CLINICAL STUDY PROTOCOL

A Randomized, Multi-Center, Investigator-Masked, Parallel Group, Equivalence Study of Once Daily Brimonidine Tartrate Ophthalmic Suspension Compared with Three Times Daily Alphagan® P in Subjects with Open Angle Glaucoma or Ocular Hypertension.

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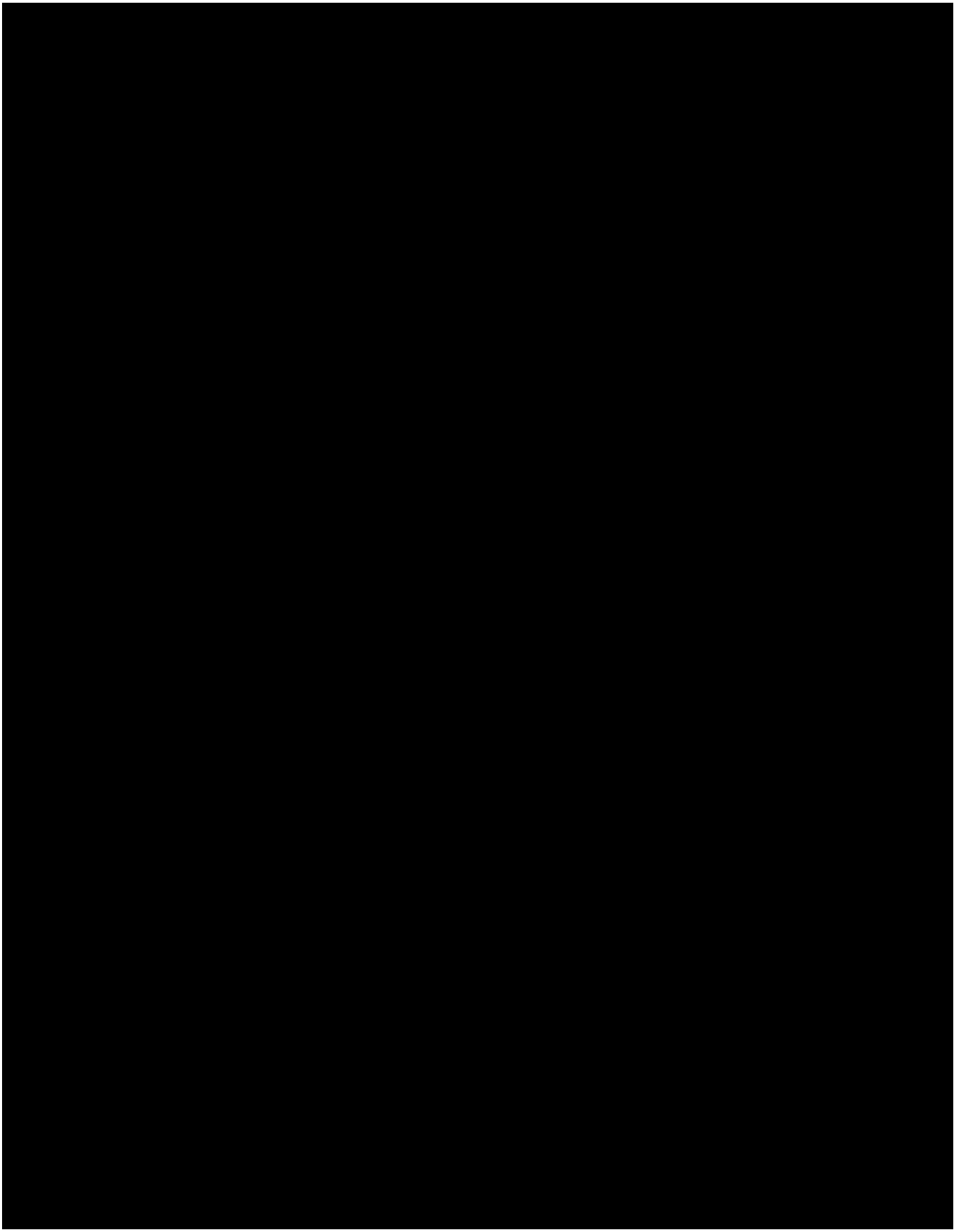

STATISTICAL ANALYSIS PLAN DETAILS

TRIAL FULL TITLE	A Randomized, Multi-Center, Investigator-Masked, Parallel Group, Equivalence Study of Once Daily Brimonidine Tartrate Ophthalmic Suspension Compared with Three Times Daily Alphagan® P in Subjects with Open Angle Glaucoma or Ocular Hypertension.
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SAP VERSION DATE	22APR2021
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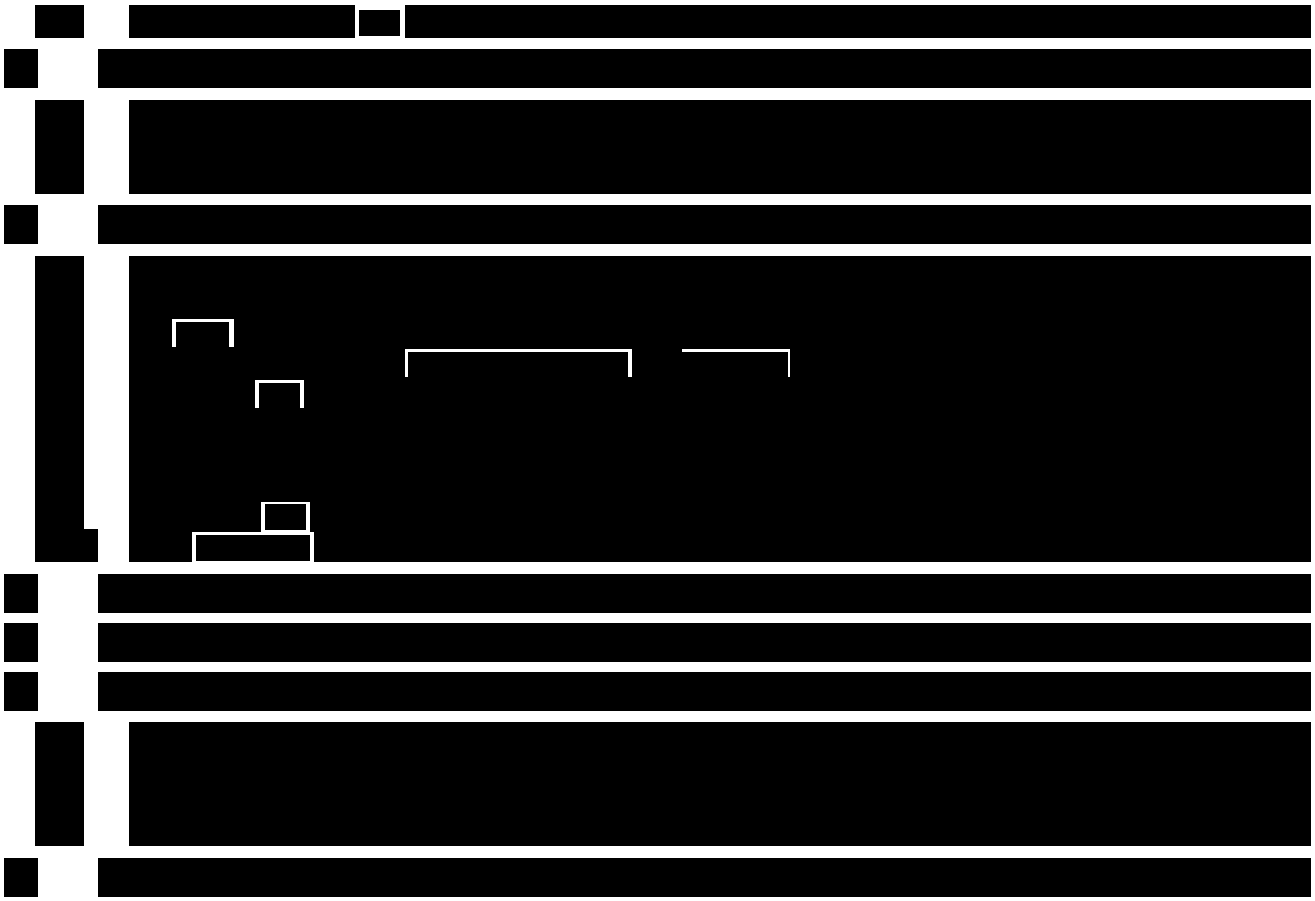

2 ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
BSCVA	Best-Spectacle Corrected Visual Acuity
CI	Confidence Interval
CRO	Contract research organization
eCRF	Electronic Case Report Form
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GAT	Goldmann Applanation Tonometry
GCP	Good clinical practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of technical requirements for pharmaceuticals for human use
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-To-Treat
LOCF	Last Observation Carried Forward
logMAR	logarithm of the Minimum Angle of Resolution
MAO	Monamine Oxidase Inhibitor
MedDRA	Medical Dictionary of Regulatory Affairs
MMRM	Mixed Model of Repeated Measures
NCT	Non-contact tonometer
OPD	(in-)Office physician dispensing
OU	Both eyes
POC	Proof-of-concept
PP	Per Protocol
PT	Preferred Term
QD	(Quaque Die) once daily
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SPARC	Sun Pharma Advanced Research Company, Ltd.
SUSAR	Suspected Unexpected Serious Adverse Reaction
TOST	Two one-sided tests
TEAE	Treatment-Emergent Adverse Event
TID	Three Times Daily

[redacted]

[redacted]

4 INTRODUCTION

4.1 Preface

Sun Pharma Advanced Research Company Ltd. (SPARC; Sponsor) has developed a once daily (QD) long-acting ophthalmic product consisting of 0.35% brimonidine tartrate suspension [redacted]

4.2 Purpose of the analyses

To evaluate the efficacy of once daily (QD) dosing of brimonidine tartrate ophthalmic suspension 0.35% compared with Alphagan® P 0.1% dosed 3 times a day (TID) in subjects with open-angle glaucoma or ocular hypertension.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Study Objectives

This study is designed to obtain estimates on the mean IOP at each of the 3 time points (8:00 AM, 10:00 AM, 4:00 PM) on [redacted] week 12 in order to compare brimonidine tartrate 0.35% ophthalmic suspension, dosed QD at 8:00 AM and Alphagan® (brimonidine tartrate ophthalmic solution 0.1%), dosed TID at approximately 8:00 AM, 2:00 PM, and 8:00 PM.

Primary Objectives:

The primary objective is to evaluate the efficacy of QD dosing with SPARC's brimonidine tartrate ophthalmic suspension 0.35% compared with Alphagan® (brimonidine tartrate ophthalmic solution 0.1%) dosed TID in subjects with open-angle glaucoma, or ocular hypertension.

[redacted]

5.2 Endpoints

Primary Efficacy Endpoint:

Primary efficacy endpoint will be the time-matched mean IOP (study eye) measures at each of the 3 time points (8:00 AM, 10:00 AM, 4:00 PM) on [redacted] week 12. These sample values will be used to compute the point estimates for the primary estimand defined by the difference across treatment groups in IOP at each of the 9 time points (3 times within each of 3 days).

[redacted]

Safety Endpoints:

- AEs
- [redacted]

[redacted]

6 STUDY METHODS

6.1 General Study Design and Plan

- This is a multicenter, investigator/ evaluator -masked, randomized, parallel group, equivalence study.

[redacted]

- The investigator or designated evaluator, masked to treatment assignment, will perform all ophthalmic examinations. Unmasked study coordinator may perform all study procedures other than ophthalmic/clinical examination, or treatment of the subjects.
- Study Duration:
    - Visit 1: (Day-42 to Day -1): Screening
    - Visit 2: (Day 0) Baseline/Randomization
    - Visit 3: (Week 2 ± 2 Days) Efficacy/Safety Evaluation
    - Visit 4: (Week 6 ± 2 Days) Efficacy/Safety Evaluation
    - Visit 5: (Week 12 ± 2 Days) Efficacy/Safety Evaluation and study exit

6.2 Inclusion-Exclusion Criteria

Inclusion Criteria:

Each subject must:

1. Be male or female, of 18 years of age or older
2. Provide signed and dated informed consent in accordance with GCP and local legislation prior to any study procedure.
3. Have open angle glaucoma, (with or without pseudo exfoliation, pigment dispersion component) or ocular hypertension in both eyes and likely to be controlled on monotherapy

[redacted]

[redacted]

7. Females of childbearing potential must not be pregnant or lactating (as confirmed by a negative urine pregnancy test with a sensitivity of less than 50 mIU/mL or equivalent units of human chorionic gonadotropin). Women of childbearing potential must agree to the use of a reliable method of contraception (e.g., total abstinence, intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], oral, transdermal, injected or implanted non- or hormonal contraceptive), throughout the study. A sterile sexual partner is not considered an adequate form of birth control. Subjects on hormonal contraceptives must have been on the same hormonal contraceptive for at least one month before the Screening and continue throughout the duration of the study. A female is considered of childbearing potential if she has had her first menses and she is either: not postmenopausal for at least 12 consecutive months prior to enrollment; or not surgically sterilized by bilateral tubal ligation, or bilateral oophorectomy, or hysterectomy. Male subjects with female partners of childbearing potential who are not using birth control as described above must use a barrier method of contraception (e.g., condom) if not surgically sterile (i.e., vasectomy).

[redacted]

9. Be able and willing to follow study instructions and complete all required visits.

[redacted]

[redacted]

Exclusion Criteria:

Each subject must not:

1. Have angle closure glaucoma or a history of acute angle closure treated with a peripheral iridotomy
2. Have uncontrolled systemic disease (e.g., diabetes) which might interfere with the study
3. Current or history of severe hepatic or renal impairment. Have severe cardiovascular disease unless his/her disease is controlled, and clearance has been obtained from the treating primary care physician or cardiologist
4. Subjects with depression, cerebral or active coronary insufficiency or orthostatic hypotension.
5. (If female of childbearing potential) Be pregnant, nursing, or planning a pregnancy during study entry and through the duration of the study.
6. Have clinically relevant, abnormally low or high blood pressure or pulse rate
7. [redacted]

[redacted]

26. Have a condition or be in a situation which, in the investigator's opinion, may put the subject at a significant risk, may confound study results, or may interfere significantly with the subject's participation in the study. This criterion provides an opportunity for the investigator to exclude subject based on clinical judgment, even if other eligibility criteria are satisfied.

[redacted]

6.4 Study Termination

If the study is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the subjects, should assure appropriate therapy and follow-up for the subjects, and, where

required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). Additionally:

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

6.5 Randomization, Masking, and Unmasking

- **Subject Number**
  At the screening visit after signing the informed consent form (ICF) each subject will be allotted a subject number. The subject number will uniquely identify each subject in the study. The subject number will appear on all study documents relating to that subject. Subject numbering is described separately in data management plan.

- **Randomization**
  Subjects who qualify inclusion and exclusion criteria will be randomly assigned to study treatment using Interactive web response system.

- **Masking**
  This is an evaluator-masked study. [redacted]

[redacted]

- **Procedures for Unmasking (if applicable)**

  When medically necessary, the investigator may need to determine what treatment has been assigned to a subject. Site will contact the designated personnel in SPARC or CRO in case the treatment code needs to be unmasked. When possible (i.e., in non-emergent situations), CRO and/or the study sponsor should be notified before unmasking investigational product.

  Unmasking details will be provided to Sponsor's designated safety physician in case of SUSAR for regulatory reporting purpose only.

  The code for all subjects will be broken when all subjects have completed the study, and all data for this period has been entered into the database and locked.

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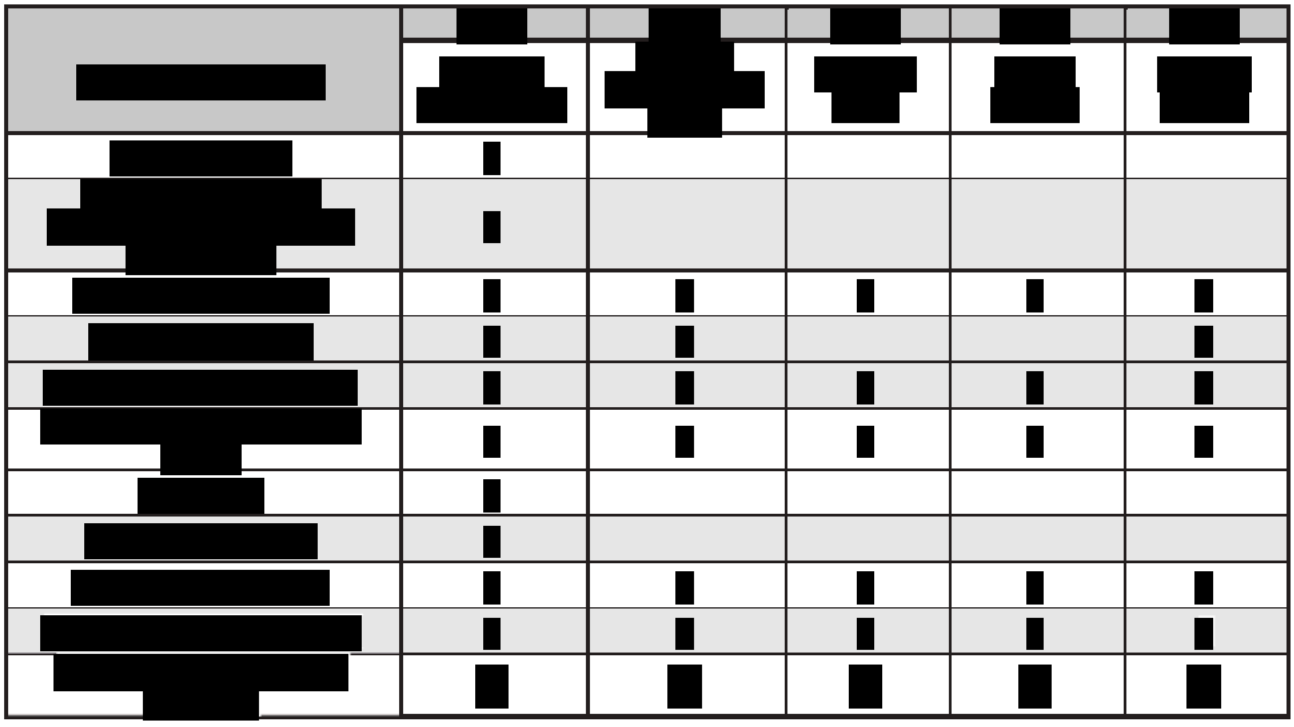

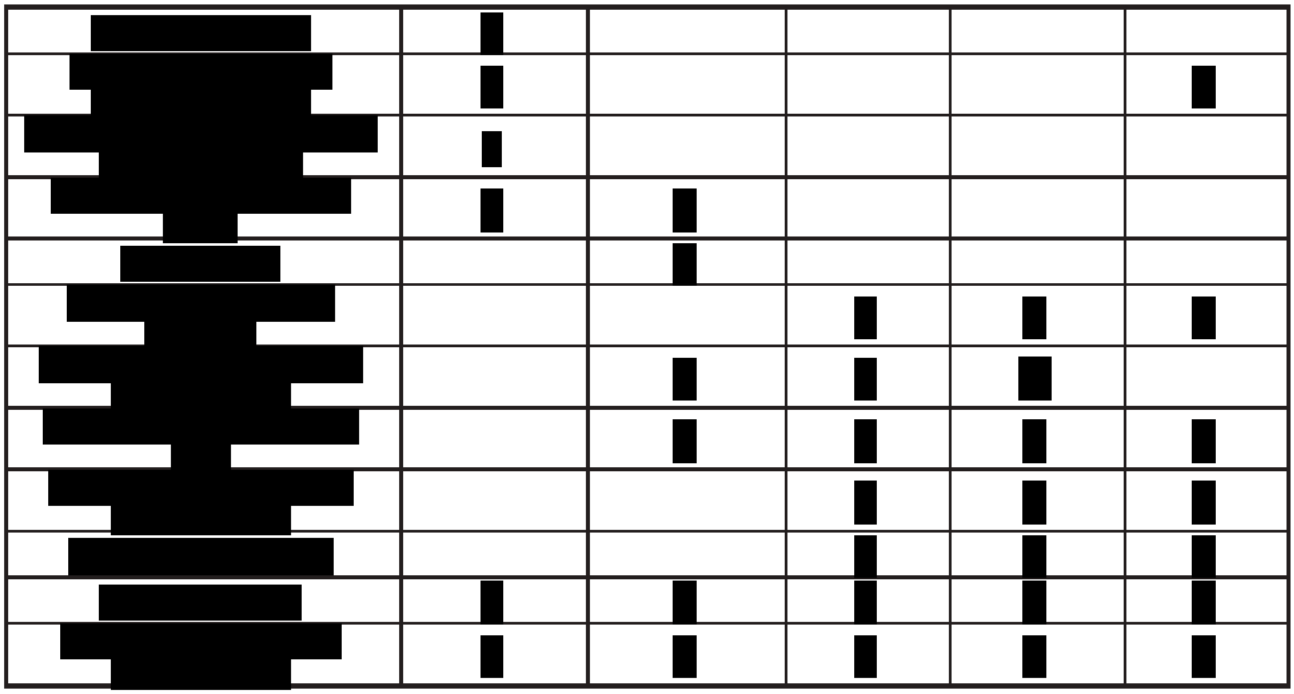

6.7 Study Variables

[redacted]

- [redacted]

[redacted]

- [redacted]

[redacted]

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

- [redacted]

[redacted]

[redacted]

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[redacted]

[redacted]

12.1 Adverse Events

AEs will be coded to System Organ Class (SOC) and Preferred Term (PT) according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA®). All AEs will be listed; however, only treatment-emergent AEs (TEAEs) will be summarized.

The primary safety analysis will summarize ocular (in either eye) and non-ocular TEAEs for all treated subjects using discrete summaries at the subject level by system organ class and preferred term for each treatment group. A TEAE will be defined as occurring after the first dose of study medication. Treatment-related ocular and non-ocular TEAEs will be summarized similarly. Ocular and non-ocular TEAEs will also be summarized by severity. This summary will provide the total number of TEAEs, the number of subjects experiencing at least one ocular or non-ocular TEAE, the number of subjects experiencing SAEs and the number of subjects experiencing TEAEs and SAEs related to IP. The overall summary of TEAEs will also include the maximum severity and maximum relationship to IP for subjects with AEs. The number and percentage of subjects at each level of severity and each level of relationship will be presented.

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