Clinical Trial Protocol: CLR_16_33

BRIMONIDINE TARTRATE OPHTHALMIC SUSPENSION

Protocol 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.
Protocol Number:	CLR_16_33
Study Phase:	3
Investigational Product Name:	Brimonidine tartrate 0.35% ophthalmic suspension
Indication:	Reduction in elevated intraocular pressure (IOP) in subjects with open angle glaucoma or ocular hypertension
Version/ amendment/Date	Amendment 03, 20Sep 2018
Previous Version/ amendment date:	Amendment 02, 08 Aug 2018
Sponsor:	Sun Pharma Advanced Research Company, Ltd. (SPARC) 17 B Mahal Industrial Estate, Mahakali Caves Rd Andheri (E), Mumbai - 400 093 India

SPONSOR APPROVAL SIGNATURE

SPONSOR'S CONTACT INFORMATION

[redacted]

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1.0 TRIAL SYNOPSIS

Title of the Study	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.
Protocol Number	CLR_16_33
Investigational Product	Brimonidine tartrate 0.35% ophthalmic suspension
Sponsor	Sun Pharma Advanced Research Company (SPARC) Limited
Trial Phase	3
Clinical Indication	Open-angle glaucoma or ocular hypertension.
Trail Design	Multi-center, investigator-masked, parallel group, stratified randomization
Controls	Brimonidine 0.1% ophthalmic solution (Alphagan P® 0.1%)
Objectives:	**Primary Objectives:** 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. **Secondary Objectives:** To evaluate the safety 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.
Study Population Characteristics	Subjects 18 years age or older with open-angle glaucoma or ocular hypertension
Number of Subjects	Approximately 666 (333 per treatment arm); subjects will complete 12

	weeks of treatment.
Route of Administration	Topical ophthalmic instillation
Dosage/Dose Regimen/ Instillation/Application/Use	Subjects will receive one drop of either: • Brimonidine tartrate 0.35% ophthalmic suspension (SPARC) at 8:00 AM ± 30 minutes • Brimonidine tartrate 0.1% ophthalmic solution (Alphagan® P 0.1%) at 8:00 AM ± 30 minutes, 2:00 PM ± 30 minutes, 8:00 PM ± 30 minutes
Duration of Participation in the Trial	Efficacy and Safety: Up to 5 visits over 12 weeks
Summary of Visit Schedule	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
Measures Taken to Reduce Bias	Subjects will be randomized to treatment sequences in visit 2 to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Investigator-masked treatment will be used to reduce the potential of bias during data collection and evaluation of clinical endpoints.
Eligibility Criteria	**Inclusion Criteria:** Subjects MUST: 1. Be male or female, of 18 years of age or older 2. Provide signed and dated informed consent in accordance with good clinical practice (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: a. not postmenopausal for at least 12 consecutive months prior to enrollment; or b. not surgically sterilized by bilateral tubal ligation, or bilateral oophorectomy, or hysterectomy c. Male subjects with partners of childbearing potential who are not using birth control as described above must use a barrier method of contraception (eg. Condom) if not surgically sterile (ie, vasectomy). [redacted]

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

Exclusion Criteria:

Subjects MUST NOT:

1. Have angle closure glaucoma or a history of acute angle closure treated with a peripheral iridotomy
2. Have uncontrolled systemic disease (eg, 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]
8. Have any known allergy or sensitivity to the study medications or their components (brimonidine tartrate, amberlite IRP 69, hypromellose, povidone, carbopol, edetate disodium, n-lauroyl sarcosine, sodium, tromethamine, benzalkonium chloride, sodium carboxymethylcellulose, sodium borate, boric acid, sodium chloride, potassium chloride, calcium chloride, magnesium chloride, Purite® - preservative).

[redacted]

11. Require the use of any ocular medications during the study other than the study medications; occasional use of artificial tears for mild dry eye or lid scrubs for mild blepharitis is allowed. [redacted]
12. Have any contraindications to brimonidine therapy
13. Have known lack of ocular hypotensive response to alpha adrenergic receptor agonist.

[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.
Efficacy Measures	**Primary Efficacy Variable(s)** The time-matched mean IOP (study eye) at each of the 3 time points (8:00 AM, 10:00 AM, 4:00 PM) on [redacted] week 12 [redacted]
Safety Measures	• Adverse events (AEs) [redacted]

	[redacted]
Statistical methods and Analyses	**General Considerations:** [redacted] **Efficacy Analyses:** [redacted]

	[redacted]
Summary of Known and Potential Risks and	[redacted]

Benefits to Human Subjects	[redacted]

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LIST OF ABBREVIATIONS

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
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

2.0 BACKGROUND INFORMATION

Glaucoma is collection of disorders characterized by a slow and progressive degeneration of retinal ganglion cells and their axons, resulting in a distinct appearance of the optic disc and a concomitant pattern of visual field loss[redacted] In 2010, 60.5 million people were estimated to be suffering from glaucoma worldwide, with a predicted increase to 79.6 million by 2020[redacted] It is a leading cause of blindness in the United States, affecting 1%-2% of individuals aged 60 and over [redacted]

There are several recognized risk factors of glaucoma including an increased intraocular pressure (IOP), aging, family history, high myopia, systemic hypertension, cardiovascular disease, migraine headaches, peripheral vasospasm and prior nerve damage[redacted] Elevated IOP is the only proven treatable risk factor in multiple forms of glaucoma[redacted] Increased IOP of greater than 21 mm Hg has traditionally been suspected to cause glaucoma[redacted] the higher the IOP, the greater the likelihood of optic nerve damage and visual field loss. With IOP > 30 mmHg, the potential risk for vision loss is 40 times greater compared to an IOP of 15 mm Hg[redacted] As IOP has been shown in several large-scale National Eye Institute-sponsored studies to be a major factor in the pathogenesis of the progression of glaucoma, pharmacologic reduction of IOP is today the mainstay of treatment for this condition[redacted]

Brimonidine is a highly selective and potent alpha$_2$-adrenergic-receptor agonist that effectively lowers IOP and is useful as a monotherapy, adjunctive therapy, and replacement therapy in glaucoma and ocular hypertension. Brimonidine functions by dual mechanism, reducing inflow of aqueous humor production and increasing uveoscleral outflow. It has a greater selectivity for α_2-ARs and lower lipid solubility than the first-generation compounds of this class, clonidine and apraclonidine. After topical administration, brimonidine readily penetrates the cornea and results in reduction of IOP within one hour. Its peak effect is achieved within two hours post-dosing and the trough effect occurs approximately 10 to 14 hours after administration[redacted]

Brimonidine tartrate is marketed and approved for use in the US only in topical ophthalmic formulations in concentrations between 0.1-0.2% (Alphagan, Alphagan® P, Combigan, and generic forms) and currently the only indication is for ocular hypertension and elevated IOP associated with open-angle glaucoma. Its pharmacology and toxicology profiles have been extensively characterized in previous US submissions. Due to its short half-life, brimonidine is dosed three times daily (TID) in the US.

Brimonidine has been shown to be safe and well-tolerated ocularly and systemically in concentrations up to 0.5% when dosed twice daily for up to 1 month for IOP-lowering in glaucoma patients[redacted] The most common side effects included dry mouth, fatigue, blurring, burning, and stinging with frequency tending to be dose-dependent.

Known barriers to compliance in glaucoma patients include adverse effects, multiple dosing, forgetfulness, age, physical disability, and complex multidrug regimens[redacted] Noncompliance with topical therapy has been identified as a critical factor associated with the development of

blindness in glaucoma [redacted] Studies on individual adherence with brimonidine tartrate ophthalmic solution for treatment of glaucoma have shown that adherence of patients was highly variable and pharmacologically insufficient for more than two third of the patients included in the study when patients were asked to take brimonidine eye drops twice daily and TID [redacted] Due to the dose-intensive schedule, patient adherence to brimonidine therapy is low suggesting that there is a need for a longer acting drug or longer acting formulation to reduce dosing frequency.

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 in a nano-bound resin. This product allows for the sustained release and activity of brimonidine over an extended period of time for the treatment of elevated IOP. This nano-size ion exchange resin technology is already in the marketed hypotensive ophthalmic suspension, Betoptic S® [redacted] While lower concentrations of brimonidine are available (0.1, 0.15%, Alphagan® P, Allergan) for the treatment of glaucoma, the Sponsor's drug-resin complex suspension product is expected provide a slow, consistent, and sustained release likely reducing the immediate exposure to drug. This feature has the potential for an improved safety profile over the higher concentrations of marketed drug and allowing for a reduced medication burden from TID to QD.

[redacted]

[redacted]

allergic conjunctivitis, conjunctival hyperemia, and eye pruritus. Adverse reactions occurring in

[redacted]

[redacted]

2.5 Compliance Statement for Study Conduct in Accordance with Protocol, Good Clinical Practice and Applicable Regulatory Requirements

The study protocol, amendments to the protocol (if applicable), Investigator's brochure, subject recruitment procedures (e.g. advertisements) and the subject's information and informed consent form as well as consent form updates (if applicable) will be submitted to the Institutional review board (IRB)/Independent ethics committee (IEC), which is constituted according to local law to obtain approval before initiation of the study and as applicable thereafter.

The study will only be initiated after receipt of the approval from the IRB/IEC. The investigator will report promptly to the IRB/IEC new information that may adversely affect the safety of the subjects or the conduct of the study.

The investigator will carry out the protocol in conformity with Good Clinical Practice (GCP) described in Guideline E6 of the ICH and applicable regulatory requirements. Before admission into the study, the written informed consent form must be personally signed and dated by the subject and by the investigator or designee who conducted the informed consent discussion.

In obtaining and documenting informed consents, the investigator must comply with the applicable regulatory requirement(s), and must adhere to GCP. The investigator must inform the subject of all pertinent aspects of the study including the written information approved/favorably assessed by the IRB.

3.0 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 week 2, week 6 and week 12 in order to compare brimonidine tartrate 0.35% ophthalmic suspension, dosed QD at 8:00 AM and brimonidine tartrate 0.1%, dosed TID at approximately 8:00 AM, 2:00 PM, and 8:00 PM.

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

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

4.0 STUDY DESIGN

This is a multicenter, investigator-masked, randomized, parallel group, equivalence study. Treatment period will consist of QD and TID dosing for 12 weeks.

Subjects who are chronically treated with ocular hypotensive medications are required to undergo appropriate washout periods prior to study entry to minimize any residual effects of other active ocular hypotensive medications.

[redacted]

4.2 Measures taken to avoid bias

4.2.1 Subject number

At the screening visit after signing the informed consent form (ICF) form 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 will be described separately in data management plan.

4.2.2 Randomization

Subjects who qualify inclusion and exclusion criteria will be randomly assigned to study treatment using [redacted]

4.2.3 Masking

This is an evaluator-masked study. 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. The investigator (if different from the evaluator) will be responsible for deciding the type of medical care a subject will get; identifying the kinds of work a subject can safely perform while in the study, and assessment of safety . In order to maintain masking, the unmasked study

coordinator will dispense IP on visit 2, 3,and 4 in a room separate from the evaluating investigator and the subjects will be asked not to discuss the treatment received with the investigator or designated evaluator in order to maintain investigator/evaluator-masking.

To minimize bias, Test and Reference bottles will be packed in an identical box with similar label.

An unmasked site personnel will instill the in-office physician dispensing (OPD) doses in a room separate from the evaluating investigator in order to maintain investigator-masking. As a means to maintain investigator masking, subjects in the SPARC 0.35% treatment group will be brought into the dosing room at each dosing time point (ie, 8:00 AM and 2:00 PM but will only receive study medication at the 8:00 AM time point).

In order to maintain masking, the Investigator will not personally retrieve/review the study medication diary; designated study personnel will collect and review the diary at each visit to ensure treatment compliance.

Subjects will be instructed not to use the study medication on the morning of a study visit; [redacted]

5.0 STUDY POPULATION

5.1 Number of Subjects (approximate)

Efficacy and Safety: Approximately 666 subjects will be enrolled.

5.2 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]

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 (eg, condom) if not surgically sterile (ie, vasectomy).

[redacted]

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[redacted] visits.

[redacted]

5.3 Exclusion Criteria

Each subject must <u>not</u>:

1. Have angle closure glaucoma or a history of acute angle closure treated with a peripheral iridotomy
2. Have uncontrolled systemic disease (eg, 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]

11. Require the use of any ocular medications during the study other than the study medications; occasional use of artificial tears for mild dry eye or lid scrubs for mild blepharitis is allowed.
12. Have any contraindications to brimonidine therapy

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]

5.5 Study Termination

The study may be stopped at any time by the Sponsor, investigator and/or IEC with appropriate notification.

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/favorable 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.

6.0 STUDY PARAMETERS

6.1 Efficacy Measures

6.1.1 Primary Efficacy Variable(s)

The time-matched mean IOP (study eye) at each of the 3 time points (8:00 AM, 10:00 AM, 4:00 PM) on week 2, week 6 and week 12.

[redacted]

6.2 Safety Measures

- AEs

[redacted]

7.0 STUDY MATERIALS

7.1 Study Treatment(s)

7.1.1 Study Treatments

- Brimonidine tartrate 0.35% ophthalmic suspension (SPARC), QD
- Brimonidine tartrate 0.1% ophthalmic solution (Alphagan P® 0.1%), TID

[redacted]

[redacted]

7.1.4 Accountability and Retention of Investigational Product

The investigational product is to only be used in accordance with this protocol. The IP must only be distributed to subjects properly qualified under this protocol to receive IP.

[redacted]

[redacted]

[redacted]

8.0 STUDY METHODS AND PROCEDURES

8.1 Subject Entry Procedures

8.1.1 Overview

Subjects as defined by the criteria in Sections 5.1, 5.2 and 5.3 will be considered for entry into this study.

8.1.2 Informed Consent

Prior to a subject's participation in the study (i.e, changes in a subject's medical treatment and/or study related procedures), the study will be discussed with each subject, and subjects wishing to participate must give written informed consent using an ICF forms. The ICF form must be the most recent version that has received approval/favorable review by a properly constituted Institutional Review Board.

[redacted]

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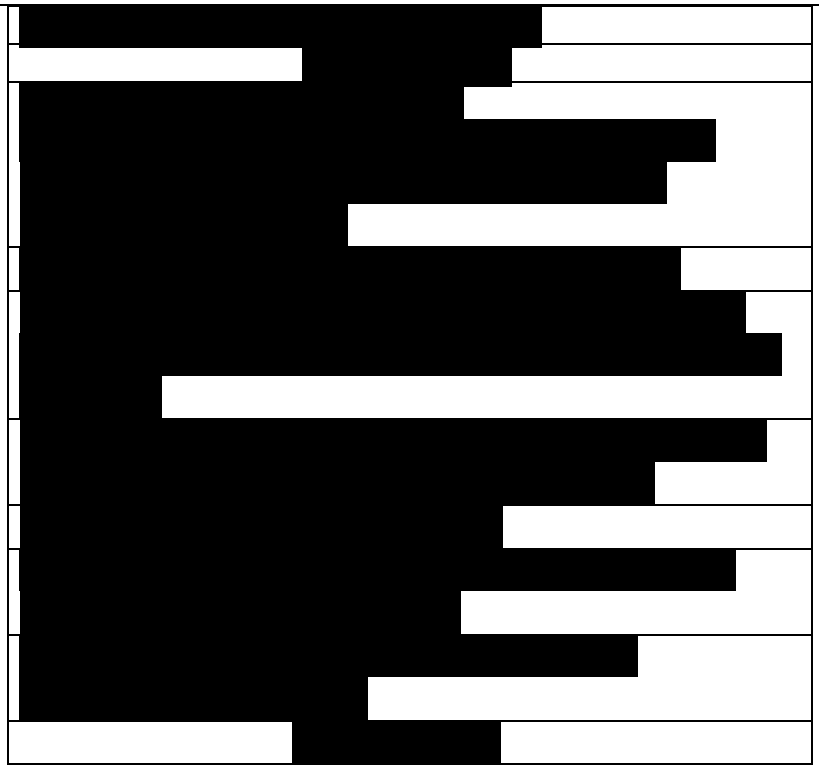

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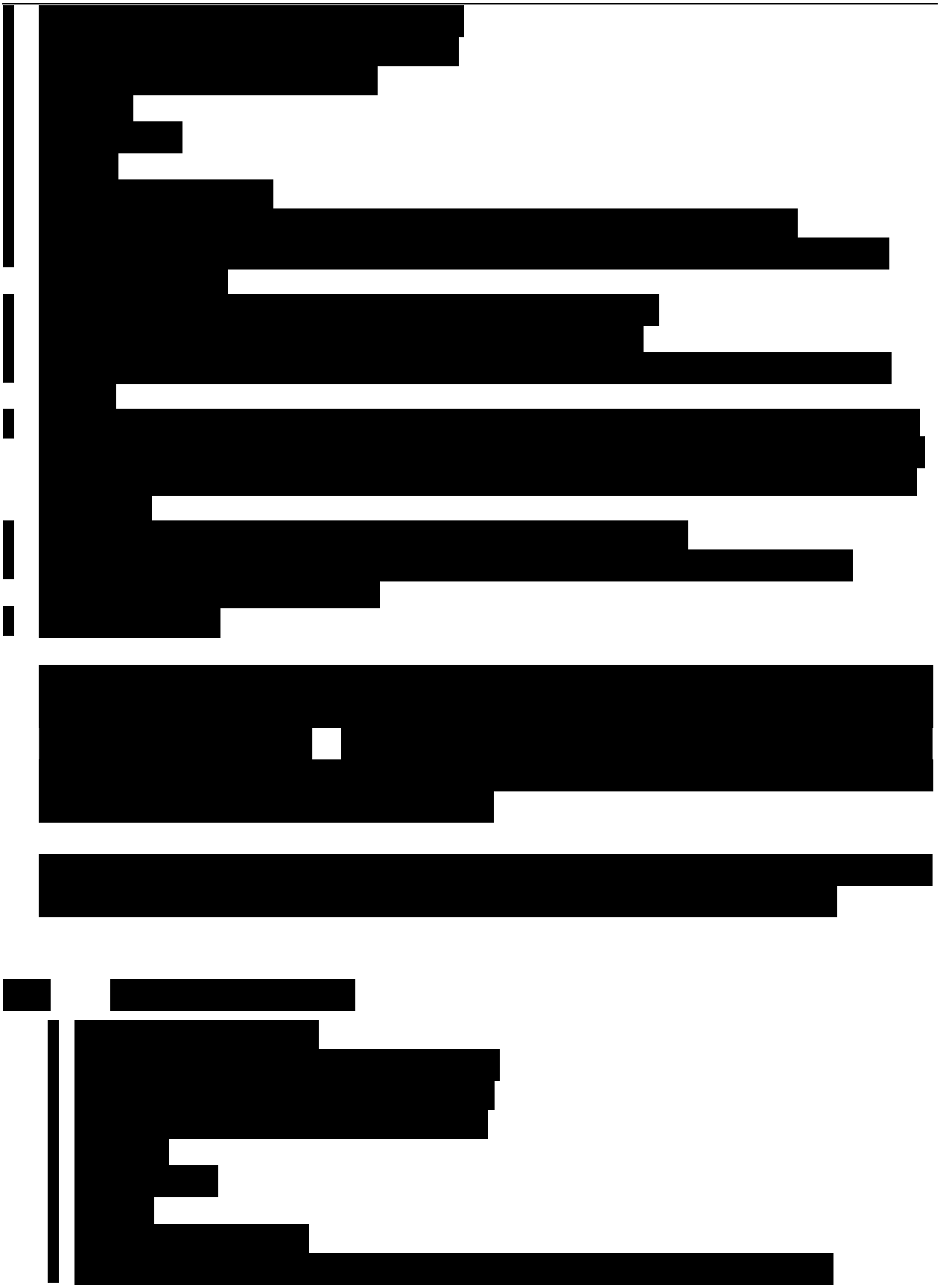

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- In-OPD study medication instillation at 2:00 PM ± 30 minutes

[redacted]

[redacted]

8.6 Compliance with Protocol

Subjects who are inappropriately enrolled will be discontinued from the study. [redacted]

8.7 Study Duration

Study will comprise 5visits.

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

8.8 Monitoring and Quality Assurance

During the course of the study CRO monitor, or designee, will make routine site visits to review protocol compliance, assess study drug accountability, and ensure the study is being conducted according to the pertinent regulatory requirements. The review of the subjects' medical records will be performed in a manner that adequately maintains subject confidentiality. Further details of the study monitoring will be outlined in a monitoring plan.

Regulatory authorities of domestic and foreign agencies, quality assurance and or its designees may carry out on-site inspections and/or audits which may include source data checks. Therefore direct access to the original source data will be required for inspections and/or audits. All inspections and audits will be carried out giving consideration to data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

9.0 SAFETY REPORTING

9.1 Reporting Adverse Events

Any AE (clinical sign, symptom, or disease) temporally associated with the use of this investigational product, whether or not considered related to the investigational product, shall be reported and documented on the CRF. All AEs reported by the subject or observed by the Principal Investigator will be individually listed. All entries should contain an event term, date of onset, date of resolution, severity, action taken, outcome, relationship to study drug, and a seriousness assessment. The investigator will document all AEs in the subject's source document. All AEs occurring during the study, including during the washout interval, will be reported and documented on the CRF.

9.1.1 Definitions

Adverse Event – Any untoward medical occurrence in a clinical investigation subject administered a drug and does not necessarily have a causal relationship with this treatment. An AE can therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Serious Adverse Event (SAE) – Any experience that is fatal or life-threatening, requires or prolongs inpatient hospitalization, results in persistent or significant disability/ incapacity, is a congenital anomaly or birth defect or an important medical event or requires medical intervention.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as an SAE. “Fatal” will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (eg, sudden death, unexplained death), the death per se might then be reported as an SAE.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event, which, hypothetically, might have caused death if it were more severe.

A planned hospitalization for pre-existing condition, or a procedure required per protocol without a serious deterioration in health or clearly not associated with an AE is not to be considered as an AE.

[redacted]

Additionally, the Principal Investigator will evaluate all AEs as follows:

Seriousness: whether or not the AE is fatal or life threatening, persistent or permanently disabling, requires or prolongs inpatient hospitalization, is a congenital anomaly or an important medical event.

Action taken:. Action taken is categorized as “none”, “study drug discontinued/withdrawn”, “study drug discontinued and restarted”, “required concomitant medication”, “required procedure”, or “other”.

Event Outcome : Event outcome , or time last follow-up is recorded is categorized as “Fatal”, “Resolved”, “Resolved with sequelae”, “Resolving”, “Not Resolved”, “Unknown”.

Intensity, to be graded as:

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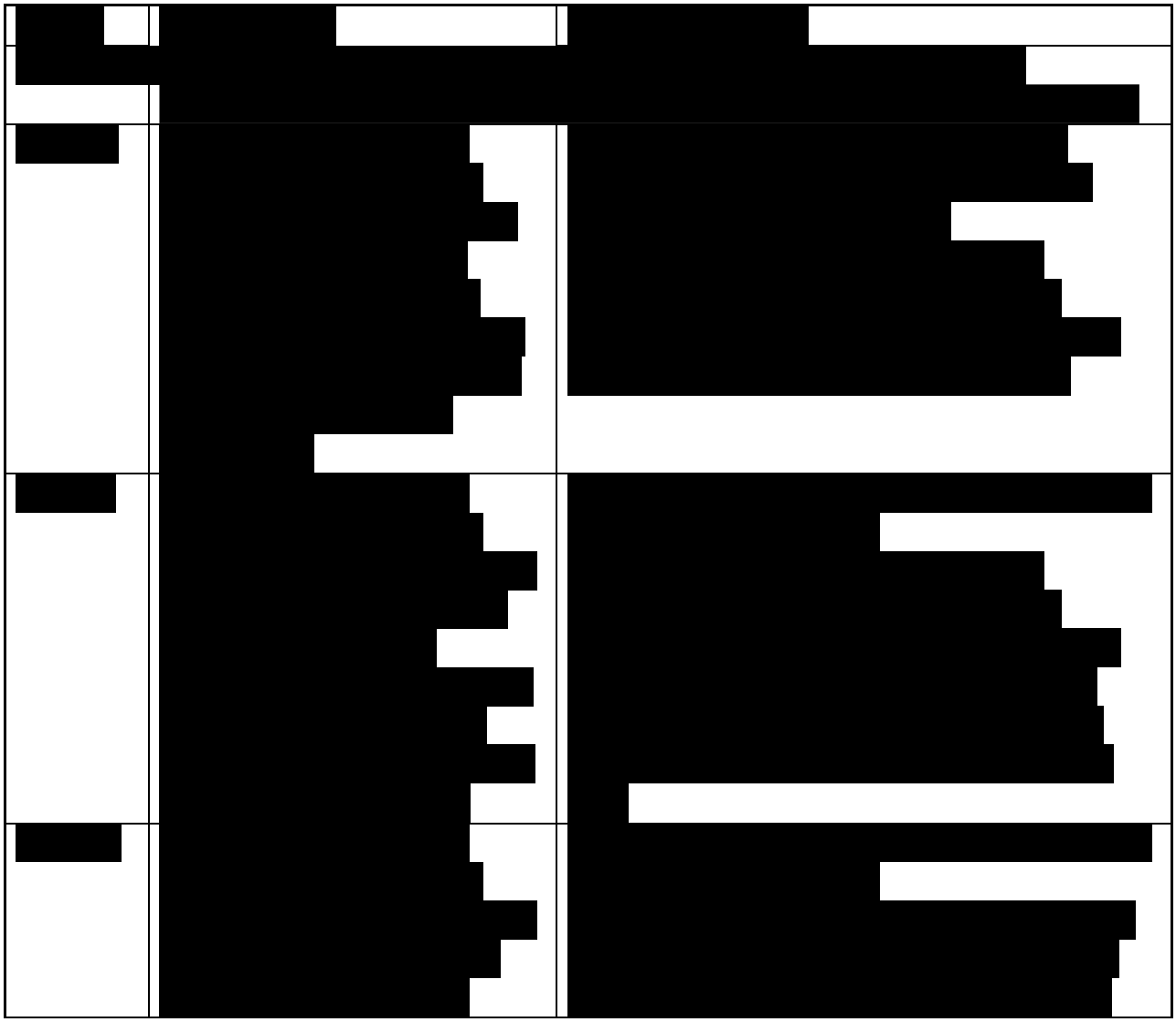

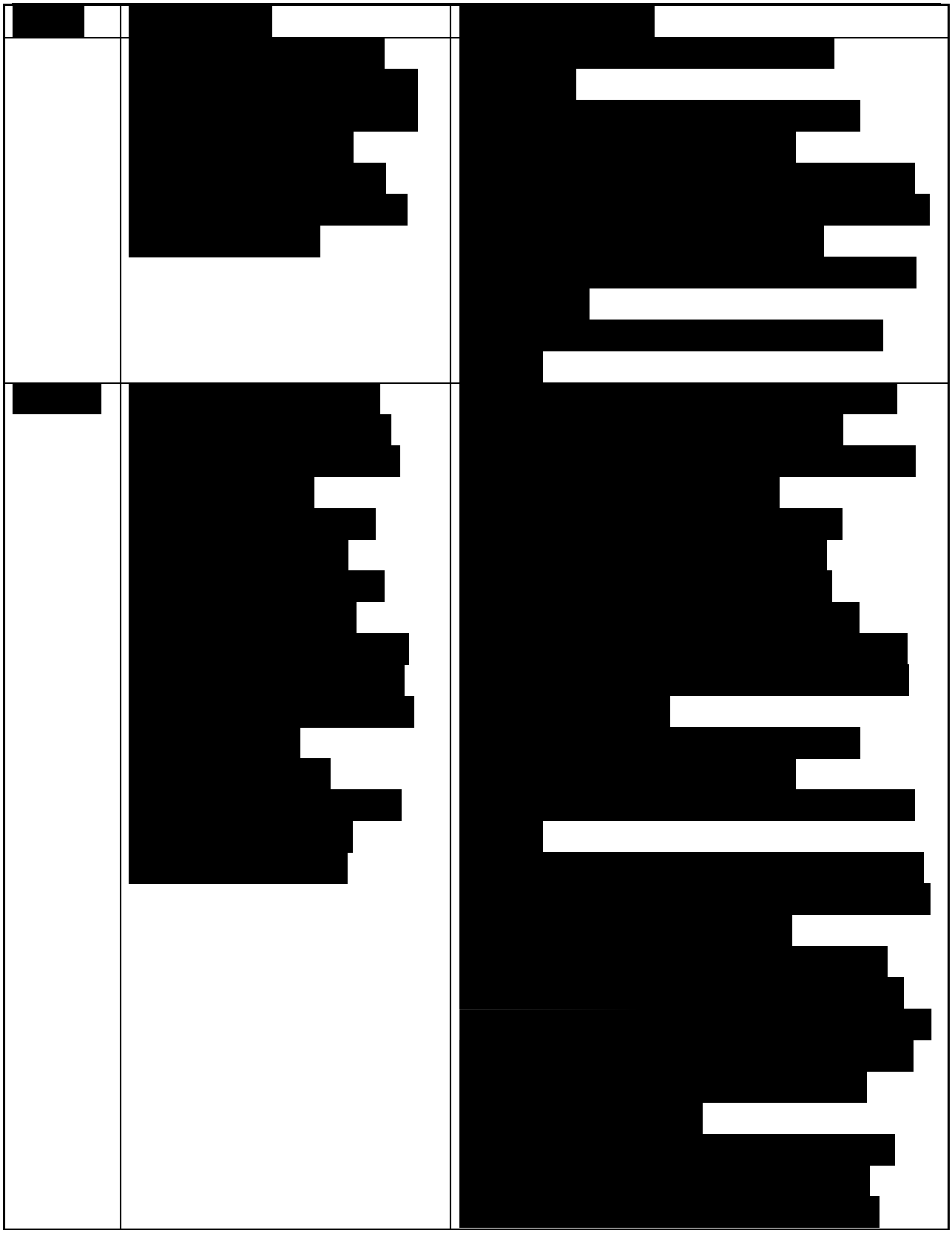

Definition of the adverse event reporting period

The AE/ SAE reporting period for safety surveillance begins when the subject sign's ICF continues till end of study or early termination visit.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (e.g., undesirable effects of any administered treatment) must be documented and reported as SAEs.

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9.2 Procedures for Reporting Serious Adverse Events (SAE) and Suspected Unexpected Serious Adverse Reaction (SUSAR)

Serious Adverse Events

All SAEs must be reported according to ICH GCP or local regulations, applying the regulation with the stricter requirements. The report will contain as much available information concerning the SAE to enable the Sponsor's safety physician/ CRO to file a report, which satisfies regulatory reporting requirements. The SAE report will be notified by Investigator within 24-hours of his/ her awareness to the Sponsor's safety physician/CRO. These timelines apply to initial reports of SAEs and to all follow-up reports.

All AEs/SAEs will be recorded on the AE Report Form and SAE report form in the eCRF and source documents.

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In the case of fatal or life-threatening events, please immediately telephone the Sponsor's safety physician/CRO also.

Additional follow-up information should be completed on an SAE follow-up form with a copy sent to the Sponsor's safety physician/CRO.

[redacted]

Requests for follow-up will usually be made via the responsible Sponsor's safety physician/CRO.

Suspected Unexpected Serious Adverse Reactions (SUSARs):

The applicable Regulatory Authorities shall be initially notified by Sponsor Safety Physician/ CRO of any SUSAR, no later than 15 calendar days from the "date learned" of the event. The applicable Regulatory Authorities will be initially notified as per regulation within 7 calendar days of any fatal or life-threatening SUSAR. If the safety report submitted within 7 calendar days is complete, an additional submission within 15 days from day 0 is not required.

All participating Investigators and Ethics committee/ Institutional Review Board shall be notified of any SUSAR by CRO as per local regulatory requirement.

[redacted]

9.3 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 (ie, 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.

9.5 Pregnancy

A pregnancy test will be performed at screening and at visits specified in the protocol. 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). Females of childbearing potential must agree to the use of a reliable method of contraception as described in Inclusion Criteria of this protocol and throughout the study. Subjects with a positive test at screening or during the study period will be excluded from study. Similarly, male subjects enrolled to the study will be instructed not father a child and avoid passage of semen to their partner by using an acceptable contraceptive method as discussed by the investigator during the enrollment to the study. However, if a female subject becomes pregnant during the study, the pregnancy will be recorded as a significant medical event and reported per SAE reporting procedure and the subject will be withdrawn from the study immediately. Similarly, if a female partner of a male subject becomes pregnant during the study, the medical event will be recorded appropriately. The 'pregnancy reporting form' will be

completed and submitted to Sponsor. The pregnancy shall be followed every three months till its outcome and up to one month post-delivery to assess the functional status of the child. If any SAE occurs during pregnancy than it will be reported using SAE forms as per timelines defined in section above.

Any congenital abnormalities or birth defects in newborn will be followed three months post-delivery.

[redacted]

10.3 Efficacy Variables

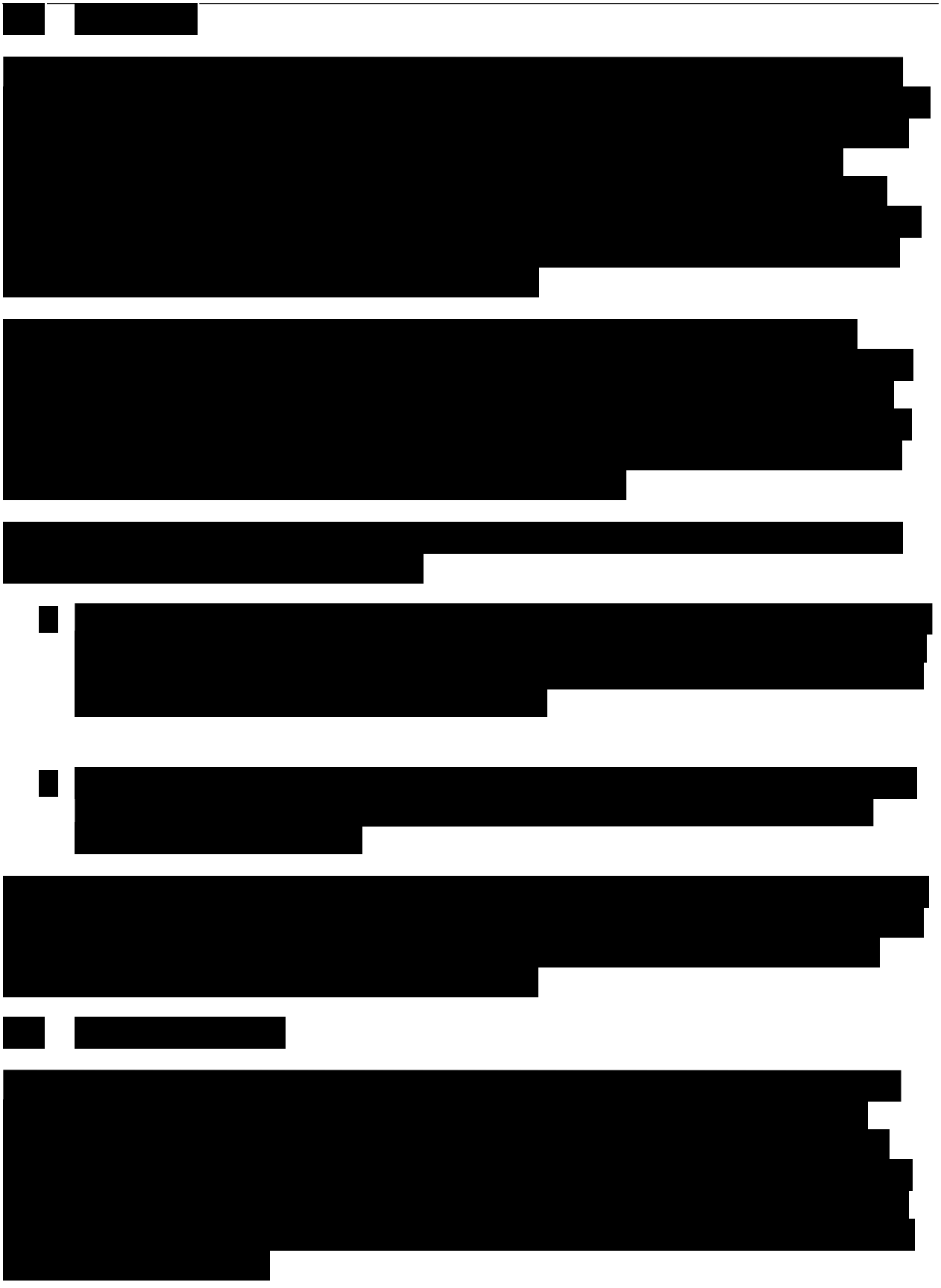
The primary efficacy variable is:

The time-matched mean IOP (study eye) at each of the 3 time points (8:00 AM, 10:00 AM, 4:00 PM) on week 12.

10.4 Safety Variables

The safety variables are:

- AEs



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11.0 COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES

This study will be conducted in compliance with the protocol, current Good Clinical Practices, including the International Conference on Harmonization (ICH) Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of IPs in the countries involved will be adhered to.

11.1 Protection of Human Subjects

11.1.1 Subject Informed Consent

Informed consent must take place before any study specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject prior to enrollment into the study. If the subject is under the legal age of consent, the consent form must be signed by a legal guardian or as required by state and/or local laws and regulations.

All informed consent forms must be approved for use by the sponsor and receive approval/favorable opinion from an IRB/IEC prior to their use. If the consent form requires revision (eg, due to a protocol amendment or significant new safety information), it is the investigator's responsibility to ensure that the amended informed consent is reviewed and approved by CRO prior to submission to the governing IRB/IEC and that it is read, signed and

dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

If informed consent is taken under special circumstances (oral informed consent), then the procedures to be followed must be determined by CRO and/or study sponsor and provided in writing by CRO and/or study sponsor prior to the consent process.

11.1.2 Institutional Review Board Approval

This study is to be conducted in accordance with Institutional Review Board regulations. The investigator must obtain appropriate IRB approval before initiating the study and re-approval at least annually. Only an IRB/ERC approved version of the ICF will be used.

11.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

11.3 Subject Confidentiality

All personal study subject data collected and processed for the purposes of this study should be maintained by the investigator and his/her staff with adequate precautions as to ensure that the confidentiality of the data in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of CRO, the sponsor, the IRB/IEC approving this study, the Food and Drug Administration (FDA), the Department of Health and Human Services, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study subject's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the IP may ultimately be marketed, but the subject's identity will not be disclosed in these documents.

11.4 Documentation

Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's study subject files, as well as the results of diagnostic tests. The investigator's copy of the electronic case report forms (eCRFs) serves as the investigator's record of a subject's study-related data.

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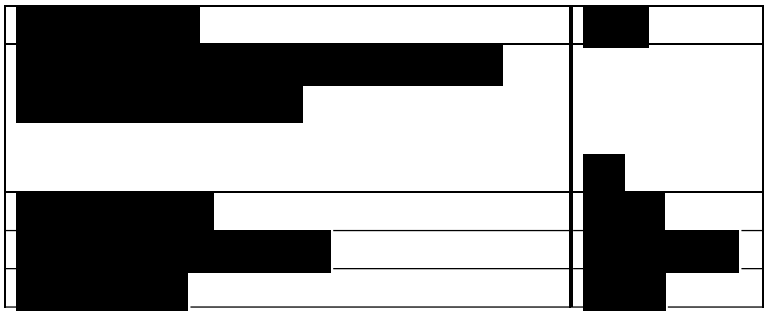

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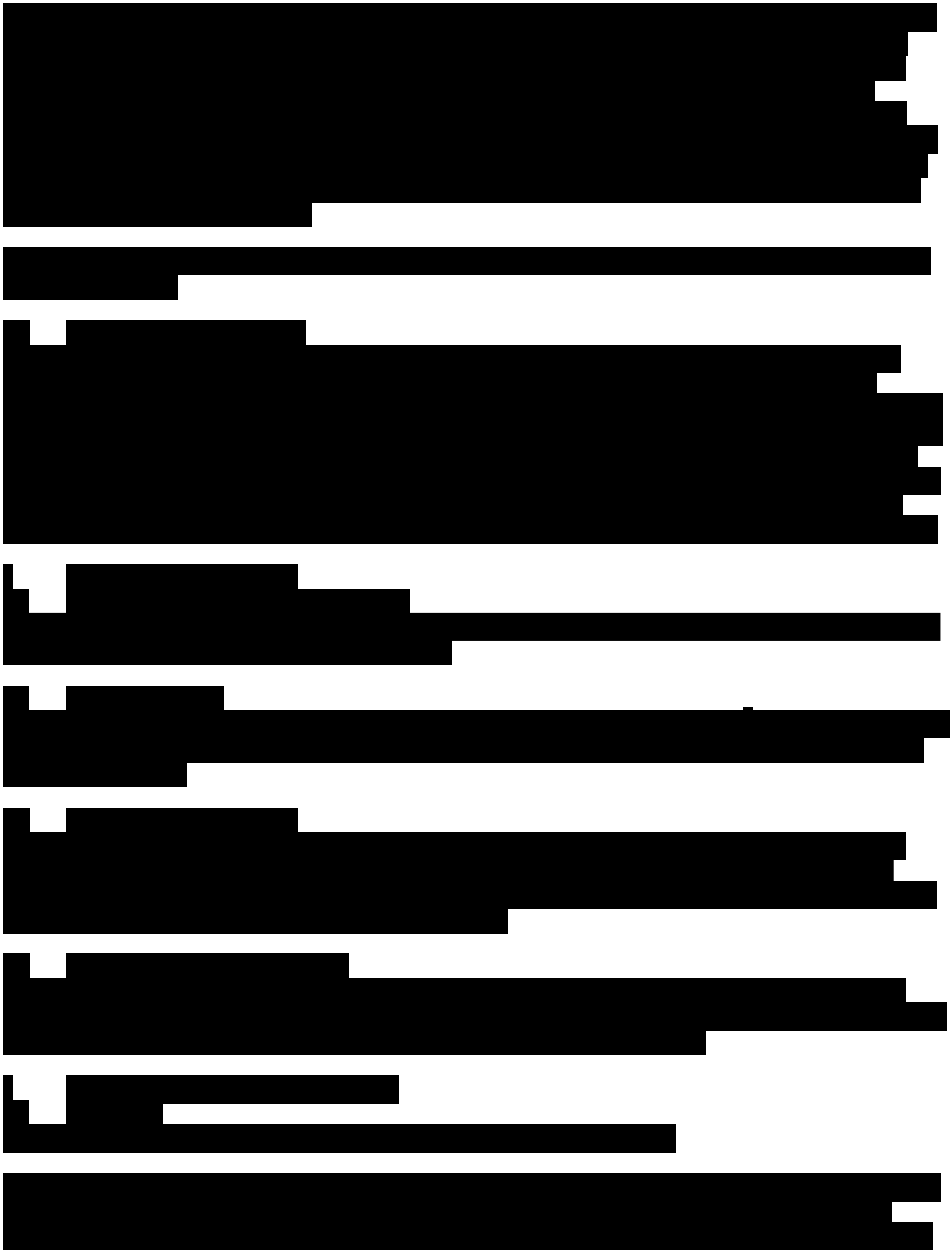

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ALPHAGAN® P has not been studied in patients with renal impairment. The effect of dialysis on brimonidine pharmacokinetics in patients with renal failure is not known.

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