A Multi-Center, Randomized, Double-Masked, Active Controlled, Parallel Group Bioequivalence Study with Clinical Endpoint Comparing Brinzolamide Ophthalmic Suspension 1% of Perrigo Pharma International DAC to Azopt® (brinzolamide ophthalmic suspension) 1% of Novartis Pharmaceuticals Corporation in the Treatment of Primary Open Angle Glaucoma or Ocular Hypertension in Both Eyes

Protocol No: PRG-NY-19-001

NCT04024072

07-01-2019

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[redacted]

Confidential

The confidential information provided in this document is for use by parties directly involved in this investigation. By accepting this document, you agree that the information contained herein will not be disclosed to any person not directly involved in this investigation without written authorization from Perrigo New York Inc.

[redacted]

[redacted]

PROTOCOL SIGNATURE PAGE

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[redacted]

[redacted]

[redacted]

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[redacted]

[redacted]

[redacted]

Synopsis

Title	A Multi-Center, Randomized, Double-Masked, Active Controlled, Parallel Group Bioequivalence Study with Clinical Endpoint Comparing Brinzolamide Ophthalmic Suspension 1% of Perrigo Pharma International DAC to Azopt® (brinzolamide ophthalmic suspension) 1% of Novartis Pharmaceuticals Corporation in the Treatment of Primary Open Angle Glaucoma or Ocular Hypertension in Both Eyes	
Protocol No.	PRG-NY-19-001	
Study Medication	Test Product:	Brinzolamide Ophthalmic Suspension, 1% [redacted]
	Reference Listed Drug:	Azopt® (brinzolamide ophthalmic suspension), 1% Novartis Pharmaceuticals Corporation
Study Objectives	To demonstrate bioequivalence of brinzolamide ophthalmic suspension 1% (Perrigo Pharma International DAC) to Azopt® (brinzolamide ophthalmic suspension) 1% (Novartis Pharmaceutical Corporation) by comparing their efficacy and safety in the treatment of subjects with Primary Open Angle Glaucoma (POAG) or Ocular Hypertension (OH) in both eyes.	
Study Design	Double-masked, randomized, multi-center, active-controlled, parallel-group, bioequivalence study with clinical endpoint.	
Study Population	Approximately [redacted] subjects will be enrolled [redacted] to obtain approximately [redacted] per protocol subjects. All efforts will be made so that the study population will consist of subjects with light colored iris and dark colored iris similar in proportion to the U. S. population.	
Dosing	The study consists of a six-week treatment (42 ± 4 days) period. At Baseline/Visit 2, eligible subjects will be randomized in a double-masked manner, [redacted] to either the test product or reference product. Subjects will apply one drop of either test product or reference product in both eyes three times daily at approximately 08:00 am, 04:00 pm and 10:00 pm for six weeks (42 ± 4 days)	
Study Visits	Clinical Evaluations will be performed at: 1. Visit 1/Screening 2. Visit 2/Day 0 (Baseline) 3. Visit 3/Week 2/Day 14 (±4 days) 4. Visit 4/Week 6/Day 42 (±4 days) (End of Study)	

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Evaluations	• Intraocular pressure [redacted] • [redacted] • Vital signs • Adverse events
Primary Endpoint	The primary efficacy endpoint is mean <u>change from baseline</u> in IOP of both eyes at four time points, i.e., at approximately 8:00 a.m. (hour 0; before the morning drop) and approximately 10:00 a.m. (hour 2) on Day 14 (Week 2) and Day 42 (Week 6) visits.
Safety	The incidence of all adverse events reported during the study will be summarized by treatment group. Test and reference product will be compared for safety by analyzing nature, severity and frequency of treatment emergent adverse events.

List of Abbreviations

AE	Adverse Event
ANOVA	Analysis of Variance
[redacted]	[redacted]
CMH	Cochran–Mantel–Haenszel test
CAI	Carbonic Anhydrous Inhibitor
CRA	Clinical Research Associate
CRO	Clinical Research Organization
dB	Decibel
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
[redacted]	[redacted]
DCF	Data Correction Form
FDA	US Food and Drug Administration
[redacted]	[redacted]
GCP	Good Clinical Practices
hr	Hour
ICH	International Conference on Harmonization
IOP	Intraocular Pressure
IRB	Institutional Review Board
IU	International Unit
IUD	Intra-Uterine Device
LogMar	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minutes
NSAID	Non-Steroidal Anti-Inflammatory Drug
OH	Ocular Hypertension
OTC	Over the counter
POAG	Primary Open Angle Glaucoma
PI	Principal Investigator
PP	Per-protocol (population)
RLD	Reference Listed Drug
Rx	Prescription
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SITA	Swedish Interactive Testing Algorithm
Sub-I	Sub-Investigator
UPT	Urine Pregnancy Test

1. BACKGROUND

[redacted]

2. STUDY OBJECTIVE

The objective of the study is to demonstrate bioequivalence of brinzolamide ophthalmic suspension 1% (Perrigo Pharma International DAC) to Azopt® (brinzolamide ophthalmic suspension) 1% (Novartis Pharmaceutical Corporation) by comparing their efficacy and safety in the treatment of subjects with Primary Open Angle Glaucoma (POAG) or Ocular Hypertension (OH) in both eyes.

2.1. Endpoint

The primary efficacy endpoint is mean change from baseline in IOP of both eyes at four time points, i.e., at approximately 8:00 a.m. (hour 0; before the morning drop) and approximately 10:00 a.m. (hour 2) on Day 14 (Week 2) and Day 42 (Week 6) visits.

2.2. Safety

Safety of the test and reference products will be compared by evaluating the nature, severity and frequency of their adverse event profiles. All adverse events that occur during the study will be recorded whether or not they are considered to be related to the study medication. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution. Comparisons between the treatment groups will be made by tabulating the frequency of subjects with one or more adverse events (classified into MedDRA terms) during the study. Pearson's Chi-Square test or Fisher's Exact test, whichever is most appropriate, will be used to compare the proportion of subjects in each treatment group with any adverse event. The adverse events reported by at least five percent of the subjects in any treatment group will be summarized descriptively.

3. STUDY DESIGN

The study will be conducted as a multi-center, double-masked, randomized, active-controlled, parallel-group study, comparing the test product, brinzolamide ophthalmic suspension 1%, to the reference product, Azopt® (brinzolamide) ophthalmic suspension 1%, in subjects diagnosed with open angle glaucoma or ocular hypertension in both eyes.

Eligible subjects will be randomized in a double-masked manner, [redacted] to either the test product or reference product. The study consists of a run-in phase and a six-week treatment (42 ± 4 days) period.

Screening and run-in phase: [redacted]

Randomization and double-masked treatment phase: [redacted].

[redacted]

3.1. Patient Population

[redacted] subjects will be enrolled [redacted] to obtain approximately per protocol subjects. [redacted]

4. STUDY SUBJECT SELECTION

4.1. Inclusion Criteria

1. Subjects 18 years or older must sign an Institutional Review Board (IRB) approved written informed consent prior to any study related procedures being performed. [redacted]
2. Male or non-pregnant females aged at least 18 years.
3. Subjects with Primary Open Angle Glaucoma (POAG) or Ocular Hypertension (OH) in both eyes.
4. [redacted]
5. [redacted]

[redacted]

[redacted]

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

[redacted]

[redacted]

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

*[redacted]

6. Baseline (Day 0/hour 0) IOP of ≥ 22 mm Hg and ≤ 34 mm Hg in **each eye** and any asymmetry of IOP between the eyes no greater than 5 mm Hg.

[redacted]

8. [redacted]

9. Subjects are willing and able to understand and comply with the requirements of the study, apply ophthalmic drops in both eyes as instructed (or have a caregiver who is able to apply the ophthalmic drops), return for the scheduled study visits, and comply with therapy prohibitions.

4.2. Exclusion Criteria

1. Females who are pregnant, breast feeding, or planning a pregnancy during the study.
2. Females of childbearing potential who do not agree to use an adequate form of contraception (Section 5.9).
3. Known or suspected substance abuse (e.g., alcohol, marijuana, etc.) and/or any other medical or psychological condition(s) that in the investigator's opinion precludes study enrollment.
4. [redacted]
7. [redacted].
8. Current disease or in the opinion of the investigator have a history of significant ocular disease, [redacted] within three months prior to baseline.
9. [redacted]
16. [redacted].
17. Contraindication to brinzolamide or sulfonamide or known hypersensitivity to any component of the study medication or sulfonamide therapy.
18. [redacted]

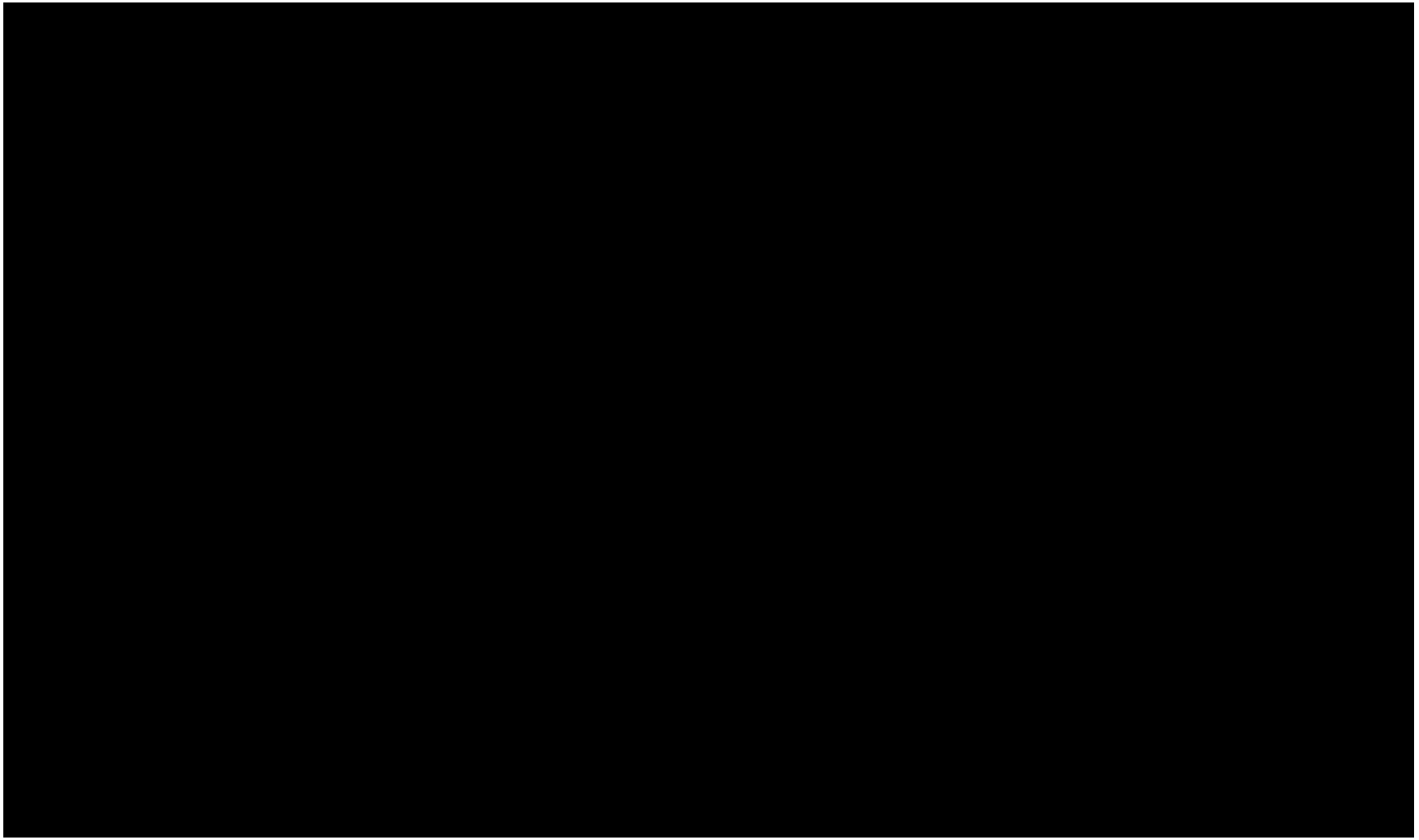
[redacted]

30. Participation (randomized) in any clinical study involving an investigational product, agent and/or device in the thirty (30) days prior to the Screening Visit.
31. [redacted]

33. Subject who in the opinion of the investigator, is unlikely to be able to follow the restrictions of the protocol and complete the study.
34. Have a condition/circumstance which, in the Investigator's opinion, may put the subject at a significant risk, may confound study results, and/or may interfere significantly with the subject's participation in the study.

4.3. Prohibited Medications and Activities

The following medications and procedures are prohibited as outlined below.



4.4. Precautions

The precautions below are to be discussed with and followed by subjects during this study.

Hygiene: Subjects must wash their hands prior to and after applying the study medication.

[redacted]

5. STUDY PROCEDURES

5.1. Study Medication Masking

[redacted]

[redacted]

5.2. Dosing Regimen Overview

Eligible subjects [redacted] will return for baseline assessments at Visit 2/Day 0. Subjects who meet the inclusion criteria and do not meet any of the exclusion criteria at Visit 2 will be randomized [redacted] to either the test or reference product for six (6) weeks (42± 4 days) of treatment. During the treatment phase, subjects will apply one drop of the study medication in each eye three (3) times daily at approximately 8:00 am, 4:00 pm and 10:00 pm.

[redacted]

[redacted]

[redacted]

Study medication compliance will be assessed following review of subject diaries.

5.3. Subject Screening and Informed Consent

The study personnel will review the IRB approved informed consent form with each subject, give the subject an opportunity to have all questions answered, and ensure that the consent form is executed prior to any study related procedures being performed. Subjects 18 years or older must sign an Institutional Review Board (IRB) approved written informed consent. [redacted]

5.4. Assignment of Subject Number

Once potential subjects sign the informed consent document, they will be given a Screening Number. [redacted]

At Visit 2/ Day 0, subjects that qualify for the randomized treatment phase of the study will be dispensed a kit which will identify their **Subject Number**. [redacted]

5.5. Medical History

A demographic profile and complete medical history will be recorded prior to dispensing study medication. The medical history will include a complete review of all current diseases and their respective treatments.

5.6. Ocular History

A complete ocular and surgical history will be recorded prior to starting study medication. The ocular history will include a complete review of all prior and current ocular diseases and their respective treatments.

5.7. Prior and Concomitant Medications

Concomitant medications and any medications taken [redacted] prior to signing informed consent will be recorded as prior/concomitant medications (using their generic name, if known) with the corresponding indication. [redacted] The medications to be recorded will include prescription and over-the-counter (OTC) medications and dietary supplements. All medications taken on either a regular or "prn" basis, including vitamins, should be recorded on this page prior to starting the study medication. An update of medication taken by the subject during the study is to be recorded at each study visit.

5.8. Vital Signs

Vital signs will be obtained at all visits. Sitting blood pressure and sitting heart rate (after resting for 5 minutes), and temperature will be obtained.

5.9. Pregnancy Test

A urine pregnancy test will be conducted on women of child bearing potential at Visit 1, Visit 2 (Day 0) and Visit 4/Day 42 (±4 days), and if warranted at an unscheduled visit. An investigator may repeat the pregnancy test anytime during the study visit if there is any suspicion or possibility that the subject may be pregnant. [redacted]

5.10. External Eye Exam

External eye exam will be performed at Visit 1. [redacted]

5.11. Iris Color

At Screening/Visit 1, the Investigator will classify the color of the iris [redacted] s Light Iris, [redacted] Dark Iris.

[redacted]

[redacted]

[redacted]

5.12. Intraocular Pressure (IOP) Measurement

The intraocular pressure of both eyes will be measured [redacted]

[redacted]			

[redacted]

As much as possible, the same staff should obtain the IOP for a given subject across all visits.

[redacted]

Subjects whose condition worsens (e.g., IOP ≥ 36 mm Hg in either eye) and require alternate or supplemental therapy for the treatment of their primary open angle glaucoma or ocular

hypertension during the study should be discontinued and provided with effective or alternative treatment.

[redacted]

The time the IOP was measured and the time the dose was instilled will be recorded.

[redacted]

[redacted]

[redacted]		

[redacted]

[redacted]

5.19. Study Medication Dispensing, Dosing and Diary Cards.

Baseline Visit 2/Day 0

At baseline, Visit 2/Day 0, upon meeting the study entry criteria and being randomized, the investigator [redacted] assign a kit (not previously assigned) to the subject. [redacted]

[redacted]

[redacted]

Week 2: Visit 3/Day 14 (±4 days)

At Visit 3, the subjects will return with the used bottle and completed diaries. [redacted]

Week 6: Visit 4/Day 42 (± 4 days)

At Visit 4, the subjects will return with the used bottle(s) and completed diaries. [redacted]

[redacted]

5.20. Schedule of Assessments By Visit

Visit 1 Screening

[redacted]

- [redacted]

[redacted]

[redacted]

Visit 2/Day 0, Baseline

All assessments will be performed on the same day.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Visit 3/Day 14 (± 4 days) or Week 2

[redacted]

Visit 4/Day 42 (± 4 Days) or Week 6. End of Study/Early Termination

[redacted]

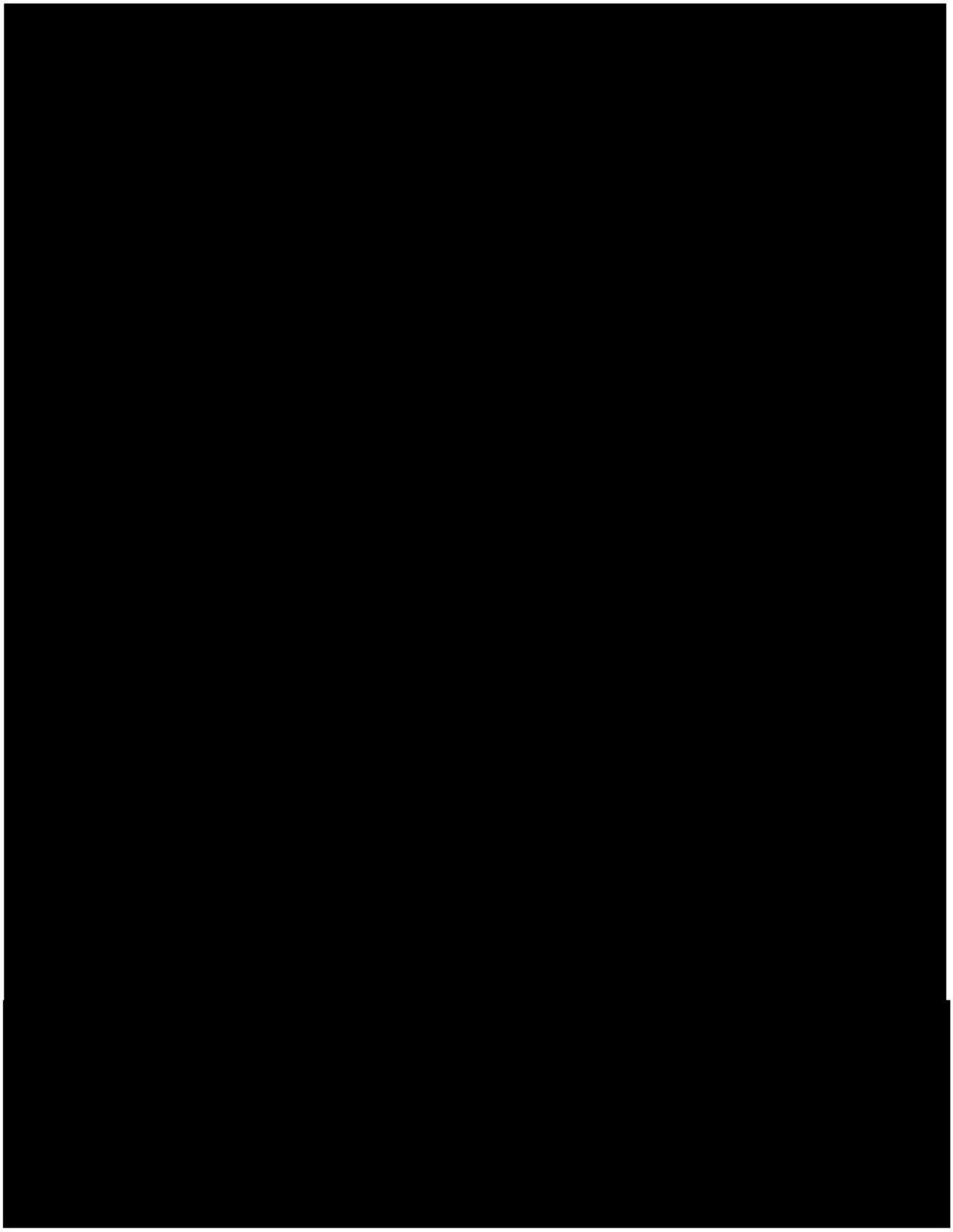
[redacted]

Unscheduled Visits

An unscheduled visit is allowed at any time if in the investigator's opinion it is warranted due an AE or safety concern. [redacted]

[redacted]

5.21. Schedule of Assessments



[redacted]

5.22. Screen Failures

Screen failures are not included in any data analyses. A screen failure is a subject who received information about the study, including signing an informed consent/assent, and possibly underwent some study-related procedures but was not enrolled, dispensed study medication, nor applied the investigational product.

[redacted]

5.23. Protocol Deviations and Violations

This study will be conducted as described in this protocol except for an emergency in which the protection, safety, and well-being of the subject requires immediate intervention, based on the judgment of the investigator or a responsible, appropriately trained and credentialed professional(s) designated by the investigator. In the event of a significant deviation from the protocol due to an emergency, accident or mistake, the investigator or designee must contact Perrigo /CRO contacts at the earliest possible time.

[redacted]

[redacted]

5.24. Subject Treatment Compliance

Compliance will be verified by use of diary cards in which subject will record daily all missed or completed applications. Subjects will be considered compliant if they apply at least [redacted] and not more than [redacted] and do not miss [redacted] consecutive days [redacted] of study medication for either eye

[redacted]

[redacted]

5.25. Reasons for Discontinuation/Withdrawal

The reasons for withdrawal from this study may include but are not limited to:

1. The subject withdraws his or her consent for any reason.
2. In the opinion of the investigator, the IOP is not adequately controlled for a subject's current ocular condition or the subject's condition has worsened to the degree that the investigator feels it is unsafe for the subject to continue in the study or requires an alternative therapy.
3. Adverse event
4. Study treatment is unmasked by either the subject or study staff [redacted]
5. The subject is lost to follow-up. The investigator will document efforts to attempt to reach the subject (at least twice by telephone and via certified letter) before considering that subject lost to follow-up.
6. The subject becomes pregnant during the study.
7. Investigator discretion (e.g. non-compliant to study protocol requirements or subject is deceptive with information provided.)
8. Subject did not meet or no longer meets the entry criteria
9. Other

5.26. Procedures for Early Termination

If a subject withdraws or is removed from the study for any reason, Early Termination Visit/Visit 4 procedures will be completed. Reason for withdrawal, date of the discontinuation, and date of the last dose of study medication should be recorded in the source and eCRF.

If a subject discontinues from the study at any time due to an adverse event, the reason for discontinuation, the nature of the event and its clinical course must be fully documented. For such a subject, the investigator must strive to follow the subject until the adverse event has resolved, become clinically insignificant, is stabilized, or the subject is lost to follow-up.

After a subject has been discontinued, he/she will not be allowed to re-enroll in the study at any facility. Study medication assigned to the withdrawn subject may not be re-assigned to another subject.

6. STUDY MEDICATION AND SUPPLIES

6.1. Study Medication

The study medication supplied by Perrigo will consist of:

Test Product:
Brinzolamide Ophthalmic suspension 1%, 10 mg/ml, 10 ml per bottle
[redacted]

Reference Listed Drug:
Azopt® (Brinzolamide Ophthalmic suspension) 1%, 10 mg/ml, 10 ml per bottle
Novartis Pharmaceutical Corporation
Distributed by Alcon

[redacted]

6.2. Randomization Code

Randomization will be performed by a third party vendor according to a computer-generated randomization schematic [redacted] where each Kit Number will be assigned one of two treatment assignments. An independent clinical packaging vendor will generate and hold the randomization codes throughout the study until formally released after database lock.

6.3. Packaging and labels

Both products are provided in 10 ml plastic dispenser bottles with a dispensing tip and cap.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.4. Procedure for Breaking the Blind

The investigator and the study staff performing the efficacy and safety assessments will be masked to the subject's treatment assignment. In the event of an emergency, the specific subject treatment may be identified by removing the overlay of the blinded label for each subject at each investigator site, which is attached to the study medication log; however, every effort should be made to maintain the blind. **The investigator must not scratch off the**

occluding layer of the label unless absolutely necessary to provide medical treatment to a subject in an emergency situation only and should seek prior authorization by Perrigo or designee when possible. The reason for breaking the blind must be clearly documented in the source documentation and eCRF and the subject must be discontinued from the study. Perrigo must be notified immediately upon all unblinding situations.

6.5. Retention Samples

Each investigational site where study medication is dispensed to at least one subject will be required to randomly select [redacted] retain (reserve) samples. The investigator will maintain [redacted] randomly selected blocks of study medication for each shipment of study medication received. As per the Code of Federal Regulations Part 21, Section 320.38(e), "Each reserve sample shall be stored under conditions consistent with product labeling and in an area segregated from the area where testing is conducted and with access limited to authorized personnel even after the study has concluded. Each reserve sample shall be retained for a period of at least 5 years following the date on which the application or supplemental application is approved, or, if such application or supplemental application is not approved, at least 5 years following the date of completion of the bioavailability study in which the sample from which the reserve sample was obtained was used." The investigator will store the retain sample study medication until such time as notification is received from Perrigo that the samples are no longer required.

6.6. Storage and Test Article Accountability

The investigator should ensure that the study medication is stored under adequate security and regularly monitored and recorded and at temperature of 4°-30°C (39°-86°F).

The investigator will not supply study medication to any person not enrolled in this study, or to any physician or scientist except those named as sub-investigators.

The third party dispenser and study monitor (CRA) will perform drug accountability and reconciliation tasks. A running inventory of dispensed study medication will be kept that will include kit number, the date each bottle of study medication was dispensed, and date returned. A study medication accountability form will be provided to the investigator to document all medication bottles received and used by each subject.

At the conclusion of the study all returned unused, partially used, and empty bottles will be inventoried by the CRA and/or third party dispenser and returned to Perrigo's designee for destruction.

7. ADVERSE REACTIONS

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

7.1. Departure From the Protocol For Individual Subjects

When an emergency occurs requiring a subject departure from the protocol, departure will be only for that subject. In such circumstances, the investigator or other physicians in attendance will contact the Medical Monitor or Perrigo by telephone and follow-up with a written description as soon as possible. The overseeing IRB should also be notified in accordance with the IRB's guidelines.

7.2. Definitions

An adverse event (AE) is defined as any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

A serious adverse event (SAE) is an adverse event that results in any of the following outcomes:

- death
- life-threatening event (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death
- requires in-subject hospitalization or prolongs hospitalization
- a persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- congenital anomaly/birth defect

- Other adverse events that may be considered serious based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Immediately Reportable Adverse Events (IRAE): Any serious AE or any AE that necessitates discontinuation of study medication, including pregnancy.

Unexpected Adverse Event: An unexpected event is any adverse drug experience, the specificity or severity of which is not consistent with the current approved product labeling (package insert) for the study medication, the Investigator's Brochure, or as described in the clinical protocol and consent materials.

Intensity of Adverse Events:

The maximum intensity of an AE during a day should be recorded on the CRF. If the intensity of an AE changes over a number of days, then separate entries should be made having distinct onset dates for the changes in severity.

Mild - AEs are usually transient, requiring no special treatment, and do not interfere with subject's daily activities.

Moderate - AEs typically introduce a low level of inconvenience or concern to the subject and may interfere with daily activities but are usually ameliorated by simple therapeutic measures.

Severe - AEs interrupt a subject's usual daily activity and traditionally require systemic drug therapy or other treatment.

Causal Relationship to Study Medication

The following criteria should be used in assessing the apparent causal relationship of an AE to study medication.

Definitely- The AE follows a reasonable temporal sequence from study medication administration abates upon discontinuation of the study medication (dechallenge) is confirmed by reappearance of the reaction on repeat exposure

Probably - The AE follows a reasonable temporal sequence from study medication administration abates upon discontinuation of the study medication (dechallenge) cannot be reasonably explained by the known characteristics of the subject's state.

Possible - The AE follows a reasonable temporal sequence from study medication administration but that could readily be produced by a number of other factors.

Unlikely - The AE follows a reasonable temporal sequence from study medication administration could have been produced by either the subject's clinical state or by study medication administration.

Not related - The AE does not have a reasonable temporal association with the administration of study medication has some other obvious explanation for the event.

7.3. Eliciting and Reporting of Adverse Events

The investigator will periodically assess subjects for the occurrence of adverse events. [redacted] All adverse events (as defined in Section 7.2), either observed by the investigator or one of his/her medical collaborators, or reported by the participant spontaneously, or in response to direct questioning, will be reported and documented in the source document and the study reporting forms. When reporting an adverse event, the investigator must assign a severity grade to each event and declare an opinion on the relatedness of the event to the study medication or procedure. Serious or unexpected adverse events must be reported [redacted] within 24 hours of when the investigator first learns of the occurrence of the event.

Adverse events will be documented in the source document and recorded in a timely manner on the eCRFs. Adverse events that are identified at the last assessment visit (or the early termination visit) must be recorded on the AE eCRF with the status of the AE noted.

Adverse event reporting begins from the signing of informed consent. Adverse events should be followed until resolved or 30 days after the final study treatment. In any case, serious adverse events that are not resolved or considered to be chronic within 30 days of the final study treatment must be followed by the investigator until they become resolved or are considered to be chronic (stabilized for at least 30 days). All events that are ongoing at this time will be recorded as ongoing on the eCRF.

7.4. Expedited Reporting Responsibilities of the Study Center

For any serious or unexpected adverse event, [redacted] must be notified within 24 hours of when the investigator first learns of the occurrence of the event. Expedited reporting requirements for serious adverse events are described below. Adequate information must be collected with supporting documentation to complete a standard report for submission to Perrigo. The adverse event term on the AE eCRF and the SAE report should agree exactly. Special attention should be given to recording hospitalizations and concomitant medications.

Subjects with unresolved adverse event(s) or serious adverse event(s) should be followed by the investigator until the events are resolved, events determined to be chronic, or the subject is lost to follow-up. Resolution means the subject has returned to the baseline state of health, or the investigator does not expect any further improvement or worsening of the adverse

event. The investigator should continue to report any significant follow-up information to the sponsor up to the point that the event has resolved. Any serious adverse event reported by the subject to the investigator that occurs within 30 days after the last assessment and is determined by the investigator to be reasonably associated with the use of the study medication, should be reported to the sponsor within 24 hours of when the investigator first learns of the occurrence of the event.

When reporting an SAE, the investigator (or designated study staff) will promptly report any serious adverse event or pregnancy by telephone [redacted] or by [redacted] immediately after the investigator becomes aware of the event. An SAE form should be completed and sent by fax, email, or overnight courier [redacted] within 24 hours of knowledge of the event by the site. In many cases, only preliminary information will be available. Appropriate follow-up information should be sought (hospital discharge summaries, operative reports, etc.) and a follow-up SAE report form submitted. A designation of causality from the study medication should always be included with a follow-up report. Assess and report the causality of the event.

7.5. Submitting an Expedited Safety Report to the IRB

[redacted] supporting documentation for the reported event, the Medical Monitor, in conjunction with Perrigo, will determine if the safety report is eligible for expedited review. [redacted] the initial event and will notify the sponsor that an event has been reported within 1 business day after initial receipt. [redacted] the review of the event. This form, as well as other supporting documentation, will be forwarded [redacted] for review. [redacted] finalize the report and distribute it to the sponsor within 1 day (one) after initial receipt. When expedited safety reporting to regulatory authorities is indeed required, the investigator should review and update any newly available materials at once. Follow-up queries may be sent to the study center to further clarify the event.

Each expedited safety report will routinely include a brief cover memorandum, the completed report, and any additional pertinent information recommended by [redacted] Perrigo, or the study Medical Monitor. Once the report is assembled, the Principal Investigator must submit the expedited safety report to the IRB within the required reporting timeframe. Follow-up reports should be submitted when requested or when pertinent information becomes available.

When a Principal Investigator receives an expedited safety report from [redacted] the sponsor detailing adverse events occurring at other study centers under this protocol, it must be promptly submitted to the study center's IRB. The Principal Investigator must retain a copy of such reports as submitted to his/her IRB in the site's study Regulatory Binder.

7.6. SAE & AEs Requiring Discontinuation of Study Drug, including Pregnancies

ANY SAE THAT OCCURS AFTER A SUBJECT HAS ENTERED THE STUDY, WHETHER OR NOT RELATED TO STUDY MEDICATION, MUST BE REPORTED [redacted] IMMEDIATELY (WITHIN 24 HOURS) VIA TELEPHONE OR FACSIMILE. IF INITIALLY REPORTED VIA TELEPHONE, THIS MUST BE FOLLOWED-UP BY A FACSIMILE OF THE WRITTEN SAE REPORT WITHIN 24 HOURS OF THE CALL [redacted]

Non-serious events that require discontinuation of study medication (including laboratory abnormalities) should be reported [redacted] immediately and within 1 working day. Subjects who discontinue due to experiencing adverse events should be followed clinically until their health has returned to baseline status or until all parameters have returned to normal. It is expected that the investigator will provide or arrange appropriate supportive care for the subject.

A subject who experiences a severe adverse event related to study drug will be discontinued from the study.

The notification about any serious adverse event should be directed to:

CRO will forward to:

[redacted]

7.7. Pregnancy

At the time some Principal Investigator or site personnel becomes aware that a study participant became pregnant following study participation, the Principal Investigator or designee will report the pregnancy immediately by phone and/or by faxing a completed Pregnancy Report to CRO **within one working day** of being notified of the pregnancy report.

The report will include the following elements:

- Participant (mother's) coded study identifier;
- Date of participant's last menstrual period;
- Total accumulated dose of study treatment administered to date;
- Date of study medication administration.

The investigator will follow the subject until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days within completion of the pregnancy.

Upon delivery, miscarriage or abortion, the Principal Investigator or designee must forward a follow-up Pregnancy Report with any relevant information on the present condition of the fetus [redacted] including:

- Mother's coded study identifier(s);
- Gestational age at delivery, miscarriage or abortion;
- Birth weight, gender, length and head circumference, if available;
- Apgar scores recorded after birth, if available;
- Any abnormalities.

If the outcome of the pregnancy **meets the criteria for immediate classification of an SAE** (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the investigator will report the event by phone and by faxing a completed SAE report form to CRO within one working day of being notified of the pregnancy report.

If the study is completed before the outcome of the pregnancy is known, CRO will assume the responsibility for following up on the pregnancy. CRO will contact the Investigator or Study coordinator on or around the potential expected date of delivery to follow-up on the outcome of pregnancy and will also check on the status of the infant 8 weeks post-delivery. Upon awareness of the pregnancy outcome and known status of the infant following 8 weeks

of delivery, the investigator will complete the applicable pregnancy report forms and fax [redacted] within 1 day of being notified.

7.8. Post Study Events

Non-serious Adverse Events

Adverse events that are identified at the last assessment visit (or the early termination visit) must be recorded on the AE eCRF with the status of the AE noted. These adverse events must be followed by the investigator until the events are resolved, events determined to be chronic or the subject is lost to follow-up. Resolution means the subject has returned to the baseline state of health or the investigator does not expect any further improvement or worsening of the adverse event.

Serious Adverse Events

Serious adverse events that are identified on the last assessment visit (or the early termination visit) must be recorded on the AE eCRF page and reported to Perrigo according to the procedures outlined above. Subjects with unresolved previously reported serious adverse events, or any new serious adverse events identified on the last assessment visit, should be followed by the investigator until the events are resolved, or the subject is lost to follow-up. Resolution means the subject has returned to the baseline state of health or the investigator does not expect any further improvement or worsening of the adverse event. The investigator should continue to report any significant follow-up information to Perrigo up to the point that the event has resolved. Any serious adverse event reported by the subject to the investigator that occurs after the last assessment and is determined by the investigator to be reasonably associated with the use of the study drug, should be reported to Perrigo.

8. Statistical Analysis

8.1. Statistical Analysis Plan

A statistical analysis plan (SAP) will be prepared separately from this protocol to describe the statistical methods, models, hypotheses and subject populations to be analyzed. The SAP will be completed and approved before locking the database and unmasking the study.
All statistical tests will be 2-sided with a significance level alpha=0.05. Data will be summarized using descriptive statistics (number of subjects [n], mean, standard deviation [SD], median, minimum, and maximum) for continuous variables and frequency and percentage for discrete variables. Subject listings of all data from the eCRFs as well as any derived variables will be presented.

8.2. Analysis Populations

The following populations are defined for analyses:

- The Safety Population

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

- Per Protocol (PP) Population:

  The accepted PP population used for BE evaluation includes all randomized subjects who:
  - meet all inclusion/exclusion criteria,
  - received and used study medication
  - [redacted]
  - complete IOP evaluations for both eyes at Visit 3/Day 14 (week 2) and Visit 4/Day 42 (week 6) within the designated visit window (i.e. +/- 4 days for each visit),
  - have no significant protocol violations that could have interfered with the administration of the treatment or the precise evaluation of treatment efficacy.

[redacted]

8.3. Planned Analysis

The safety analysis will be performed for the safety subjects while the efficacy analysis will be conducted on the PP population.

8.4. Sample Size

[redacted]

8.5. Efficacy Measures and Analysis

Clinical endpoints

The primary efficacy endpoint is mean change from baseline in IOP of both eyes at four time points, i.e., at approximately 8:00 a.m. (hour 0; before the morning drop) and approximately 10:00 a.m. (hour 2) at Day 14 (Week 2) and Day 42 (Week 6) visits. The IOP at hour 8:00 a.m. (hour 0) on day 0 will serve as baseline for IOP at hour 8 a.m. for days 14 and 42, while IOP at hour 10 a.m. (hour 2) on day 0 will serve as baseline for IOP at hour 10 a.m. for days 14 and 42. The hypothesis testing for statistical bioequivalence at each of the four time points [redacted]

For test formulation to be considered bioequivalent to the reference formulation, the limits of each two-sided 95% confidence interval of the treatment difference (test – reference) for mean change from baseline IOP of both eyes at all four follow-up points (i.e., at approximately 8:00 a.m. (hour 0; before the morning drop) and 10:00 a.m. (hour 2) at the Day 14 (week 2) and Day 42 (week 6) visits must be within ± 1.5 mm Hg using the PP and within ± 1.0 mm Hg using the PP population for the majority of time points measured.

[redacted]

[redacted]

8.6. Safety Analysis

The frequency and percent of subjects with adverse events will be summarized by MedDRA system organ class and preferred term and by severity and relationship to study drug for all two treatment groups. [redacted] comparable safety of the Test and Reference treatments will be evaluated by statistical comparison of the proportion of subjects who reported any adverse events. Safety comparisons will be performed on the safety population.

9. CONSENT/ASSENT CONSIDERATIONS AND PROCEDURES

It will be made clear to the subject that, for the purposes of the study, they are consenting only for ophthalmic application of the test or reference product. Investigators may discuss the availability of the study and the possibility for entry with a potential subject without first obtaining consent/assent. However, informed consent/assent must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from current medication(s). When this is done in anticipation of, or in preparation for, the research, it is considered to be part of the research.

The study must be approved in writing by an appropriate IRB as defined by FDA regulations. A copy of the Letter of Approval from the IRB, which also contains specific identification of the documents approved, must be received by Perrigo prior to study commencement.

Periodic status reports must be submitted to the IRB at least annually as required by the site's IRB, as well as notification of completion of the study. A copy of all reports submitted to the IRB by the sites must be sent to Perrigo.

The investigator(s) has both ethical and legal responsibility to ensure that each subject being considered for inclusion in this study is given a full explanation of the protocol. This shall be delivered in the form of a written informed consent/assent form, which shall be approved by the same Institutional Review Board (IRB) responsible for approval of this protocol. Each informed consent/assent form shall include the elements required by FDA regulations in 21 CFR Part 50. The investigator agrees to obtain approval from Perrigo of any written informed consent/assent form used in the study, preferably prior to submission to the IRB.

Once the appropriate essential information has been provided to the subject and fully explained by the investigators (or a qualified delegated designee) the subject has had the opportunity to have all questions answered, and it is felt that the subject understands the implications of participating, the IRB-approved written informed consent/assent form shall be signed by the subject (or their parent/legally authorized representative) and the person

obtaining consent/assent (investigator or designee). The subject shall be given a copy of the signed informed consent/assent form and the investigator shall keep the original on file.

If the subject fails to meet the inclusion/exclusion criteria at the conclusion of the screening phase, the subject will be withdrawn from study participation. In the event that the subject is re-screened for study participation 30 days or more beyond the initial screening, a new informed consent/assent form must be signed.

9.1. Subject Confidentiality

All participants are concerned for the individual subject's privacy and, therefore, all subject data will be identified only by a subject identification number and subject initials. However, in compliance with federal guidelines regarding the monitoring of clinical studies and in fulfillment of his/her obligations to Perrigo, it is required that the investigator permit the study monitor, any Perrigo authorized representative, and/or FDA representatives to review that portion of the subject's medical record that is directly related to the study. This shall include all study relevant documentation including but not limited to subject medical histories to verify eligibility, laboratory test results to verify transcription accuracy, admission/discharge summaries for hospital stays occurring while the subject is enrolled in the study and autopsy reports for deaths occurring during the study.

As part of the required content of informed consent, the subject must be informed that his/her medical chart may be reviewed by Perrigo or their authorized representative, or a representative of the FDA. Should access to the medical record require a separate waiver or authorization, it is the investigator's responsibility to obtain such permission from the subject in writing

To preserve the subject's confidentiality, the data collected will be available only to the investigators of the study, their support staff, Perrigo or their authorized representative and possibly the FDA.

All reports and communications relating to the subject in the study will identify each subject only by the subject's initials and by the Subject Number. The investigator agrees to furnish Perrigo with complete subject identification.

10. CONDUCT OF STUDY

The investigational site is to maintain complete documentation of all subject procedures and when they occur.

10.1. Completion of Study

The investigational site will complete the study and complete all documentation required in satisfactory compliance with the protocol.
It is agreed that, the investigator or Perrigo may terminate this study before completion and shall provide written notice of such termination.

10.2. Protocol Amendments

The Investigator will not make any changes to this protocol nor intentionally deviate from this protocol without prior written consent from Perrigo and subsequent approval by the IRB. Any permanent change to the protocol, whether it is an overall change or a change for specific study center(s), must be handled as a protocol amendment.

When in the judgment of the reviewing IRB, the investigators and/or Perrigo, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the subject, the currently approved written informed consent form will require similar modification. In such cases, additional informed consent will be obtained from subjects enrolled in the study before expecting continued participation.

11. RECORDS MANAGEMENT

11.1. Data Collection

Database set-up will be performed [redacted] using an appropriate fully validated, 21 CFR Part 11 compliant Electronic Data Capture (EDC) system. eCRFs will be provided to each site via a secured web link. All applicable study data collected on each subject will be recorded by approved site personnel into the eCRF. Only authorized site personnel will be able to enter/modify/correct data to the eCRF.

Approved staff at the CRO will verify all data entered into eCRFs for completeness and accuracy with reference to the source documents and records and will issue data queries to correct missing data or discrepancies found against the source within the EDC system.

Data validation will consist of automated and manual edit checks that are created directly into EDC. Automated edit checks will be executed on all data points defined and documented by the study team and data management. Study metrics will be reported from the EDC system.
After all data have been verified by approved staff at the CRO, an Investigator or Sub-Investigator (listed on Form FDA 1572) is required to review and approve all eCRFs prior to database lock and breaking of the blind.
Quality assurance verification via a 10% database audit of eCRF data will be conducted before the treatment assignment code is broken.

During each subject's visit to the clinic, a designee participating in the study will record progress notes to document all significant observations. At a minimum, these notes will contain the following information about the following procedure at the visits they occur:

a) Documentation of the informed consent process (when obtained)
b) The date of the visit and the corresponding Visit or Week in the study schedule;
c) General subject status remarks, including any significant medical findings. The severity, frequency, and duration of any adverse events and the investigator's assessment of relationship to study medication must also be recorded.

d) Any changes in concomitant medications or dosages;
e) A general reference to the procedures completed; and
f) The signature (or initials) and date of all clinicians who made an entry in the progress notes.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above.

Any changes to information in the study progress notes and other source documents, will be entered in **black or blue ink**, **initialed** and **dated** by the authorized person making the correction/addition. Changes will be made by striking a single line through erroneous data, and clearly entering the correct data. (e.g., ~~wrong data~~ right data). Entries may not be erased or masked with white-out fluid. If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change by the clinician.

For transmission to Perrigo, information from the study progress notes and other source documents will be entered into the database. The database also contains a complete audit trail to capture all regulatory components of data corrections (e.g. initial entry, new value, initials and date of the change).

11.2. Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, progress notes and screening logs. All source documents pertaining to this study will be maintained by the investigators and made available for inspection by authorized persons. The original signed informed consent form for each participating subject shall be filed with records kept by the investigators and a copy given to the subject.

11.3. File Management at the Study Site

It is the responsibility of the investigator to ensure that the study center file is maintained in accordance with Section 8 of the International Conference on Harmonization (ICH) Guideline for Good Clinical Practices (GCP).

Records Retention at the Study Site

FDA regulations require all investigators participating in clinical drug studies to maintain detailed clinical data for one of the following periods:

a) A period of at least two years following the date on which a New Drug Application is approved by the FDA;
b) A period of two years after Perrigo notifies the investigator that no further application is to be filed with the FDA.

The investigator must not dispose of any records relevant to this study without either (1) written permission from Perrigo or (2) providing an opportunity for Perrigo to collect such

records. The investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study, including any data correction forms (DCFs) received from CRO. Such documentation is subject to inspection by Perrigo and the FDA.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Monitoring

Perrigo has ethical, legal and scientific obligations to carefully follow this study in a detailed and orderly manner in accordance with established research principles and FDA regulations. All medical records (source documents) of the subjects participating in this study must be presented for review and verification of eCRFs.

12.2. Auditing

Perrigo (or representative) may conduct audits at the study center(s). Audits will include, but are not be limited to drug supply, presence of required documents, the informed consent process, and comparison of case report forms with source documents. The investigator agrees to participate with audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may also audit the investigator during or after the study. The investigator should contact Perrigo immediately if notified of such an audit and must fully cooperate with the audits conducted at a reasonable time in a reasonable manner.

13. ETHICS AND RESPONSIBILITY

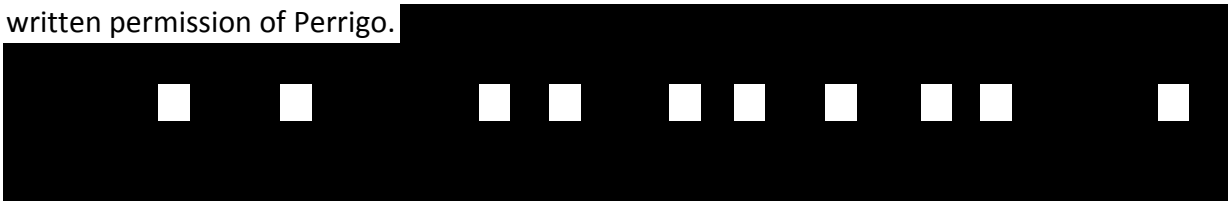
This study must be conducted in compliance with the protocol, the United States Food and Drug Administration (FDA) regulations, any other countries regulations, and ICH GCP Guidelines.

14. USE OF INFORMATION AND PUBLICATION

All information supplied by Perrigo in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, data, materials (i.e. the clinical protocol, case report forms), equipment, experience (whether of a scientific, technical, engineering, operational, or commercial nature), designs, specifications, know-how, product uses, processes, formulae, costs, financial data, marketing plans and direct selling systems, customer lists and technical and commercial information relating to customers or business projections used by Perrigo in its business. Any data, inventions, or discoveries collected or developed, as a result of this study is considered confidential. This confidential information shall remain the sole property of Perrigo, shall not be disclosed to any unauthorized person or used in any unauthorized manner without written consent of Perrigo, and shall not be used except in the performance of the study. As such, confidential study-related information should not be included on the curriculum vitae of any participating investigator or study staff.

The information developed during the course of this clinical study is also considered confidential and will be used by Perrigo in connection with the development of the drug. The information may be disclosed as deemed necessary by Perrigo to allow the use of the information derived from this clinical study, the investigator is obliged to provide Perrigo with complete test results and all data developed in the study. The information obtained during this study may be made available to other investigators who are conducting similar studies.

The investigator shall not make any publication related to this study without the express written permission of Perrigo.



INVESTIGATOR AGREEMENT

PROTOCOL NUMBER: PRG-NY-19-001

PROTOCOL TITLE:

A Multi-Center, Randomized, Double-Masked, Active Controlled, Parallel Group Bioequivalence Study with Clinical Endpoint Comparing Brinzolamide Ophthalmic Suspension 1% of Perrigo Pharma International DAC to Azopt® (brinzolamide ophthalmic suspension) 1% of Novartis Pharmaceuticals Corporation in the Treatment of Primary Open Angle Glaucoma or Ocular Hypertension in Both Eyes.

I have carefully read 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, ICH Guidelines for Good Clinical Practices, the Code of Federal Regulations, the Health Insurance Portability and Accountability Act (HIPAA) and any local regulatory requirements and will attempt to complete the study within the time designated. I will provide access to copies of the protocol and all other information relating to pre-clinical and prior clinical experience submitted by Perrigo to all personnel responsible to me who participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study. I agree to keep records on all subject information in accordance with FDA regulations.

_____

Principal Investigator's Printed Name

_____

Principal Investigator's Signature

_____

Date

15. APPENDICES

15.1. Appendix A: Study Personnel Contacts

15.2. Appendix B: Subject Instructions

SUBJECT INSTRUCTIONS
Perrigo Study # PRG-NY-19-001

Check Visit Dispensed: Visit 2: ☐ Visit 3: ☐ Unscheduled visit: ☐ Date: _____

SUBJECT INITIALS: ___ ___ ___ SITE NUMBER ____ ____ SUBJECT NUMBER: ___ ___ ___ ___

STORAGE AND HANDLING

STORE THE STUDY MEDICATION AT 4°- 30°C (39°-86°F). DO NOT FREEZE, AVOID HIGH TEMPERATURE BY NOT LEAVING IN YOUR CAR.

[redacted]

[redacted]

APPOINTMENT

You are scheduled to return at:

_____AT _____ Visit 3, Treatment Week 2
DATE TIME

Reminder:
Don't forget to instill the evening dose the evening before your study visit at about 10:00 pm.
Do not instill the morning dose of study medication on the day of your study visit.

_____ AT_____ Visit 4, Treatment Week 6
DATE TIME

ALL APPOINTMENTS ARE IMPORTANT! IF YOU NEED TO RE-SCHEDULE YOUR APPOINTMENT, PLEASE CALL YOUR STUDY DOCTOR'S OFFICE IMMEDIATELY.

_____
NAME AND TELEPHONE NUMBER OF STUDY COORDINATOR/STUDY SITE

16. References