Glaucoma/Brimonidine Clinical Trial

Draft Protocol for Discussion with Investigators/KOLs

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Draft Clinical Study Protocol

A Multicenter, Randomized, Double-Masked, Parallel, Two-Arm Study to Determine the Therapeutic Equivalence by Assessing Intraocular Pressure Outcomes of Generic Brimonidine Tartrate 0.1% Manufactured by Sponsor Compared With Alphagan® P (Brimonidine Tartrate Ophthalmic Solution) 0.1% in Patients With Chronic Open-Angle Glaucoma or Ocular Hypertension

Study Phase:	Bioequivalence study
Investigational Product:	Brimonidine tartrate 0.1%
Indication:	Elevated intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension
Investigator Agreement:	I have read the clinical study described herein, recognize its confidentiality, and agree to conduct the described trial in compliance with Good Clinical Practices, the ethical principles contained within the Declaration of Helsinki, this protocol, and all applicable regulatory requirements.
Investigator Signature:	_____ Signature Date
Investigator Name, Affiliation, and Address:	Investigator name Practice name Address City

PROTOCOL APPROVAL AND SIGNATURE PAGE

Title of Protocol: A Multicenter, Randomized, Double-Masked, Parallel, Two-Arm Study to Determine the Therapeutic Equivalence by Assessing Intraocular Pressure Outcomes of Generic Brimonidine Tartrate 0.1% Manufactured by Sponsor Compared With Alphagan® P (Brimonidine Tartrate Ophthalmic Solution) 0.1% in Patients With Chronic Open-Angle Glaucoma or Ocular Hypertension

Investigator's Agreement

I have carefully read and understand the foregoing protocol and agree that it contains all the necessary information for conducting this study safely. I will conduct this study in strict accordance with this protocol, International Conference on Harmonisation guidelines for Good Clinical Practice, the Code of Federal Regulations, the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and local regulatory guidelines. I will attempt to complete the study within the time designated. I will ensure that the rights, safety, and welfare of patients under my care are protected. I will ensure control of the investigational product under investigation in this study. I will provide copies of the protocol and all other study-related information supplied by Sponsor to all personnel responsible to me who participate in the study. I will discuss this information with them to ensure that they are adequately informed regarding the investigational product and conduct of the study. I agree to keep records on all patient information (case report forms, shipment and drug return forms, and all other information collected during the study) and drug disposition in accordance with Food and Drug Administration regulations. I will not enroll any patients into this protocol until institutional review board/independent ethics committee approval and Sponsor's approval are obtained.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

EMERGENCY CONTACT INFORMATION

Project Manager		
Medical Monitor		
Serious Adverse Event Reporting		

1. SYNOPSIS

Name of investigational product Brimonidine tartrate 0.1% manufactured by Sponsor
Title of study A Multicenter, Randomized, Double-Masked, Parallel, Two-Arm Study to Determine the Therapeutic Equivalence by Assessing Intraocular Pressure Outcomes of Generic Brimonidine Tartrate 0.1% Manufactured by Sponsor Compared With Alphagan® P (Brimonidine Tartrate Ophthalmic Solution) 0.1% in Patients With Chronic Open-Angle Glaucoma or Ocular Hypertension
Study center(s) Up to 13 study centers
Study duration Estimated date first patient enrolled: Estimated date last patient completed:
Phase of development Bioequivalence study
Target number of patients To be decided based on statistical plan
Objectives The primary objective is to demonstrate the bioequivalence of brimonidine tartrate 0.1% from Sponsor to marketed Alphagan P 0.1% for the reduction of intraocular pressure (IOP) due to chronic open-angle glaucoma or ocular hypertension.
Study treatments (dosage, mode of administration) Investigational product: Brimonidine tartrate ophthalmic solution 0.1% administered topically 1 drop 3 times daily in both eyes, at approximately 8:00 am (±30 min), 4:00 pm (±30 min), and 10:00 pm (±30 min), for 6 weeks Reference therapy: Alphagan® P (brimonidine tartrate ophthalmic solution) 0.1% administered topically 1 drop 3 times daily in both eyes, at approximately 8:00 am (±30 min), 4:00 pm (±30 min), and 10:00 pm (±30 min), for 6 weeks
Study design and methods

This is a randomized, double-masked, parallel, two-arm, multicenter study of the efficacy and safety of brimonidine tartrate 0.1% versus Alphagan P 0.1% in patients 18 years of age or older with chronic open-angle glaucoma or ocular hypertension. Patients will be randomly assigned 1:1 to either brimonidine tartrate or Alphagan P 0.1% dosed topically 1 drop 3 times daily, at approximately 8:00 am (±30 min), 4:00 pm (±30 min), and 10:00 pm (±30 min), in both eyes for 6 weeks.

Patients will be followed for assessment of IOP reduction and safety. IOP will be measured at 8:00 am (prior to study drug instillation) and at 10:00 am at Baseline, Week 2, and Week 6. Analysis of IOP effect (primary endpoint) will be based on the mean change in IOP of the 2 eyes from Baseline to Week 2 (8:00 am and 10:00 am time points) and from Baseline to Week 6 (8:00 am and 10:00 am time points). Safety will be monitored with adverse events (AEs), Snellen best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, automated perimetry, fundoscopy, and resting blood pressure and pulse rate.

Inclusion criteria

1. Eighteen years of age or older, of either gender and any race/ethnicity, diagnosed with bilateral chronic open-angle glaucoma or ocular hypertension
2. Requires treatment of both eyes
3. Able to discontinue use of all ocular hypotensive medication(s) or switch ocular hypotensive medications and undergo appropriate washout period:
   a. Four days for parasympathomimetics (eg, pilocarpine, carbachol) and systemic or topical carbonic anhydrase inhibitors (eg, acetazolamide, dorzolamide, brinzolamide)
   b. Two weeks for sympathomimetics (eg, dipivefrin, epinephrine) and alpha-agonists (eg, apraclonidine, brimonidine tartrate, brimonidine tartrate + brinzolamide)
   c. Four weeks for beta-adrenergic blocking agents (eg, timolol, timolol maleate + dorzolamide, timolol maleate + brimonidine tartrate, levobunolol, betaxolol, metipranolol, carteolol) and prostaglandin analogs (eg, latanoprost, travoprost, bimatoprost, tafluprost)

   In order to minimize potential risk to patients due to IOP elevations during the washout period, investigator may choose to substitute a parasympathomimetic or carbonic anhydrase inhibitor in place of a sympathomimetic, alpha-agonist, beta-adrenergic blocking agent, or prostaglandin analog; however, all patients must have discontinued all ocular hypotensive medications for the minimum washout period
4. Baseline IOP ≥22 mmHg and ≤34 mmHg in each eye and any asymmetry of IOP between the eyes ≤5 mmHg, both at the 8:00 am time point
5. Baseline BCVA equivalent to 20/200 or better in each eye
6. Able and willing to read, comprehend, and give both informed consent and authorization for use or disclosure of protected health information (according to Health Insurance Portability and Accountability Act of 1996 [HIPAA])
7. Able and willing to fully comply with all visits and study procedures scheduled by the study site, as evidenced by written informed consent

8. Women of child-bearing potential (those not surgically sterilized or not postmenopausal for at least 2 years) must have a negative pregnancy test at screening and must agree to practice an adequate method of birth control, including intrauterine device; oral, transdermal ("patch"), implant, or injected contraceptives; or barrier methods with spermicide

Exclusion criteria

1. Any form of glaucoma (such as secondary, congenital, angle-closure, or normal-tension glaucoma) in either eye other than chronic open-angle glaucoma or ocular hypertension
2. Shaffer angle grade <2 in either eye, as measured by gonioscopy (extreme narrow angle with complete or partial closure)
3. Cup/disc ratio >0.8 (horizontal or vertical measurement) in either eye
4. Functionally significant visual field loss in either eye, or evidence of deterioration within the last 12 months
5. Current corneal abnormalities in either eye that would prevent accurate IOP readings with a Goldmann applanation tonometer
6. History of (within 2 months prior to baseline) or current significant ocular disease (eg, corneal edema, uveitis, ocular infection, or ocular trauma) in either eye
7. Any history of allergic/toxic local reaction with use of brimonidine
8. Any other significant ophthalmic condition, such as proliferative diabetic retinopathy, retinal detachment, or age-related macular degeneration in either eye
9. Any other intraocular surgery (eg, cataract surgery) within 6 months prior to baseline
10. Refractive surgery within 12 months prior to baseline, or filtering surgery or laser surgery for IOP reduction within 6 months prior to baseline
11. Use of topical ophthalmic corticosteroid or topical corticosteroid within 4 weeks prior to baseline
12. Use of any of the following within 1 month prior to baseline, or expected use during the study duration:
    a. Systemic corticosteroid
    b. Monoamine oxidase inhibitor therapy
    c. Any antidepressant that affects noradrenergic transmission (eg, tricylic antidepressants, mianserin)
    d. Adrenergic-augmenting psychotropic drug (eg, desipramine, amitriptyline)
13. Use of intravitreal or subtenon injection of ophthalmic corticosteroid within 6 months prior to baseline
14. Use of intraocular corticosteroid implant at any time prior to baseline
15. Use of any additional topical or systemic ocular hypotensive medication (over-the counter drops, ointment, or gel) in either eye during the study period other than the study ocular hypotensive medication

16. Pregnancy, lactation, or planning a pregnancy during the course of the study (for women of childbearing potential)
17. Less than 30 days' stable dosing regimen before the Screening visit of any medications or substances administered by any route and used on a chronic basis that may affect IOP
18. Current or recent (within 30 days prior to baseline) participation in a drug, device, or other investigational research study
19. Any other conditions, including severe illness, which would make the patient, in the opinion of the investigator, unsuitable for the study

Criteria for evaluation

Efficacy: The primary efficacy endpoint is the mean difference in IOP of the 2 eyes between the 2 treatment groups at 4 time points (ie, at approximately 8:00 am [before the morning dose] and 10:00 am) at the Week 2 and Week 6 visits.

Safety: Safety endpoints are AEs, BCVA results, slit-lamp biomicroscopy findings, automated perimetry results, fundoscopy results, and resting blood pressure and pulse rate.

Statistical methods

Sample size: Assuming a standard deviation of IOP of 3.0 mmHg and an equivalence limit of 1.5 mmHg, 86 patients per group are required in the per-protocol (PP) population to have at least 90% power to establish equivalence. Assuming a dropout rate of 25%, 216 patients (108 patients/group) are targeted to meet the primary objective of the study.

Interim analysis: An administrative blinded interim analysis is planned when approximately 50% of patients have been randomized, received treatment, and been observed to Week 6. This blinded interim analysis will only present the pooled standard deviation for the primary efficacy endpoint. This information will then be used to revisit the original sample size assumptions and recalculate the sample size itself, if necessary. No other statistical inferences will be made.

Efficacy: The PP population will be used to establish equivalence in the efficacy endpoints, and the intent-to-treat population will be used as the secondary population. The adjusted estimate of difference between groups at each post-Baseline visit will be obtained from a restricted maximum likelihood repeated measures mixed model on change from Baseline values with Baseline as a covariate, treatment group as a fixed factor and observations from both eyes and visit and its interaction treatment group, as repeated measures using an unstructured covariance structure. The adjusted estimate of difference between groups and 95% confidence limits will be tabulated for the 8:00 am and 10:00 am results on Week 2 and Week 6.

To establish non-inferiority, the limits of each two-sided 95% confidence interval of the treatment difference for mean IOP of both eyes at all four follow-up points must be within ± 1.5 mm Hg using the PP population for all time points measured and within ± 1.0 mm Hg using the PP population for the majority of time points measured.

Inasmuch as the criterion for success requires meeting the endpoint at multiple time points and in the 2 eyes, no adjustment for multiple testing is required. All other efficacy variables will be analyzed using appropriate statistical techniques.

Safety: The safety population will be used to examine the safety of the study drugs. The occurrence of AEs at each visit will be summarized by frequency, severity (mild, moderate, severe), and relationship (unlikely, possible, probable). All other safety measures will be summarized by treatment group and visit.

2. TABLE OF CONTENTS AND LISTS OF TABLES AND FIGURES

LIST OF TABLES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations are used in this study protocol.

Table 1: List of Abbreviations

Abbreviation	Explanation
AE	adverse event
BCVA	best-corrected visual acuity
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH E6(R1)	International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice E6(R1)
IOP	intraocular pressure
IRB	institutional review board
ITT	intent-to-treat
IWRS	Interactive Web Response System
PP	per protocol
SAE	serious adverse event
SAP	statistical analysis plan
US	United States
US CFR Title 21	Title 21 of the United States Code of Federal Regulations

4. INTRODUCTION

Primary open-angle glaucoma is a chronic, progressive optic neuropathy in adults in which there is a characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons.[1] It is frequently associated with elevated intraocular pressure (IOP) that, when not properly treated, can produce retinal ganglion cell death and optic nerve damage, both of which can lead to an irreversible loss of vision.[1] Glaucoma is the second leading cause of blindness worldwide,[2] and more than 120,000 Americans are blind due to glaucoma.[3] Although glaucoma is currently incurable, evidence from multiple studies shows not only that topical ocular hypotensive medications can control IOP,[4] but also that IOP control can effectively delay or prevent disease progression and vision loss.[5,6]

Brimonidine is an alpha-adrenergic receptor agonist (alpha-agonist), one of the classes of typical ocular hypotensive medications shown to control IOP in patients with open-angle glaucoma or ocular hypertension.[7] The original formulation and concentration for topical brimonidine was 0.2% and was preserved with benzalkonium chloride, which has been shown to be associated with corneal surface damage.[8] The more recent formulations of 0.15% and 0.1% were developed to improve the drug's tolerability while maintaining its IOP-lowering efficacy. These reformulations are preserved with Purite®, a stabilized oxychloro complex and oxidative preservative that is nontoxic to mammalian cells. In its pivotal study, brimonidine tartrate 0.1% (Alphagan® P 0.1%) demonstrated similar efficacy to brimonidine 0.2% (Alphagan®) with a better safety profile.[7]

Sponsor has manufactured a generic version of Alphagan® P 0.1%. This bioequivalence study will compare the efficacy and safety of generic brimonidine tartrate ophthalmic solution 0.1% with Alphagan P 0.1%. Similar to the pivotal brimonidine 0.1% vs 0.2% study, the current study will use a randomized, double-masked, parallel, two-arm, *in vivo*, multicenter design to examine the efficacy and safety of brimonidine tartrate 0.1% versus Alphagan P 0.1% in patients ≥18 years of age with open-angle glaucoma or ocular hypertension. Patients will be randomly assigned 1:1 to either brimonidine tartrate or Alphagan P 0.1% dosed topically 1 drop 3 times daily in both eyes for 6 weeks.

5. TRIAL OBJECTIVES AND PURPOSE

The primary objective of this trial is to demonstrate the bioequivalence of brimonidine tartrate 0.1% from Sponsor to marketed Alphagan P 0.1% for the reduction of IOP due to chronic open-angle glaucoma or ocular hypertension.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This randomized, double-masked, parallel, two-arm, in vivo, multicenter trial will study the efficacy and safety of brimonidine tartrate 0.1% versus Alphagan P 0.1% in the treatment of patients 18 years of age or older with chronic open-angle glaucoma or ocular hypertension. Patients will be randomly assigned 1:1 to either brimonidine tartrate or Alphagan P 0.1% dosed topically 1 drop 3 times daily, at approximately 8:00 am (±30 min), 4:00 pm (±30 min), and 10:00 pm (±30 min), in both eyes for 6 weeks. The primary efficacy endpoint is the mean change in IOP of the 2 eyes from Baseline to Week 2 (8:00 am and 10:00 am time points) and from Baseline to Week 6 (8:00 am and 10:00 am time points).

6.2. Number of Patients

To be decided based on statistical plan.

6.3. Treatments Administered

Investigational product: Brimonidine tartrate ophthalmic solution 0.1% (manufactured by Sponsor administered topically 1 drop 3 times daily, at approximately 8:00 am (±30 min), 4:00 pm (±30 min), and 10:00 pm (±30 min), in both eyes for 6 weeks

Reference therapy: Alphagan® P (brimonidine tartrate ophthalmic solution) 0.1% (manufactured by Allergan, Inc.; Irvine, CA) administered topically 1 drop 3 times daily, at approximately 8:00 am (±30 min), 4:00 pm (±30 min), and 10:00 pm (±30 min), in both eyes for 6 weeks

Patients who wear contact lenses should remove lenses before dosing and reinsert lenses no sooner than 15 minutes post-instillation.

All study drugs will be supplied in identical opaque bottles with masked labels indicating that the product is for investigational use only and will be identified both by kit and protocol number. Each bottle will be filled to a volume of 10 mL with either investigational product or reference therapy. Bottles must be stored at room temperature (15°-25°C or 59°-77°F).

6.4. Criteria for Study Termination

Although the Sponsor intends to complete the study, the Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons, or if required by regulatory agencies. If the Sponsor discontinues the study, all study treatment will be discontinued and the investigator will be responsible to prescribe any additional therapy to be administered.

6.5. Schedule of Assessments

Lists the overall schedule of assessments for the study.

Table 2: Schedule of Assessments

Activity	Screening	Therapy period			Unscheduled visit	Early termination visit
		Baseline (Day 0)	Week 2 (Day 14±4)	Week 6 (Day 42±4)		
Informed consent[a]	X					
Demographics	X					
Medical history	X					
Inclusion/Exclusion criteria	X					
Pulse/Blood pressure[b]	X	X	X	X	X	X
Urine pregnancy test[c]	X			X	X	X
Randomization		X				
Best-corrected visual acuity	X	X	X	X	X	X
Slit-lamp biomicroscopy	X	X	X	X	X	X
Dilated fundus exam	X			X	X	X
Automated perimetry	X			X	X	X
Intraocular pressure (Goldmann)	X	X[d,e]	X[e]	X[e]	X[e]	X[e]
Gonioscopy	X					
Dispense study drug		X[f]				
Dispense diary		X				
Instill study drug in office		X	X	X	X	X
Review diary for compliance			X	X	X	X
Collect study drug				X		X
Concomitant meds	X	X	X	X	X	X
Adverse events		X	X	X	X	X

[a]Must be signed and dated before any study procedures are performed.
[b]Patients should be sitting for 5 minutes prior to assessment of pulse and blood pressure.
[c]Required for all female patients of childbearing potential.
[d]If subject IOP does not meet eligibility criteria at 8:00 am, the 10:00 am IOP assessment will not be performed.
[e]To be performed at 8:00 am and 10:00 am.
[f]Patients who wear contact lenses will be instructed to remove lenses before dosing and reinsert lenses no sooner than 15 min post-instillation. These patients should be reminded to wear or bring their glasses on study visit days.

7. ELECTION AND WITHDRAWAL OF PATIENTS

7.1. Patient Inclusion Criteria

1. Eighteen years of age or older, of either gender and any race/ethnicity, diagnosed with bilateral chronic open-angle glaucoma or ocular hypertension
2. Requires treatment of both eyes
3. Able to discontinue use of all ocular hypotensive medication(s) or switch ocular hypotensive medications and undergo appropriate washout period:
4. Four days for parasympathomimetics (eg, pilocarpine, carbachol) and systemic or topical carbonic anhydrase inhibitors (eg, acetazolamide, dorzolamide, brinzolamide)
5. Two weeks for sympathomimetics (eg, dipivefrin, epinephrine) and alpha-agonists (eg, apraclonidine, brimonidine tartrate, brimonidine tartrate + brinzolamide)
6. Four weeks for beta-adrenergic blocking agents (eg, timolol, timolol maleate + dorzolamide, timolol maleate + brimonidine tartrate, levobunolol, betaxolol, metipranolol, carteolol) and prostaglandin analogs (eg, latanoprost, travoprost, bimatoprost, tafluprost)
7. In order to minimize potential risk to patients due to IOP elevations during the washout period, investigator may choose to substitute a parasympathomimetic or carbonic anhydrase inhibitor in place of a sympathomimetic, alpha-agonist, beta-adrenergic blocking agent, or prostaglandin analog; however, all patients must have discontinued all ocular hypotensive medications for the minimum washout period
8. Baseline IOP ≥22 mmHg and ≤34 mmHg in each eye and any asymmetry of IOP between the eyes ≤5 mmHg, both at the 8:00 am time point
9. Baseline best-corrected visual acuity (BCVA) equivalent to 20/200 or better in each eye
10. Able and willing to read, comprehend, and give both informed consent and authorization for use or disclosure of protected health information (according to Health Insurance Portability and Accountability Act of 1996 [HIPAA])
11. Able and willing to fully comply with all visits and study procedures scheduled by the study site, as evidenced by written informed consent

Women of child-bearing potential (those not surgically sterilized or not postmenopausal for at least 2 years) must have a negative pregnancy test at screening and must agree to practice an adequate method of birth control,

12. including intrauterine device; oral, transdermal ("patch"), implant, or injected contraceptives; tubal ligation; or barrier methods with spermicide

7.2. Patient Exclusion Criteria

1. Any form of glaucoma (such as secondary, congenital, angle-closure, or normal-tension glaucoma) in either eye other than chronic open-angle glaucoma or ocular hypertension
2. Shaffer angle grade <2 in either eye, as measured by gonioscopy (extreme narrow angle with complete or partial closure)
3. Cup/disc ratio >0.8 (horizontal or vertical measurement) in either eye
4. Functionally significant visual field loss in either eye, or evidence of deterioration within the last 12 months
5. Current corneal abnormalities in either eye that would prevent accurate IOP readings with a Goldmann applanation tonometer
6. History of (within 2 months prior to baseline) or current significant ocular disease (eg, corneal edema, uveitis, ocular infection, or ocular trauma) in either eye
7. Any history of allergic/toxic local reaction with use of brimonidine
8. Any other significant ophthalmic condition, such as proliferative diabetic retinopathy, retinal detachment, or age-related macular degeneration in either eye
9. Any other intraocular surgery (eg, cataract surgery) within 6 months prior to baseline
10. Refractive surgery within 12 months prior to baseline, or filtering surgery or laser surgery for IOP reduction within 6 months prior to baseline
11. Use of topical ophthalmic corticosteroid or topical corticosteroid within 4 weeks prior to baseline
12. Use of any of the following within 1 month prior to baseline, or expected use during the study duration:
13. Systemic corticosteroid
14. Monoamine oxidase inhibitor therapy
15. Any antidepressant that affects noradrenergic transmission (eg, tricylic antidepressants, mianserin)
16. Adrenergic-augmenting psychotropic drug (eg, desipramine, amitriptyline)
17. Use of intravitreal or subtenon injection of ophthalmic corticosteroid within 6 months prior to baseline
18. Use of intraocular corticosteroid implant at any time prior to baseline

19. Use of any additional topical or systemic ocular hypotensive medication (over-the counter drops, ointment, or gel) in either eye during the study period other than the study ocular hypotensive medication

20. Pregnancy, lactation, or planning a pregnancy during the course of the study (for women of childbearing potential)

21. Less than 30 days' stable dosing regimen before the Screening visit of any medications or substances administered by any route and used on a chronic basis that may affect IOP

22. Current or recent (within 30 days prior to baseline) participation in a drug, device, or other investigational research study

23. Any other conditions, including severe illness, which would make the patient, in the opinion of the investigator, unsuitable for the study

7.3. Patient Rescreening

Patients may repeat the screening procedures once to qualify for the study with approval from the medical monitor (a new screening number will be issued). Patients may rescreen if they:

- Used a topical ophthalmic corticosteroid and/or a topical corticosteroid within 2 weeks prior to baseline (rescreening may be performed 2 weeks or more after discontinuation of these agents)
- Used a systemic corticosteroid, monoamine oxidase inhibitor therapy, any antidepressant that affects noradrenergic transmission (eg, tricylic antidepressants, mianserin), an adrenergic-augmenting psychotropic drug (eg, desipramine, amitriptyline), high doses of systemic salicylates (>1g daily), and/or any investigational drug within 1 month prior to baseline (rescreening may be performed 1 month or more after discontinuation of these agents)
- Used an intravitreal or subtenon injection of ophthalmic corticosteroid within 6 months prior to baseline (rescreening may be performed 6 months or more after discontinuation of this agent)

Failed screening because of operational challenges (rescreening may be performed no fewer than 2 weeks from the date of screen failure)

7.4. Patient Withdrawal and Discontinuation

Patients have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. Furthermore, the investigator may discontinue a patient from study drug or terminate the patient from the study. The reason for a patient's withdrawal or discontinuation from the study will be recorded in an electronic case report form (eCRF).

7.4.1. Patient Discontinuation Criteria

Discontinuation refers to a patient stopping administration of study drug. Reasons for study drug discontinuation may include the following:

- Occurrence of an adverse event (AE)
- Change in medical status that leads the investigator to be concerned about the patient's welfare
- Protocol violations
- Administrative reasons (eg, inability to continue, lost to follow up)
- Sponsor termination of the study
- Voluntary withdrawal
- Pregnancy during the study
- Investigator unblinding

Patients who are discontinued from study drug should attend an early termination visit and undergo all study assessments scheduled for that visit, if possible.

7.4.2. Patient Termination Criteria

Termination refers to a patient stopping study drug and all study assessments and visits. Reasons for study termination include the following:

- Administrative reasons (eg, inability to continue, lost to follow-up)
- Death

Patients who terminate the study for any reason may not re-initiate study drug at any time.

8. TREATMENT OF PATIENTS

8.1. Description of Study Drug

Brimonidine tartrate ophthalmic solution 0.1% is a generic formulation of Alphagan P 0.1%. Aside from the active agent (brimonidine tartrate 0.1%), it contains hydroxypropyl methyl cellulose; boric acid; sodium borate, deca hydrate; sodium chloride; calcium chloride, dihydrate; potassium chloride; magnesium chloride, hexahydrate; hydrochloric acid; sodium hydroxide, and water for injection and is preserved with benzododecinium bromide. Brimonidine tartrate 0.1% is manufactured by Sponsor .

Alphagan P 0.1% contains the active agent (brimonidine tartrate 0.1%), the preservative Purite® 0.005% (stabilized oxychloro complex), and the following inactive ingredients: sodium carboxymethylcellulose, sodium borate, boric acid, sodium chloride, potassium chloride, calcium chloride, magnesium chloride, purified water, and hydrochloric acid and/or sodium hydroxide to adjust pH. Alphagan P 0.1% is manufactured by Allergan, Inc. in Irvine, CA.

Sponsor will provide sufficient quantities of brimonidine tartrate 0.1% and Alphagan P 0.1% at the Baseline visit to allow for completion of the study. To provide masking, both investigational product and reference therapy will be packaged in an opaque bottle with X. At the Baseline visit, a trained technician will instill the first drop of study drug and will instruct the patient on the use of the study drug.

8.2. Prior and Concomitant Medications

8.2.1. Prohibited Medications

Patients who have taken any of the following drugs within 2 weeks prior to baseline will be excluded from the study:

Topical ophthalmic corticosteroid

Topical corticosteroid

Patients who have taken any of the following drugs within 1 month prior to baseline will be excluded from the study:

Systemic corticosteroid

Monoamine oxidase inhibitor therapy

Any antidepressant that affects noradrenergic transmission (eg, tricylic antidepressants, mianserin)

Adrenergic-augmenting psychotropic drug (eg, desipramine, amitriptyline)

High doses of systemic salicylates (>1g daily)

Any investigational drug

Patients who have taken any of the following drugs within 6 months prior to baseline will be excluded from the study:

Intravitreal or subtenon injection of ophthalmic corticosteroid

Patients who have had an intraocular corticosteroid implant at any time prior to baseline will be excluded from the study.

8.2.2. Permitted Medications

Patients taking concomitant medication chronically are permitted, as authorized by the treating physician, as long as they have been taking the medication for the last 30 days and are maintained on those same doses and dose schedules throughout the study period, as medically feasible.

Compliance With Study Drug

The investigator or designee will only dispense study drug to patients randomized in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

All patients will return study drug bottles at the Week 6 visit. Patients will be provided a dosing diary to document that drops were instilled as instructed as well as the date and time of dosing. To be considered compliant with study drug, patients can miss no more than 25% of the total planned doses (ie, 32 doses) during the study. Out-of-window doses will not be considered missed doses. Patients who exceed the number of allowed missed doses will be considered noncompliant with dosing. Patients who dose at home prior to a scheduled visit should have their visit rescheduled. Protocol deviations should be recorded for dosing noncompliance.

8.3. Randomization

Patients will be randomly assigned 1:1 to brimonidine tartrate 0.1% or Alphagan P 0.1%. Randomization will be generated using a centralized Interactive Web Response System (IWRS). Patients will be stratified by site, with a target minimum enrollment of 10 patients per arm per site.

8.4. Masking

To maintain masking, investigators will distribute masked study drug to patients as assigned by the IWRS. All Sponsor staff, patients, investigators,

and site personnel with direct involvement in the conduct of the study or their designees will be masked to treatment assignments and appropriate measures will be taken to ensure the masking is maintained to reduce potential bias.

The only people with access to treatment assignments will be those individuals who develop and maintain the randomization code, the IWRS group, and safety personnel without direct involvement in the conduct of the study who are assigned to report unmasked data to regulatory authorities as required.

8.5. Patient Unmasking

Under rare circumstances, unmasking may be considered medically necessary. Unless faced with a life-threatening medical situation, the investigator should contact the medical monitor to discuss if there is a medically compelling reason to unmask the patient's treatment assignment. After the discussion, the investigator may proceed to unmask the patient, as appropriate. If unmasking is required, the investigator will utilize the IWRS to perform the unmasking. If the investigator cannot reach the medical monitor in a timely manner and unmasks the patient, the investigator should notify the medical monitor immediately but not more than 24 hours after unmasking. In addition, the investigator should provide a report of the circumstances surrounding the unmasking to the medical monitor within 5 business days. If a study drug assignment is unmasked, a description of the event that required unmasking must be documented by the investigator in the patient's source documents. Patients must discontinue taking study drug if their treatment assignment has been unmasked to the investigator (or designee) and attend an early termination visit, undergoing all study assessments scheduled for that visit, if possible. Patient treatment assignments must not be unmasked in the case of an AE or serious adverse event (SAE), except as described above.

8.5.1. Unmasking for Regulatory Submission

In situations where a regulatory body requires unmasking and reporting of a particular SAE, the appropriate bodies (eg, ethics committees, IRBs) must be provided with unmasked information according to the applicable regulatory requirement. In these circumstances, unmasking will be performed by the Sponsor or its designee. This information must not be conveyed to the investigator, site personnel, or patient; therefore, this type of unmasking does not necessitate that the patient discontinue taking study drug.

8.6. Unscheduled Visits

Unscheduled visits are allowed for the following reasons:

Patient rescreening

Management of an AE or SAE

Performance of a serum pregnancy test to confirm a possible pregnancy

If the investigator feels that it is clinically appropriate for patient safety

8.7. Pregnancy

8.8. Women of Childbearing Potential

Women of childbearing potential are female patients who are not surgically sterile (no history of bilateral tubal ligation, hysterectomy, or bilateral salpingo-oophorectomy) and are not postmenopausal for at least 2 years.

Methods of Birth Control

From the Screening visit, while taking study drug, and until 1 month after taking the final dose of study drug, women of childbearing potential must agree to practice one of the following methods of birth control:

Use of a double-barrier contraception method, defined as male use of a condom and female use of a barrier method (eg, contraceptive sponge, spermicidal jelly or cream, diaphragm [always use with spermicidal jelly/cream])

Use of hormonal contraceptives (oral, transdermal, implant, or injected) for at least 1 month prior to study drug administration

Use of an intrauterine device

Complete abstinence from sexual intercourse

8.8.1. Suspected Pregnancy

During the study, all women of childbearing potential must be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, late or missed menstrual period). If a patient or investigator suspects that the patient may be pregnant, the study drug must be withheld until the results of a serum pregnancy test are available. If pregnancy is confirmed with a serum pregnancy test, the patient should discontinue taking study drug and attend an early termination visit, undergoing all study assessments scheduled for that visit, if possible. The investigator must immediately report a pregnancy associated with study drug exposure and record the event on X pregnancy form.

Pregnancy is not considered an AE; however, the investigator must follow a pregnant patient and report follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants resulting from such pregnancies should be followed for a minimum of 8 weeks. The Sponsor or its designee may contact the investigator to request additional information throughout the course of the pregnancy.

The following pregnancy outcomes must be considered SAEs and will require additional reporting in the eCRF and on an SAE form:

- Congenital anomaly/birth defect
- Stillbirth
- Spontaneous miscarriage

8.9. Study Procedures

To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determination completes all subsequent assessments.

8.9.1. Informed Consent

Written informed consent (Section 15.3) must be obtained from the patient (1) before any study-related procedures are performed, and (2) if there is a change in the study procedures that could affect the patient's willingness to participate.

8.9.2. Demographics and Baseline Disease Characteristics

Demographic data, including sex, age, race, and ethnicity, and baseline disease characteristics will be collected at the time indicated in Table 2.

8.9.3. Medical History

A complete medical history (eg, per patient report) that includes medical history within the past 5 years and all ocular medical history (no time limit) will be collected and recorded at the time indicated in Table 2.

8.9.4. Inclusion/Exclusion Criteria

Inclusion and exclusion criteria should be reviewed at the time indicated inTable 2. Patients must meet all of the inclusion criteria and none of the exclusion criteria for entry into the study.

8.9.5. Pulse/Blood Pressure

Pulse and blood pressure measurements should be taken at the times indicated in Table 2. Patients should be sitting for 5 minutes prior to assessment of pulse and blood pressure.

8.9.6. Urine Pregnancy Test

Women of childbearing potential (see Section 8.8) will complete a pregnancy test at the times indicated in Table 2. Negative test results are required at the Baseline visit before study drug administration. Any patient who becomes pregnant during the study must discontinue taking study drug immediately. See Section 8.8.1 for a description of procedures to be followed in case of pregnancy.

8.9.7. Randomization

Patients who qualify for the study will be randomized with a 1:1 assignment ratio to receive brimonidine tartrate 0.1% or Alphagan P 0.1% at the time indicated in Table 2.

8.9.8. Best-Corrected Visual Acuity

BCVA should be assessed for each eye at the times indicated in Table 2.

8.9.9. Slit-Lamp Biomicroscopy

Slit-lamp biomicroscopy should be assessed for each eye at the times indicated in Table 2.

8.9.10. Dilated Fundus Exam

Dilated fundus exam, including the retina, optic disc, choroid, and blood vessels, should be performed for each eye at the times indicated in Table 2. Any abnormalities should be noted on the eCRF.

8.9.11. Automated Perimetry

Automated perimetry should be performed for each eye at the times indicated in Table 2.

8.9.12. Intraocular Pressure

IOP will be assessed in both eyes using Goldmann tonometry at the times indicated in Table 2. IOP will be measured in a way that minimizes observer bias. An unmasked observer (investigator or other qualified study personnel) will place the applanator tip on the corneal apex and obtain a desired

endpoint (ie, mires of equal size, centered in the field, with the inner surfaces of the circles "kissing"). At that point, the tip will be withdrawn from the cornea. A masked observer, separated from the subject by an opaque screen such that he or she is are unable to see or interact with the subject, will read and record the pressure from the scale on the knob on the side of the tonometer. After reading and recording the pressure, the masked observer will reset the tonometer knob to "10".

At each specified time point, the IOP of each eye will be measured twice, alternating between the eyes. However, if the second measurement on a given eye is more than ±2 mmHg from the first measurement for an eye, a third measurement will be taken. All measurements taken will be recorded. In the case of 2 measurements, the average of the 2 values will be used for analysis, and in the case of 3 measurements, the average of the 2 closest values of the 3 will be used for analysis for that eye at that specific time point. In the instances when 3 readings are of equal difference (eg, 20, 23, and 26 mmHg), the median of the 3 is to be recorded as the IOP.

8.9.13. Gonioscopy

Gonioscopy should be performed for each eye at the time indicated in Table 2.

8.9.14. Study Drug and Diary Dispensation

Two bottles of study drug will be dispensed to the patient at the time indicated in Table 2, along with instructions for use. Patients who wear contact lenses will be instructed to remove lenses before dosing and reinsert lenses no sooner than 15 min post-instillation. These patients should be reminded to wear or bring their glasses on study visit days.

A diary will be given to the patient at the time indicated in Table 2, along with instructions for its completion.

8.9.15. Study Drug Administration

At the Baseline visit, a trained technician will instill the first drop of study drug and will instruct the patient on the use of the study drug. Patients should instill 1 drop of study drug 3 times daily, at approximately 8:00 am (±30 min), 4:00 pm (±30 min), and 10:00 pm (±30 min), in both eyes for 6 weeks. At the Week 2 and Week 6 visits, the patient will wait to instill the first morning dose in the clinic after the 8:00 am IOP measurement.

8.9.16. *Review of Study Drug Diary*

The study drug diary should be reviewed at the times indicated in Table 2. Compliance with study drug instillation should be encouraged, and noncompliance should be noted in the eCRF

8.9.17. *Collection of Study Drug*

The study drug should be collected from the patient at the time indicated in Table 2.

8.9.18. *Prior and Concomitant Medications*

Information on prior and concomitant medications will be collected at the times indicated in Table 2. The name, dose, and frequency of all medications that the patient is taking or has taken within 90 days prior to the Baseline visit must be recorded during the study and until the final visit. All allowed and excluded medications should be recorded, including all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Trade or generic drug names should be used whenever possible.

8.9.19. *Adverse Event Collection*

Patients should be observed for general appearance, presence of illness or injury, or signs indicative of a concurrent illness at the times indicated in Table 2. Patients should be instructed to volunteer any information regarding AEs at any time during the study. The study physician or the study staff should also query patients with an open question regarding any AEs they may be experiencing (eg, “How do you feel?” or “How have you been feeling since your last visit?”). Any findings are to be documented.

8.9.20. *Exit From Study*

Patients will be exited at the Week 6 visit upon completion of the study.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

Bottles containing either brimonidine tartrate ophthalmic solution 0.1% or Alphagan P 0.1%, as described in Table 3, will be used in this study.

Table 3: Study Drug Information

Description	Brimonidine tartrate ophthalmic solution 0.1%	Alphagan® P 0.1%
Ingredients	Brimonidine tartrate 0.1% (1 mg/mL); benzododecinium bromide; hydroxypropyl methyl cellulose; boric acid; sodium borate, deca hydrate; sodium chloride; calcium chloride, dihydrate; potassium chloride; magnesium chloride, hexahydrate; water for injection; and hydrochloric acid and sodium hydroxide (to adjust pH)	Brimonidine tartrate 0.1% (1 mg/mL), Purite® 0.005% (0.05 mg/mL), sodium carboxymethylcellulose, sodium borate, boric acid, sodium chloride, potassium chloride, calcium chloride, magnesium chloride, purified water, hydrochloric acid and/or sodium hydroxide (to adjust pH)
Manufacturer	Sponsor	Allergan, Inc. 2525 Dupont Dr Irvine, CA

9.2. Study Drug Packaging and Labeling

Alphagan P will be packaged in its commercial bottle but with a masked label added for the study. The study drug therapy will be packaged in a similar bottle with a masked label. Each bottle will contain a volume of 10 mL with either investigational product or reference therapy. The label on the bottle will include the following information:

- Medication ID number
- Caution statement: New Drug – Limited by Federal Law to Investigational Use (United States)
- Storage: Controlled room temperature, 15°C to 25°C (59°C to 77°C)
- Sponsor name, address, and contact information
- Contents: One bottle containing 10 mL of brimonidine tartrate 0.1% or Alphagan P 0.1%
- Directions for use: Instill 1 drop study drug topically 3 times daily, at approximately 8:00 am (±30 min), 4:00 pm (±30 min), and 10:00 pm (±30 min), in both eyes for 6 weeks
- Keep out of sight and reach of children
- FOR OPHTHALMIC USE ONLY

9.3. Study Drug Storage

Investigative sites must store the investigational product in a secure location under controlled room temperature conditions of 15°C to 25°C (59°F to 77°F). Sites must maintain a temperature log of the storage conditions. Temperature logs must be available for review at each monitor site visit. If a temperature within the storage location at the site is noted to be outside the excursion range for 24 hours or more or exceeds 40°C, the Sponsor must be notified.

9.4. Study Drug Administration

Please refer to Section 8.9.15 for details on study drug administration. Patients will receive enough drug at Baseline for continuous dosing 3 times daily until the end of the study. Clear instructions will be provided to the patient regarding study drug administration at each study drug administration time point listed in Table 2. A reminder call will be made from the site the day before the week 2 visit and the week 6 visit, reminding each patient of the upcoming visit and to avoid taking the study drug that morning.

9.5. Study Drug Accountability

The investigator or designee will maintain a record of all study drug received, dispensed, and returned to the Sponsor or its designee. No study drug shall be destroyed by the clinical site unless directed to do so by the Sponsor or its designee. Study drug bottles should be returned by the patient to the study staff at the Week 6 visit.

9.6. Study Drug Handling and Disposal

At the conclusion of the study, the Sponsor or its designee will direct the site regarding the final disposition of any remaining study drug.

10. EFFICACY ASSESSMENTS

10.1. Efficacy Parameter: Intraocular Pressure

At each specified time point, the IOP of each eye will be measured twice, alternating between the eyes. However, if the second measurement on a given eye is more than ±2 mmHg from the first measurement for that eye, a third measurement will be taken. All measurements taken will be recorded. In the case of 2 measurements, the average of the 2 values will be used for analysis, and in the case of 3 measurements, the average of the 2 closest values of the 3 will be used for analysis for that eye at that specific time point. In the instances when 3 readings are of equal difference (eg, 20, 23, and 26 mmHg), the median of the 3 is to be recorded as the IOP.

11. SAFETY ASSESSMENTS

11.1. Safety Parameters

Safety parameters are AEs, BCVA, slit-lamp biomicroscopy, fundoscopy, automated perimetry, and resting blood pressure and pulse rate.

11.2. Adverse Events and Serious Adverse Events

11.2.1. Definition of Adverse Events

11.2.1.1. Adverse Event

An AE is defined as any untoward medical occurrence in a patient regardless of its causal relationship to study treatment. An AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study drug related. Included in this definition is any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug.

All AEs that are observed or reported by the patient during the study (from the time of the first dose of study drug until the final visit or 30 days following final study dose for patients who terminate early) must be reported, regardless of their relationship to study drug or their clinical significance. All AEs that are observed or reported by the patient from the time of informed consent until the first dose of study drug should be recorded as part of medical history.

11.2.1.2. Serious Adverse Event

An SAE is any AE occurring at any dose and regardless of causality that:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly or birth defect in an offspring of a patient taking study drug
- Is an important medical event

The term "life threatening" refers to an event in which the patient was at immediate risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Important medical events are those that may not meet any of the criteria defined above; however, they may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the SAE definition.

Pregnancy is not considered an AE; however, information will be collected for any pregnancies that occur during the study (from the time of first dose of study drug until the final visit). Certain pregnancy outcomes will require submission as an SAE (Section 8.8.1).

The investigator is responsible for reporting to the Sponsor or its designee all AEs and SAEs that are observed or reported by the patient during the study (from the time of first dose of study drug until the final visit), regardless of their relationship to study drug or their clinical significance. All SAEs reported or observed during the study must be followed to resolution or until the investigator deems the event to be chronic or the patient to be stable. The Sponsor or its designee may contact the investigator to obtain additional information on any SAE that has not resolved at the time the patient completes the study.

11.3. Eliciting Adverse Event Information

At every study visit, patients must be asked a standard, non-directed question, such as, "How do you feel?" or "How have you been feeling since your last visit?", to elicit any medically related changes in their well-being. They may also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (including prescription drugs, over-the-counter medications, vitamins, herbal products, and minerals). Responses should be recorded in the source documents.

In addition to patient observations, AEs must be documented for any clinically significant diagnosis resulting from physical examination findings or other documents that are relevant to patient safety.

11.4. Assessment of Causality

The investigator must use the following classifications and criteria to characterize the relationship or association of the study drug in causing or contributing to the AE:

- Unrelated: This relationship suggests that there is no association between the study drug and the reported event
- Unlikely: This relationship suggests that the temporal sequence of the event with study drug administration makes a causal relationship improbable and/or other factors also provide plausible explanations
- Possible: This relationship suggests that treatment with the study drug caused or contributed to the AE. That is, the event follows a reasonable temporal sequence from the time of study drug administration and/or follows a known response pattern to the study drug but could have been produced by other factors
- Probable: This relationship suggests that a reasonable temporal sequence of the event with study drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with study drug administration seems likely

11.5. Assessment of Severity

The investigator will grade the severity of the AEs as mild, moderate, or severe using the following definitions:

- Mild: Symptoms causing no or minimal interference with usual social and functional activities
- Moderate: Symptoms causing greater than minimal interference with usual social and functional activities
- Severe: Symptoms causing inability to perform usual social and functional activities

11.6. Recording Adverse Events

All conditions present prior to the first dose of study drug should be documented as medical history. All drug-related (characterized as possibly or probably related; Section 11.4) AEs reported or observed during the study must be followed to resolution (either return to baseline or within normal limits). All other AEs will be followed through the final visit (ie, end of study or early termination). Information to be collected includes type of event, date of onset, date of resolution, investigator-specified assessment of severity and relationship to study drug, seriousness, as well as any action taken.

While an AE is ongoing, changes in the severity (eg, worsening or improving) should be noted in the source documents but when documenting the AE, only the total duration and greatest severity should be recorded in the eCRF.

AEs characterized as intermittent require documentation of onset and duration.

AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. Pre-existing conditions (present before the start of the AE collection period) are considered concurrent medical conditions and should NOT be recorded as AEs. However, if the patient experiences a worsening or complication of such a concurrent condition, the worsening or complication (except disease progression) should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Each AE should be recorded to represent a single diagnosis. Accompanying signs or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded as an AE(s).

Elective procedures (surgeries or therapies) that were scheduled prior to the start of AE collection are not considered AEs. These elective procedures should not be recorded as AEs but should be documented in the patient's source documents as elective (eg, elective periodontal surgery). However, if a preplanned procedure is performed early (eg, as an emergency) because of a worsening of the pre-existing condition, the worsening of the condition should be captured as an AE.

11.7. Reporting Serious Adverse Events

Any AE that meets the criteria of serious according to the previously described criteria must be reported within 24 hours from the time when site personnel first learn about the event. To report the SAE, the completed SAE form must be emailed to XX (email address listed below in Table 4) within 24 hours of awareness.

Table 4: Serious Adverse Event Reporting Contact Information

For questions regarding SAE reporting, contact your study manager, monitor, or medical monitor:

The investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies. Within 24 hours of receipt of new

information, the updated follow-up SAE form, along with any supporting documentation (eg, patient discharge summary or autopsy reports), should be emailed to ……..(Table 4).

The Sponsor or its designee will notify regulatory agencies of any fatal or life-threatening unexpected events associated with the use of the study drug as soon as possible but no later than 7 calendar days after the initial receipt of the information. Initial notification will be followed by a written report within the timeframe established by the appropriate regulatory agency. For other SAEs that do not meet the fatal or life-threatening unexpected criteria but are deemed by the investigator to be associated with the use of the study drug (that is, "possible" or "probable" in causality assessment), the Sponsor or its designee will notify the appropriate regulatory agencies in writing within the timeframe established by those regulatory agencies. The Sponsor or its designee will provide copies of any reports to regulatory agencies regarding serious and unexpected SAEs to the investigators for their information and submission to their IRB, as appropriate.

Principal investigators are responsible for informing their IRB of any SAEs at their site, as appropriate. SAE correspondence with regulatory authorities or IRBs must be submitted to the Sponsor or its designee for recording in the study file.

12. STATISTICS

12.1. Sample Size

Assuming a standard deviation of IOP of 3.0 mmHg and an equivalence limit of 1.5 mmHg, 86 patients per group are required in the per-protocol (PP) population to have at least 90% power to establish equivalence. Assuming a dropout rate of 25%, 216 patients (108 patients/group) are targeted in the intent-to-treat (ITT) population to meet the primary objective of the study.

12.2. Data Sets to be Analyzed

The ITT population will include data from all patients who were randomized, received study medication, and had at least 1 post-Baseline observation. The PP population will include all patients included in the ITT population who met all entry criteria and had no major protocol violations. The safety population will include all patients who were randomized and received study medication.

12.3. Demographics and Baseline Characteristics

Demographic (eg, age, sex, ethnicity, race) and baseline characteristics (eg, baseline IOP) will be summarized for the ITT population. Descriptive statistics in accordance with the scale of each variable will be presented overall and by treatment group.

12.4. Efficacy Analyses

The efficacy variable is IOP.

The PP population will be used to establish equivalence in the efficacy endpoints, and the intent-to-treat population will be used as the secondary population. The adjusted estimate of difference between groups at each post-Baseline visit will be obtained from a restricted maximum likelihood repeated measures mixed model on change from Baseline values with Baseline as a covariate, treatment group as a fixed factor and observations from both eyes (presented as a mean change in IOP of the 2 eyes) and visit and its interaction treatment group, as repeated measures using an unstructured covariance structure. The adjusted estimate of difference between groups and 95% confidence limits will be tabulated for the 8:00 am and 10:00 am results on Week 2 and Week 6. Inasmuch as the criterion for success requires meeting the endpoint at multiple time points and in both eyes, no adjustment for multiple testing is required. All other efficacy variables will be analyzed using appropriate statistical techniques.

12.5. Interim Analysis

An administrative blinded interim analysis is planned when approximately 50% of patients have been randomized, received treatment, and been observed to Week 6. This blinded interim analysis will only present the pooled standard deviation for the primary efficacy endpoint. This information will then be used to revisit the original sample size assumptions and recalculate the sample size itself, if necessary. No other statistical inferences will be made.

12.6. Safety Analyses

The safety variables are AEs, BCVA, slit-lamp biomicroscopy, fundoscopy, automated perimetry, and resting blood pressure and pulse rate.

The safety population will be used to examine the safety of the study drugs. The occurrence of AEs at each visit will be summarized by frequency, severity (mild, moderate, severe), and relationship (unlikely, possible, probable). All other safety measures will be summarized by treatment group and visit.

12.7. Statistical Analyses

A statistical analysis plan (SAP) detailing the analyses described below will be developed prior to the database lock. The SAP will serve as the final arbiter of all statistical analyses. Data will be summarized overall using descriptive statistics. Continuous data will be summarized with number of patients (n), mean, median, minimum, maximum, standard deviation, and coefficient of variation. Other continuous safety and ordinal categorical variables will be analyzed in a manner similar to those proposed for the primary efficacy variable.

To establish bioequivalence, the limits of each two-sided 95% confidence interval of the treatment difference for the mean IOP of the 2 eyes at all four follow-up points must be within ± 1.5 mm Hg using the PP population for all time points measured and within ± 1.0 mm Hg using the PP population for the majority of time points measured.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

The study monitor, as a representative of the Sponsor, has the obligation to follow the study conduct closely. In doing so, the monitor will visit the principal investigator and study facilities periodically, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current knowledge of the study activity of the investigator and his/her staff through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigators and staff.

The Sponsor or its designee will monitor all aspects of the study for compliance with applicable government regulation with respect to the International Conference on Harmonisation Harmonised Tripartite Guideline for GCP E6(R1), abbreviated as ICH E6(R1), and current standard operating procedures.

Each principal investigator is expected to make a reasonable effort to accommodate the monitor when monitoring visits are necessary and to be available during the site visit. Furthermore, the monitor should be provided direct access to source data and documents for trial-related monitoring and to the internet during the visit.

13.2. Audits and Inspections

Principal investigators and institutions involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to all study records. In the event of an audit, the principal investigator agrees to allow the Sponsor, representatives of the Sponsor, the Unites States (US) Food and Drug Administration (FDA), or other relevant regulatory authorities access to all study records.

The principal investigator or designee should promptly notify the Sponsor or designee of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor or its designee.

14. QUALITY CONTROL AND QUALITY ASSURANCE

14.1. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Please see Section 13.2 for more details regarding the audit process.

14.2. Financial Disclosure

Principal investigators and subinvestigators are required to provide financial disclosure information prior to starting the study. In addition, the principal investigator and subinvestigators must provide the Sponsor or its designee with updated information, if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Any potential investigator who has a vested financial interest in the success of this study may not participate in this study.

14.3. Sponsor Obligations

The Sponsor or its designee is not financially responsible for further testing/treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, the Sponsor or its designee is not financially responsible for treatment of non–study-related fatalities, physical injuries, or damage to health that may occur during the clinical study, as well as the patient's underlying disease.

14.4. Investigator Documentation

Before beginning the study, the principal investigator will be asked to comply with ICH E6(R1), Section 8.2 and Title 21 of the US Code of Federal Regulations, abbreviated as US CFR Title 21, by providing the essential documents to the Sponsor or its designee, which include but are not limited to the following:

- An original investigator-signed investigator agreement page of the protocol
- The IRB approval of the protocol
- The IRB-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardians
- A Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572

- Curricula vitae for the principal investigator and each subinvestigator listed on Form FDA 1572. A curriculum vitae and current licensure, as applicable, must be provided. The curricula vitae must have been signed and dated by the principal investigators and subinvestigators within 2 years before study start-up to indicate the documents are accurate and current
- Completed financial disclosure forms (Section 14.2) to allow the Sponsor or its designee to submit complete and accurate certification or disclosure statements required under US CFR Title 21, Part 54. In addition, the investigators must provide to the Sponsor or its designee a commitment to update this information promptly if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study

14.5. Clinical Study Insurance

In accordance with the respective national drug laws, the Sponsor has taken out patient liability insurance for all patients who give their consent and enroll in this study. This insurance covers potential study-related fatalities, physical injuries, or damage to health that may occur during the clinical study.

14.6. Use of Information

All information regarding brimonidine tartrate ophthalmic solution 0.1% supplied by the Sponsor to the investigator is privileged and confidential. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. Furthermore, the investigator is obligated to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of brimonidine tartrate ophthalmic solution 0.1% and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants, as required.

15. ETHICS

15.1. Institutional Review Board Review

The protocol and the proposed ICF must be reviewed and approved by a properly constituted IRB before study start. Each site must provide the Sponsor or its designee a signed and dated statement that the protocol and ICF have been approved by the IRB before consenting patients. Prior to study initiation, the investigator is required to sign a protocol signature page, confirming agreement to conduct the study in accordance with this protocol and to give access to all relevant data and records to the Sponsor, its designee, and regulatory authorities, as required.

The IRB chairperson or designee must sign all IRB approvals and must identify the IRB by name and address, the clinical protocol, and the date approval and/or favorable opinion was granted.

The principal investigator is responsible for obtaining reviews of the clinical research at intervals specified by the IRB, but not exceeding 1 year. The principal investigator must supply the Sponsor or its designee with written documentation of reviews of the clinical research.

15.2. Ethical Conduct of the Study

This clinical study was designed and shall be implemented and reported in accordance with the ICH E6(R1), with applicable local regulations (eg, US CFR Title 21), and with the ethical principles of the Declaration of Helsinki.

The principal investigator agrees to conduct the study in accordance with the ICH E6(R1) and the principles of the Declaration of Helsinki. The principal investigator must conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

15.3. Written Informed Consent

Because the study will be conducted under a US Investigational New Drug Application, a signed ICF, in compliance with US CFR Title 21, Part 50, will be obtained from each patient before the patient enters the study. An informed consent template may be provided by the Sponsor or its designee to the investigators. The consent must be reviewed by the Sponsor or its designee before IRB submission. Once reviewed, the consent will be submitted by the principal investigator to his or her IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all participants affected by the revision must sign the revised IRB-approved consent form.

Before enrollment, each prospective patient will be given a full explanation of the study and be allowed to read the approved ICF. Once the principal investigator or designee is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing the ICF.

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB-approved informed consent. Informed consent must be obtained before conducting any study-specific procedures (ie, all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Any changes to the proposed consent form suggested by the investigator must be agreed to by the Sponsor before submission to the IRB, and a copy of the approved version and the notice of approval must be provided to the Sponsor's designated monitor after IRB approval.

The principal investigator or designee will provide a copy of the ICF (signed copy to be provided per applicable law) to the patient and/or legal guardian. The original form will be maintained in the patient's medical records at the site.

15.4. Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, the FDA or applicable regulatory authorities, or the IRB.

The principal investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished confidential information disclosed to them for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

15.5. Modification of the Protocol

Any changes that arise after the approval of the protocol must be documented as protocol amendments. FDA must be notified of protocol amendments. The changes will become effective only after approval of the Sponsor, the principal investigator, and the IRB. In cases where the protocol is modified

to enhance patient safety, changes may be implemented and the amendment must be immediately submitted to the IRB.

The principal investigator is responsible for informing the IRB of all problems involving risks to patients according to national legislation. In case of urgent safety measures, the Sponsor will immediately notify FDA in accord with US CFR Title 21, Part 312, Section 32.

15.6. Protocol Deviations

The principal investigator or designee must document any protocol deviations. The IRB must be notified of all protocol deviations in a timely manner by the investigator, as appropriate. Protocol deviations will be documented by the site personnel and reviewed by the responsible monitor during monitoring visits, and those observations will be communicated to the investigator.

If there is an immediate hazard to a patient, the principal investigator may deviate from the protocol without prior Sponsor and IRB approval. The Sponsor and IRB must be notified of the deviation.

16. DATA HANDLING AND RECORDKEEPING

16.1. Retention of Records

The investigator will maintain all study records according to ICH E6(R1) and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application is approved or 2 years after formal discontinuation of the clinical development of the investigational product. If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

16.2. Case Report Forms

All case report form data will be entered in electronic forms at the investigational site. The electronic data capture system used to capture data electronically for all randomized patients will be US CFR Title 21, Part 11 compliant.

17. PUBLICATION POLICY

The Sponsor reserves the right to review all planned communications and manuscripts based on the results of this study. This reservation of the right is not intended to restrict or hinder publication or any other dissemination of study results, but to allow the Sponsor to confirm the accuracy of the data, to protect proprietary information, and to provide comments based on information that may not yet be available to the study investigators. The Sponsor supports communication and publication of study results whatever the findings of the study. The Sponsor also encourages disclosure of any conflict of interest from all authors or investigators when manuscripts are submitted for publication.

Those individuals who have contributed greatly to this study, as determined by the Sponsor, will serve on any publications committee for the study.

18. LIST OF REFERENCES

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19. APPENDICES

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ALPHAGAN® P safely and effectively. See full prescribing information for ALPHAGAN® P.

ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.1% and 0.15%
Initial U.S. Approval: 1996

INDICATIONS AND USAGE
ALPHAGAN® P is an alpha adrenergic receptor agonist indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. (1)

DOSAGE AND ADMINISTRATION
One drop in the affected eye(s), three times daily, approximately 8 hours apart. (2)

DOSAGE FORMS AND STRENGTHS
Solution containing 1 or 1.5 mg/mL brimonidine tartrate. (3)

CONTRAINDICATIONS
Neonates and infants (under the age of 2 years). (4.1)

WARNINGS AND PRECAUTIONS
Potentiation of vascular insufficiency. (5.1)

ADVERSE REACTIONS
Most common adverse reactions occurring in approximately 5% to 20% of patients receiving brimonidine ophthalmic solution (0.1%-0.2%) included allergic conjunctivitis, burning sensation, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, hypertension, ocular allergic reaction, oral dryness, and visual disturbance. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-433-8871 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
- Antihypertensives/cardiac glycosides may lower blood pressure. (7.1)
- Use with CNS depressants may result in an additive or potentiating effect. (7.2)
- Tricyclic antidepressants may potentially blunt the hypotensive effect of systemic clonidine. (7.3)
- Monoamine oxidase inhibitors may result in increased hypotension. (7.4)

USE IN SPECIFIC POPULATIONS
Use with caution in children ≥ 2 years of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 09/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.1% or 0.15% is an alpha adrenergic receptor agonist indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

2 DOSAGE AND ADMINISTRATION

The recommended dose is one drop of **ALPHAGAN® P** in the affected eye(s) three times daily, approximately 8 hours apart. **ALPHAGAN® P** ophthalmic solution may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic product is to be used, the different products should be instilled at least 5 minutes apart.

3 DOSAGE FORMS AND STRENGTHS

Solution containing 1 mg/mL or 1.5 mg/mL brimonidine tartrate.

4 CONTRAINDICATIONS

4.1 Neonates and Infants (under the age of 2 years)

ALPHAGAN® P is contraindicated in neonates and infants (under the age of 2 years).

4.2 Hypersensitivity Reactions

ALPHAGAN® P is contraindicated in patients who have exhibited a hypersensitivity reaction to any component of this medication in the past.

5 WARNINGS AND PRECAUTIONS

5.1 Potentiation of Vascular Insufficiency

ALPHAGAN® P may potentiate syndromes associated with vascular insufficiency. **ALPHAGAN® P** should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.

5.2 Severe Cardiovascular Disease

Although brimonidine tartrate ophthalmic solution had minimal effect on the blood pressure of patients in clinical studies, caution should be exercised in treating patients with severe cardiovascular disease.

5.3 Contamination of Topical Ophthalmic Products After Use

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (see **PATIENT COUNSELING INFORMATION**, 17).

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 rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Adverse reactions occurring in approximately 10-20% of the subjects receiving brimonidine ophthalmic solution (0.1-0.2%) included: allergic conjunctivitis, conjunctival hyperemia, and eye pruritus. Adverse reactions occurring in approximately 5-9% included: burning sensation, conjunctival folliculosis, hypertension, ocular allergic reaction, oral dryness, and visual disturbance.

Adverse reactions occurring in approximately 1-4% of the subjects receiving brimonidine ophthalmic solution (0.1-0.2%) included: abnormal taste, allergic reaction, asthenia, blepharitis, blepharoconjunctivitis, blurred vision, bronchitis, cataract, conjunctival edema, conjunctival hemorrhage, conjunctivitis, cough, dizziness, dyspepsia, dyspnea, epiphora, eye discharge, eye dryness, eye irritation, eye pain, eyelid edema, eyelid erythema, fatigue, flu syndrome, follicular conjunctivitis, foreign body sensation, gastrointestinal disorder, headache, hypercholesterolemia, hypotension, infection (primarily colds and respiratory infections), insomnia, keratitis, lid disorder, pharyngitis, photophobia, rash, rhinitis, sinus infection, sinusitis, somnolence, stinging, superficial punctate keratopathy, tearing, visual field defect, vitreous detachment, vitreous disorder, vitreous floaters, and worsened visual acuity.

The following reactions were reported in less than 1% of subjects: corneal erosion, hordeolum, nasal dryness, and taste perversion.

6.2 Postmarketing Experience

The following reactions have been identified during postmarketing use of brimonidine tartrate ophthalmic solutions in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to brimonidine tartrate ophthalmic solutions, or a combination of these factors, include: bradycardia, depression, hypersensitivity, iritis, keratoconjunctivitis sicca, miosis, nausea, skin reactions (including erythema, eyelid pruritus, rash, and vasodilation), syncope, and tachycardia. Apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving brimonidine tartrate ophthalmic solutions.

7 DRUG INTERACTIONS

7.1 Antihypertensives/Cardiac Glycosides

Because **ALPHAGAN® P** may reduce blood pressure, caution in using drugs such as antihypertensives and/or cardiac glycosides with **ALPHAGAN® P** is advised.

7.2 CNS Depressants

Although specific drug interaction studies have not been conducted with **ALPHAGAN® P**, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be considered.

7.3 Tricyclic Antidepressants

Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with **ALPHAGAN® P** in humans can lead to resulting interference with the IOP lowering effect. Caution is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

7.4 Monoamine Oxidase Inhibitors

Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine and potentially result in an increased systemic side-effect such as hypotension. Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B: Teratogenicity studies have been performed in animals.

Brimonidine tartrate was not teratogenic when given orally during gestation days 6 through 15 in rats and days 6 through 18 in rabbits. The highest doses of brimonidine tartrate in rats (2.5 mg/kg/day) and rabbits (5.0 mg/kg/day) achieved AUC exposure values 360- and 20-fold higher, or 260- and 15-fold higher, respectively,

than similar values estimated in humans treated with **ALPHAGAN® P** 0.1% or 0.15%, 1 drop in both eyes three times daily.

There are no adequate and well-controlled studies in pregnant women; however, in animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. Because animal reproduction studies are not always predictive of human response, **ALPHAGAN® P** should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether brimonidine tartrate is excreted in human milk, although in animal studies, brimonidine tartrate has been shown to be excreted in breast milk. Because of the potential for serious adverse reactions from **ALPHAGAN® P** in nursing infants, 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

ALPHAGAN® P is contraindicated in children under the age of 2 years (see **CONTRAINDICATIONS**, 4.1). During postmarketing surveillance, apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving brimonidine. The safety and effectiveness of brimonidine tartrate have not been studied in children below the age of 2 years.

In a well-controlled clinical study conducted in pediatric glaucoma patients (ages 2 to 7 years) the most commonly observed adverse reactions with brimonidine tartrate ophthalmic solution 0.2% dosed three times daily were somnolence (50-83% in patients ages 2 to 6 years) and decreased alertness. In pediatric patients 7 years of age (>20 kg), somnolence appears to occur less frequently (25%). Approximately 16% of patients on brimonidine tartrate ophthalmic solution discontinued from the study due to somnolence.

8.5 Geriatric Use

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

8.6 Special Populations

ALPHAGAN® P has not been studied in patients with hepatic impairment.

ALPHAGAN® P has not been studied in patients with renal impairment. The effect of dialysis on brimonidine pharmacokinetics in patients with renal failure is not known.

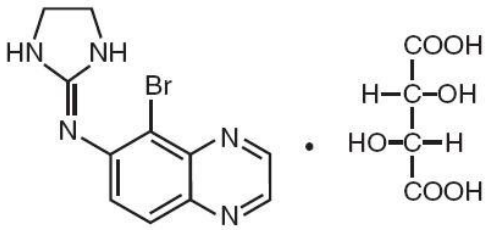
10 OVERDOSAGE

Very limited information exists on accidental ingestion of brimonidine in adults; the only adverse reaction reported to date has been hypotension. Symptoms of brimonidine overdose have been reported in neonates, infants, and children receiving **ALPHAGAN® P** as part of medical treatment of congenital glaucoma or by accidental oral ingestion (see **USE IN SPECIFIC POPULATIONS**, 8.4). Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

11 DESCRIPTION

ALPHAGAN® P (brimonidine tartrate ophthalmic solution) 0.1% or 0.15%, sterile, is a relatively selective alpha-2 adrenergic receptor agonist (topical intraocular pressure lowering agent).

The structural formula of brimonidine tartrate is:



5-Bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate; MW= 442.24

In solution, **ALPHAGAN® P** (brimonidine tartrate ophthalmic solution) has a clear, greenish-yellow color. It has an osmolality of 250-350 mOsmol/kg and a pH of 7.4-8.0 (0.1%) or 6.9-7.4 (0.15%).

Brimonidine tartrate appears as an off-white to pale-yellow powder and is soluble in both water (0.6 mg/mL) and in the product vehicle (1.4 mg/mL) at pH 7.7.

Each mL of **ALPHAGAN® P** contains the active ingredient brimonidine tartrate 0.1% (1 mg/mL) or 0.15% (1.5 mg/mL) with the inactive ingredients sodium carboxymethylcellulose; sodium borate; boric acid; sodium chloride; potassium chloride; calcium chloride; magnesium chloride; PURITE® 0.005% (0.05 mg/mL) as a preservative; purified water; and hydrochloric acid and/or sodium hydroxide to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ALPHAGAN® P is a relatively selective alpha-2 adrenergic receptor agonist with a peak ocular hypotensive effect occurring at two hours post-dosing.

Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action by reducing aqueous humor production and increasing uveoscleral outflow.

12.3 Pharmacokinetics

Absorption

After ocular administration of either a 0.1% or 0.2% solution, plasma concentrations peaked within 0.5 to 2.5 hours and declined with a systemic half-life of approximately 2 hours.

Distribution

The protein binding of brimonidine has not been studied.

Metabolism

In humans, brimonidine is extensively metabolized by the liver.

Excretion

Urinary excretion is the major route of elimination of brimonidine and its metabolites. Approximately 87% of an orally-administered radioactive dose of brimonidine was eliminated within 120 hours, with 74% found in the urine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No compound-related carcinogenic effects were observed in either mice or rats following a 21-month and 24-month study, respectively. In these studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 1 mg/kg/day in rats achieved 150 and 120 times or 90 and 80 times, respectively, the plasma C_{max} drug concentration in humans treated with one drop of **ALPHAGAN® P** 0.1% or 0.15% into both eyes 3 times per day, the recommended daily human dose.

Brimonidine tartrate was not mutagenic or clastogenic in a series of *in vitro* and *in vivo* studies including the Ames bacterial reversion test, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, and three *in vivo* studies in CD-1 mice: a host-mediated assay, cytogenetic study, and dominant lethal assay.

Reproduction and fertility studies in rats with brimonidine tartrate demonstrated no adverse effect on male or female fertility at doses which achieve up to approximately 125 and 90 times the systemic exposure following the maximum recommended human ophthalmic dose of **ALPHAGAN® P** 0.1% or 0.15%, respectively.

14 CLINICAL STUDIES

Elevated IOP presents a major risk factor in glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss. Brimonidine tartrate has the action of lowering intraocular pressure with minimal effect on cardiovascular and pulmonary parameters.

Clinical studies were conducted to evaluate the safety, efficacy, and acceptability of **ALPHAGAN® P** (brimonidine tartrate ophthalmic solution) 0.15% compared with **ALPHAGAN®** administered three-times-daily in patients with open-angle glaucoma or ocular hypertension. Those results indicated that **ALPHAGAN® P** (brimonidine tartrate ophthalmic solution) 0.15% is comparable in IOP lowering effect to **ALPHAGAN®** (brimonidine tartrate ophthalmic solution) 0.2%, and effectively lowers IOP in patients with open-angle glaucoma or ocular hypertension by approximately 2-6 mmHg.

A clinical study was conducted to evaluate the safety, efficacy, and acceptability of **ALPHAGAN® P** (brimonidine tartrate ophthalmic solution) 0.1% compared with **ALPHAGAN®** administered three-times-daily in patients with open-angle glaucoma or ocular hypertension. Those results indicated that **ALPHAGAN® P** (brimonidine tartrate ophthalmic solution) 0.1% is equivalent in IOP lowering effect to **ALPHAGAN®** (brimonidine tartrate ophthalmic solution) 0.2%, and effectively lowers IOP in patients with open-angle glaucoma or ocular hypertension by approximately 2-6 mmHg.

16 HOW SUPPLIED/STORAGE AND HANDLING

ALPHAGAN® P is supplied sterile, in teal opaque plastic LDPE bottles and tips, with purple high impact polystyrene (HIPS) caps as follows:

0.1%

5 mL in 10 mL bottle	NDC 0023-9321-05
10 mL in 10 mL bottle	NDC 0023-9321-10
15 mL in 15 mL bottle	NDC 0023-9321-15

0.15%

5 mL in 10 mL bottle	NDC 0023-9177-05
10 mL in 10 mL bottle	NDC 0023-9177-10
15 mL in 15 mL bottle	NDC 0023-9177-15

Storage: Store at 15°-25°C (59°-77°F).

17 PATIENT COUNSELING INFORMATION

Patients should be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, 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 (see **WARNINGS AND PRECAUTIONS**, 5.3). Always replace the cap after using. If solution changes color or becomes cloudy, do not use. Do not use the product after the expiration date marked on the bottle.

Patients also should be advised 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.

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

As with other similar medications, **ALPHAGAN® P** may cause fatigue and/or drowsiness in some patients. Patients who engage in hazardous activities should be cautioned of the potential for a decrease in mental alertness.

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Notes