A Multi-Center, Double-Masked, Randomized, Two-Arm, Parallel-Group, Safety and Efficacy Study to Compare Perrigo Pharmaceuticals International DAC Brinzolamide and Brimonidine Tartrate Ophthalmic Suspension 1%/0.2% to Novartis Pharmaceuticals Simbrinza® (brinzolamide/brimonidine tartrate 1%/0.2% ophthalmic suspension) in the Treatment of Chronic Open Angle Glaucoma or Ocular Hypertension in both Eyes

Protocol No.: PRG-NY-20-002

NCT04944290

Protocol Date: May 27, 2021

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Protocol No.: PRG-NY-20-002

[redacted]

Confidential

PROTOCOL SIGNATURE PAGE

PROTOCOL NUMBER: PRG-NY-20-002

PROTOCOL TITLE: Multi-Center, Double-Masked, Randomized, Two-Arm, Parallel-Group, Safety and Efficacy Study to Compare Perrigo Pharmaceuticals International DAC Brinzolamide and Brimonidine Tartrate Ophthalmic Suspension 1%/0.2% to Novartis Pharmaceuticals Simbrinza® (brinzolamide/brimonidine tartrate 1%/0.2% ophthalmic suspension) in the Treatment of Chronic Open Angle Glaucoma or Ocular Hypertension in both Eyes

[redacted]

Contents

[redacted]

STUDY SYNOPSIS

Title:	Multi-Center, Double-Masked, Randomized, Two-Arm, Parallel-Group, Safety and Efficacy Study to Compare Perrigo Pharmaceuticals International DAC Brinzolamide and Brimonidine Tartrate Ophthalmic Suspension 1%/0.2% to Novartis Pharmaceuticals Simbrinza® (brinzolamide/brimonidine tartrate 1%/0.2% ophthalmic suspension) in the Treatment of Chronic Open Angle Glaucoma or Ocular Hypertension in both Eyes
Study Period:	6 weeks (42 Days)
Study Medication:	1. Brinzolamide and Brimonidine Tartrate Ophthalmic Suspension 1%/0.2% Perrigo Pharmaceuticals International DAC, [redacted] 2. Simbrinza® (brinzolamide/brimonidine tartrate 1%/0.2% ophthalmic suspension), manufactured by Novartis Pharmaceuticals.
Study Objectives:	To compare the safety and efficacy profiles of Perrigo Pharmaceuticals International DAC Brinzolamide and Brimonidine Tartrate Ophthalmic Suspension 1%/0.2% to Novartis Pharmaceuticals Simbrinza® (brinzolamide/brimonidine tartrate 1%/0.2% ophthalmic suspension), in order to prove bioequivalence between them in the treatment of chronic open angle glaucoma or ocular hypertension in both eyes.
Study Design:	Subjects in this multi-center, double-masked, randomized, Two Arm, parallel-group study will be admitted into the study only after written informed consent/assent (as applicable) has been obtained and after all inclusion/exclusion criteria have been met. Male and female subjects at least 18 years with chronic open angle glaucoma or ocular hypertension in both eyes will be eligible for enrollment.
Study Population:	Approximately [redacted] healthy males and females, at least 18 years of age, inclusive, who meet the inclusion/exclusion criteria, will be enrolled to obtain approximately [redacted] per-protocol (PP) subjects.
Dosing:	Subjects will be randomized [redacted] to either the test product or reference product treatment group, respectively, and will apply one drop in both eyes three (3) times daily at approximately 8:00 am, 4:00 pm, and 10:00 pm with all doses having a ± 1 hour window for 6 weeks (42 days).
Study Visits:	Clinical Evaluations will be performed at: Visit 1/Screening Visit 2/Week 1/ Day 0 (Baseline) Visit 3/Week 2/Day 14 (±4 days)(Interim) Visit 4/Week 6/Day 42 (±4 days)(End of study or Early Termination) Safety will be assessed by monitoring adverse events at each visit.
Evaluations:	At Visit 1/Screening the following evaluations: [redacted].

	The intraocular pressure (IOP)/ Goldmann Applanation Tonometry (GAT) [redacted] will be performed and recorded at Visit 2/Baseline and all subsequent visits.
Endpoints:	The primary efficacy endpoint will be the mean change from Baseline in intraocular pressure (IOP) of both eyes at all four time points (e.g., at approximately 8:00 am (hour 0, before the morning drop) and 10:00 am (hour 2) at Visit 3/Week 2/Day 14 (±4 days) and Visit 4/Week 6/Day 42 (±4 days)
Safety:	The incidence of all adverse events reported during the study will be summarized by treatment group. Equivalence of the test and reference with regard to safety will be evaluated by comparing the nature, severity and frequency of their adverse event profiles.

ABBREVIATIONS

AE	Adverse Event
[redacted]	[redacted]
CAI	Carbonic Anhydrous Inhibitor
CI	Confidence Interval
CRA	Clinical Research Associate
COAG	Chronic Open Angle Glaucoma
CRO	Contract Research Organization
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
[redacted]	[redacted]
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
ITT	Intent- to-treat (population)
IU	International Unit
IUD	Intra-Uterine Device
LogMar	Logarithm of the Minimum Angle of Resolution
LS	Least squares
MR	Manifest refraction
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minutes
NSAID	Non-Steroidal Anti-Inflammatory Drug
OH	Ocular Hypertension
OTC	Over the counter
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 OBJECTIVES

The objectives of this study are to compare the efficacy and safety profiles of Perrigo Pharmaceuticals International DAC Brinzolamide and Brimonidine Tartrate Ophthalmic Suspension 1%/0.2% to Novartis Pharmaceuticals Simbrinza® (brinzolamide/brimonidine tartrate 1%/0.2% ophthalmic suspension), in order to prove bioequivalence between them in the treatment of chronic open angle glaucoma or ocular hypertension in both eyes.

2.1 Endpoint

The primary efficacy endpoint will be the mean change from Baseline in intraocular pressure (IOP) of both eyes at all four time points (e.g., at approximately 8:00 am (hour 0, before the morning drop) and 10:00 am (hour 2) at Visit 3/Week 2/Day 14 (±4 days) and Visit 4/Week 6/Day 42 (±4 days).

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. Descriptions of reactions or complaints will include the approximate date of onset, the date the adverse event ended, the severity of the adverse event, and the outcome. 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

3.1 Type/Design of Study

Subjects in this multi-center, double-masked, randomized, parallel-group study who meet eligibility criteria at Visit 2 /Baseline (Day 0), will be assigned [redacted] to test product or reference product, respectively. One drop of the assigned study medication will be applied in both eyes three (3) times daily at approximately 8:00 am, 4:00 pm, and 10:00 pm for 6 weeks (42 days).

Males and females, at least 18 years of age with chronic open angle glaucoma or ocular hypertension in both eyes will be eligible for enrollment. Visits to the study site are scheduled at Visit 1 /Screening, Visit 2/Baseline (Day 0), Visit 3/Week 2/Day 14 (±4 days) and Visit 4/ Week 6/Day 42 (±4 days).

The study consists of a run-in phase and a six-week treatment (42 ±4 days) duration.

3.1.1 Screening and Run-In Phase

[redacted]

3.1.2 Randomization and Double-Masked Treatment Phase

[redacted]

[redacted]

3.2 Study Population

Male and female subjects, at least 18 years of age, with chronic open angle glaucoma or ocular hypertension in both eyes.

[redacted] healthy male and female subjects will be enrolled at approximately [redacted] per-protocol (PP) subjects.

As much as possible, the study population should consist of subjects with light colored irises and subjects with dark colored irises in similar proportion to the US population.

4 SELECTION AND WITHDRAWAL OF STUDY SUBJECTS

4.1 Inclusion Criteria

Subjects **must** meet all of the following criteria:

1. Subjects must sign an Institutional Review Board (IRB) approved written informed consent for this study before enrolling into the study. [redacted]
2. Subjects must be male or female, at least 18 years of age with chronic open angle glaucoma or ocular hypertension in both eyes.
3. [redacted]

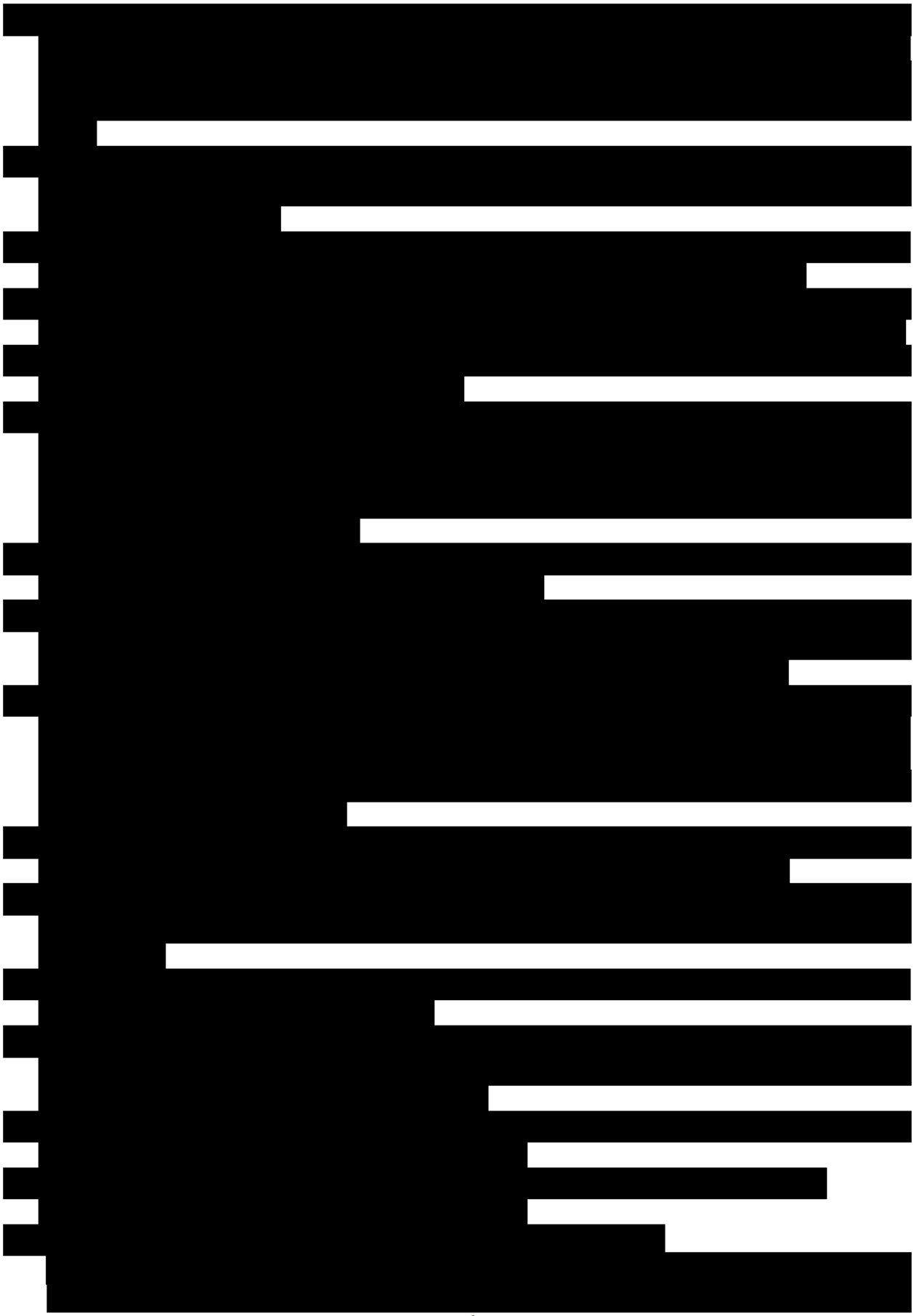
[redacted]

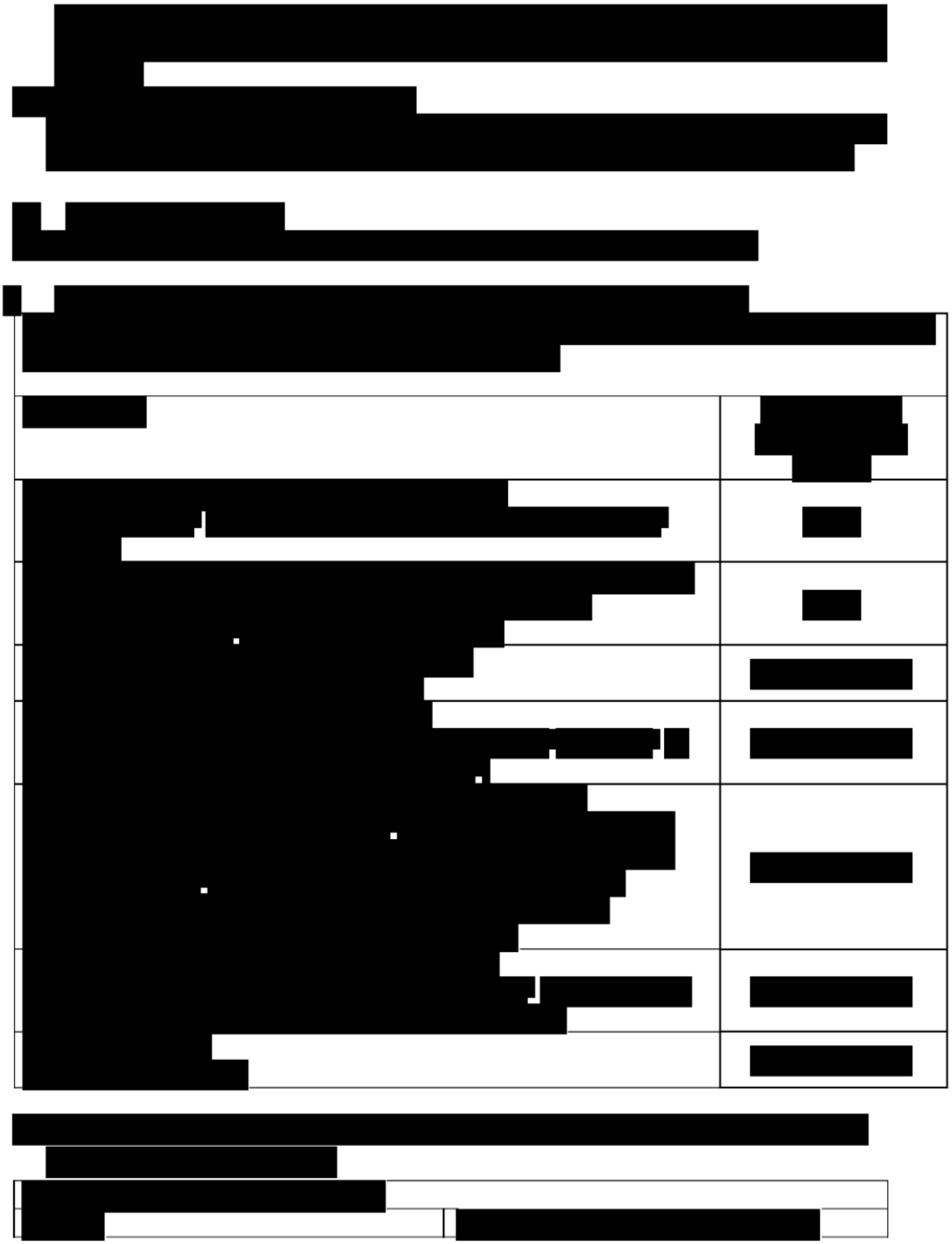
[redacted]

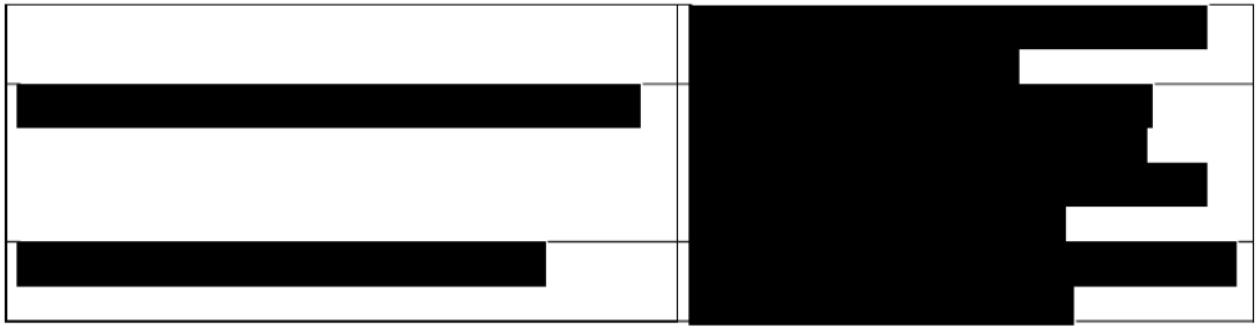
4.2 Exclusion Criteria

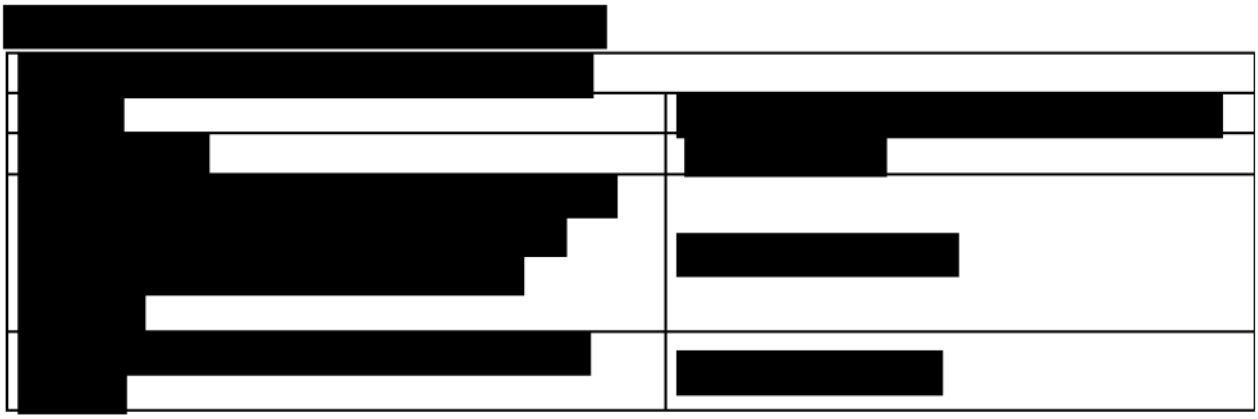
Subjects may **not** be selected if any of the following criteria exist:

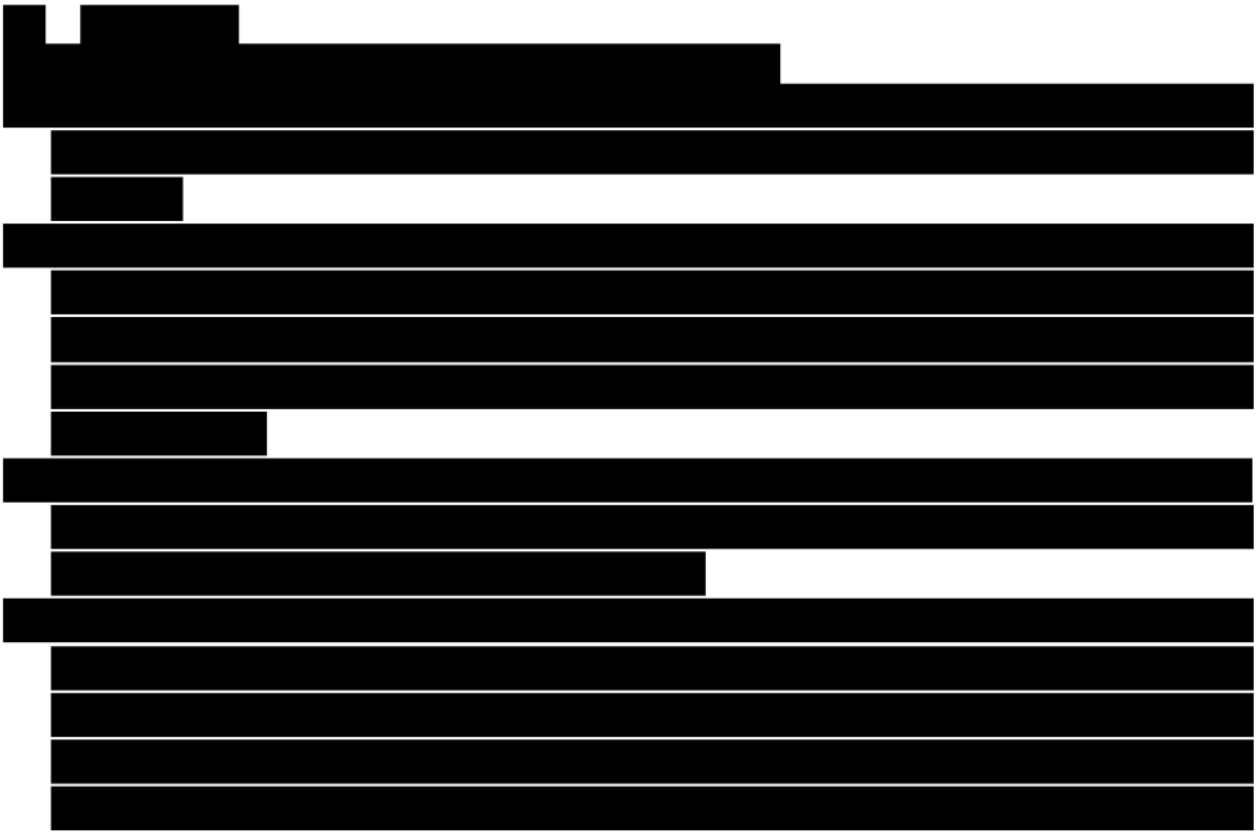
1. Subjects who are pregnant, breastfeeding or planning a pregnancy within the study participation period.
2. Subjects who are females, of childbearing potential who do not agree to utilize an adequate form of contraception.
3. [redacted]











[redacted]

5 PROCEDURES

5.1 Subject Screening, Informed Consent and Enrollment

The study personnel will review the IRB approved informed consent form and assent form (if applicable), with each subject and give the subject an opportunity to have all questions answered before proceeding. The IRB approved informed consent/assent form must be signed by each subject before the subject is enrolled into the study. A copy of the signed consent/assent will be given to every participant (or legally authorized representative) and the original will be maintained with the participant's records. [redacted]

Subjects that require a wash-out of more than 30 days from their initial informed consent/assent signing must be re-consented before any further study procedures can begin.

5.1.1 Assignment of Subject Number

[redacted]

5.2 Demographics/Medical History

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

5.3 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.

[redacted]

[redacted]

5.6 Urine Pregnancy Test

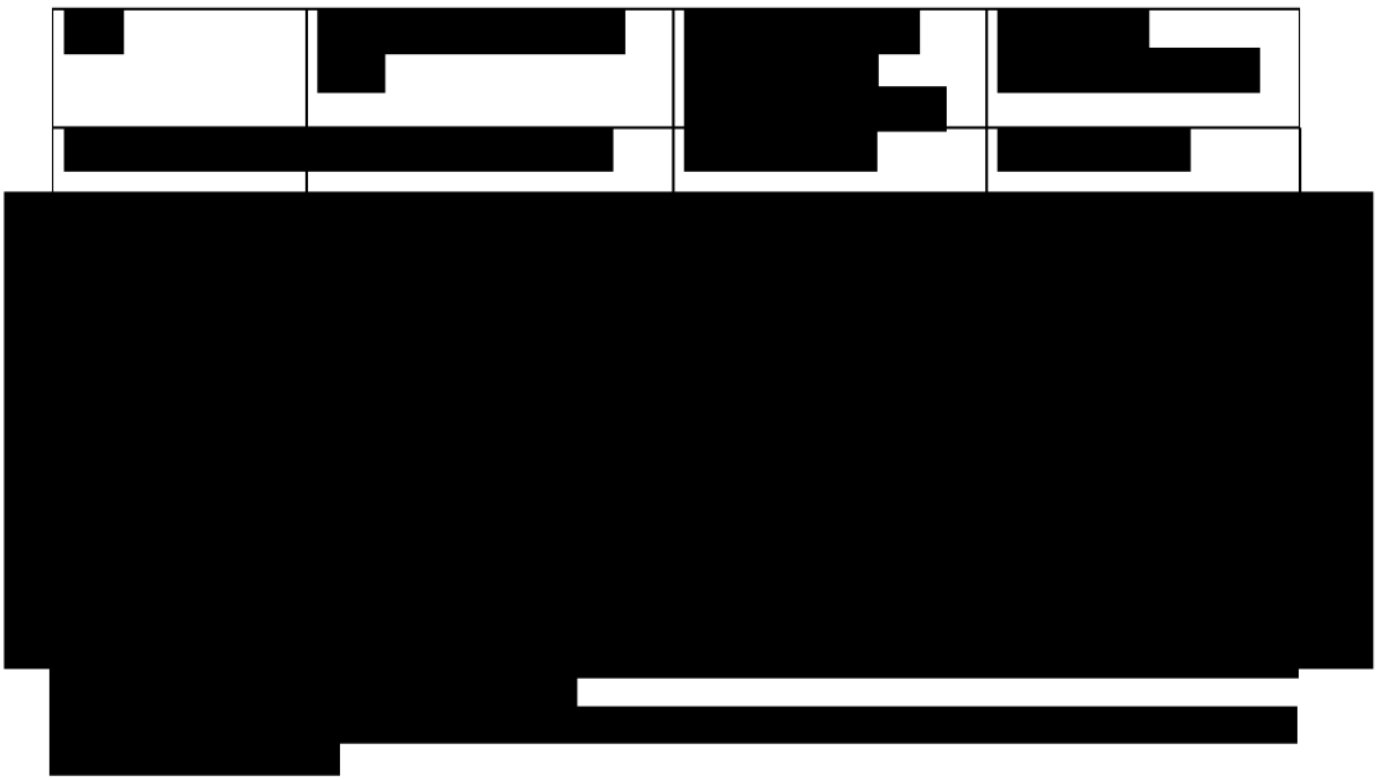
A urine pregnancy test will be conducted at Visit 1/Screening, Visit 2/Baseline /Day 0 (before the subjects applies the first dose of the study medication at the site) and Visit 4/ Week 6/Day 42(+/- 4 days). An investigator may repeat the pregnancy test anytime during the study visit if there is any suspicion or possibility that the subject may be pregnant. Females of childbearing potential (excluding women who are surgically sterilized or post- menopausal for at least 2 years), must have a negative urine pregnancy test at baseline, and must be willing to use an acceptable form of birth control during the study.

[redacted]

[redacted]

5.7.1 Iris Color

At Visit 1/Screening, the investigator or designee will classify the color of the iris of each eye to one of the following categories: Blue, Gray, Green, Hazel, Brown. In the electronic case report forms (eCRFs), [redacted]



[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

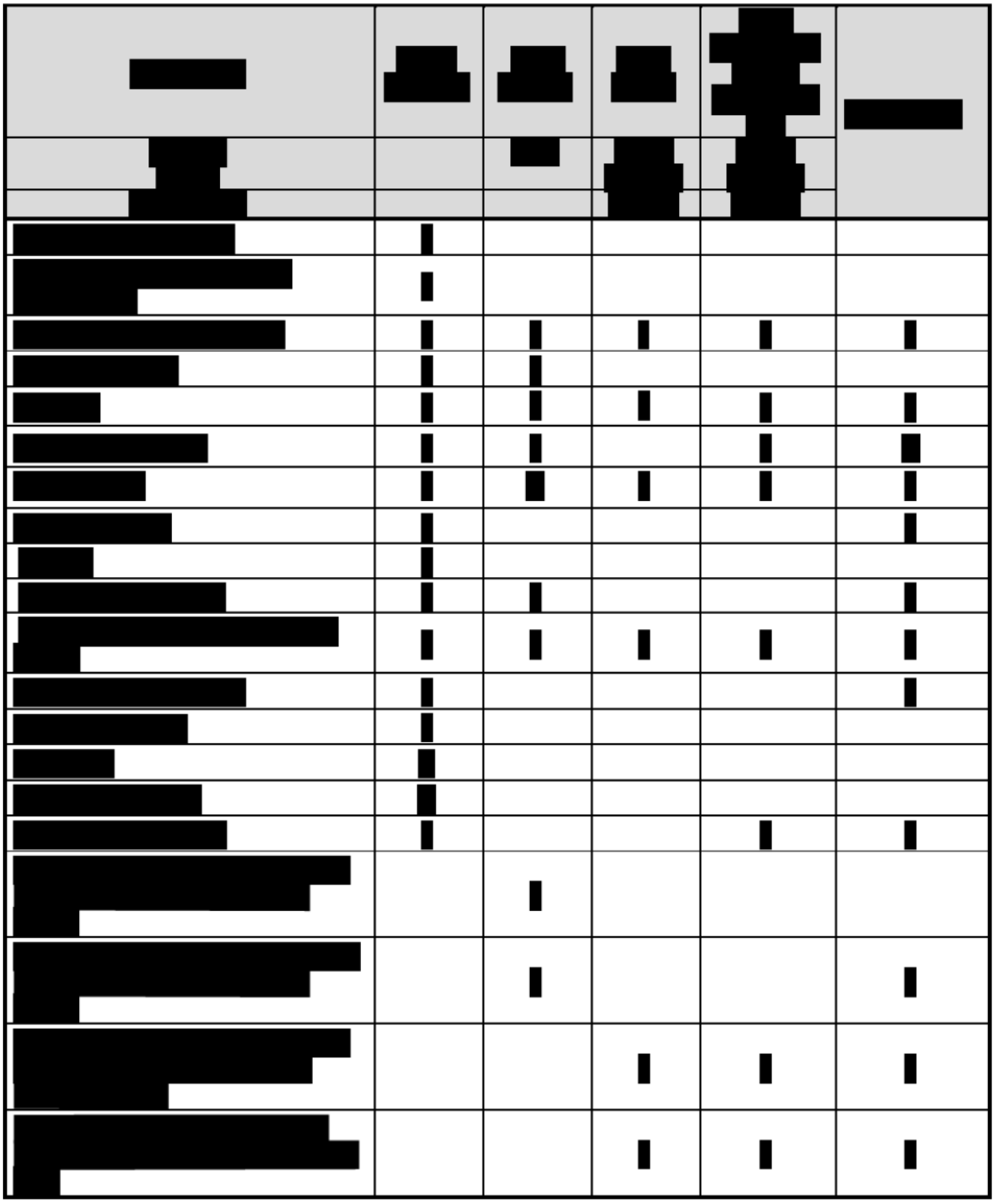
[redacted]





[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.20 Subject/Treatment Compliance

Subjects will instill 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] for 6 weeks (42 days). Subjects should avoid allowing the tip of the dispensing container to come into contact with their eye or the area surrounding the eyes, or other surfaces.

On Day 0, subjects/caregiver will apply their initial dose of study medication at the study site under the supervision of the third-party dispenser staff. Compliance will be determined from the diary card, in which the subject will be instructed to record all applications made or missed. [redacted]

follow-up.

6 MATERIALS AND SUPPLIES

6.1 Study Medication

The study medication supplied by Perrigo will consist of:

Test Product: Brinzolamide and Brimonidine Tartrate Ophthalmic Suspension 1%/0.2%, Perrigo Pharmaceuticals International DAC, [redacted]

Reference Product: Simbrinza® (brinzolamide/brimonidine tartrate 1%/0.2% ophthalmic suspension), manufactured by Novartis Pharmaceuticals.

6.2 Medication Management

6.2.1 Labeling, Packaging and Distribution

[redacted]

All study medications will be supplied to the subjects in 10ml plastic bottles. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.2.2 Retention Samples

Each investigational site where study medication is dispensed to at least one subject will be required to randomly select [redacted] study medication to be maintained as retain samples. The investigator will maintain [redacted] study medication from 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 (in an upright position away from heat and protected from light at temperature, 2°C-25°C (36°F-77°F) even after the study has concluded. At the conclusion of the study, each investigational site should continue to track and record daily the temperature of the storage room where the retention samples are stored and report any temperature excursion to Perrigo and Symbio for the duration of the retention period. Each retention 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 or 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.

6.2.3 Storage and Test Article Accountability

Study articles used to conduct this study will be maintained under adequate security by the investigator or designee. Each investigator site will ensure that the temperature of study medication is monitored and recorded throughout the study. The study medication should be stored at temperature in a secured area with limited access, 2°C-25°C (36°F-77°F), and bottles must be kept in an upright position and tightly closed. The medication should not be frozen, should be protected from light, kept away from children, heat and kept tightly closed. 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 at each investigator site will keep a running inventory of study medication dispensed that will include subject numbers assigned and the date each bottle of study medication is dispensed and returned. A study medication accountability form will be provided to the investigator to document all medications received, dispensed by and used by each subject. The third-party dispenser and monitor will perform drug accountability and reconciliation tasks of the study medication throughout the study.

At the conclusion of the study all unused, partially used, and empty bottles must be inventoried by the third-party dispenser and /or the monitor and returned to Perrigo, or designee, for destruction, with the exception of retention samples which shall remain at the investigator site.

6.2.4 Randomization

[redacted]

6.2.5 Procedure for Breaking the Blind

[redacted]

7 ADVERSE REACTIONS

The potential adverse reactions of generic Brinzolamide and Brimonidine Tartrate Ophthalmic Suspension 1%/0.2%, are anticipated to be similar to those observed in Simbrinza® (brinzolamide/brimonidine tartrate 1%/0.2%) ophthalmic suspension),

The following adverse reactions occurred in 3% to 5% of patients treated with Simbrinza® include blurred vision, eye irritation, dysgeusia (bad taste), dry mouth, and eye allergy may occur.

Other adverse reactions reported with individual active ingredients of Simbrinza® Ophthalmic Suspension

The most frequently reported adverse reactions occurring in 1% to 5% of patients treated with Brinzolamide ophthalmic suspension 1% in clinical studies 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 in 1% of patients treated with Brinzolamide ophthalmic suspension 1%: allergic reactions, chest pain, conjunctivitis, diarrhea, diplopia, dizziness, dry mouth, dyspnea, dyspepsia, eye fatigue, hypertonia, keratoconjunctivitis, keratopathy, kidney pain, lid margin crusting or sticky sensation, nausea, pharyngitis, tearing and urticaria.

The most frequently reported adverse reactions occurring in 10% to 30% of patients treated with Brimonidine Tartrate 0.2% ophthalmic suspension in clinical studies were oral dryness, ocular hyperemia, burning and stinging, headache, blurring, foreign body sensation, fatigue/drowsiness, conjunctival follicles, ocular allergic reactions and ocular pruritus. The following adverse reactions were reported in 3% to 9% of patients treated with Brimonidine Tartrate 0.2% ophthalmic suspension: corneal staining/erosion, photophobia, eyelid erythema, ocular ache/pain, ocular dryness, tearing, upper respiratory symptoms, eyelid edema, conjunctival edema, dizziness, blepharitis, ocular irritation, gastrointestinal symptoms, asthenia, conjunctival blanching, abnormal vision and muscular pain. The following adverse reactions were reported in ≤ 3% of patients treated with Brimonidine Tartrate 0.2% ophthalmic suspension: lid crusting, conjunctival hemorrhage abnormal taste, insomnia, conjunctival discharge, depression, hypertension, anxiety, palpitations/arrhythmias, nasal dryness and syncope.

There is no post marketing experience with Simbrinza® ophthalmic suspension. The following adverse reactions have been identified during post-approval use of brimonidine tartrate ophthalmic solutions in clinical practice, a similar drug containing brimonidine tartrate as an active ingredient are bradycardia, hypersensitivity, iritis, keratoconjunctivitis sicca, miosis, nausea, skin reactions (including erythema, eyelid pruritus, rash, and vasodilation) and tachycardia. pain of skin, pruritus, swelling face, conjunctivitis, skin discoloration, rash, eczema, throat tightness and allergic contact dermatitis.

7.1 Departure from the Protocol for Individual Subjects

When an emergency occurs requiring a departure from the protocol for a subject, departure will be only for that subject. In such circumstances, the investigator or other physician 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 (e.g., 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] ll 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 to [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 (e.g., worsening of chronic open angle glaucoma or ocular hypertension define as IOP ≥ 36 mm Hg in either eye) 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/assent. 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.

7.3.1 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 are 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 a serious adverse event (SAE) the Investigator (or the Study Coordinator) will promptly report any serious adverse event or pregnancy by telephone [redacted] immediately after the investigator becomes aware of the event. An SAE form should be completed and sent by fax, email, or overnight courier to Symbio 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.

7.3.2 Submitting an Expedited Safety Report to the IRB

Once [redacted] receives all supporting documentation for the reported event, the Medical Monitor, in conjunction with [redacted], will determine if the safety report is eligible for expedited review. [redacted] will log the initial event and will notify the sponsor that an event has been reported within 1 business day after initial receipt. [redacted] will complete the review of the event, enter information into their safety database and generate the report. This form, as well as other supporting documentation, will be forwarded to [redacted] Medical Monitor for review. [redacted]

will 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 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] or 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 their IRB in the site's study Regulatory Binder.

7.4 SAE & AEs Requiring Discontinuation of Study Drug, including Pregnancies

ANY SAE, WHICH OCCURS AFTER A SUBJECT HAS ENTERED THE STUDY, WHETHER OR NOT RELATED TO STUDY MEDICATION, MUST BE REPORTED TO [redacted] AND PERRIGO IMMEDIATELY (WITHIN 24 HOURS, OF WHEN THE INVESTIGATOR FIRST LEARNS OF THE OCCURENCE) 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 TO [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:

[redacted]

7.4.1 Pregnancy

At the time a 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 Symbio 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 Symbio within one working day of being notified of the pregnancy report.

If the trial is completed before the outcome of the pregnancy is known, Symbio will assume the responsibility for following up on the pregnancy. Symbio 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 [redacted] within 1 day of being notified.

7.5 Post Study Adverse Events

7.5.1 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.

7.5.2 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 are determined by the investigator to be reasonably associated with the use of the study drug, should be reported to Perrigo.

8 Statistical Analysis

The sections that follow highlight sample size determination and the planned analyses for this study. A statistical analysis plan (SAP) will be prepared separately from this protocol which gives descriptions of the statistical methods, models, hypotheses and subject populations to be analyzed. The SAP will be completed and approved before locking the database and unblinding the study and will serve as a companion to the protocol and the *de facto* documentation of the proposed statistical evaluation. The SAP will be completed and finalized prior to breaking the blind.

8.1 Statistical Analysis Plan

8.1.1 Analysis Populations

The following populations are defined for the purpose of analyses:

- Intent-to-Treat (ITT) (safety population): Any subject that was enrolled, randomized, received and used study medication.

- Per Protocol (PP): Any subject who:
  - met inclusion/exclusion criteria,
  - was randomized, received and used study medication,
  - [redacted]
  - completed IOP evaluations for both eyes at Visit 3/Week 2/Day 14 and Visit 4/Week 6/Day 42 within the designated visit window (±4 days) for each visit
  - had no significant protocol violations that could have interfered with the administration of the treatment or the precise evaluation of treatment efficacy.

[redacted]

8.1.2 Planned Analysis

The safety analysis will be performed for the ITT subjects. The efficacy analysis will be conducted on the PP subjects . Two-sided hypothesis testing will be conducted. Resulting p-values less than 0.05 will be considered statistically significant. No adjustments of p-values for multiple comparisons will be made. No interim analyses are planned. SAS software will be used for all data analyses and tabulations.

The treatment response will be summarized by treatment group.

The primary efficacy endpoint will be the mean change from Baseline in intraocular pressure (IOP) of both eyes at four time points (e.g., at approximately 8:00 am (hour 0, before the morning drop) and 10:00 am (hour 2) at Visit 3/week 2/Day 14 (±4 days) and Visit 4/week 6/Day 42 (±4 days)

[redacted]

[redacted]

[redacted]

8.1.4 Efficacy Measures and Analysis

Clinical endpoints

The primary efficacy measure is the mean change from baseline in IOP of both eyes at four (4) time points (e.g., at approximately 8:00 am (hour 0, before the morning drop) and approximately at 10:00 am (hour 2) at Visit 3/week 2/Day 14 and Visit 4/Week 6/Day 42. The IOP at hour 0 (8:00 am) on Day 0 will serve as baseline for the IOP at hour 8:00am for Day 14 and Day 42, while the IOP at hour 2 (10:00am) on Day 0 will serve as baseline for the IOP at hour 10:00am for Days 14 and Day 42. The hypothesis testing for statistical bioequivalence at each of the four time points will be

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.1.5 Safety and Adverse Events 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 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 only for the safety intent-to-treat population.

8.2 Comparability of Subjects at Baseline

Descriptive statistics will be presented, by treatment group, for subject baseline characteristics. The significance of any obvious treatment group differences will be discussed in the CSR.

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 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 and a final report within three months of study completion or termination. A copy of all reports submitted to the IRB 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

documented on 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 designee) and it is felt that the subject understands the implications of participating and had the opportunity to have all questions answered, 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, thirty days (30) 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 representative 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 subject medical histories to verify eligibility, laboratory test result reports 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 before the subject is entered into the study.

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, if necessary on a confidential follow-up form, which will be used for the purpose of a long-term follow-up, if needed. This will be treated with strict adherence to

professional standards of confidentiality and will be filed at Perrigo under adequate security and restricted accessibility.

10 CONDUCT OF STUDY

The investigational site is to maintain complete documentation of all events and the times at which 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, within 3.5 months of enrollment of the last subject and extending beyond as needed to complete necessary data queries.

It is agreed that, for reasonable cause, either the investigator or Perrigo may terminate this study before completion provided written notice is submitted at a reasonable time in advance of intended termination. Any extension of this study must be mutually agreed upon in writing by both the investigator and Perrigo.

10.2 Protocol Amendments

The Investigator will not make any changes to 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. Any amendment to the protocol that appears indicated as the study progresses will be fully discussed between Symbio LLC and Perrigo. If agreement is reached regarding the need for an amendment, the amendment will be written by Perrigo. The written amendment must be submitted to the chairman of the IRB identified with this responsibility. Except for 'administrative amendments', investigators must await IRB approval of protocol amendments before implementing the change(s). Administrative amendments are defined to have no effect on the safety of the research subjects, scope of the investigation, or quality of the trial. However, a protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately, and the IRB notified within five days. Perrigo will submit protocol amendments to the FDA or other regulatory agencies.

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, repeat informed consent will be obtained from subjects enrolled in the study before expecting continued participation.

10.3 COVID-19 Risk Mitigation

The study center will use risk mitigation to prevent COVID-19 spread. Processes and procedures implemented will be in accordance with guidelines and recommendations issued by World Health Organization (WHO), Centers for Disease Control (CDC), local, federal and Investigator guidelines. Such guidelines shall include pre-screening procedures including questionnaires pertaining to

symptoms of and exposure to COVID-19, encouragement of hand washing and sanitizing, staff use of personal protective equipment (PPE), subjects' and staff use of masks, cleaning and disinfecting procedures of equipment and furniture, and social distancing in the study unit.

10.4 Alternative protocol assessments during the COVID-19 Pandemic only

To mitigate any risks that may occur due to the COVID-19 pandemic that might impact the conduct of the trial, the following may be considered if a site is not able to participate at full capacity or on-site subject participation is compromised due to local regulations caused by COVID-19 restrictions (e.g., temporary site closures, subjects unable to complete on-site visit):

- Sites may be placed on a temporary enrollment hold.
- Remote monitoring visits may be conducted.

10.4.1 Subject Disposition due to COVID-19 Infection

If a subject is confirmed to have tested positive for COVID-19, the investigator will be instructed to record the event as an AE or SAE. The subjects should further be immediately discontinued from study medication and study participation and instructed to quarantine.

10.4.2 Regulatory and Study Oversight Considerations

Remote monitoring may be substituted for physical visits to the site(s) in the event that the CRA or Sites are not able to conduct an on-site visit due to site closure, local or federal guidelines, or safety guidelines in relation to COVID-19.

10.4.3 Documentation of Protocol Deviations related to COVID-19

All protocol violations and protocol deviations (PV/PD) that occur as a result of the COVID-19 pandemic should be documented in the source documents as PV/PDs specifically occurring due to the COVID-19 pandemic. As much as possible, detailed reasons for the PV/PD (e.g., subject is ill, site closed, subject unable to travel to site) should be included in the source documents, including any procedures/activities not undertaken or visits missed as a result of COVID-19. All protocol deviations and AEs impacted by COVID-19 will be documented in the COVID-19 eCRF form.

11 RECORDS MANAGEMENT

11.1 Data Collection

Database set-up will be performed [redacted] in collaboration with the Electronic Data Capture (EDC) vendor, using an appropriate fully validated, 21 CFR Part 11 compliant 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 Symbio will verify all data entered into eCRFs for completeness and accuracy with reference to the source documents and records and will issue manual 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 Symbio, 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.

After database lock, each site will be provided with a password protected USB that will include the eCRF data from their site for local archival purposes.

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:

a) Documentation of the informed consent process;
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 promptly 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/assent 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).

11.4 Records Retention at the Study Site

FDA regulations 21 CFR§312.57 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. Such documentation is subject to inspection by Perrigo and Regulatory authorities such as the Food & Drug Administration.

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 electronic 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 (e.g., the clinical protocol, eCRFs), 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. [redacted]

15 INVESTIGATOR AGREEMENT

PROTOCOL NUMBER: PRG-NY-20-002

PROTOCOL TITLE:

A Multi-Center, Double-Masked, Randomized, Active-Controlled, Parallel-Group, Safety and Efficacy Study to Compare Perrigo Pharmaceuticals International DAC Brinzolamide and Brimonidine Tartrate Ophthalmic Suspension 1%/0.2% to Novartis Pharmaceuticals Simbrinza® (brinzolamide /brimonidine tartrate 1%/0.2% ophthalmic suspension) in the Treatment of Chronic 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

16 APPENDICES

16.1 Appendix A: Study Personnel Contacts

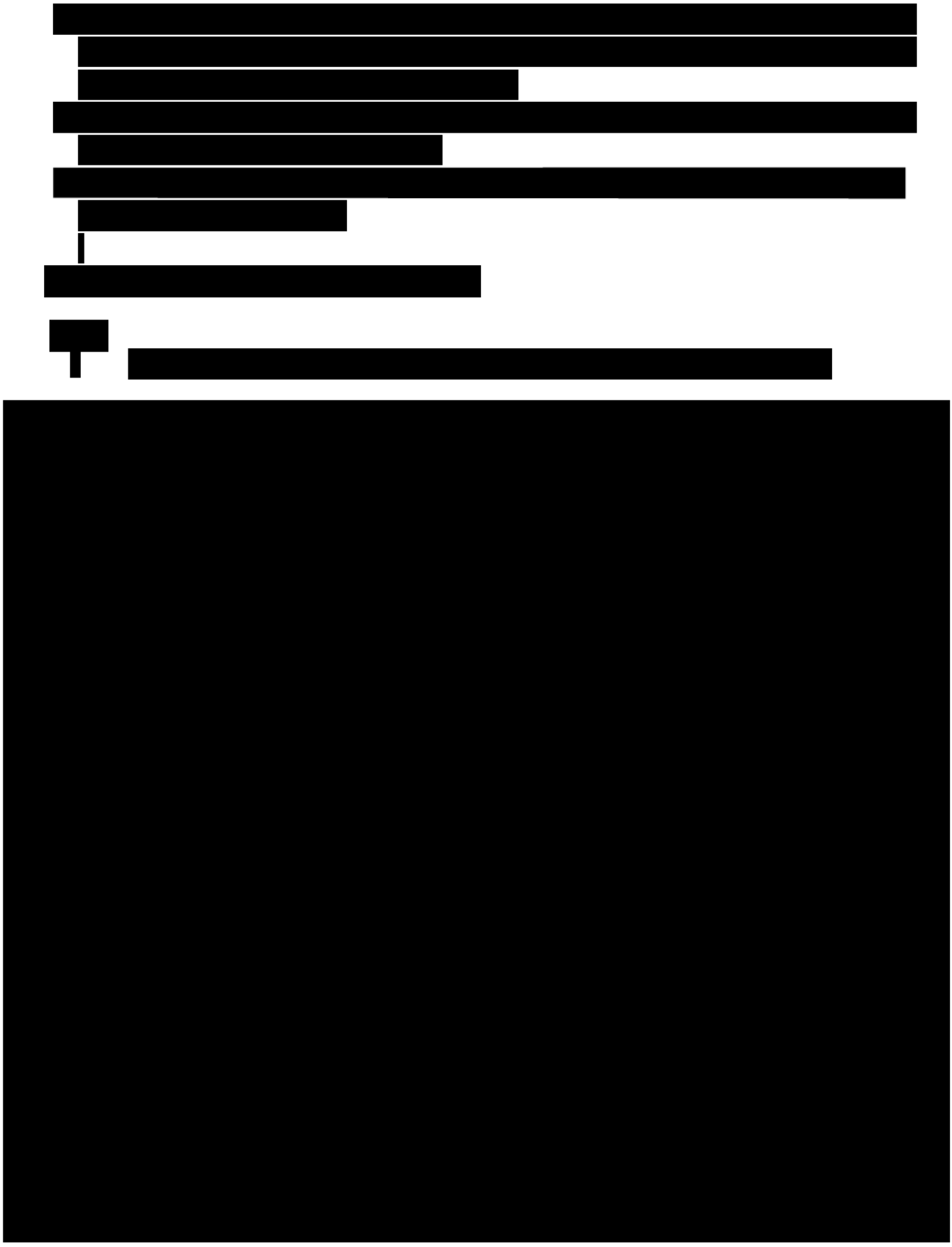
16.2 Appendix B: Instructions for the Subject

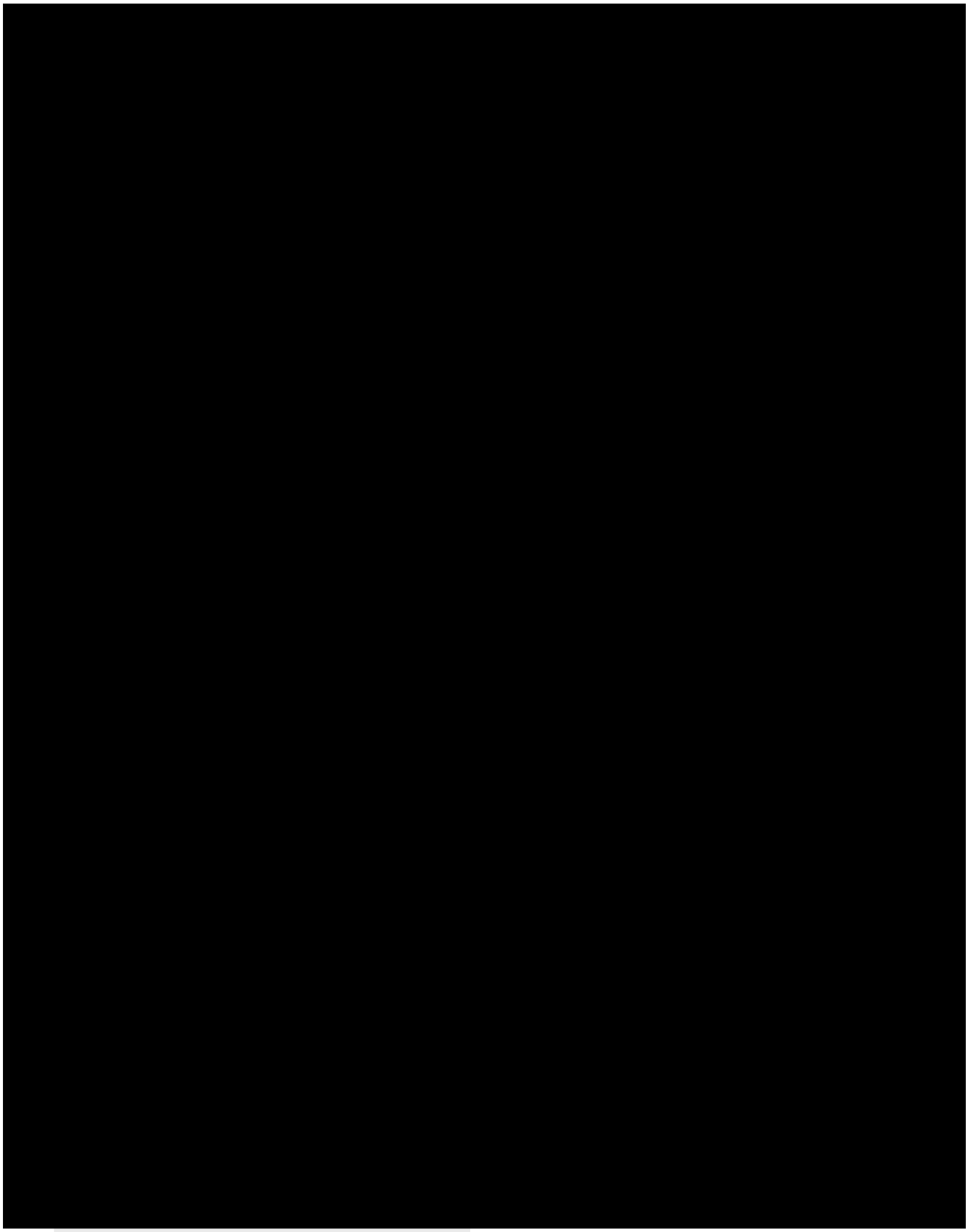
Check Visit Dispensed:
☐ Visit 2: ☐ Visit 3: ☐ Unscheduled visit: ☐ Date: _____

SUBJECT INITIALS: _____ SUBJECT NUMBER: _____
SITE NUMBER: _____

1. Your doctor has given you the study medication, for your use in the study. Store the study medication at temperature 2ºC-25ºC (36ºF-77ºF) in a secured area and bottles must be kept in an upright position and tightly closed. Keep this and all medications out of the reach of children. Keep the study medication bottle tightly closed, protect it from light and heat. For ophthalmic use only. Not for oral, topical, or intranasal use.

[redacted]





[redacted]

You are scheduled to return at:

_____on _____ (Visit 3, Study Week 2)
(Time) (Date)

_____on _____ (Visit 4, Study Week 6)
(Time) (Date)

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