: **Active ingredient:** brinzolamide 10 mg. **Preservative:** Benzalkonium chloride 0.1 mg. **Inactives:** mannitol, carbomer 974P, tyloxapol, edetate disodium, sodium chloride, purified water, with hydrochloric acid and/or sodium hydroxide to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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 carbonic anhydrase 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 intraocular pressure (IOP).

AZOPT (brinzolamide ophthalmic suspension) 1% contains brinzolamide, an inhibitor of carbonic anhydrase II (CA-II). Following topical ocular administration, brinzolamide inhibits aqueous humor formation and reduces elevated intraocular pressure. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss.

12.3 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 (<10 ng/mL). Binding to plasma proteins is approximately 60%. Brinzolamide is eliminated predominantly in the urine as unchanged drug. N-Desethyl brinzolamide is also found in the urine along with lower concentrations of the N-desmethoxypropyl and O-desmethyl metabolites.

An oral pharmacokinetic study was conducted in which healthy volunteers received 1 mg capsules 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. RBC 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Brinzolamide caused urinary bladder tumors in female mice at oral doses of 10 mg/kg/day and in male rats at oral doses of 8 mg/kg/day in 2 year studies. Brinzolamide was not carcinogenic in male mice or female rats dosed orally for up to 2 years. The carcinogenicity appears secondary to kidney and urinary bladder toxicity. These levels of exposure cannot be achieved with topical ophthalmic dosing in humans. The following tests for mutagenic potential were negative: (1) *in vivo* mouse micronucleus assay; (2) *in vivo* sister chromatid exchange assay; and (3) Ames *E. coli* test. The *in vitro* mouse lymphoma forward mutation assay was negative in the absence of activation, but positive in the presence of microsomal activation. In reproduction studies of brinzolamide in rats, there were no adverse effects on the fertility or reproductive capacity of males or females at doses up to 18 mg/kg/day (375 times the recommended human ophthalmic dose).

14 CLINICAL STUDIES

In two, three-month clinical studies, AZOPT® (brinzolamide ophthalmic suspension) 1% dosed three times per day in patients with elevated intraocular pressure (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 three times per day in the same studies.

In two clinical studies in patients with elevated intraocular pressure, AZOPT (brinzolamide ophthalmic suspension) 1% was associated with less stinging and burning upon instillation than TRUSOPT* 2%.

16 HOW SUPPLIED/STORAGE AND HANDLING

AZOPT (brinzolamide ophthalmic suspension) 1% is supplied in plastic DROP-TAINER† dispensers with a controlled dispensing-tip as follows:

10 mL NDC 0065-0275-10

15 mL NDC 0065-0275-15

Storage and Handling

Store AZOPT (brinzolamide ophthalmic suspension) 1% at 4-30°C (39-86°F). Shake well before use.

17 PATIENT COUNSELING INFORMATION

17.1 Sulfonamide Reactions

Advise patients that if serious or unusual ocular or systemic reactions or signs of hypersensitivity occur, they should discontinue the use of the product and consult their physician.

17.2 Temporary Blurred Vision

Vision may be temporarily blurred following dosing with AZOPT (brinzolamide ophthalmic suspension) 1%. Advise patients to exercise care in operating machinery or driving a motor vehicle.

17.3 Avoiding Contamination of the Product

Instruct patients to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures or other surfaces, since the product can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

17.4 Intercurrent Ocular Conditions

Advise patients that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

17.5 Concomitant Topical Ocular Therapy

If more than one topical ophthalmic drug is being used, the drugs should be administered at least ten minutes apart.

17.6 Contact Lens Wear

The preservative in AZOPT (brinzolamide ophthalmic suspension) 1%, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of AZOPT (brinzolamide ophthalmic suspension) 1%, but may be reinserted 15 minutes after instillation.

U.S. Patent Nos: 6,071,904.

*TRUSOPT is a registered trademark of Merck & Co., Inc.

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