A Double-Masked Comparison of Apraclonidine Hydrochloride Ophthalmic Solution to Vehicle for the Reduction of Ocular Redness

STUDY ID

DEW422-C001

PROTOCOL

NCT06444529

Alcon

Clinical Study Protocol

Study Title:	A Double-Masked Comparison of Apraclonidine Hydrochloride Ophthalmic Solution to Vehicle for the Reduction of Ocular Redness
Study Short Name:	A Double-Masked Comparison of FID 123320 Ophthalmic Solution to Vehicle for the Reduction of Ocular Redness
Study Number:	DEW422-C001
Study Phase:	Phase 3
Product Name:	FID 123320 (Apraclonidine HCl Ophthalmic Solution 0.125%)
Indication:	Reduction of ocular redness due to minor eye irritations
Investigators:	Multicenter, located in the United States
Sponsor:	Alcon Research, LLC, and its affiliates (“Alcon”) 6201 South Freeway Fort Worth, Texas 76134-2099

Investigator Agreement:

- I have read the clinical study described herein, recognize its confidentiality, and agree to conduct the described study in compliance with Good Clinical Practice (GCP), the ethical medical research principles contained within the Declaration of Helsinki, this protocol, all applicable laws, regulatory authority regulations, and conditions of approval imposed by the reviewing IRB or regulatory or governmental authority.
- I will supervise all testing of the investigational medicinal product(s) involving human research subjects and ensure that the requirements relating to obtaining informed consent and IRB review and approval are met in accordance with applicable local and governmental laws and regulations.
- I have read and understand the appropriate use of the IMP(s) as described in the protocol, current IB, product information, or other sources provided by the sponsor.
- I understand the potential risks and side effects of the investigational medicinal product(s).
- I agree to maintain adequate and accurate records in accordance with applicable government laws and regulations and to make those records available for inspection.
- I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements of the sponsor and government agencies.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed of their obligations in meeting the above commitments.

Have you ever been disqualified as an investigator by any Regulatory Authority? ☐ No ☐Yes
Have you ever been involved in a study or other research that was terminated? ☐ No ☐Yes If yes, please explain here:

Principal investigator:

_____

Signature Date

Name and professional position:

Address:

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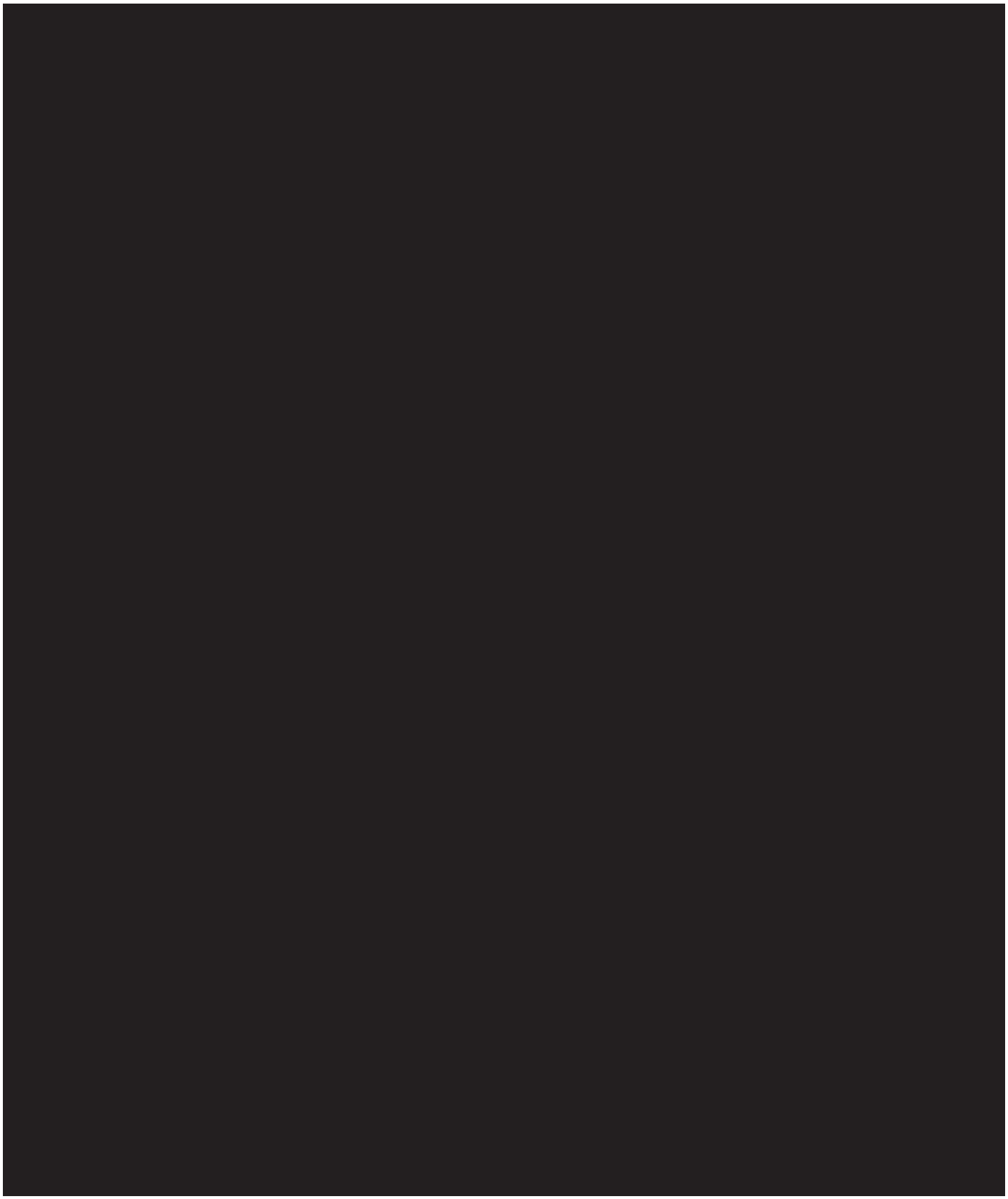


Table of Contents

Clinical Study Protocol 1

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Table of Contents 4

List of Tables 8

List of Figures 9

1 GLOSSARY OF TERMS 10

2 PROTOCOL SUMARRY 13

2.1 Protocol Synopsis 13

2.1.1 Primary and Secondary Objectives and Endpoints 13

2.1.2 Overall Design 14

2.1.3 Arms and Duration 17

2.1.4 Masking 17

2.1.5 Committees: 17

2.2 Study Schema 17

2.3 Schedule of Study Procedures and Assessments 18

3 INTRODUCTION 21

3.1 Purpose of Study 21

3.2 Summary of Benefits and Risks 21

3.3 Benefit Summary 22

3.3.1 Risk Summary and Mitigation Strategy 22

3.3.2 Overall Benefit: Risk Conclusion 24

4 STUDY OBJECTIVES AND ENDPOINTS 24

4.1 Primary Objective 24

4.2 Secondary Objective 25

[redacted]

4.4 Safety Objective 26

5 STUDY DESIGN 27

5.1 Description of Study Design 27

5.1.1 Description of Study Duration....27
5.2 Rationale for Study Design....27
5.2.1 Rationale for Comparator....28
6 STUDY POPULATION....28
6.1 Selection of Study Population....28
6.2 Inclusion Criteria....28
6.3 Exclusion Criteria....29
6.4 Lifestyle Considerations....31
6.4.1 Caffeine, Alcohol, Tobacco, and Other Substances....31
6.5 Screen Failures....31
6.6 Study Eye Selection Criteria....31
7 STUDY INTERVENTION AND CONCOMITANT THERAPY....32
7.1 Description of Study Intervention....32
7.2 Rationale for Study Intervention....32
7.3 Dosing and Administration....33
7.4 Treatment of Overdose....33
7.5 Handling, Storage, and Accountability....34
7.5.1 Handling and Storage of Study Intervention....34
7.5.2 Accountability of Study Intervention....35
7.5.3 Receipt of Study Intervention....35
7.5.4 Dispensing of Study Interventions....35
7.5.4.1 Return of Study Intervention....35
7.6 Subject Assignment, Randomization, and Masking....36
7.6.1 Subject Assignment....36
7.6.2 Subject Randomization....36
7.6.3 Masking....36
7.6.4 Emergency Unmasking....36
7.7 Study Intervention Compliance....37
7.8 Concomitant Therapy....38
7.8.1 Prohibited Medications/Treatments....38
8 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT WITHDRAWAL FROM STUDY....40
8.1 Discontinuation of Study Intervention....40
8.1.1 Criteria for Permanent Discontinuation of Study Intervention....40

8.1.2 Temporary Discontinuation or Interruption of Study Intervention ...41
8.1.3 Rechallenge ...41
8.2 Subject Withdrawal from the Study ...41
8.3 Lost to Follow-up ...41
8.4 Follow-up of Subjects After Study Participation has Ended ...42
9 STUDY ASSESSMENTS AND PROCEDURES ...42
9.1 Assessments and Procedures ...42
9.1.1 Informed Consent ...42
9.1.2 Demographics ...42
9.1.3 Medical/Ophthalmic History ...43
9.1.4 Prior and Concomitant Medication Assessments ...43
9.1.5 Washout Intervals ...43
9.1.6 Urine Pregnancy Test ...43
9.1.7 Investigator-Assessed Ocular Redness ...43
9.1.8 Adverse Event Collection ...43
9.1.9 Best-Corrected Visual Acuity ...43
9.1.10 Slit Lamp Biomicroscopy ...44
9.1.11 Intraocular Pressure ...44
9.1.12 Dilated Ophthalmoscopy ...44
9.1.13 Physical Examination ...44
9.1.14 Resting Blood Pressure and Pulse Rate ...44
9.2 Visit Assessments and Procedures ...44
9.2.1 Visit 1 (Day -7 to Day -1) ...45
9.2.2 Visit 2 (Day 1) ...46
9.2.3 Visit 3 (Day 14±2) ...47
9.2.4 Visit 4 (Day 28±2) ...48
9.2.5 Visit 5/Early Exit (Day 56±2) ...49
9.2.6 Visit 6/Exit (Day 63+1) ...50
9.3 Unscheduled Visits ...51
9.4 Adverse Events and Serious Adverse Events ...52
9.4.1 Definitions of AEs and SAEs ...52
9.4.2 Time Period and Frequency for Collecting AE and SAE Information ...54
9.4.3 Identifying AEs and SAEs ...54
9.4.4 Recording of AEs and SAEs ...54
9.4.5 Follow-up of AEs and SAEs ...55
9.4.6 Reporting of SAEs ...56

9.4.7 Regulatory Reporting Requirements for SAEs 56
9.4.8 Adverse Events of Special Interest 57
9.4.9 Disease-related Events or Outcomes Not Qualifying as AEs or SAEs 57
9.5 Pregnancy and Postpartum Information 57
9.5.1 Subjects Who Become Pregnant During the Study 57
9.6 Technical Issues with Study Test Articles or Ophthalmic Delivery Device 58
10 STATISTICAL CONSIDERATIONS 58
10.1 Analysis Set 58
10.2 Analyses Supporting Primary Objective(s) 59
10.2.1 Statistical Model, Hypothesis, and Method of Analysis 59
10.2.1 Handling of Intercurrent Events of Primary Estimand(s) 60
10.2.2 Handling of Missing Data Not Related to Intercurrent Events 60
[redacted]
10.3 Analysis Supporting Secondary Objective(s) 61
[redacted]
10.6 Safety Analyses 63
[redacted]
10.8 Interim Analyses 64
10.9 Sample Size Determination 65
11 Protocol Deviations 65
12 GENERAL CONSIDERATIONS: REGULATORY, ETHICAL, AND STUDY OVERSIGHT 66
12.1 Regulatory and Ethical Considerations 66
12.2 Committees 67
12.2.1 Data Monitoring Committee 67
12.3 Informed Consent Process 67
12.4 Privacy and Data Protection 68
12.5 Early Site Closure or Study Termination 68
13 GENERAL CONSIDERATIONS: RISK MANAGEMENT AND QUALITY ASSURANCE 69
13.1 Quality Tolerance Limits 69

13.2 Data Quality Assurance 69
13.3 Source Data....69
14 APPENDIX: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS – DEFINITIONS, SEVERITY, AND CAUSALITY 70
14.1 Severity 70
14.2 Causality 71
14.3 Expectedness 71
15 APPENDIX: DEFINITIONS AND SUPPORTING OPERATIONAL DETAILS 72
15.1 Contraception and Pregnancy Testing 72
15.1.1 Definitions Related to Childbearing 72
15.1.2 Contraception 72
15.1.3 Pregnancy Testing....73
[redacted]
16 PUBLICATIONS....74
17 REFERENCES 74
17.1 Internal References 74
17.2 External References....74

List of Tables

Table 1-1 List of Terms 10
Table 1-2 List of Acronyms and Abbreviations 11
Table 2-1 Primary and Secondary Objectives and Endpoints....13
Table 2-2 Schedule of Study Procedures and Assessments 19
Table 4-1 Primary Objective and Endpoint....24
Table 4-2 Secondary Objective and Endpoints 25
[redacted]
Table 4-4 Safety Objective and Endpoints....26
Table 7-1 Study Arms....33

Table 7-2 Prohibited Concomitant Therapies 39

List of Figures

Figure 2-1 Study Design.....18

1 GLOSSARY OF TERMS

Table 1-1 List of Terms

Term	Definition
Enrollment	The process of registering or entering a subject into a clinical study. Once a subject has been enrolled, the subject would then follow the clinical study protocol. Clinical investigations are designed to enroll a set number of subjects to increase the likelihood of answering the study questions.
Randomization	Subjects who are enrolled in the study will be randomized to one of the study intervention arms at the Day 1 (Visit 2) visit.
Screening	A process of active evaluation of potential subjects for enrollment in a study. After a subject is recruited, screening occurs during the enrollment period to see if they meet the inclusion and exclusion criteria. If they meet the criteria, the subject is eligible to enroll in the study.
Screen Failure	A subject who did not meet one or more criteria that were required for participation in the study.
Study Intervention	Study intervention is defined as any investigational medicinal product(s) (IMP), marketed product(s), placebo, vehicle(s), or medical device(s) intended to be administered to a study subject according to the study protocol

Table 1-2 List of Acronyms and Abbreviations

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
BCVA	Best corrected visual acuity
BID	Twice a day
bpm	Beats per minute
C	Celsius
CBD	Cannabidiol
CFR	Code of Federal Regulations
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COV	Close out visit
CRF	Case report form
CRO	Contract research organization
CSM	Clinical site manager
CSR	Clinical study report
DMC	Data monitoring commitee
eCRF	Electronic case report form
EDC	Electronic data capture
F	Fahrenheit
FAS	Full analysis set
FDA	US Food and Drug Administration
FID	Formulation identification
GCP	Good Clinical Practice
HCl	Hydrochloride
ICF	Informed consent form
IB	Investigator’s brochure
ICH	International Conference on Harmonization
IOP	Intraocular pressure
IMP	Investigational medicinal product
IND	Investigational new drug
IMV	Interim monitoring visit
IMP	Investigational medicinal product

Abbreviation	Definition
IOP	Intraocular pressure
IP	Investigational product
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LAM	Lactational amenorrhoea method
LDPE	Low-density polyethylene
logMAR	Logarithm of the minimum angle of resolution
MAO	Monoamine oxidase
ml	Milliliter
mmHg	Millimeters of mercury
MMRM	Mixed model repeated measure
MNAR	Missing not at random
MOP	Manual of procedures
N/A	Not applicable
NSAID	Nonsteroidal anti-inflammatory drug
PD	Protocol deviation
pH	Potential of hydrogen
PI	Principal investigator
[redacted]	[redacted]
QID	Four times a day
QTL	Quality tolerance limit
R&D	Research and development
REML	Restricted maximum likelihood
RTSM	Randomization and trial supply management
SAE	Serious adverse events
SAR	Serious Adverse Reaction
SAV	Site activation visit
SLE	Slit lamp examination
SOP	Standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
US	United States
USP	United States Pharmacopeia
VA	Visual acuity

Abbreviation	Definition
WOCBP	Woman of childbearing potential

2 PROTOCOL SUMARRY

2.1 Protocol Synopsis

Compound Number(s):	AL-02145
Compound Name(s):	Apraclonidine Hydrochloride Ophthalmic Solution
Study Phase:	Phase 3
Brief Summary of Protocol:	A multicenter, double-masked, randomized, vehicle-controlled, parallel-group study to assess the safety and efficacy of Apraclonidine Hydrochloride (HCl) Ophthalmic Solution 0.125%, when compared to vehicle, in relieving redness of the eye due to minor eye irritations in healthy adults. Eligible subjects who have a history of using (or expressed a desire to use) redness relief drops within the last 6 months and who show a baseline redness of > 1 unit in both eyes on Day 1 will be randomized to receive the assigned study intervention. Approximately 240 subjects will be screened to achieve ~120 subjects randomized into the study. There will be 6 visits over a period of approximately 10 weeks. The expected outcome will be to determine the safety and efficacy of test article relative to vehicle.
Local Sponsor Name and Address:	Alcon Research, LLC, and its affiliates (“Alcon”) 6201 South Freeway Fort Worth, Texas 76134-2099
Regulatory Agency Identifier Number(s):	IND Number 158742

2.1.1 Primary and Secondary Objectives and Endpoints

Table 2-1 lists the objectives and endpoints. For more information, see Section 4.

Table 2-1 Primary and Secondary Objectives and Endpoints

Primary Objective To demonstrate superiority of Apraclonidine Hydrochloride (HCl) Ophthalmic Solution 0.125%, when compared to vehicle at	Primary Endpoint Mean change from baseline in investigator-assessed ocular redness at 15-minutes and

15-minutes and 10-hours (600-minutes) postinstillation, in relieving redness of the eye due to minor eye irritations.	10-hours (600-minutes) postinstillation on Day 1.
Secondary Objective To demonstrate superiority of Apraclonidine Hydrochloride (HCl) Ophthalmic Solution 0.125%, when compared to vehicle, at 1-minute, 8-hours (480-minutes), and 12-hours (720-minutes) postinstillation timepoints.	Secondary Endpoint • Mean change from baseline in investigator-assessed ocular redness at 1-minute postinstillation on Day 1. • Mean change from baseline in investigator-assessed ocular redness at 8-hours (480-minutes) postinstillation on Day 1. • Mean change from baseline in investigator-assessed ocular redness at 12-hours (720-minutes) postinstillation on Day 1.

2.1.2 Overall Design

Several key aspects of the study design are summarized below.

Intervention Model:	Parallel group
Control:	Vehicle
Active Comparator:	N/A
Study Intervention Assignment Method:	Randomization All eligible subjects will be randomized in a 1:1 ratio to one of the two treatment arms at Visit 2, which occurs 1-7 days after the Screening Visit.
Population Type:	Adult subjects
Population Diagnosis or Condition:	Ocular redness
Population Age:	Minimum: 18 years – Maximum: N/A
Number of Subjects:	Planned number of subjects assigned to study intervention: ~120 (~60 test, ~60 control)
Number of Arms:	2
Site Distribution:	Planned number of clinical sites: Approximately 5 sites Planned locations: US

Eligible subjects are expected to attend 6 in-office visits in this study.

Screening Period:
At Visit 1, subjects will sign the informed consent form (ICF) and baseline assessments will be performed.

Treatment Period:
At Visit 2, qualifying subjects will be randomized in a 1:1 ratio to receive one of the following:

- Apraclonidine Hydrochloride (HCl) Ophthalmic Solution 0.125%
- Vehicle of Apraclonidine Hydrochloride (HCl) Ophthalmic Solution

A trained study technician will instill one drop of the assigned investigational product into each eye. Drop comfort assessments will be performed immediately upon instillation, at 30 seconds, and at 2-minutes postinstillation, and a subject-reported drop comfort descriptor query will be administered at 3-minutes postinstillation.

The investigator will assess ocular redness predose, and at 1 (+0.5), 5 (+1), 15 (+1), 60 (+10), 240 (+15), 480 (+15), 600 (+15), and 720 (+15) minutes postinstillation.

Subjects will be dispensed the assigned investigational product and instructed to dose bilaterally, one drop per eye, two times daily (BID; approximately 12 hours apart) from Day 2 onwards for approximately 2 weeks until the day prior to Visit 3. [redacted] On the day of Visit 3, subjects should not dose at home. The last dose on the previous day should occur at least 12 hours prior to their scheduled Visit 3.

At Visit 3, a trained study technician will instill one drop of the assigned investigational product into each eye. [redacted]

The investigator will assess ocular redness predose, and at 1 (+0.5), 5 (+1), and 15 (+1) minutes postinstillation.

Subjects will be instructed to dose bilaterally, one drop per eye, BID (approximately 12 hours apart) from the day of Visit 3 onwards for the next 2 weeks until the day prior to Visit 4.

[redacted] On the day of Visit 4, subjects should not dose at home. The last dose on the previous day should occur at least 12 hours prior to their scheduled Visit 4.

At Visit 4, a trained study technician will instill one drop of the assigned investigational product into each eye. [redacted]

The investigator will assess ocular redness predose, and at 1 (+0.5), 5 (+1), and 15 (+1) minutes postinstillation.

Subjects will be instructed to dose bilaterally, one drop per eye, BID (approximately 12 hours apart) from the day of Visit 4 onwards for the next 4 weeks until the day prior to Visit 5.

[redacted] On the day of Visit 5, subjects should not dose at home. The last dose on the previous day should occur at least 12 hours prior to their scheduled Visit 5.

At Visit 5, a trained study technician will instill one drop of the assigned investigational product into each eye. [redacted]

The investigator will assess ocular redness predose, and at 1 (+0.5), 5 (+1), and 15 (+1) minutes postinstillation. Study dosing will end after this in-office administration.

[redacted]

At Visit 6, [redacted] final study procedures will be performed prior to study exit.

Note: During the treatment period, subjects will be provided a spare droptainer to take home. If the spare investigational product is lost, contaminated, or damaged for any reason, subjects will be required to visit the clinic for additional clinical supply.

2.1.3 Arms and Duration

Total duration of study participation for each subject: Approximately 10 weeks with 8 weeks of exposure to assigned study articles.

2.1.4 Masking

The following roles indicated below will not be made aware of the treatment group assignment during the study:

- Subjects
- Care provider
- Investigator
- Outcomes assessor: the individual who evaluates the outcome(s) of interest
- All remaining site personnel associated with the study.
- All sponsor personnel and designees, with the exception of specified member(s) of R&D quality assurance, clinical supplies, and RTSM (external third party)

For more information on masking, see Section 7.6.

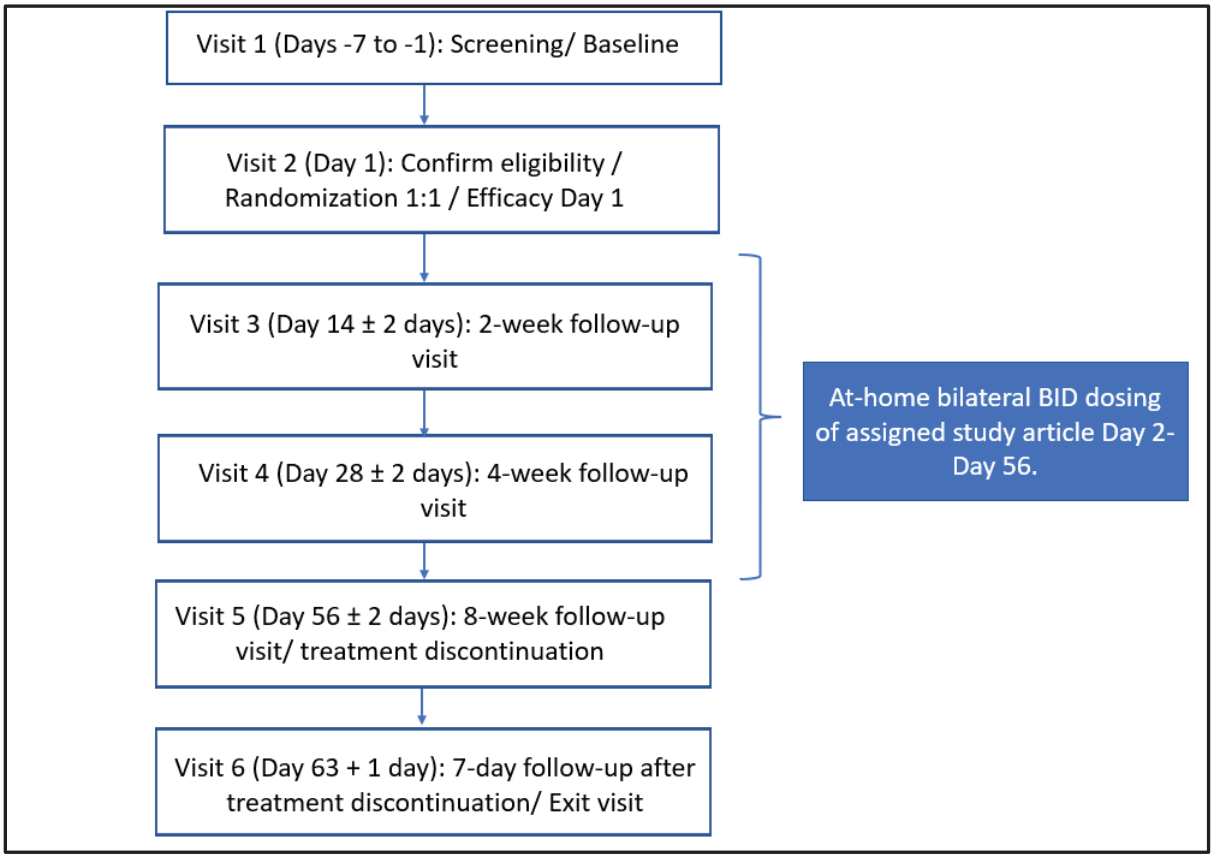
2.1.5 Committees:

N/A

2.2 Study Schema

Figure 2-1 illustrates the study design.

Figure 2-1 Study Design



2.3 Schedule of Study Procedures and Assessments

Table 2-2 provides a summary of the schedule of study procedures and assessments.

A description of the procedures to be performed at each visit can be found in the accompanying MOP.

Table 2-2 Schedule of Study Procedures and Assessments

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5 / Early Exit	Visit 6 / Exit
Study Day and Visit Window	**Day -7 to -1**	**Day 1**	**Day 14 ± 2**	**Day 28 ± 2**	**Day 56 ± 2**	**Day 63 + 1**
Informed Consent/Enrollment	X					
Demographics	X					
Medical and Medication History	X					
Medical and Medication History Update		X	X	X	X	X
Resting Blood Pressure and Pulse	X	X[3]	X	X	X	
Full Physical Examination	X				X	
Urine Pregnancy Test[2]	X	X			X	
BCVA with Manifest Refraction utilizing Snellen Chart ≠	X	X	X	X	X	X
Slit Lamp Biomicroscopy	X	X[3]	X	X	X	X
Intraocular Pressure	X			X	X	X
Dilated Ophthalmoscopy	X				X	
Review of Inclusion/Exclusion Criteria	X	X				
Randomization		X				
In-Office IP Instillation		X	X	X	X	
In-Office Alertness Evaluation[4]		X	X	X	X	
Adverse Events	X	X	X	X	X	X
Investigator-Assessed Ocular Redness		X[5]	X[6]	X[6]	X[6]	X
[redacted]						
IP Dispensation for At-Home Dosing		X		X		

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5 / Early Exit	Visit 6 / Exit
Study Day and Visit Window	**Day -7 to -1**	**Day 1**	**Day 14 ± 2**	**Day 28 ± 2**	**Day 56 ± 2**	**Day 63 + 1**
Dosing Compliance Review			X	X	X	
IP Collection (used and unused)				X	X	
[redacted]						
Study Exit						X

[2] For females of childbearing potential.

[3] Assessments to be completed predose and following the 12 hours (720 minutes) redness assessment.

[4] In-Office Alertness Evaluation will be performed predose and postdose at Visit 2 (12 hours postinstillation), and will be performed postdose at Visits 3, 4, and 5.

[5] Investigator-Assessed Ocular Redness assessments to be completed predose, and 1 (+0.5), 5 (+1), 15 (+1), 60 (+10), 240 (+15), 480 (+15), 600 (+15), and 720 (+15) minutes postinstillation in-office.

[6] Investigator-Assessed Ocular Redness assessments to be completed pre-dose, and 1 (+0.5), 5 (+1), and 1 5(+1) minutes postinstillation in-office.

[redacted]

≠ Visits 2 to 5: BCVA to be performed pre- and postinstillation. BCVA will be assessed 12 hours postinstillation on Day 1 (Visit 2).

See Section 9.2 for additional details by visit.

3 INTRODUCTION

3.1 Purpose of Study

Apraclonidine hydrochloride, a relatively selective alpha-adrenergic receptor agonist, is an active ingredient of the previously approved ophthalmic products IOPIDINE 0.5% and IOPIDINE 1.0%. IOPIDINE is effective in reducing intraocular pressure (IOP) and has an established safety profile (Abrams 1987, Abrams 1989, Yuksel 1992). Apraclonidine HCl's vasoconstrictive effects are being assessed for a new indication, i.e., to relieve the redness of the eye due to minor eye irritations. The investigational product is being developed by the sponsor to provide prolonged ocular redness relief that lasts approximately 8 hours or more.



The purpose of this study is to assess the safety and efficacy of Apraclonidine Hydrochloride (HCl) Ophthalmic Solution 0.125%, when compared to vehicle, in relieving redness of the eye due to minor eye irritations.

The study sponsor assures that the key designs of this protocol will be registered on public databases where required by current regulations, and, as applicable, results will be posted.

3.2 Summary of Benefits and Risks



The following are key Contraindications and Warnings/Precautions for use for Apraclonidine 0.5%:

Contraindications:

- Subjects with a history of severe or unstable and incontrollable cardiovascular disease including severe uncontrolled hypertension.

Warnings/Precautions:

- Caution should be exercised in subjects with a history of vasovagal attack.
- Caution should be exercised in subjects with a history of angina, severe coronary insufficiency, recent myocardial infraction, overt cardiac failure, hypertension, cardiovascular disease (including apoplexy), cerebrovascular disease, Parkinson's syndrome, chronic renal failure, Raynaud's disease, or thromboangiitis obliterans.
- Caution and monitoring of depressed subjects are advised since apraclonidine has been rarely associated with depression.

The potential benefit from exposure to Apraclonidine HCl 0.125% is ocular redness relief associated with minor eye irritations. [redacted]

3.3 Benefit Summary

Potential benefits include ocular redness relief with BID dosage of the investigational product, and the convenience of not having to dose frequently compared to other ocular redness relief products available on the market that may require more frequent dosing ([redacted]

3.3.1 Risk Summary and Mitigation Strategy

The newly formulated product Apraclonidine Hydrochloride (HCl) Ophthalmic Solution 0.125% is a preserved, isotonic, and pH balanced ophthalmic solution intended for reduction of ocular redness due to minor irritations. Preclinical data have shown the investigational product to be nontoxic and biocompatible for in-eye use. [redacted]

[redacted]

Apraclonidine at concentrations higher (IOPIDINE 0.5% and 1.0%) than the newly formulated product has been marketed in the United States for over 30 years with proven efficacy, safety, and patient acceptance profile, albeit for different indications, e.g., for lowering intraocular pressure (IOP). [redacted]

Study subjects must be advised of potential ocular allergic-like reactions associated with treatment. If such symptoms occur, the use of investigational drug may be discontinued based on investigators' medical judgement. Also, subjects with a known history of allergies to any of the components of the new formulation must not be enrolled in this clinical study. Subjects must be advised that administration of a topical ocular drop may temporarily cause blurred vision right after instilling in the eye(s). They must be advised not to drive, use machinery, or do any activity that requires clear vision until they are sure that they can perform such activities safely.

The investigational product has not been studied via controlled clinical studies thus far in special populations such as pediatric, pregnant or lactating, or renal or hepatic impaired populations. Based on available pharmacokinetic data for IOPIDINE 0.5%, close monitoring of cardiovascular parameters in subjects with renal or hepatic impairments is recommended. Subjects with renal or hepatic impairment are excluded from this clinical study. Subjects that are pregnant and/or lactating are currently excluded from participation.

Risks associated with participation in the study related to anesthetic drops for Goldmann tonometry measurement and dilating drops include transient stinging, burning, and conjunctival redness. Risks associated with dilation of pupils for fundus exam include transient blurred vision and photophobia lasting a few hours.

Appropriate safeguards will be maintained to protect the privacy and confidentiality of the subject's personal data in accordance with local, state, and federal laws and regulations. Each subject will be assigned with a unique subject identification number.

[redacted]

[redacted]

3.3.2 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk for subjects involved in this study, the potential risks identified in association with Apraclonidine HCl Ophthalmic Solution 0.125% are justified by the anticipated benefits that may be afforded to subjects with relieving redness of the eye due to minor eye irritations.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of Apraclonidine HCl Ophthalmic Solution 0.125% can be found in the IB.

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 Primary Objective

Table 4-1 Primary Objective and Endpoint

Objective	Endpoint
To demonstrate superiority of Apraclonidine Hydrochloride (HCl) Ophthalmic Solution 0.125%, when compared to vehicle at 15-minutes and 10-hours (600-minutes) postinstillation, in relieving redness of the eye due to minor eye irritations.	Mean change from baseline in investigator-assessed ocular redness at 15-minutes and 10-hours (600-minutes) postinstillation on Day 1.

4.2 Secondary Objective

Table 4-2 Secondary Objective and Endpoints

Objective	Endpoint(s)
To demonstrate superiority of Apraclonidine Hydrochloride (HCl) Ophthalmic Solution 0.125%, when compared to vehicle, at 1-minute, 8-hours (480-minutes), and 12-hours (720-minutes) postinstillation timepoints.	• Mean change from baseline in investigator-assessed ocular redness at 1-minute postinstillation on Day 1. • Mean change from baseline in investigator-assessed ocular redness at 8-hours (480-minutes) postinstillation on Day 1. • Mean change from baseline in investigator-assessed ocular redness at 12-hours (720-minutes) postinstillation on Day 1.





4.4 Safety Objective

Table 4-4 Safety Objective and Endpoints

Objective	Endpoints
To evaluate the safety profile of the investigational products.	• Adverse events • Intraocular pressure • Biomicroscopy findings • Dilated ophthalmoscopy • Best-corrected visual acuity (BCVA) at distance • Full physical examination • Blood pressure • Pulse rate • [redacted] • Alertness

5 STUDY DESIGN

5.1 Description of Study Design

This will be a phase 3, multicenter, vehicle-controlled, double-masked, randomized, parallel-group study conducted at approximately 5 sites in the US. Approximately 240 subjects will be enrolled and screened to achieve approximately 120 subjects randomized. All subjects enrolled will have a history of using (or expressed a desire to use) redness relief drops within the last 6 months and who show a baseline redness of > 1 unit in both eyes on Day 1.

5.1.1 Description of Study Duration

The study is expected to be completed in approximately 7 months. The expected study duration for each subject is approximately 10 weeks with approximately 8 weeks (56 days) of IP exposure.

The study will consist of 6 scheduled visits: Screening and/or Baseline visit (Day -7 to -1), Eligibility confirmation/Randomization/1st Treatment visit on Day 1, 2-week follow-up visit on Day 14, 4-week follow-up visit on Day 28, 8-week follow-up/Treatment discontinuation visit on Day 56, and 7-day follow-up after treatment discontinuation/Exit visit on Day 63.

Refer to Figure 2-1 for an outline of the study.

5.2 Rationale for Study Design

[redacted]

[redacted] The primary and secondary endpoints were selected to fulfill the primary and secondary objectives of the study, with the intent to generate data to support the indication for which the drug is being developed. The exposure duration, [redacted] and assessment methods were chosen to provide a reliable

and valid measurement of the intended intervention effect, and to aid in overall interpretation of the efficacy and safety outcomes.

5.2.1 Rationale for Comparator

Existing clinical data (Investigator's Brochure for Apraclonidine Hydrochloride Ophthalmic Solution), and the fact that many pivotal clinical studies for topical ocular redness relief approved in the United States and overseas have used vehicle as the comparator (Ackerman 2019), fully support the choice of vehicle control for the Phase 3 study design.

6 STUDY POPULATION

6.1 Selection of Study Population

The study population will consist of healthy male and female subjects (age ≥ 18) at the time of informed consent, who have a history of using (or expressed a desire to use) redness relief drops within the last 6 months, and who show a baseline redness of > 1 unit in both eyes at Visit 2 (Day 1).

Approximately 240 subjects will be screened to achieve ~120 subjects randomized in approximately 5 sites in the US with a target of 102 completed subjects. The anticipated screen fail rate is 45 to 50% based on previous study and experience.

6.2 Inclusion Criteria

Subjects must meet all of the inclusion criteria to enroll into the study. All procedures to determine eligibility must be completed prior to the randomization and administration of study intervention. Individuals who do not meet criteria for study eligibility must not be enrolled via protocol waivers or exemptions. Eligibility criteria are assessed at Visit 1 and Visit 2.

1. Capable of giving signed informed consent as described in Section 12.3 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
2. Be at least 18 years of age at Visit 1, of either gender and any race.
3. Be willing and able to follow all instructions and attend all study visits.
4. Be able to self-administer eye drops in the opinion of the investigator.

5. Have a history of vasoconstrictor (redness relief drop) use within the last 6 months, or have an interest to use OTC vasoconstrictor eye drops for redness relief, or would benefit from the use of redness relief drops as per the Investigator's opinion.
6. For females capable of becoming pregnant, agree to have urine pregnancy testing performed at Visit 1 (must be negative), Visit 2 (must be negative), and at Visit 5; and must agree to use a medically acceptable form of birth control[1] throughout the study duration, for at least 14 days prior to the first dose of study drug (Visit 2), and for 1 month after the last dose of study drug (Visit 5). Women considered capable of becoming pregnant include all females who have experienced menarche and have not experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) or have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy).
7. Have ocular health within normal limits, including distance best-corrected visual acuity (BCVA) of 20/40 (0.3 logarithm of the minimum angle of resolution [logMAR]) or better in each eye as measured using a Snellen chart.
8. At Visit 2, have a baseline ocular redness score of > 1 unit in both eyes on a 0 to 4 unit scale as scored by the investigator using the Investigator Ocular Redness Scale.
9. Have stable ocular health (defined as no ocular conditions requiring therapy or surgical intervention) during the study.

Note: [1]Acceptable forms of birth control are spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of partner. For nonsexually active females, abstinence will be considered an acceptable form of birth control.

6.3 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded and may not participate in this study. Criteria are assessed at Visit 1 and Visit 2.

1. Have known contraindications or sensitivity to the use of any of the investigational drug(s) or their components, or any other medication required by the protocol.
2. Have had ocular surgical intervention within 6 months prior to Visit 1 or during the study.
3. Any history of lid surgery.

4. Have any ocular condition that, in the opinion of the investigator, could affect the subject's safety or study parameters (i.e., could affect ocular redness, IOP, or eyelid position).
5. Have any abnormality of the lids, ocular surface, or lacrimal duct system that, in the investigator's opinion, could affect ophthalmic drop absorption.
6. Have a known history of retinal detachment, diabetic retinopathy, or active retinal disease.
7. Have an active ocular infection (bacterial, viral, or fungal) or positive history of an ocular herpetic infection.
8. Have had Botox injection into lateral canthal rhytids (crow's feet) in the past 6 months.
9. Use of any of the following disallowed medications or devices during the period indicated prior to Visit 2 and for the duration of the study:
    - Contact lenses: 5 days
    - Artificial tear products, eye whiteners (e.g., vasoconstrictors), ocular decongestants, ocular antihistamines (including over-the-counter and herbal topical ophthalmic medications), ocular corticosteroids, any other topical ophthalmic agents (including phenylephrine dilating drops), lid scrubs, systemic antihistamines or decongestants, prostaglandins or prostaglandin derivatives, or ocular, topical, or systemic nonsteroidal anti-inflammatory drugs (NSAIDs): 7 days
    - Systemic corticosteroids or mast cell stabilizers, and/or any other systemic medications which the investigator feels may confound study data or interfere with subject's study participation: 14 days
    - Depot corticosteroids: 45 days
    - Cancer chemotherapy or immunosuppressive agents: 60 days
    - Monoamine oxidase (MAO) inhibitors: current use or previous use within the last 6 months
    - Antidepressants that affect the noradrenergic transmission such as tricyclic and tetracyclic antidepressants: current use or previous use within the last 6 months
10. Have prior (within 7 days of beginning investigational drug) or currently active significant illness (ocular or systemic) that could compromise participation, in the opinion of the investigator.

11. Have prior (within 30 days of beginning investigational drug) or anticipated concurrent use of an investigational drug or device during the study period.
12. Have an ocular or systemic condition or a situation which, in the investigator's opinion, may put the subject at increased risk, confound study data, or interfere significantly with the subject's study participation (e.g., renal or hepatic impairment).
13. Have planned surgery (ocular or systemic) during the study period or within 30 days after the study period.
14. Have abnormal blood pressure at rest at Visit 1 or Visit 2 defined as ≤ 90 or ≥ 160 mmHg (systolic) or ≤ 60 or ≥ 100 mmHg (diastolic).
15. Have an abnormal pulse at rest at Visit 1 or Visit 2 defined as < 60 or > 90 bpm.
16. Have abnormal intraocular pressure at Visit 1 defined as < 9 or > 22 mmHg and/or be currently using any IOP lowering medications.
17. Be currently breastfeeding or planning to breastfeed during the study period, or is a female who is currently pregnant, is planning a pregnancy, or has a positive urine pregnancy test at Visit 1 or at Visit 2.

6.4 Lifestyle Considerations

No restrictions are required during this study.

6.4.1 Caffeine, Alcohol, Tobacco, and Other Substances

Subjects must not use cannabidiol (CBD) within 3 days of screening or throughout the study.

6.5 Screen Failures

A screen failure occurs when a subject who consents to participate in the clinical study is not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Subjects who do not meet the criteria for participation in this study (screen failures) may not be rescreened.

6.6 Study Eye Selection Criteria

Study subjects will be dosed in both eyes.

7 STUDY INTERVENTION AND CONCOMITANT THERAPY

7.1 Description of Study Intervention

Study intervention is defined as any investigational medicinal product(s) (IMP), marketed product(s), placebo, vehicle(s), or medical device(s) intended to be administered to a study subject according to the study protocol.

The investigational products will be packaged with a 5 ml fill in a multidose 8 ml opaque, white, low-density polyethylene (LDPE) bottle with a natural LDPE dispensing plug and white polypropylene closure. The sponsor will mask the identity of test and vehicle by affixing investigational product labels that are identical except the kit number listed.

Each study intervention bottle will be labeled with an investigational label with the following minimal information: study number, kit number, and storage statement, including the statement, “Caution – New Drug – Limited by Federal (US) Law to Investigational Use”.

Apraclonidine HCl Ophthalmic Solution drug product is a sterile, colorless to light yellow, aqueous solution with a pH of approximately 6.8. It is preserved with benzalkonium chloride at 0.005% (50 parts per million). In addition to the drug substance and preservative, the formulation contains the following standard pharmacopeia excipients: Hypromellose, sodium chloride, sodium citrate (dihydrate), citric acid monohydrate, sodium hydroxide/hydrochloric acid to adjust pH, and purified water.

Vehicle of Apraclonidine HCl Ophthalmic Solution is a sterile, colorless to light yellow, aqueous solution with a pH of approximately 6.8. It is preserved with benzalkonium chloride at 0.005% (50 parts per million). In addition to the preservative, the vehicle contains the following standard pharmacopeia excipients: Hypromellose, sodium chloride, sodium citrate (dihydrate), citric acid monohydrate, sodium hydroxide/hydrochloric acid to adjust pH, and purified water.

More information on the test product can be found in the IB.

7.2 Rationale for Study Intervention

The topical ocular administration was selected on the basis of the route of administration of marketed Apraclonidine HCl 0.5% and 1%, [redacted]

[redacted]

[redacted]

7.3 Dosing and Administration

Table 7-1 Study Arms

Intervention:	Apraclonidine Hydrochloride (HCl) Ophthalmic Solution 0.125%	Vehicle for Apraclonidine Hydrochloride (HCL) Ophthalmic Solution
Dosing Regimen:	At Visit 2 (Day 1), subjects will receive one drop of the assigned IP into each eye. Subjects will dose one drop in each eye at home BID (approximately 12 hours apart, but not less than 11.5 hours apart) beginning the day following Visit 2 up until the day prior to Visit 5, except that the first dose on the day of Visits 3 and 4 will occur in-office instead of dosing at home. o On the day of Visit 3, subjects will receive 1 dose in-office in each eye, and will instill 1 dose at home for a total of 2 doses that day. o On the day of Visit 4, subjects will receive 1 dose in-office in each eye and will instill 1 dose at home for a total of 2 doses that day. On the day of Visit 5, subjects will only receive 1 dose in-office and then treatment will be discontinued.	

7.4 Treatment of Overdose

No information regarding overdose of Apraclonidine Hydrochloride (HCl) Ophthalmic Solution 0.125% is currently known. The active component of the investigational product is

apraclonidine. The label of IOPIDINE 0.5% Ophthalmic Solution (same active ingredient) contains the following regarding overdose:

> "Ingestion of IOPIDINE 0.5% Ophthalmic Solution has been reported to cause bradycardia, drowsiness, and hypothermia.
>
> Accidental or intentional ingestion of oral clonidine has been reported to cause apnea, arrhythmias, asthenia, bradycardia, conduction defects, diminished or absent reflexes, dryness of the mouth, hypotension, hypothermia, hypoventilation, irritability, lethargy, miosis, pallor, respiratory depression, sedation or coma, seizure, somnolence, transient hypertension, and vomiting.
>
> Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained. Hemodialysis is of limited value since a maximum of 5% of circulating drug is removed."

For more information refer to IB, package insert, and product label.

7.5 Handling, Storage, and Accountability

7.5.1 Handling and Storage of Study Intervention

Study interventions will be supplied in identical kits across treatment arms. Prior to dispensing to the subject, all study interventions must be stored in a secure location at the recommended storage condition of 2 to 25ºC (36 to 77ºF) with strictly limited access. Only authorized persons may dispense study intervention. Labeling of investigational product:

Each study intervention bottle will be labeled with a masked, investigational label.

Storage of investigational product:

The IP must be stored in a secure area accessible only to the investigator and his/her designees. The IP will be administered only to subjects entered into the clinical study, in accordance with the conditions specified in this protocol.

The subject should be instructed that, once opened, the product may be kept at room temperature (up to 25ºC [77ºF]) for the duration of the intended treatment period (i.e., approximately 30 days).

For more information refer to the pharmacy manual.

7.5.2 Accountability of Study Intervention

The investigator or delegate must keep an accurate accounting of the number of IMP units delivered to the site, dispensed to subjects, returned to the investigator by the subject, and returned to the sponsor or other disposition during and at the completion of the study.

7.5.3 Receipt of Study Intervention

Upon receipt of the study interventions, the investigator or delegate must conduct an inventory. The assigned study personnel at the investigator's site will verify study intervention shipment records by comparing the shipping documentation accompanying the study intervention to the study intervention actually received at the investigator's site. If a discrepancy, damage, or temperature excursion is observed, the sponsor must be notified immediately according to the instruction included with the shipment.

7.5.4 Dispensing of Study Interventions

During the study, the investigator or designated study personnel must dispense the study interventions to the subjects in accordance with their randomization assignment. Throughout the study, the investigator or delegate must maintain records of study intervention dispensation and collection for each subject. This record must be made available to the study monitor for the purposes of verifying the accounting of study intervention supplies. Any discrepancies and/or deficiencies between the observed disposition and the written account must be recorded along with an explanation. All study interventions sent to the investigator must be accounted for by study sponsor personnel, and in no case be used in an unauthorized situation.

7.5.4.1 Return of Study Intervention

When the site is closed, the study is completed, or is terminated by the sponsor, all study material including unused IMP will be returned to the sponsor (or the sponsor's designee). All IMP reconciliation procedures must be completed before the study is concluded. The responsible person at the investigator's institution must account for all used and unused IMP. The IMP storage manager or designee will complete a study drug returns form or equivalent that will be signed by the investigator or designee prior to returning the unused IMP to the sponsor's designee.

7.6 Subject Assignment, Randomization, and Masking

7.6.1 Subject Assignment

Subjects will be randomized at Visit 2 in a 1:1 ratio to receive treatment with Test product or Control product.

A randomization list will be generated based on the study requirements using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. Subjects will be assigned treatment according to the randomization list [redacted].

At Visit 2, after confirming eligibility, all subjects will be randomized [redacted] to one of the treatment arms. [redacted]

7.6.2 Subject Randomization

Randomization will be stratified by site and will be generated [redacted] based on the study requirements.

7.6.3 Masking

[redacted] Unmasking will occur only after all planned study data have been validated and the database locked.

Study personnel must avoid seeking information that may compromise masking.

7.6.4 Emergency Unmasking

Masked information on the identity of the assigned study treatment should not be disclosed during the study. Treatment assignment(s) may be made available to the investigator in case of a medical emergency or occurrence of an AE that, in the opinion of the investigator, warrants unmasking. If the investigator feels it is necessary to unmask a subject's treatment assignment, the investigator is asked to contact the sponsor/sponsor representative first. [redacted]

[redacted] The treatment assignment will be revealed on a subject-by-subject basis, thus leaving the masking on remaining subjects intact. In the case of such unmasking in an emergency, the investigator must contact the sponsor/sponsor representative immediately thereafter and document the unmasking in writing, recording the date, time, and reason for unmasking the study drug treatment in the source documentation. Additionally, the study sponsor may be required to unmask the information in order to fulfill expedited regulatory reporting requirements.

7.7 Study Intervention Compliance

Compliance with study intervention will be assessed at all follow-up visits. Compliance will be assessed [redacted] direct questioning during the site visits and counting returned bottles during the last site visit. Compliance will be documented in the source documents or relevant form. Deviation(s) from the prescribed dosage regimen will be recorded.

A record of the quantity of study intervention dispensed to and administered by each subject must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays will also be recorded.

These guidelines will be used by the investigator for determining the subject's necessary compliance for the study and for recording deviations from this compliance.

Subjects who are inappropriately enrolled may be discontinued from the study. The reason for such discontinuation will be recorded as "protocol deviation" in the source document and on the appropriate page in the CRF.

Subjects will be asked if they changed their dosing regimen since their previous visit and the response will be recorded in the source document and on the CRF at Visits 3, 4, and 5.

Interruptions to dosing during the study period must be avoided, unless deemed necessary by the investigator due to an AE. Subjects should contact the investigator before interrupting treatment, and investigators should contact the sponsor if possible. Any interruptions or intermittent dosing will be reported as protocol deviations unless necessary due to an AE.

Dosing compliance throughout the 8-week exposure to the study articles will be reviewed [redacted] Subjects are considered noncompliant if they had dosing compliance < 80% or > 120%.

7.8 Concomitant Therapy

Pharmacologic and nonpharmacologic therapies and surgeries/procedures will be queried during all study visits.

The use of any concurrent medication, prescription or over-the-counter medication, is to be recorded on the subject's source document and corresponding case report form (CRF) along with the reason the medication was taken.

Concurrent enrollment in another investigational drug or medical device study is not permitted.

7.8.1 Prohibited Medications/Treatments

The table below outlines all prohibited prior and concomitant therapies. Subjects must discontinue the use of any of the therapies or interventions listed in Table 7-2 for the specified period prior to the specified visit and these therapies or interventions must not be used during the course of the study. Use of any of these therapies or interventions during the course of the study must be documented as a protocol deviation.

Lid scrubs, lid hygiene, or lid heating must be discontinued 7 days prior to screening Visit 2 and are prohibited during the study.

Systemic therapy with agents that could have a substantial effect on ocular redness or IOP (e.g., β-adrenoceptor antagonists, corticosteroid-containing drugs regardless of route of administration) must be avoided throughout the study. Changes in systemic medication that could have a substantial effect on ocular redness and IOP are prohibited throughout the study.

Table 7-2 Prohibited Concomitant Therapies

Treatment/Intervention/Therapy	Washout/ Discontinuation Required	Precaution(s) and Action(s) to be Taken	Rationale
Contact lenses	5 days prior to Visit 2	Prohibited throughout the study	Confounding factor
Artificial tear products	7 days prior to Visit 2	Prohibited throughout the study	Confounding factor
Eye whiteners (e.g., vasoconstrictors)	7 days prior to Visit 2	Prohibited throughout the study	Confounding factor
Lid scrubs	7 days prior to Visit 2	Prohibited throughout the study	Confounding factor
Systemic antihistamines or decongestants	7 days prior to Visit 2	Prohibited throughout the study	Confounding factor
Prostaglandins or prostaglandin derivatives	7 days prior to Visit 2	Prohibited throughout the study	Confounding factor
Ocular, topical, or systemic NSAIDs	7 days prior to Visit 2	Prohibited throughout the study	Confounding factor
Ocular decongestants, ocular antihistamines (including over-the-counter and herbal topical ophthalmic medications), ocular corticosteroids, any other topical ophthalmic agents (including phenylephrine dilating drops)	7 days prior to Visit 2	Prohibited throughout the study	Confounding factor
Systemic corticosteroids or mast cell stabilizers and/or any other systemic medications which the investigator feels may confound study data, or interfere with subject's study participation	14 days prior to Visit 2	Prohibited throughout the study	Confounding factor
Depot corticosteroids	45 days prior to Visit 2	Prohibited throughout the study	Confounding factor
Cancer chemotherapy or immunosuppressive agents	60 days prior to Visit 2	Prohibited throughout the study	Confounding factor
Monoamine oxidase (MAO) inhibitors	6 months prior to Visit 2	Prohibited throughout the study	Confounding factor
Antidepressants that affect the noradrenergic transmission such as tricyclic and tetracyclic antidepressants	6 months prior to Visit 2	Prohibited throughout the study	Confounding factor
Botox injection into lateral canthal rhytids (crow's feet)	6 months prior to Visit 2	Prohibited throughout the study	Confounding factor

8 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT WITHDRAWAL FROM STUDY

8.1 Discontinuation of Study Intervention

Discontinuation of study intervention for a subject occurs when study intervention is stopped earlier than the protocol planned duration.

8.1.1 Criteria for Permanent Discontinuation of Study Intervention

A subject may be discontinued from the study at the discretion of the investigator or the medical monitor. Other reasons that a subject may be discontinued from the study may include, but are not limited to:

- Adverse event(s) (AEs including, in the opinion of the investigator, clinically relevant laboratory abnormalities, and intercurrent diseases reported by the subject or observed by the investigator)
- Death
- Lack of efficacy
- Lost to follow-up
- Pregnancy
- Protocol violation which, in the opinion of the investigator and/or sponsor, precludes continued study participation
- Study terminated by sponsor
- Technical problems
- Withdrawal of consent by subject
- Investigator decision where participation in the study poses a risk to the safety of the subject and/or integrity of the study

The investigator must document the reason for study or treatment discontinuation in the subject's case history source documents and must complete all exit procedures according to Schedule of Procedures and Assessments and Section 2.3 if the subject is willing and able, and if, in the opinion of the investigator, it is safe for the subject to do so. To ensure the safety of all subjects who discontinue early, investigators must assess each subject and, if necessary, advise them of any therapies and/or medical procedures that may be needed to maintain their health.

8.1.2 Temporary Discontinuation or Interruption of Study Intervention

Subjects who temporarily discontinue trial intervention should remain in the trial unless discontinuation from the trial is deemed necessary by the investigator due to a safety-related event.

Subjects who miss an instillation(s) of IP should resume instillation at their earliest convenience [redacted].

8.1.3 Rechallenge

Subjects that experience an AE and have discontinued IP will not be rechallenged. However, this does not apply to suspected or expected AEs (e.g., eye redness, ocular discomfort, or temporary blurring of vision) that are reported without subject discontinuation/will not be considered rechallenged.

8.2 Subject Withdrawal from the Study

A subject may exit the study by their own volition. Any subject may decide to voluntarily withdraw from the study at any time without prejudice. The sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If possible, an early discontinuation visit should be conducted, in accordance with the schedule of activities (Section 2.3). Study intervention will be discontinued upon subject exit.

The investigator must document the reason for study or IP discontinuation in the subject's case history source documents.

To ensure the safety of all subjects who discontinue early, investigators must assess each subject and, if necessary, advise them of any therapies and/or medical procedures that may be needed to maintain their health.

8.3 Lost to Follow-up

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain whether the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls, and if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

8.4 Follow-up of Subjects After Study Participation has Ended

Following this study, the subject will return to their eye care professional for their routine eye care.

9 STUDY ASSESSMENTS AND PROCEDURES

Detailed descriptions of assessments and procedures are provided in the MOP. The investigator is responsible for ensuring responsibilities for all procedures and assessments are delegated to appropriately qualified site personnel.

9.1 Assessments and Procedures

9.1.1 Informed Consent

The investigator or delegate must explain the purpose and nature of the study, and have the subject read, sign, and date the IRB-approved ICF. The subject must sign the ICF BEFORE any study-specific procedures or assessments can be performed, including study-specific screening procedures. Additionally, have the individual obtaining consent from the subject and a witness, if applicable, sign and date the ICF.

The Investigator or delegate must provide a copy of the signed document to the subject and place the original signed document in the subject's chart, or provide documentation as required by local regulations.

9.1.2 Demographics

Obtain relevant demographic information including age, race, ethnicity, sex, [redacted]

9.1.3 Medical/Ophthalmic History

Significant medical and ophthalmic history will be collected, including:

- Current medical/ophthalmic conditions
- Medical/ophthalmic conditions that occurred within the last 6 months
- Resolved medical/ophthalmic conditions that are deemed relevant by the investigator
- Relevant past surgeries/procedures

9.1.4 Prior and Concomitant Medication Assessments

Any medication (including vaccines, over-the-counter or prescription medicines, vitamins, and/or herbal supplements) will be queried and recorded on the appropriate case report form (CRF) and updated at each visit. Ongoing or prior medications taken up to 30 days prior to Visit 1 must also be recorded.

9.1.5 Washout Intervals

Subjects will adhere to the medication washout intervals according to Table 7-2 during the period indicated prior to Visit 2 and will refrain from using these medications during the study.

9.1.6 Urine Pregnancy Test

All females of childbearing potential must have negative urine pregnancy tests at Visits 1 and 2 (for eligibility), must agree to use an adequate method of contraception, and the urine pregnancy test will be repeated at Visit 5.

9.1.7 Investigator-Assessed Ocular Redness

Ocular redness will be assessed by the investigator using the 0 to 4 unit Investigator Ocular Redness Scale (see MOP).

9.1.8 Adverse Event Collection

Assess and record adverse events that are observed or reported since the previous visit, including those associated with changes in concomitant medication dosing.

9.1.9 Best-Corrected Visual Acuity

Best-corrected visual acuity at distance (with manifest refraction) will be assessed using a Snellen chart at all visits.

BCVA will be performed pre- and postinstillation at Visits 2-5. BCVA will be assessed 12 hours postinstillation on Day 1 (Visit 2). For pre-instillation acuity assessment, BCVA should be evaluated at the beginning of each of these visits in the study as applicable, i.e., prior to slit-lamp examination, intraocular pressure measurement, the administration of topic anesthetic agents, or any examination requiring contact with the anterior segment.

9.1.10 Slit Lamp Biomicroscopy

SLE of the cornea, conjunctiva, eyelids, and ocular surface must be performed in both eyes at each visit.

9.1.11 Intraocular Pressure

Intraocular pressure will be measured (see Manual of Procedures). The ocular anesthetic agent and dye, fluorescein sodium and benoxinate hydrochloride ophthalmic solution USP, will be used for the intraocular pressure assessment.

9.1.12 Dilated Ophthalmoscopy

A dilated ophthalmoscopy will be performed by the investigator to evaluate the presence or absence of clinically significant fundus abnormalities and vitreous pathology (see Manual of Procedures). Dilating eye drops will be used.

9.1.13 Physical Examination

A physical examination will be performed (see Manual of Procedures).

9.1.14 Resting Blood Pressure and Pulse Rate

Resting blood pressure and pulse rate will be taken (see Manual of Procedures).

9.2 Visit Assessments and Procedures

All ophthalmic procedures will be performed in both eyes.

The Schedule of Study Procedures and Assessments is provided in Table 2-2. Procedures for each visit are outlined below.

9.2.1 Visit 1 (Day -7 to Day -1)

- Informed Consent
- Demographic Information Collection
- Medical and Medication (Ocular and Nonocular) History. Collect and record all medical history, any medications, and any underlying condition(s). Current underlying conditions, including those that occurred within the last 6 months must be recorded. Record any medications the subject is taking, as well as those the subject may have taken but discontinued within the 30 days prior to screening
- Resting Blood Pressure and Pulse Rate
- Physical Exam (see Manual of Procedures)
- Urine Pregnancy Test (for females of childbearing potential). Women of childbearing potential must have a negative urine pregnancy test to continue in the study and must agree to use an adequate method of contraception specified in the protocol in order to be enrolled
- BCVA at Distance with Manifest Refraction utilizing a Snellen Chart. Subjects must have a VA score of 20/40 (0.3 logMAR) or better in each eye in order to qualify (see Manual of Procedures)
- Slit Lamp Biomicroscopy. A slit lamp exam will be performed to exclude subjects with disallowed ocular conditions (see Manual of Procedures)
- Intraocular pressure will be measured (see Manual of Procedures). Subjects who have an IOP < 9 or > 22 mmHg will be excluded
- Dilated Ophthalmoscopy will be performed by the investigator to evaluate the presence or absence of clinically significant fundus abnormalities and vitreous pathology (see Manual of Procedures)
- Review of Inclusion/Exclusion Criteria
- Adverse Events Query
- Schedule Visit 2

9.2.2 Visit 2 (Day 1)

Prior to first dose:

- Update Medication History. Collect and record any changes or new medications that may have started or that require follow-up from the last visit. If a subject uses a disallowed medication, that subject will be excluded from the study
- Adverse Events Query
- Urine Pregnancy Test (for females of childbearing potential)
- BCVA at Distance with Manifest Refraction utilizing a Snellen Chart
- Slit Lamp Biomicroscopy
- Investigator-Assessed Ocular Redness. Redness will be assessed by the investigator using the 0 to 4 unit Investigator Ocular Redness Scale. Subjects must have ocular redness >1 unit in both eyes to continue in the study
- Resting Blood Pressure and Pulse Rate
- In-Office Alertness Evaluation (baseline)
- Review of Inclusion/Exclusion Criteria
- Randomization
- Investigational Product Instillation

Subsequent to first dose:

[redacted]

- Postinstillation Investigator-Assessed Ocular Redness. Redness will be assessed by the investigator at 1 (+0.5), 5 (+1), 15 (+1), 60 (+10), 240 (+15), 480 (+15), 600 (+15), and 720 (+15) minutes after investigational product instillation using the 0 to 4 unit Investigator Ocular Redness Scale
- In-Office Alertness Evaluation
- BCVA at Distance (with Manifest Refraction) utilizing a Snellen Chart

- Slit Lamp Biomicroscopy (Postinstillation following 12-hour redness assessment)
- Resting Blood Pressure and Pulse Rate (Postinstillation following 12-hour redness assessment)



- Adverse Events Query
- Schedule Visit 3

9.2.3 Visit 3 (Day 14±2)

Prior to in-office administration of investigational product at this visit:

- Update Medication History
- Adverse Events Query



- BCVA at Distance (with Manifest Refraction) utilizing a Snellen Chart
- Investigator-Assessed Ocular Redness Assessment
- Investigational Product Instillation

Subsequent to in-office administration of investigational product at this visit:



[redacted]

- Postinstillation Investigator-Assessed Ocular Redness. Redness will be assessed by the investigator at 1 (+0.5), 5 (+1), and 15 (+1) minutes after investigational product instillation using the 0 to 4 unit Investigator Ocular Redness Scale
- In-Office Alertness Evaluation
- BCVA at Distance (with Manifest Refraction) utilizing a Snellen Chart
- Slit Lamp Biomicroscopy
- Resting Blood Pressure and Pulse Rate

[redacted]

- Adverse Events Query
- Schedule Visit 4

9.2.4 Visit 4 (Day 28±2)

Prior to in-office administration of investigational product at this visit:

- Update Medication History
- Adverse Events Query

[redacted]

- IP Collection (used and unused)
- BCVA at Distance (with Manifest Refraction) utilizing a Snellen Chart
- Investigator-Assessed Ocular Redness
- Investigational Product Instillation

Subsequent to in-office administration of investigational product at this visit:

[redacted]

- Postinstillation Investigator-Assessed Ocular Redness. Redness will be assessed by the investigator at 1 (+0.5), 5 (+1), and 15 (+1) minutes after investigational product instillation using the 0 to 4 unit Investigator Ocular Redness Scale
- Alertness Evaluation
- BCVA at Distance (with Manifest Refraction) utilizing a Snellen Chart
- Slit Lamp Biomicroscopy
- Intraocular Pressure
- Resting Blood Pressure and Pulse Rate

[redacted]

- Adverse Events Query
- Schedule Visit 5

9.2.5 Visit 5/Early Exit (Day 56±2)

Prior to in-office administration of investigational product at this visit:

- Update Medication History
- Adverse Events Query
- Urine Pregnancy Test (for females of childbearing potential)

[redacted]

- IP Collection (used and unused)
- BCVA at Distance (with Manifest Refraction) utilizing a Snellen Chart
- Investigator-Assessed Ocular Redness
- Investigational Product Instillation

Subsequent to in-office administration of investigational product at this visit:

[redacted]

- Postinstillation Investigator-Assessed Ocular Redness. Redness will be assessed by the investigator at 1 (+0.5), 5(+1), and 15 (+1) minutes after investigational product instillation using the 0 to 4 unit Investigator Ocular Redness Scale.
- Alertness Evaluation
- Resting Blood Pressure and Pulse Rate
- BCVA at Distance (with Manifest Refraction) utilizing a Snellen Chart
- Slit Lamp Biomicroscopy
- Intraocular Pressure
- Physical Exam

[redacted]

- Dilated Ophthalmoscopy
- Adverse Events Query
- Schedule Visit 6

9.2.6 Visit 6/Exit (Day 63+1)

- Update Medication History
- Adverse Events Query

[redacted]

- BCVA at Distance (with Manifest Refraction) utilizing a Snellen Chart
- Slit Lamp Biomicroscopy
- Investigator-Assessed Ocular Redness
- Intraocular Pressure
- Adverse Events Query
- Study Exit

Adverse Events (AEs) (both elicited and observed) will be monitored throughout the study. All AEs (both elicited and observed) will be promptly reviewed by the investigator for accuracy and completeness. All AEs will be documented on the appropriate CRF.

If a female has a positive pregnancy test during the study, then the investigator will notify Alcon immediately. The investigator shall request from the subject and/or the subject's physician copies of all related medical reports during the pregnancy and shall document the outcome of the pregnancy. The investigator will retain these reports together with the subject's source documents and will provide a copy of all documentation to Alcon.

9.3 Unscheduled Visits

An unscheduled visit may occur between two regularly scheduled study visits, as required. For unscheduled visits, the reason for the visit should be clearly documented on the appropriate CRF, including findings from all evaluations that are completed.

An unscheduled visit may be performed to ensure subject safety. All information gathered at unscheduled visits should be recorded on the Source Document and the data will be collected on the corresponding CRF (if the assessments were performed by delegated study personnel). Any AE, concomitant medication, or PD identified during the visit should be documented.

Evaluations may be conducted at an unscheduled visit as per the investigator’s discretion, and include but are not limited to:

- Update to Medical/Medication History
- Resting Blood Pressure and Pulse
- Physical Examination
- Urine Pregnancy Test
- BCVA at Distance (with Manifest Refraction) utilizing a Snellen chart
- Slit Lamp Biomicroscopy
- IOP
- Dilated Ophthalmoscopy
- In-Office Alertness Evaluation
- Assessment of Adverse Events
- Investigator-Assessed Ocular Redness
- Review of Dosing Compliance
- IP Dispensation for At-Home Dosing
- IP Collection (used and unused)

9.4 Adverse Events and Serious Adverse Events

9.4.1 Definitions of AEs and SAEs

The following definitions of terms apply to this section:

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

Adverse drug reaction (ADR): All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. Responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. See Appendix 14

Adverse event of special interest (AESI): Adverse event (serious or nonserious) of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the study sponsor to other parties (e.g., regulators) might also be warranted.

Life-threatening AE or life-threatening ADR: An AE or ADR is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or ADR that, had it occurred in a more severe form, might have caused death.

Serious adverse event (SAE) or serious adverse reaction (SAR): An AE or AR is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening or sight-threatening AE
- A subject hospitalization or prolongation of existing hospitalization,

  Note: Planned hospitalization for a pre-existing condition, without serious deterioration in health, is not considered a serious adverse event. Therefore,

neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as a serious adverse event when the hospitalization or prolonged hospitalization was for an elective surgical procedure or for a preexisting condition. In general, hospitalization signifies that the individual remained at the hospital or emergency ward for observation and/or treatment (usually involving an overnight stay) that would not have been appropriate in the physician's office or an outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, the event should be considered serious.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (disability)
- A congenital anomaly/birth defect
- An important medical event or reaction that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse.

Note: Medical and scientific judgment should be exercised in deciding whether other situations should be considered as serious such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also be considered serious.

Suspected unexpected SAR (SUSAR): Adverse drug reaction that is both unexpected and meets the definition of a serious adverse event.

Unexpected AE or unexpected ADR: An AE or ADR is considered "unexpected" if it is not listed in the investigator's brochure or is not listed at the specificity or severity that has been observed; or, if an investigator's brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

Additional details and clarifications for AEs and SAEs are in Appendices 14.1 and 14.2.

9.4.2 Time Period and Frequency for Collecting AE and SAE Information

AEs and SAEs should be documented from the time the subject provides informed consent until Visit 6/Exit. Any SAE experienced after study Exit should only be reported to the sponsor if the investigator suspects a causal relationship to study treatment.

9.4.3 Identifying AEs and SAEs

AE information may be volunteered by the subject or solicited by study personnel through nonleading questions. At each visit, after the subject has had the opportunity to spontaneously mention any problems, the investigator should inquire about AEs by asking the standard questions shown below and report as applicable:

- "Have you had any health problems since your last study visit?"
- "Have there been any changes in the medicines you take since your last study visit?"

AEs should be reported for any clinically relevant change, as determined by the investigator, in concomitant medication(s) that is the result of an untoward (unfavorable and unintended) change in a subject's medical health.



9.4.4 Recording of AEs and SAEs

All AEs occurring during the study, regardless of the assumption of causal relationship, must be documented on the respective CRF. Qualified study staff responsible for assessing AEs will be listed on the Site Authorization and Delegation Log. This includes assessment of AE severity and relationship to treatment.

Documentation of AEs/adverse reactions will include AE description, start date and stop date, severity, relationship, action(s) taken, seriousness, and outcome.

When recording an AE, the following information should be provided on the study AE CRF:

Action Taken with Study Intervention:

- Dose Increased
- Dose Not Changed
- Dose Rate Reduced
- Dose Reduced
- Drug Interrupted
- Drug Withdrawn
- Not Applicable
- Unknown
- Other

AE Outcome:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with sequelae
- Unknown/Lost to Follow-up

Further details on assessing severity and causality of AEs and SAEs are in Appendices 14.1 and 14.2.

9.4.5 Follow-up of AEs and SAEs

After the initial report of an AE/SAE, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up.

Any unresolved AEs at the time of the subject's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the EDC. The sponsor retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

The investigator is responsible for adequate and safe medical care of subjects during the study and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the study. Any additional data from these follow-up procedures must be documented and available at the sponsor's request.

9.4.6 Reporting of SAEs

An investigator must immediately (i.e., within 24 hours of the investigator's or site's knowledge of the event) report any SAE or SAR (see Appendix 14) to the sponsor or sponsor representative, whether or not considered study intervention-related, including those listed in the protocol or investigator's brochure. The investigator must use the SAE report form (eCRF or email as a back-up) and include an assessment of whether there is a reasonable possibility that the study intervention caused the event. The investigator must report any SAE or SAR that occurs or is observed during the study. In case of incomplete information, the investigator must provide follow-up information as soon as possible, again using the SAE report form. The details for SAE/SAR report submission are listed below.

Report SAEs/SARs within 24 hours via electronic data capture (EDC) system or, in the case of the EDC system not being available, the provided SAE source document will be completed and sent via the instructions noted on the form to the sponsor (or representative) within the expected reporting time frame.

SAE/SAR reports will be evaluated by the medical monitor. Regulatory authorities, IRB, and investigators at each of the study sites will be informed as required (See Section 9.4.7 below).

An assessment of seriousness will also be performed for all adverse events by a sponsor physician utilizing the same criteria. If an adverse event reported for an investigator's subject is upgraded to a serious adverse event by a sponsor physician, the investigator will receive a notification from the sponsor.

9.4.7 Regulatory Reporting Requirements for SAEs

The sponsor is responsible for making regulatory submissions of SUSARs to the FDA as IND Safety Reports to comply with 21 CFR 312.32 I(1)(i). In the event of a SUSAR, the sponsor will also notify all study investigators via an investigator notification letter.

In addition to reporting of SAEs to the sponsor, it is the responsibility of the investigator to report SAEs to IRBs according to their requirements.

9.4.8 Adverse Events of Special Interest

Not applicable for this study.

9.4.9 Disease-related Events or Outcomes Not Qualifying as AEs or SAEs

Any medical condition present prior to informed consent which remains unchanged or improved should not be recorded as an AE at subsequent visits. However, an AE should be recorded if the frequency, intensity, or the character of a pre-existing condition worsens, in the medical opinion of the investigator, during the study period beyond what would be expected from the natural progression of that condition.

Surgery should not be reported as an adverse event nor as an outcome of an adverse event if the purpose of the surgery was diagnostic and the outcome was uneventful. However, if the surgery resulted from a new condition or worsening of an existing condition, the condition should be reported as an AE.

If there is a question as to whether a medical development should be reported as an adverse event, it is recommended the investigator contact the sponsor for guidance. The study manual of procedures provides the sponsor contact information.

9.5 Pregnancy and Postpartum Information

9.5.1 Subjects Who Become Pregnant During the Study

Pregnancies occurring in subjects enrolled in the study must be reported and followed to outcome. No further study treatments will be administered to pregnant subjects; however, the subject will be encouraged to complete all visits in the study.

If a woman is of childbearing potential, she must have a pregnancy test performed at Visit 1 and Visit 2 prior to confirmation of eligibility (and prior to start of study treatment). Additional pregnancy tests may also be required per local regulatory guidelines. Subjects with a positive pregnancy test result must be excluded from the study. Subjects with a negative pregnancy test result must agree to use a highly effective contraception method during the study.

While pregnancy itself is not considered to be an AE, pregnancy reports are tracked by the sponsor or sponsor representative. The investigator must complete the Pregnancy Report Form and email or fax the form to the sponsor or sponsor representative. Following delivery or termination of the pregnancy, the Pregnancy Report Form is to be completed and sent by email or fax to the sponsor or sponsor representative.

Premature terminations including miscarriage, spontaneous abortion, or elective termination of a pregnancy for medical reasons will be reported as a serious adverse event (SAE). Other pregnancy complications should be reported as SAEs if they meet the seriousness criteria. Should the pregnancy result in a congenital anomaly or birth defect, a separate SAE must be submitted for the child. Furthermore, all neonatal deaths that occur within 30 days of birth, without regard to causality, should be reported as SAEs.

9.6 Technical Issues with Study Test Articles or Ophthalmic Delivery Device

Any technical issues concerning the test article formulations or the ophthalmic delivery device (i.e., droptainer) must be reported to the sponsor. Instructions on how to report to the sponsor are provided in the study manual of procedures.

10 STATISTICAL CONSIDERATIONS

10.1 Analysis Set

10.1.1 Efficacy Analysis Sets

The following analysis populations will be considered:

- Full Analysis Set (FAS): The Full Analysis Set (FAS) includes all randomized subjects who have received at least 1 instillation of the study treatment and completed at least 1 postinstillation ocular redness assessment on Day 1. Subjects will be analyzed according to the treatment to which they were randomized. The primary efficacy analysis will be based on FAS.



10.1.2 Safety Analysis Set

The Safety Analysis Set includes all randomized subjects who have received at least 1 instillation of the study treatments. All subjects in the Safety Analysis Set will be analyzed accordingly to the treatment they received. All safety analyses will be based on the safety population.

10.2 Analyses Supporting Primary Objective(s)

The co-primary comparison in this study will be between Apraclonidine Hydrochloride (HCl) Ophthalmic Solution 0.125% versus vehicle at 15-minutes and 600-minutes after investigational drug instillation at Visit 2 (Day 1) for the FAS using the following estimand.

The primary estimand is formally defined as follows:

- Population: Subjects with ocular redness as defined by the eligibility criteria with at least 1 postinstillation ocular redness assessment (FAS).
- Endpoint: Mean change from baseline in investigator-assessed ocular redness at 15-minutes and 10-hours (600-minutes) postinstillation on Day 1.
- Treatment: Apraclonidine Hydrochloride (HCl) Ophthalmic Solution 0.125% compared to vehicle
- Intercurrent event:
  - Nonoptimal compliance is ignored [treatment policy strategy].
  - Use of prohibited medication is ignored [treatment policy strategy].
  - Withdrawal due to adverse events (AEs) or lack of efficacy (assumed to be missing not at random [MNAR]) will be imputed employing a control-based mean method if the rate of missing data due to AEs and lack of efficacy exceeds 10%. Otherwise, a mixed model repeated measures (MMRM) analysis will be used to handle the missingness due to these intercurrent events [hypothetical strategy].
- Population-level summary: Difference in least-square mean change from baseline and associated standard error in investigator-assessed ocular redness at 15-minutes and 600-minutes postinstillation between Apraclonidine HCl 0.125% and vehicle.

10.2.1 Statistical Model, Hypothesis, and Method of Analysis

To address the co-primary efficacy objective, the flowing hypotheses will be formulated:

1- H_0: $\mu_{(v)} = \mu_{(t)}$ vs H_a: $\mu_{(v)} \neq \mu_{(t)}$

where μ(v) and μ(t) denote the mean change from baseline in investigator-assessed redness score at 15-minute postinstillation on Day 1 with vehicle and Apraclonidine HCl 0.125%, respectively.

2- $H_0: \mu_{(v)} = \mu_{(t)}$ vs $H_a: \mu_{(v)} \neq \mu_{(t)}$

Where μ(v) and μ(t) denote the mean change from baseline in investigator-assessed redness score at 600-minute postinstillation on Day 1 with vehicle and Apraclonidine HCl 0.125%, respectively.

Both co-primary null hypotheses must be rejected in favor of Apraclonidine HCl 0.125% at the 0.05 (two-sided) significance level to claim efficacy.

To evaluate the hypothesis that the mean change from baseline in ocular redness with Apraclonidine HCl Ophthalmic Solution 0.125% is lower than mean change from baseline in ocular redness with vehicle at 15-minutes and 600-minutes (10-hours) postinstillation on Day 1, a mixed model repeated measures (MMRM) analysis will be employed. The mixed model will include fixed effect terms for baseline (predose) ocular redness score, treatment, site, discrete time (1-minute, 5-minutes, 15-minutes, 60-minutes, 240-minutes, 480-minutes, 600-minutes, and 720-minutes postinstillation), and treatment-by-time interaction, with restricted maximum likelihood (REML) and Kenwood-Roger approximation for the degrees of freedom. Within subject correlation due to bilateral ocular redness assessment across eyes as well as correlation due to repeated measures over discrete time will be accounted for using a Kronecker product variance-covariance structure. In the event of a lack of convergence using the MMRM with the Kronecker variance-covariance matrix, we will propose an updated covariance matrix for the model. The specifics of this and other updates to the modeling analyses will be outlined in the statistical analysis plan, which will take precedence over the protocol in the event of any disparities between the two documents.

10.2.1 Handling of Intercurrent Events of Primary Estimand(s)

See primary objective Section 10.2.

10.2.2 Handling of Missing Data Not Related to Intercurrent Events

Missing data not related to intercurrent events will be handled by a mixed model repeated measures (MMRM) analysis. This analysis assumes that the missing data mechanism is at random; that is, given the observed data, the likelihood of missingness is independent of the unobserved measurements. Valid inferences can be obtained through an MMRM analysis

without the need for explicit modeling of the dropout process, provided that the missingness is considered ignorable.



10.3 Analysis Supporting Secondary Objective(s)

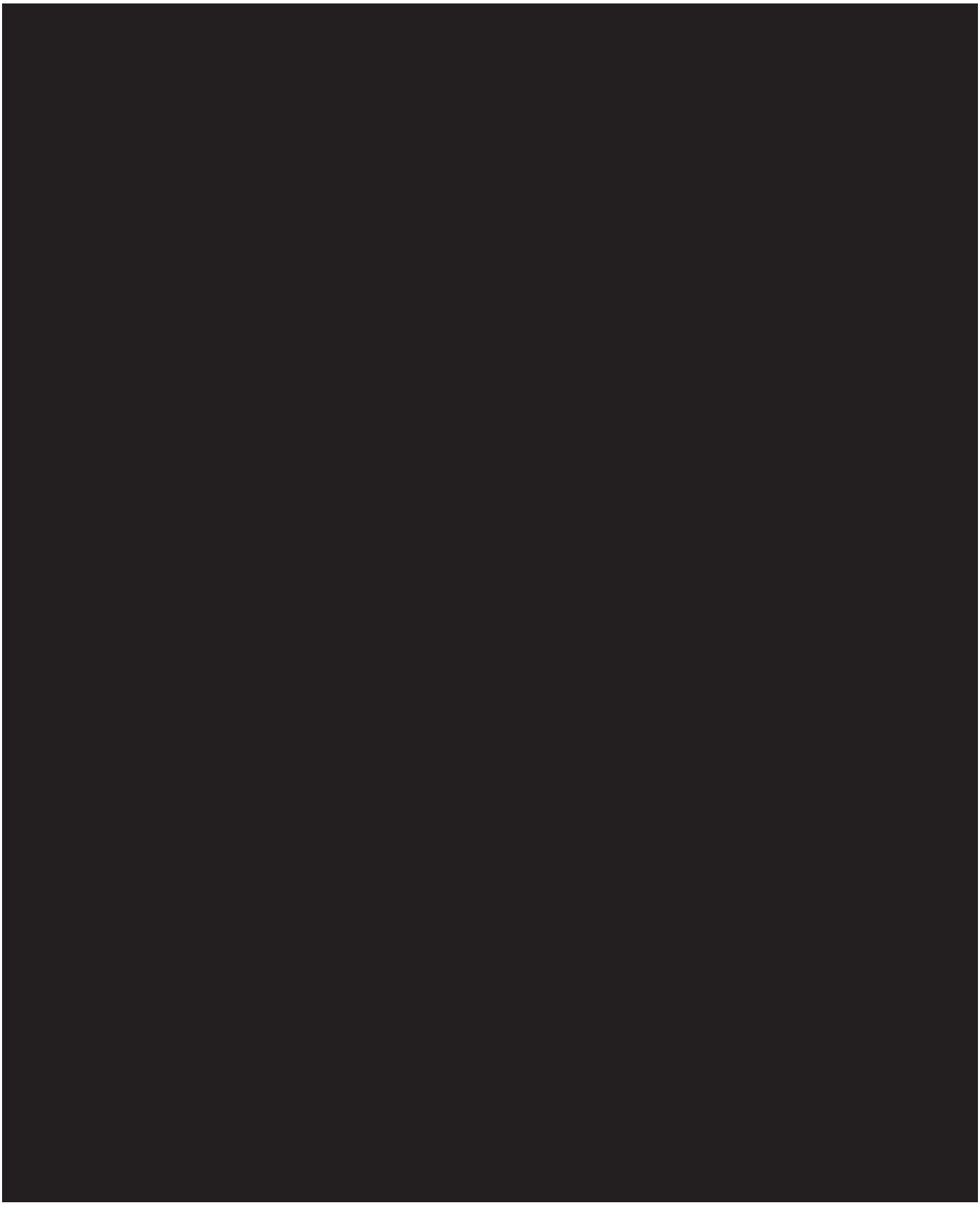
The secondary objective in this study will be to demonstrate superiority of Apraclonidine Hydrochloride (HCl) Ophthalmic Solution 0.125%, when compared to vehicle, at 1-minute, 8-hours (480-minutes), and 12-hours (720-minutes) postinstillation discrete timepoints.

Secondary efficacy endpoints will be evaluated hierarchically, as follows:

1. Mean change from baseline in investigator-assessed ocular redness at 1-minute postinstillation on Day 1.
2. Mean change from baseline in investigator-assessed ocular redness at 8-hours (480-minutes) postinstillation on Day 1.
3. Mean change from baseline in investigator-assessed ocular redness at 12-hours (720-minutes) postinstillation on Day 1.

Estimand definition as applicable to the secondary endpoints will be consistent with that employed for the co-primary endpoints as described in Section 10.2.





[redacted]

10.6 Safety Analyses

The following safety endpoints and variables will be recorded:

- Extent of exposure
- Adverse events
- Intraocular pressure
- Biomicroscopy findings/Slit Lamp Examinations
- Dilated ophthalmoscopy
- Best corrected visual acuity (BCVA) at distance
- Full physical examination

- Vital signs (resting blood pressure and pulse rate)
- Alertness (6-point scale: fully alert, alert, lethargy, obtunded, stupor, coma)

[redacted]

All adverse events occurring from the time a subject signs informed consent to study exit will be accounted for in the reporting. Safety analyses will be conducted using the safety analysis set on a treatment-emergent basis. Descriptive summaries (counts and percentages) for ocular and nonocular AEs will be presented by Medical Dictionary for Regulatory Activities Preferred Terms. AEs leading to study discontinuation and SAEs will be identified.

Individual subject listings will be provided for AEs that occur after signing informed consent but prior to exposure to IMP, as well as after exposure to IMP.

Each biomicroscopy parameter will be tabulated by its grade. For each biomicroscopy parameter, counts and percentages of eyes that experience an increase ≥ 2 grades from baseline (last assessment prior to IMP exposure) to any subsequent visit will be presented. A supportive listing will be provided.

[redacted]

10.8 Interim Analyses

There is no interim analysis planned for this study.

10.9 Sample Size Determination

The study will randomize 120 subjects between Apraclonidine HCl Ophthalmic Solution 0.125% and vehicle in a 1:1 ratio, targeting 102 evaluable subjects. The total number of randomized subjects has been adjusted to account for dropout rate, early termination due to cause, and evaluability (15%).



11 Protocol Deviations

Per ICH E6 (GCP) R2 Section 4.5.1, the investigator/institution should conduct the study in compliance with the protocol agreed upon with the sponsor and, if required, by the regulatory authority and which was given approval/favorable opinion by IRB.

Protocol waivers or deviations from the protocol inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The site will contact the sponsor for clarification of inclusion and/or exclusion criteria as needed prior to enrollment of a study subject. The sponsor or their representative will

document clarification requests and responses. If a subject does not meet any of the eligibility criteria, that subject may not be enrolled into the study.

If the investigator feels that, in his/her clinical judgment, it is necessary to promptly implement reasonable alternatives to, or deviations from, the protocol in consideration of the safety of study subjects, the sponsor is to be notified of these alternatives and deviations, and the reasons for such changes are to be documented in the study records. The investigator is to also notify his/her IRB of any such changes.

If a significant protocol deviation is identified by the investigator or through site monitoring activities, an immediate submission to the IRB may be required (as per IRB guidelines). The sponsor will assess any protocol deviation and decide whether any of these noncompliances should be reported to the relevant competent authority as a serious breach of Good Clinical Practice (GCP) and the protocol. If, per the relevant competent authorities' requirements, the protocol deviation is not required to be reported immediately but is still required to be reported to the IRB, the specific protocol deviation will be added to the annual progress report.

The sponsor will review, designate, and/or approve all protocol deviations prior to the database lock.

12 GENERAL CONSIDERATIONS: REGULATORY, ETHICAL, AND STUDY OVERSIGHT

12.1 Regulatory and Ethical Considerations

The study will be conducted according to this clinical protocol and will be governed by all applicable governmental rules and regulations concerning the conduct of clinical studies on human subjects. This includes, but is not limited to:

- The approval of IRB
- The Helsinki Declaration (World Medical Association 2013)
- US Code of Federal Regulations, Title 21
- International Conference on Harmonization (ICH) Consolidated Good Clinical Practice Guideline (E6 R2)
- Standard operating procedures (SOPs) of the sponsor and any other vendors participating in the conduct of the study

- Investigator responsibilities include ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of drugs under investigation. An investigator shall, obtain the informed consent of each human subject to whom the drug is administered.
- Sponsor responsibilities include selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation, ensuring the investigation is conducted in accordance with the general investigational plan and protocols contained in the IND, maintaining an effective IND with respect to the investigations, and ensuring that the FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug.

12.2 Committees

12.2.1 Data Monitoring Committee

This study will not use a data monitoring committee (DMC) for ongoing monitoring of safety or efficacy. Safety will be monitored by the study team with the oversight of the medical monitor.

12.3 Informed Consent Process

Prior to any study procedures, the study will be discussed with each subject and subjects wishing to participate must give written informed consent including appropriate privacy authorization, as applicable. The verbal explanation of the study will cover all the elements specified in the written information provided for the subject. The investigator will inform the subject of the aims, methods, anticipated benefits, and potential hazards of the study, including any discomfort it may entail. The subject must be given every opportunity to clarify any points he/she does not understand and, if necessary, may ask for more information. At the end of the interview, the subject should be given time to reflect. The subjects and/or legally authorized representative then will be required to sign and date the informed consent form (ICF). Consent procedures must follow local legal requirements of the study site. A copy of the signed and dated consent document will be given to each subject. The original signed and dated informed consent document must be maintained in the study files at the investigator’s site.

The investigator or staff is responsible for ensuring that no subject undergoes any study related examination or activity before the subject has given written informed consent. It

should be emphasized that the subject is at liberty to withdraw consent to participate at any time, without penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give, or withdraw, written informed consent may not be included or continued in this study and should be notified that discontinuation from the study will not impact their subsequent care.

If the subject is part of a vulnerable population, including without limitation minors, or requires any special needs, ensure that a parent or legal guardian signs the informed consent and that the subject signs an IRB-approved assent document as required.

12.4 Privacy and Data Protection

The investigator must ensure that the subject's identity is kept confidential throughout the course of the study. In particular, the investigator must maintain appropriate safeguards to prevent unauthorized use or disclosure of, or access to, subject data, and keep an enrollment log with confidential identifying information that corresponds to the subject numbers and initials of each study subject. The study sponsor may collect a copy of the enrollment log ***without any directly identifying subject information***.

The study sponsor may share subject-level data collected in this study with qualified researchers to help facilitate product development or enhancements in research that are not directly related to the study objectives. The informed consent explains this to the study subject.

12.5 Early Site Closure or Study Termination

The study sponsor reserves the right to suspend or close the investigational site or suspend or terminate the study in its entirety at any time. The investigator may terminate the site's participation in the study for reasonable cause.

If the clinical study is prematurely terminated or suspended:

- The study sponsor must:
    - Immediately notify the investigator(s) and subsequently provide instructions for study termination.
    - Inform the investigator and the regulatory authorities of the termination/suspension and the reason(s) for the termination/suspension.
- The investigator must:

- Promptly notify the IRB of the termination or suspension and of the reasons.
- Provide subjects with recommendations for poststudy treatment options as needed.

13 GENERAL CONSIDERATIONS: RISK MANAGEMENT AND QUALITY ASSURANCE

13.1 Quality Tolerance Limits

Quality tolerance limits (QTLs) will be predefined through an internal risk management process and monitored on an ongoing basis, with documentation of QTLs that are met summarized in the CSR.

13.2 Data Quality Assurance

Regulatory authorities of domestic and foreign agencies, Alcon quality assurance, and/or its designee may carry out on-site inspections and/or audits which may include source data checks. 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.

Additionally, the progress of the study will be monitored by on-site, written, and telephone communications between personnel at the investigator's site and the clinical site manager. The investigator will provide all required personnel (sponsor and regulatory) access to all study records for review to confirm compliance with the protocol and regulatory requirements.

13.3 Source Data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities (in a clinical investigation) used for the reconstruction and evaluation of the study. Source documents may include: hospital records, subject diaries, pharmacy dispensing lists, test results, x-rays, lab records, etc. Investigators are responsible for adequately maintaining all subject data collected and documented.

Access to source data is critical to permit review, ensuring adequate protection of the rights, welfare, and safety of human subjects and the quality and integrity of the clinical investigation data. Monitors, auditors, and other authorized representatives of Alcon, the IRB approving this study, and government regulatory authorities must be granted directed access

to the study subject's original medical and study records for verification of the data and clinical study procedures.

Clinical site managers (CSMs) will be responsible for monitoring the study sites and study activities. Clinical site managers will contact and visit the investigator at regularly scheduled intervals. The actual frequency of monitoring visits will be determined based on subject enrollment and study site performance. The following items will be reviewed:

- Study progress
- Compliance with the protocol
- Completion of eCRFs
- Storage and accountability of study interventions
- Source data verification
- AE and SAE reporting
- Essential documents

Critical data points will be 100% source verified and will include, but are not limited to: subject identification, informed consent, selection criteria, and primary and safety parameters (i.e., all AEs). All other data will be subject to a risk-based targeted approach to source data verification. Specific details will be outlined in the protocol monitoring plan.

Monitoring visits (SAVs, IMVs, and COVs) are planned to be conducted on site. In exceptional circumstances (nonenrollment, pandemic, etc.), monitoring may be conducted remotely. Specific details will be outlined in the protocol monitoring plan.

14 APPENDIX: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS – DEFINITIONS, SEVERITY, AND CAUSALITY

14.1 Severity

Severity of an AE is defined as a qualitative assessment of the level of discomfort or the degree of intensity of an AE as determined by the investigator or reported to them by the subject. The assessment of severity is made irrespective of study medication relationship or seriousness of the event and should be evaluated according to the following scale:

- 1 = Mild: present and noticeable, but not distressing, and no disruption of normal daily activities

- 2 = Moderate: bothersome, discomfort sufficient to possibly reduce or affect normal daily activity
- 3 = Severe: incapacitating, with inability to work or perform normal daily activity

A change in increased severity for a reported AE will require a stop date for the previous severity and a new start and stop date for the new severity, e.g., a change in severity may go from mild to moderate, or from moderate to severe. In either case, the start and stop dates should be recorded.

Note: A severe AE is not the same as a serious AE. Seriousness of an AE (NOT severity) serves as a guide for defining regulatory reporting obligations (see Section 9.4.1 for further information on SAEs, SARs, and suspected unexpected serious adverse reactions [SUSARs]).

14.2 Causality

Relationship between the AE and the study intervention or study procedure will be determined by the Investigator, as applicable, for each AE using these explanations:

Not Related: The event is clearly related to other factors such as subject's clinical condition, therapeutic interventions, concomitant disease, or therapy administered to the subject and does not follow a known response pattern to the product or procedure.

Related: The event follows a reasonable, temporal sequence from the time of study medication administration or study procedure and/or follows a known response pattern to the product or procedure and cannot be reasonably explained by other factors such as subject's clinical state, therapeutic interventions, or concomitant therapy administered to the subject, and either occurs immediately following study medication administration or procedure, or improves on stopping the study medication, or reappears on repeat exposure, or there is a positive reaction at the application site.

14.3 Expectedness

AEs or ARs are considered "unexpected" if they are not listed in the Reference Safety Information section of the Investigator's Brochure for Apraclonidine Hydrochloride (HCl) Ophthalmic Solution 0.125% or are not listed at the specificity or severity that has been observed. "Unexpected," as used in this definition, also refers to AEs or ARs that are mentioned in the investigator's brochure as occurring with this class of drugs or as anticipated from the pharmacological properties of Apraclonidine Hydrochloride (HCl) Ophthalmic Solution 0.125% and are not specifically mentioned as occurring with the study drug, e.g., under this definition, hepatic necrosis would be unexpected (by virtue of greater

severity) if the investigator's brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator's brochure listed only cerebral vascular accidents.

An investigator must immediately (i.e., within 24 hours from time of awareness) report any SAE or SAR (see Section 9.4.6 for definitions) to the sponsor or its CRO representative, whether or not considered drug-related, including those listed in the protocol or investigator's brochure.

It is ultimately the sponsor's responsibility to determine expectedness of related SAEs (SARs) for purposes of regulatory reporting, based upon the Reference Safety Information.

15 APPENDIX: DEFINITIONS AND SUPPORTING OPERATIONAL DETAILS

15.1 Contraception and Pregnancy Testing

15.1.1 Definitions Related to Childbearing

An adult woman is considered to be of childbearing potential (WOCBP) unless she is at least 1-year postmenopause (no menses for 12 months or more without an alternative medical cause) or at least 3 months postsurgical sterilization.

15.1.2 Contraception

Subjects must not intend to become pregnant during the study and must properly use an acceptable effective method of contraception.

Acceptable effective contraceptive methods when used consistently and in accordance with both the product label and the instructions of the physician (Clinical Trials Facilitation Group 2020), include:

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception (oral, injectable, implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner

  - Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP study subject and that the vasectomized partner has received medical assessment of the surgical success.

- Sexual abstinence
  - Sexual abstinence is considered to be an acceptable method of contraception when defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject
- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide

Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are **NOT** acceptable methods of contraception.

15.1.3 Pregnancy Testing

A urine pregnancy test (dipstick) conducted at Visit 1, 2, and 5 for WOCBP is required for this study.



[redacted]

16 PUBLICATIONS

There are no immediate plans to submit the results of this study for publication; however, the results may be offered for publication if they are of scientific interest, or if the results relate to a product that is subsequently approved or cleared for marketing.

17 REFERENCES

17.1 Internal References

- Pharmacy manual
- Manual of procedures
- Investigator brochure
- Statistical analysis plan

[redacted]

17.2 External References

- 21 CFR Part 11 - Electronic Records; Electronic Signatures
- 21 CFR Part 50 - Protection of Human Subjects
- 21 CFR Part 56 - Institutional Review Boards
- 21 CFR Part 54 - Financial Disclosure by Clinical Investigators
- 21 CRF Part 312.32 (c)(1)(i) – Serious and Unexpected Suspected Adverse Reaction
- International Conference on Harmonization (ICH) Consolidated Good Clinical Practice Guideline (E6 R2)
- The Helsinki Declaration (World Medical Association 2013)
- US Code of Federal Regulations, Title 21

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- IOPIDINE 1.0 % Ophthalmic Solution [package insert]. Nashville, TN: Harrow Eye, LLC; 2023.
- IOPIDINE 0.5% Ophthalmic Solution [package insert]. Fort Worth TX: ALCON LABORATORIES, INC.; 2016.
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