PROTOCOL: SHP639-101

TITLE:	A Randomized, Double-masked, Placebo-controlled Phase 1 Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single Daily and Multiple Daily Ascending Doses of SHP639 Topical Ophthalmic Solution in Subjects with Ocular Hypertension or Primary Open-angle Glaucoma (POAG)
DRUG:	SHP639
IND:	130,425
EUDRACT NO.:	Not applicable
SPONSOR:	Shire HGT 300 Shire Way, Lexington, MA 02421 USA
PRINCIPAL/ COORDINATING OPHTHALMOLOGIST:	Dr. PPD

PROTOCOL HISTORY:	Amendment 3 (Version 4):	11 May 2018
	Amendment 2 (Version 3):	4 Oct 2017
	Amendment 1 (Version 2.1)	16 May 2017
	Original Protocol (Version 2):	15 Feb 2017
	Original Protocol (Version 1):	12 Dec 2016

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: PPD	**Date:** PPD
Dr. PPD	

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP639-101.

Title: A Randomized, Double-masked, Placebo-controlled Phase 1 Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single Daily and Multiple Daily Ascending Doses of SHP639 Topical Ophthalmic Solution in Subjects with Ocular Hypertension or Primary Open-angle Glaucoma (POAG).

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address:	
(please hand print or type)	

Signature: _____ **Date:** _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION

See Appendix 1 for protocol history, including all amendments.

The purpose of this amendment is the addition of language to allow the unmasking of data for the interim analysis of data from the repeat of Cohort B3.

Noteworthy changes to the protocol are captured in the table below.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3**	**Amendment Date** **11 May 2018**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
Addition of the following language: **All cohorts conducted after B3 (ie Part 1 of the study) may be unmasked following completion of Day 29 to permit review of safety, tolerability and the pharmacodynamics effects of each cohort to better inform planning for additional cohorts and further clinical development options for SHP639.** A **final** unmasked analysis will be conducted when all subjects of the remaining cohorts have completed through Day 29. The Day 88/FU visit is the planned study completion for each subject.		**Section 9.5**
Minor changes to standard Shire protocol language to conform to the latest version of the protocol template		**Emergency Contact Information** **Product Quality Complaints** **Section 1.3** **Section 4.2** **Section 5** **Sections 10, 10.2.3.2, 10.5**

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event, the investigator must fax or email the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Nonserious AEs as Required by the Protocol within 24 hours to the Shire Global Drug Safety Department:
PPD

The fax number and email address are provided on the form (sent under separate cover). A copy of this form must also be sent to the contract research organization/Shire medical monitor using the details below.

PPD , MD
PPD
Clinical Research and Development
Telephone: PPD (business hours)
PPD (after business hours)
Email: PPD

For protocol- or safety-related issues, the investigator must contact the Shire medical monitor:

PPD , MD
Telephone: PPD (business hours)
PPD (after business hours)

ADDITIONAL CONTACT INFORMATION

In case of any other issues, including nonsafety-related issues or if the medical monitor is unable to be reached, the investigator must contact the Shire study manager:

PPD
PPD
Telephone: PPD (24-hour coverage)

If unavailable, please contact:

PPD MS, CCRP
PPD
Telephone: PPD (24-hour coverage)

If unavailable, please contact:

PPD , MSc, MBA
PPD
Telephone: PPD (business hours)
PPD (24-hour coverage)

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints or nonmedical complaints to Shire within 24 hours. If requested, defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products) or a product deficiency that relates to identity, quality, durability, reliability, safety and performance of the product but did not result in an AE, which include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function, eg, reconstitution difficulty
- Missing components
- Damage to the product or unit carton
- A mislabeled product (eg, potential counterfeiting/tampering)
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims

For instructions on reporting adverse events related to product complaints, see Section 8.

Please use the information below as applicable to report the Product Quality Complaint:

Origin of Product Quality Complaint	**Email Address**
North and South America	PPD

Telephone numbers (provided for reference if needed):

Shire, Lexington, MA (USA)

PPD

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ABBREVIATIONS

ADA	antidrug antibody
AE	adverse event
AMD	age-related macular degeneration
AUC_{0-t}	area under the observed concentration vs time curve from time zero (predose) to the time of the last measurable concentration
$AUC_{0-\tau}$	area under the observed concentration vs time curve over the dosing interval
$AUC_{0-\infty}$	area under the observed concentration vs time curve from time zero (predose) extrapolated to infinity
BCVA	best-corrected visual acuity
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
cGMP	cyclic guanosine monophosphate
CI	confidence interval
CL/F	apparent clearance
C_{max}	maximum observed concentration
CNP	C-type natriuretic peptide
CS	clinically significant
CRO	contract research organization
EC_{50}	half maximum effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
E_{max}	maximum percentage intraocular pressure reduction from baseline
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HVF	Humphrey visual field
IA	interim analysis
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IOP	intraocular pressure
IRB	Institutional Review Board
IRT	interactive response technology
IV	intravenous

MDTP	multiple-dose treatment period
MWOA	midwashout ophthalmic assessment
NCS	not clinically significant
NHP	nonhuman primates
NOAEL	no-observed-adverse-effect level
NPDR	nonproliferative diabetic retinopathy
NPR-A	natriuretic peptide receptor A
NPR-B	natriuretic peptide receptor B
OHT	ocular hypertension
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
POAG	primary open-angle glaucoma
QD	once daily
QID	4 times daily
QTcB	QT interval corrected for heart rate using the Bazett formula
QTcF	QT interval corrected for heart rate using the Fridericia formula
$R_{ac(AUC)}$	accumulation ratio based on area under the curve
$R_{ac(Cmax)}$	accumulation ratio based on maximum observed concentration
SAE	serious adverse event
SAP	statistical analysis plan
SDTP	single-dose treatment period
t½	apparent terminal phase elimination half-life
TE_{max}	time to the maximum reduction
TID	3 times daily
t_{max}	time to reach maximum observed concentration
US	United States
Vz/F	apparent volume of distribution

STUDY SYNOPSIS

Protocol number: SHP639-101	**Drug:** SHP639
Title of the study: A Randomized, Double-masked, Placebo-controlled Phase 1 Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single Daily and Multiple Daily Ascending Doses of SHP639 Topical Ophthalmic Solution in Subjects with Ocular Hypertension or Primary Open-angle Glaucoma (POAG).	
Number of subjects (total and for each treatment arm): Approximately 120 subjects will be screened to ensure the enrollment and completion of 84 subjects. There will be approximately 12 cohorts, each consisting of 7 subjects. Subjects may be replaced to ensure 6 out of 7 completers per dosing regimen cohort.	
Investigator(s): Dr. PPD (coordinating principal ophthalmologist)	
Site(s) and Region(s): This is a multicenter study conducted solely in the United States. Approximately 7 sites will participate in the study.	
Study period (planned): 2017 to 2018	**Clinical phase:** 1
Objectives: **Primary:** To investigate the safety and tolerability of single and multiple ascending doses of SHP639 ophthalmic solution in subjects with ocular hypertension (OHT) or with primary open-angle glaucoma (POAG). **Secondary:** To evaluate reduction of intraocular pressure (IOP), as a pharmacodynamic (PD) biomarker, following different SHP639 dosing regimens. **Exploratory:** To explore the pharmacokinetic (PK)-PD relationship of SHP639 in subjects with OHT or POAG	
Rationale: SHP639 is being developed for reduction of IOP in glaucoma patients. It is expected to act through a novel mode of action (natriuretic peptide receptor B agonism) that leads to an increase in trabecular meshwork outflow, thus reducing the IOP. SHP639-101 is a first-in-human clinical study for a topical ophthalmic formulation of SHP639. Up to 3 different concentrations (0.1%, 0.3%, and 0.6%) will be explored and safety and tolerability of SHP639 ophthalmic solution will be evaluated. As a secondary objective, the study will also aim to characterize the PD of SHP639, using IOP as a PD biomarker. The PK-PD relationship will be explored if the data permit.	
Investigational product, dose, and mode of administration: Topical ophthalmic drops of 3 SHP639 concentrations and matching placebo will be used in this study: 0.1%, 0.3%, and 0.6%. Each concentration will be given in an ascending dose fashion once daily (QD), twice daily (BID), 3 times daily (TID), and 4 times daily (QID).	
Methodology: This is a multicenter, randomized, double-masked, placebo-controlled, single- and multiple-dose escalation study. Three different SHP639 concentrations will be studied: 0.1%, 0.3%, and 0.6%. There will be up to 12 cohorts in total, 1 cohort for each dose level and different dosing regimen. Each cohort will consist of 7 subjects for a total of 84 subjects in the study. Eligible subjects will be randomized in a 5:2 ratio to receive either SHP639 or placebo, respectively.	

A sufficient number of subjects will be screened and enrolled to ensure that at least 6 of 7 subjects complete each treatment in their assigned cohort. In the event that a sufficient number of subjects do not complete a cohort, replacement subjects may be enrolled. Each replacement subject will follow the same screening procedures and randomization sequence as the subject who is discontinued, regardless of when the subject discontinued. The anticipated doses being studied for each dosing regimen are as follows:

Treatment Regimen	**Doses**	
Single-dose or QD	A1	0.1%/Placebo
	A2	0.3%/Placebo
	A3	0.6%/Placebo
BID	B1	0.1%/Placebo
	B2	0.3%/Placebo
	B3	0.6%/Placebo
TID	C1	0.1%/Placebo
	C2	0.3%/Placebo
	C3	0.6%/Placebo
QID	D1[a]	0.1%/Placebo
	D2	0.3%/Placebo
	D3	0.6%/Placebo

BID=twice daily; QD=once daily; QID= 4 times daily; TID= 3 times daily.
[a] The dose-escalation committee decided not to enroll cohort D1, agreeing that the results would not add to the understanding of the safety of SHP639.

Screening Period

For all cohorts, the maximum duration of the screening period is 42 days. On the initial visit to the site, the subject will first give informed consent. This will be the date that he/she enters the screening period. After giving consent, the subject will be evaluated against the inclusion and exclusion criteria and undergo screening procedures. During the screening period, subjects will return to the site approximately every 2 weeks for safety evaluations. If necessary, subjects will undergo a washout period from their current medications.

Following the screening visit, subjects who continue to meet the protocol-specific inclusion and exclusion criteria will return to the site on either Day-3 or Day -2, to reconfirm eligibility criteria for participation and undergo predose safety and ophthalmologic assessments.

Study Parts

The study will consist of 2 parts, Part 1 and Part 2.

- Part 1 consists of Cohorts A1, A2, and A3, each of which is a single-dose and QD multiple-dose cohort (1 cohort for each of the 3 dose levels), followed by Cohorts B1, B2, and B3, each of which is a BID multiple-dose cohort (1 cohort for each dose level).
- Part 2 consists of Cohorts C1, C2, and C3, each of which is a TID multiple-dose cohort (1 cohort for each dose level), followed by Cohorts D1, D2, and D3, each of which is a QID multiple-dose cohort (1 cohort for each dose level).

Cohorts A1-A3

In Cohorts A1, A2, and A3, there will be a single-dose treatment period (SDTP) followed by a multiple-dose treatment period (MDTP).

In the SDTP, subjects will be randomized prior to administration of investigational product on Day 1 after all entry criteria have been confirmed. One drop of investigational product will be administered topically to a designated eye. The first 3 of 7 subjects will be dosed with a minimum of 1-hour intervals between the subjects for safety purposes. The subject will then undergo safety, ophthalmologic, and PK assessments. Subjects will be observed for the next 24 hours with appropriate medical oversight. An ophthalmologist will be on call to assess ophthalmic-related medical issues. If no adverse events (AEs) occur that are consistent with the predefined stopping criteria, the rest of

the subjects in the cohort can be administered investigational product in 1 designated eye.

After completion of the assessments scheduled for Day 2 of the SDTP, subjects will enter a washout period. The duration of the washout period will last between 3 and 14 days. A dose escalation meeting will occur prior to the advancement to the multidose part of each cohort. Following a decision to commence the MDTP for Cohorts A1, A2, and A3, subjects will attend the site on Days -2 and -1 to undergo the scheduled safety and ophthalmic assessments. In Cohorts A1, A2, and A3 MDTP, all subjects will be administered investigational product in both eyes. The same dose concentration that was administered during the SDTP of Cohorts A1, A2, or A3 will be administered during the MDTP QD for the next 28 days. Subjects are to place 1 drop in each eye at approximately the same time each day.

Within each cohort (A1, A2, or A3), subjects will continue to self-administer investigational product QD for the duration of the MDTP. Between Day 2 and Day 26, subjects will return to the site for scheduled outpatient visits. On Day 26, subjects will be readmitted to the site. On Day 27, subjects will continue to self-administer investigational product while undergoing the scheduled assessments. The last dose will be administered on the morning of Day 28. Following completion of the assessments scheduled for Day 29, subjects will then be discharged from the site.

Subjects will receive a follow-up telephone call approximately 7 days after being discharged from the site. They will return to the site to undergo antidrug antibody (ADA) sampling approximately 60 days after the last dose of investigational product.

Cohorts B1-3, C1-3, and D1-3

Authorization from the sponsor to proceed from 1 cohort to the next is to be received before subjects enter the screening period for Cohorts B, C, and D. Once authorization has been received from the sponsor, subjects are to be admitted to the screening period of the appropriate cohort as previously described in this section.

Subjects will undergo the scheduled safety and ophthalmic assessments on Day -2 and Day -1. Subjects will then be administered investigational product per the sponsor's authorization to proceed to that cohort. In Cohorts B, C, and D, subjects will be administered investigational product in both eyes.

Subjects will continue to self-administer investigational product as instructed for the duration of the cohort. Between Day 2 and Day 26, subjects will return to the site for scheduled outpatient visits. On Day 26, subjects will be readmitted to the site. On Day 27, subjects will continue to self-administer investigational product while undergoing the scheduled assessments. The last dose will be administered on the morning of Day 28. After completion of the assessments scheduled for Day 29, subjects will then be discharged from the site.

Subjects will receive a follow-up telephone call approximately 7 days after being discharged from the site. They will return to the site to undergo ADA sampling approximately 60 days after the last dose of investigational product.

Inclusion and exclusion criteria:

Inclusion criteria

1. Subjects must provide written, signed and dated informed consent to participate in the study in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guideline E6 and applicable regulations, before completing any study-related procedures.
2. Subjects must be aged from 18 through 90 at the time of consent. This inclusion criterion will only be assessed at the screening visit.
3. Subjects must have OHT or stable early POAG in both eyes with acceptable Humphrey visual fields (HVF). Early POAG for this protocol is defined as healthy appearing anterior chamber angles (Shaffer classification system grade 3 or 4) and focal and/or generalized thinning of the optic disc rim characteristic of glaucomatous disease. An acceptable HVF must have been performed within approximately one year of screening, have a false- positive rate of 25% maximum, false-negative rate of 25% maximum, and fixation loss rate of 33% maximum, and mean deviation of no worse than -6.00 dB.
4. On Day -1, subjects must have a mean IOP of ≥24 mmHg at 8:00 AM and a mean IOP of ≥22 mmHg at 10:00 AM in at least 1 eye, with an IOP difference of <4 mmHg between eyes at both of these time points. If

only 1 eye meets this criterion, then it will be the designated study eye for PD analysis; this eye will also be used for dosing in Cohort A SDTP.

5. Subjects must have a best-corrected visual acuity (BCVA) in both eyes of 65 letters on the Early Treatment Diabetic Retinopathy Study chart (Snellen equivalent ~20/60) or better at the screening and baseline assessments.
6. Subjects must be males or females who are nonpregnant and nonlactating at screening (negative serum beta-human chorionic gonadotropin [β-hCG]); if sexually active during the study, they must agree to comply with the applicable contraceptive requirements of the protocol throughout the study period and for 60 days following the last dose of investigational product.
7. Subjects must have a satisfactory medical assessment with no clinically significant or relevant abnormalities as determined by medical history, physical examination, and clinical and laboratory evaluation (hematology, biochemistry, urinalysis) as assessed by the investigator.
8. Subject must understand and be able, willing, and likely to fully comply with study procedures and restrictions.
9. Subjects must be nonsmokers or have had stable use of tobacco or nicotine-containing products for a 3-month period before signing the informed consent form (ICF).
10. Subjects who drink alcohol must have had stable use of alcohol for a 3-month period before signing the ICF.

Exclusion criteria:

1. Subject has an anatomically narrow angle, synechiae or evidence of prior inflammation, angle closure glaucoma, normal tension glaucoma, pseudoexfoliation syndrome or pigmentary dispersion syndrome with or without glaucoma, or secondary glaucoma.
2. Subject has corneal endothelial cell counts of less than 2000 cells/mm^2 (measured by noncontact specular microscopy) at the screening or baseline assessments.
3. Subject has central corneal thickness less than 500 µm or greater than 620 µm at the screening or baseline assessments.
4. Subject has IOP greater than 32 mmHg in either eye before randomization.
5. Subject has used topical ocular hypotensive medications as follows: prostaglandin analogs, β-adrenoceptor antagonists, α-adrenergic agonists, or epinephrine-related medications within 4 weeks before the first dose of investigational product; or pilocarpine or carbonic anhydrase inhibitors within 7 days before the first dose of investigational product.
6. Subject has a history of angle closure, ocular surgery, microinvasive glaucoma surgery device insertion, or laser surgery, except for the following procedures, which are allowed: uncomplicated cataract surgery, laser peripheral iridotomy with resultant angle of Shaffer grade 3 or 4, and postcataract neodymium-doped yttrium-aluminum-garnet (Nd:YAG) laser posterior capsulotomy. Cataract surgery and other procedures must have occurred a minimum of 3 months before randomization.
7. Subject has a history of significant ocular trauma or ocular disease including but not limited to moderate to severe dry eye disease that requires chronic treatment or punctal plugs.
8. Subject has evidence of ocular infection, inflammation, degeneration, or dystrophy at the screening or baseline assessments, including but not limited to moderate to severe blepharitis (mild blepharitis is allowed), conjunctivitis (allergic or infectious), corneal dystrophy (epithelial, stromal, or endothelial), corneal haze of grade 1 or greater based on the Hwang Grading Scale of Corneal Haze, corneal opacities, keratitis, uveitis, or vitritis.
9. Subject has retinal disease including but not limited to: moderate or severe nonproliferative diabetic retinopathy (NPDR) (early NPDR is allowed), proliferative diabetic retinopathy, intermediate or advanced dry age-related macular degeneration (AMD) (early dry AMD is allowed), all geographic atrophy, or all wet AMD.

10. Subject has any nonglaucomatous optic neuropathy or other significant nonglaucomatous ocular disease that is likely to affect visual function.
11. Subject has any corneal or ocular surface pathology in either eye that prevents proper IOP measurement, pachymetry, or other study data collection procedures.
12. Subject has had changes to their existing prescription medication regimen for chronic disease, including those medicines that affect IOP, within 14 days or 5 half-lives before screening, whichever is longer.
13. Subject has started any new prescription drug medication for chronic disease, including those medications that affect IOP, within 14 days or 5 half-lives before screening, whichever is longer.
14. Subject has a history of corticosteroid use within 3 months before randomization, except for nonperiocular dermatologic use, which is allowed.
15. Subject has used belladonna alkaloids (scopolamine, hyoscyamine, atropine) within 7 days prior to randomization, cannabinoids or opioids within 28 days before randomization, or B-type natriuretic peptides within the past year before randomization; or a subject has an anticipated need for any of the aforementioned drugs/drug categories during the study.
16. Subject has used amantadine within 28 days before randomization.
17. Subject is unable to discontinue contact lens use during and for 60 minutes following instillation of study medication, during ophthalmologic examinations, and during study visits.
18. Subject has a current or relevant history of any physical, medical, mental, or psychiatric illness, disorder, or condition that may require treatment during the study and/or that may interfere with the subject complying with the study rules and procedures or completing the study.
19. Subject has any condition that presents undue risk from use of the investigational product, assessment tools, or procedures.
20. Subject is a woman who is pregnant (positive serum β-hCG pregnancy test at the time of screening), lactating, or less than 90 days post partum at randomization.
21. Subject has donated blood within 60 days before first dose of investigational product.
22. Subject has donated plasma within 28 days before first dose of investigational product.
23. Subject has used another investigational product within 30 days before the first dose of investigational product or is actively enrolled in a drug or vaccine clinical study.
24. Subject has a positive human immunodeficiency virus, hepatitis B surface antigen, or hepatitis C virus antibodies screen.
25. Subject has a positive drugs of abuse screen or alcohol breathalyzer test.
26. Subject has been previously enrolled in this study.
27. Subject has known hypersensitivity or allergy to any of the ingredients of the investigational product.
28. Subject consumes more than 21 units of alcohol per week or is unable to refrain from alcohol consumption within 48 hours before a scheduled visit. (1 alcohol unit=1 beer or 1 wine [5 oz/150 mL] or 1 liquor [1.5 oz/40 mL] or 0.75 oz alcohol.)
29. Subject is unable to refrain from tobacco or any products containing nicotine within 8 hours before a scheduled visit.

Maximum duration of subject involvement in the study:

The subjects' maximum duration of participation in the study is expected to be 146 days or approximately 5 months (Cohort A1, A2, and A3). The subjects' maximum duration of participation in the study for Cohorts B, C, and D is expected to be 130 days or approximately 4.5 months.

- Maximum planned duration of screening and Washout 1: 42 days
- Planned duration of treatment period: 2 days for SDTP (Cohort A only) and 29 days for MDTP (all cohorts)
- Planned duration of Washout 2 (Cohort A only): 3-14 days

Planned duration of follow-up: until Day 88±4 days

Endpoints and statistical analysis:

Study Population

The safety set will consist of all subjects who have been randomized and who have received at least 1 dose of investigational product.

The PK set will consist of all subjects in the safety set for whom the primary PK data are considered sufficient and interpretable.

The PD set will consist of all subjects in the safety set for whom the primary PD data are evaluable.

Pharmacokinetic Endpoints

Plasma concentrations of SHP639 will be measured using a fully validated bioanalytical method. If data permit, PK parameters for SHP639 will be calculated based on plasma concentration-time data using a noncompartmental approach). Pharmacokinetic parameters may include, but are not limited to, the following: maximum observed concentration (C_{max}); time to reach C_{max} (t_{max}); area under the observed concentration vs time curve from time zero (predose) to the time of the last measurable concentration (AUC_{0-t}), over the dosing interval ($AUC_{0-\tau}$) for each multiple-dose regimen, and from time zero (predose) extrapolated to infinity ($AUC_{0-\infty}$); apparent terminal phase elimination half-life (t½); apparent clearance (CL/F); apparent volume of distribution (Vz/F); and accumulation ratios based on AUC and C_{max} for each multiple-dose regimen.

Pharmacodynamic Endpoints

Intraocular pressure (IOP; mmHg) will be measured using Goldmann applanation tonometry. Pharmacodynamic parameters will be estimated as appropriate and may include, but are not limited to, the following: change from baseline in IOP; time to the maximum change from baseline in IOP; and proportion of subjects maintaining IOP reduction after specified days of treatment.
Specific endpoints in order to understand the effect of SHP639 on IOP will be defined in the SAP.

Safety Endpoints

Safety and tolerability will be assessed by monitoring AEs, vital sign measurements, clinical laboratory assays, electrocardiogram (ECG), ADA, drop comfort assessment, and ophthalmologic examinations.

Sample Size Justification

The number of subjects in this study is not based on statistical power considerations because the statistical analyses are primarily descriptive in nature. However, if at least 7 subjects complete each cohort, then there will be at least 65- 85% probability of observing at least 1 occurrence of any AE with a true incidence rate for a given dose group of at least 15- 25%, respectively.

It is estimated that dose escalation will occur for up to 3 dose levels (4 cohorts within each dose level). Each cohort will include 5 subjects randomized to active drug and 2 subjects randomized to placebo for an estimated total of at least 84 subjects.

For each cohort, the number of subjects will be increased as needed based on safety and IOP response. Any cohort can be repeated to confirm findings with regard to safety or IOP response.

Statistical Methodology for Pharmacokinetic Endpoints

All plasma PK analyses will be performed using the PK set. Summary statistics (number of observations, mean, standard deviation [SD], coefficient of variation, median, maximum [max], minimum [min], and geometric mean) will be determined for all plasma PK parameters and will be presented by dose, cohort, treatment period (single dose or multiple dose; Cohort A only), and study day. Plasma concentrations at each nominal sampling time will also be summarized using descriptive statistics.

For accumulation ratios, the 95% confidence interval (CI) for the arithmetic mean of the difference (for example, $AUC_{0-\tau}$ [Day 27] - $AUC_{0-\tau}$ [Day 1]) on the logarithmic scale (natural base) will be calculated. The results will be back-transformed to give the ratio of geometric means together with the corresponding 95% CI.

Before statistical comparisons, dose-dependent parameters (C_{max}, AUC_{0-t}, $AUC_{0-\tau}$, and $AUC_{0-\infty}$) will be normalized to a common dose, assuming linearity. Additionally, the linear dose proportionality will be evaluated for C_{max}, $AUC_{0-\tau}$, AUC_{0-t}, and $AUC_{0-\infty}$ using the power function model (eg, $C_{max}=\alpha \cdot Dose^{\beta}$ or equivalently $\log[C_{max}]=\log[\alpha]+\beta \cdot \log[Dose]$, where C_{max} is considered to increase linearly proportional to dose if β is not significantly different from 1.0.

Statistical Methodology for Pharmacodynamic Endpoints

All PD analyses will be performed using the PD set.

Descriptive summary statistics for IOP (number of subjects, mean, SD, median, min, and max) will be provided by dose, cohort, treatment period (single dose or multiple dose; Cohort A only), and study day. Additionally, 95% CIs for each estimate and summary statistics of change from baseline along with 95% CIs will be calculated. Pharmacodynamic parameters will be calculated and summarized by dose, cohort, treatment period (single dose or multiple dose; Cohort A only), and study day as applicable.

All IOP data will be listed by dose, cohort, subject, treatment period (single dose or multiple dose; Cohort A only), and study day.

Statistical methodology for PK/PD relationship

The relationship between dose of SHP639 ophthalmic solution, plasma PK parameters, and changes in IOP may be explored using graphical and/or regression methods if the data permit.

Statistical Methodology for Safety Endpoints

All safety analyses will be performed using the safety set. The placebo subjects will be pooled together as a pooled placebo group.

All vital sign, clinical laboratory, ECG, ADA, drop comfort assessment, and ophthalmologic examination data (per schedule of events) will be listed by dose, cohort, subject, treatment period (single dose or multiple dose; Cohort A only), visit, day, and time point (for days with multiple assessments per day). If the ranges are available then abnormalities will be flagged. Summary statistics with number of subjects, mean, standard deviation, median, minimum, and maximum will be provided by dose, cohort, treatment period (single dose or multiple dose; Cohort A only), visit, day, and time point (for days with multiple assessments per day).

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. The number of events, incidence, and percentage of treatment-emergent AEs will be calculated overall and by system organ class and preferred term by dose and cohort. Treatment-emergent AEs will be further summarized by severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, serious AEs, and deaths will be similarly summarized/listed. All information obtained on AEs will be displayed by dose, cohort, subject, treatment period (single dose or multiple dose; Cohort A only), visit, and day. A subject with multiple AEs within a body system will be counted only once.

STUDY SCHEDULES

Table 1 Overall Schedule of Events

Study Visit	Screening and WO 1[a,t]		SDTP Baseline[b]		SDTP (Cohort A)[b]		WO 2[c]	MDTP Baseline[d]		MDTP[d] (Cohorts A, B, C, and D)														
Study Day	-28	-14/ MWOA[t]	-2	-1	1	2		-2	-1	1	2	3-6	7	8-13	14	15-20	21	22-25	26	27	28[e]	29/ ET[f,t]	FU Call[g]	88/ FU[s], [v]
Study Day Window (Days)	-14	±2			0	0				0	0		±2		±2		±2					0	±2	±4
Informed consent	X																							
Inclusion/exclusion criteria	X[h]		X					X																
Randomization					X					X[i]														
In-house overnight stay[u]			X	X	X					X									X	X	X			
Demography and medical/medication history	X																							
Physical examination	X		X			X		X							X				X			X		
Height and weight	X																							
HIV, HBsAg, and HCV Ab	X																							
Drugs of abuse[j]	X[k]	X	X					X	X	X					X		X		X					
Alcohol breath test[j]	X[k]	X	X					X	X	X					X		X		X					
Serum pregnancy test (female subjects)	X		X					X		X									X			X		
Vital signs[l]	X	X	X	X	X	X		X	X	X	X		X		X		X		X	X	X	X		
Biochemistry, hematology, and urinalysis	X		X			X		X		X			X		X		X		X	X		X		
Electrocardiogram	X		X	X	X	X		X	X	X	X		X		X		X		X	X		X		
PK blood sampling					X					X										X				
Antidrug Ab blood sampling								X							X							X		X
Drop comfort assessment[m]					X					X			X		X		X			X	X			

Table 1 Overall Schedule of Events

Study Visit	Screening and WO 1[a,t]		SDTP Baseline[b]		SDTP (Cohort A)[b]		WO 2[c]	MDTP Baseline[d]		MDTP[d] (Cohorts A, B, C, and D)															
Study Day	-28	-14/ MWOA[t]	-2	-1	1	2		-2	-1	1	2	3-6	7	8-13	14	15-20	21	22-25	26	27	28[e]	29/ ET[f,t]	FU Call[g]	88/ FU[s], [v]
Study Day Window (Days)	-14	±2			0	0				0	0		±2		±2		±2					0	±2	±4
BCVA[n]	X	X	X	X	X	X		X	X	X	X		X		X		X			X	X	X		
Manifest refraction[o]	X		X					X														X		
Slit lamp examination of anterior segment	X[r]	X	X	X	X	X		X	X	X	X		X		X		X			X	X	X[r]		
Conjunctival redness[p]	X	X	X	X	X	X		X	X	X	X		X		X		X			X	X	X		
Corneal haze	X	X	X	X	X	X		X	X	X	X		X		X		X			X	X	X		
Corneal epithelial integrity using fluorescein stain	X	X	X	X	X	X		X	X	X	X		X		X		X			X	X	X		
Anterior chamber cell and flare	X	X	X	X	X	X		X	X	X	X		X		X		X			X	X	X		
Lens opacification	X[r]																					X[r]		
IOP[w]	X	X	X	X	X	X		X	X	X	X		X		X		X			X	X	X		
Posterior segment examination, dilated[n]	X																					X		
Posterior segment examination, nondilated			X					X																
Gonioscopy	X							X[i]														X		
Specular microscopy, noncontact	X			X		X			X						X							X		
Corneal pachymetry	X			X	X	X			X	X	X		X		X							X		
Adverse events reporting	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant medication	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1 Overall Schedule of Events

Study Visit	Screening and WO 1[a,t]		SDTP Baseline[b]		SDTP (Cohort A)[b]		WO 2[c]	MDTP Baseline[d]		MDTP[d] (Cohorts A, B, C, and D)														
Study Day	-28	-14/ MWOA[t]	-2	-1	1	2		-2	-1	1	2	3-6	7	8-13	14	15-20	21	22-25	26	27	28[e]	29/ ET[f,t]	FU Call[g]	88/ FU[s,v]
Study Day Window (Days)	-14	±2			0	0				0	0		±2		±2		±2					0	±2	±4
IP Administration (Per Cohort for Each Dose Level)[q]																								
Cohort A					X					X	X	X	X	X	X	X	X	X	X	X	X			
Cohort B										X	X	X	X	X	X	X	X	X	X	X	X			
Cohort C										X	X	X	X	X	X	X	X	X	X	X	X			
Cohort D										X	X	X	X	X	X	X	X	X	X	X	X			

Ab=antibody; BCVA=best-corrected visual acuity; ET=early termination; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IOP=intraocular pressure; IP=investigational product; MDTP=multiple-dose treatment period; MWOA=midwashout ophthalmic assessment; PK=pharmacokinetic; SDTP=single-dose treatment period; WO=washout.

[a] Subjects in all cohorts are to be washed out of current medications for up to 28 days, as specified in Section 5.2.2. The washout may start from Day -28 onwards, depending on the length of washout required. A MWOA will be performed on both eyes either 14±2 days after a subject starts the washout period or 14±2 days after a previous MWOA. Subjects will continue not to take prohibited medications until discharge from the site on Day 29 of the MDTP.

[b] The SDTP will occur in Cohort A only. Subjects in Cohort A will be admitted to the unit on Day -3 (optional early check-in to unit if more convenient for the subject) or Day -2 before the morning assessments and will be discharged on Day 2 after completion of the evening assessments. All subjects must have checked in to the unit before the ophthalmologic assessments on Day -2.

[c] For Cohort A only, there will be a washout period of 3-14 days between the SDTP and the MDTP.

[d] For the MDTP, subjects in Cohorts A, B, C, and D will arrive at the unit before the morning assessments and depart after the evening assessments on Days -2 and -1. They will be admitted to the unit on the morning of Day 1 and discharged from the unit after completing the Day 2 assessments. They will arrive at the unit before the morning assessments and depart after the evening assessments on Days 7, 14, and 21. They will be admitted to the unit on the evening of Day 26 and discharged from the unit after completing the assessments on the morning of Day 29. While admitted to the unit, subjects must remain within the unit unless otherwise specified.

[e] The final dose will be at approximately 8:00 AM on Day 28.

[f] Subjects who are prematurely discontinued from the study will complete the Day 29/ET assessments as fully as possible.

[g] A follow-up telephone call will take place 7±2 days post discharge from the clinic (Day 29 of MDTP).

[h] All eligibility criteria except IOP-related criteria (inclusion criterion 4 and exclusion criterion 4) will be assessed at screening.

[i] Excluding Cohort A (previously performed during the SDTP baseline).

[j] Breathalyzer test for alcohol and urine screening for drugs of abuse.

[k] These assessments will be performed at initial screening and may also be performed at any visit during the screening period.

[l] Vital signs include blood pressure, pulse rate, and temperature.

Table 1 Overall Schedule of Events

Study Visit	Screening and WO 1[a,t]		SDTP Baseline[b]		SDTP (Cohort A)[b]		WO 2[c]	MDTP Baseline[d]		MDTP[d] (Cohorts A, B, C, and D)														
Study Day	-28	-14/ MWOA[t]	-2	-1	1	2		-2	-1	1	2	3-6	7	8-13	14	15-20	21	22-25	26	27	28[e]	29/ ET[f,t]	FU Call[g]	88/ FU[s], [v]
Study Day Window (Days)	-14	±2			0	0				0	0		±2		±2		±2					0	±2	±4

[m] Drop comfort assessments will be performed immediately and 1, 2, and 3 minutes after instillation of the investigational product; to be assessed at morning doses only. If the score is not ≤3 at minute 3, the drop comfort assessment should be repeated at minutes 5, 10, and 15 until the score is ≤3. If the score is >3 at minute 15, it should be recorded as an adverse event.

[n] If BCVA decreases by 6 or more letters, then a dilated posterior segment examination should be performed.

[o] Manifest refraction should be repeated if the BCVA in either eye decreases by 10 or more letters.

[p] Conjunctival redness will be evaluated using the Efron scale.

[q] SDTP dosing (Cohort A only): investigational product (SHP639 ophthalmic solution or placebo) will be administered once on the morning of Day 1. MDTP dosing: Cohort A=once daily, Cohort B=twice daily, Cohort C=3 times daily, Cohort D=4 times daily; the final dose will be administered on the morning of Day 28. Dose administration will occur during waking hours.

[r] Lens opacification is graded at screening and Day 29, during the scheduled dilated exam. The lens assessment that is part of the slit lamp exam on those days should not report graded opacification findings, but should report other lens-related findings that are visible during the non-dilated exam.

[s] The Day 88 visit is 60 days post last dose (Day 28 of MDTP).

[t] For Screening, MWOA, and Day 29 visits only one round of ophthalmic assessments needs to be done in the morning.

[u] At check-in for overnight stays the following assessments will be performed: physical exam, drugs of abuse screening, alcohol breathalyzer, vital signs, hematology, chemistry, urinalysis, and a single ECG.

[v] The Day 88/FU visit is labeled "Day 88" based on a subject's duration of participation from Day 1 (1st dose) of the MDTP. Subjects in cohort A1, A2, and A3 will have been in the study for a longer duration due to the SDTP.

[w] At screening IOP may be done at any time during the day. At MWOA (D-14), IOP should be done at 10:00am +3 hours. IOP only needs to be done at one time during screening, MWOA, and Day 29.

Refer to Section 7.1 for guidance on the priority order of assessments. Refer to Table 2 (Cohort A), Table 3 (Cohort B), Table 4 (Cohort C), and Table 5 (Cohort D), for details of time points within each visit.

Table 2 Detailed Schedule of Events – Cohort A

Assessment	Days Performed (Screening through D29)[f]	Predose/ Morning[a]	0 m	30 m	1 h	2 h	3 h	4 h	6 h	8 h	12 h
Assessment Window (minutes)			0	±5	±15	±15	±15	±15	±15	±15	±15
Dosing	SDTP: D1. MDTP: D1 through D28[g]		X								
PK blood sampling	SDTP: D1. MDTP: D1, D27	X		X	X	X	X		X		
Drop comfort assessment[b]	SDTP: D1. MDTP: D1, D7, D14, D21, D27, D28		X								
Physical examination	SCR. SDTP: D-2, D2. MDTP: D-2, D14, D26, D29	X									
Vital signs	All visits except Day 88/FU	X		X			X			X	
ECG	All visits except MWOA, Day 28, and Day 88/FU[h]	X		X			X			X	
BCVA	All visits except Day 26 and Day 88/FU	X			X						X
Manifest refraction	SCR. SDTP: D-2 MDTP: D-2, D29.	X									
Slit lamp examination of anterior segment[c]	SCR, D-14, SDTP: D-2, D-1, D1, D2. MDTP: D-2 and D-1, D1, D2, D7, D14, D21, D27, D28, D29	X			X						X
Conjunctival redness	SCR, D-14, SDTP: D-2,D-1, D1, D2. MDTP: D-2 and D-1, D1, D2, D7, D14, D21, D27, D28, D29.	X			X		X		X		X
Corneal haze	SCR, D-14. SDTP:D-2,D-1, D1, D2. MDTP: D-2 and D-1), D1, D2, D7, D14, D21, D27, D28, D29	X			X		X		X		X
Corneal epithelial integrity using fluorescein stain	SCR, D-14, SDTP: D-2, D-1, D1, D2. MDTP: D-2,D-1, D1, D2, D7, D14, D21, D27, D28, D29	X				X		X		X	X
Anterior chamber cell and flare	SCR, D-14, SDTP: D-2, D-1, D1, D2. MDTP: D-2, D-1), D1, D2, D7, D14, D21, D27, D28, D29	X			X						X
Lens opacification	SCR, D29	X									
IOP, abbreviated schedule	SCR[e], D-14[d], MDTP: D7, D14, D21, D29[d]	X				X		X		X	X
IOP, full schedule	SDTP: D-2, D-1, D1, D2. MDTP: D-2 and D-1, D1, D2, D27, D28.	X		X	X	X	X	X	X	X	X
Posterior segment examination	SCR (dilated). SDTP: D-2; nondilated. MDTP: D-2; nondilated, D29 (dilated)	X									
Gonioscopy[e]	SCR,D29	X									
Specular microscopy, noncontact	SCR. SDTP: D-1, D2. MDTP: D-1, D14, D29	X									
Corneal pachymetry	SCR. SDTP: D-1D1, D2. MDTP: D-1, D1, D2, D7, D14, D29	X			X	X		X			X
Antidrug Ab blood sampling	D-2, D14, D29, D88/FU.	X									
Drugs of abuse	SCR, D-14, SDTP: D-2, MDTP: D-2 and D-1, D1, D14, D21, D26.	X									

Table 2 Detailed Schedule of Events – Cohort A

Assessment	Days Performed (Screening through D29)[f]	Predose/ Morning[a]	0 m	30 m	1 h	2 h	3 h	4 h	6 h	8 h	12 h
Assessment Window (minutes)			0	±5	±15	±15	±15	±15	±15	±15	±15
Alcohol breath test	SCR, D-14, SDTP: D-2, MDTP: D-2 and D-1, D1, D14, D21, D26.	X									
Serum pregnancy test (female subjects)	SCR, SDTP: D-2, MDTP: D-2, D1, D26, D29	X									
Biochemistry, hematology, and urinalysis	SCR, SDTP: D-2, D2. MDTP: D-2, D1, D7, D14, D21, D26, D27, D29.	X									

Ab=antibody; BCVA=best-corrected visual acuity; D=day; ECG=electrocardiogram; FU=follow up; h=hours; IOP=intraocular pressure; m=minutes; MDTP=multiple-dose treatment period; PK=pharmacokinetic; SCR=screening; SDTP=single-dose treatment period.

[a] Assessments will take place 60-30 minutes before dosing or in the morning on nondosing days.

[b] Drop comfort assessments will be obtained immediately, 1, 2, and 3 minutes after instillation of the investigational product; to be assessed at morning doses only. If the score is not ≤3 at minute 3, the drop comfort assessment should be repeated at minutes 5, 10, and 15 until the score is ≤3. If the score is >3 at minute 15, it should be recorded as an adverse event.

[c] Slit lamp examination of anterior segment will be performed only during the morning assessment on the following days: Screening, Day -14, SDTP Day -2, SDTP Day -1, MDTP Day -2, MDTP Day -1, and Day 29.

[d] At screening IOP may be done at any time during the day. At MWOA (D-14), IOP should be done at 10:00am ±3 hours. IOP only needs to be done at one time during screening, MWOA, and Day 29.

[e] Gonioscopy at screening can be done at any time of day. Gonioscopy on Day 29 will be performed at the morning time point.

[f] Ophthalmologic assessments on screening, MWOA (D-14), and Day 29 need to be done one time during the day only.

These assessments include: BCVA, Manifest Refraction (Screening), Slit Lamp examination of anterior segment, Conjunctival Redness, Corneal Haze, Corneal Epithelial integrity using fluorescein stain, Anterior Chamber cell and flare, Lens Opacification, IOP, Posterior Segment Examination, dilated (Screening and Day 29), Specular Microscopy, Noncontact (Screening and Day 29), Corneal Pachymetry (Screening and Day 29)

[g] Subjects will be administered the last dose of study drug on the morning of Day 28.

[h] ECG is to be performed at one time point only on Day 26 and Day 29

Timings relate to dose administration or the equivalent morning assessment. Refer to Section 7.1 for guidance on the priority order of assessments. Assessments on nondosing days (screening, baseline, and Day 29) will take place once in the morning only unless otherwise specified.

Table 3 Detailed Schedule of Events – Cohort B

Assessment	Days Performed (Screening through D29)[f]	Predose/ Morning[a]	0 m	30 m	1 h	2 h	3 h	4 h	6 h	8 h	12 h
Assessment Window (minutes)			0	±5	±15	±15	±15	±15	±15	±15	±15
Dosing	D1 through D28[g]		X								X
PK blood sampling	D1, D27	X		X	X	X	X		X		
Drop comfort assessment[b]	D1, D7, D14, D21, D27, D28		X								
Physical examination	SCR, D-2, D14, D26, D29	X									
Vital signs	All visits except Day 88/FU	X		X			X			X	
ECG	All visits except MWOA, Day 28, and Day 88/FU[h]	X		X			X			X	
BCVA	All visits except Day 26 and Day 88/FU	X			X						X
Manifest refraction	SCR, D-2, D29	X									
Slit lamp examination of anterior segment[c]	SCR, D-14, D-2,D-1, D1, D2, D7, D14, D21, D27, D28, D29	X			X						X
Conjunctival redness	SCR, D-14,D-2,D-1, D1, D2, D7, D14, D21, D27, D28, D29	X			X		X		X		X
Corneal haze	SCR, D-14, D-2,D-1, D1, D2, D7, D14, D21, D27, D28, D29	X			X		X		X		X
Corneal epithelial integrity using fluorescein stain	SCR, D-14, D-2,D-1, D1, D2, D7, D14, D21, D27, D28, D29	X				X		X		X	X
Anterior chamber cell and flare	SCR, D-14. D-2,D-1, D1, D2, D7, D14, D21, D27, D28, D29	X			X						X
Lens opacification	SCR, D29	X									
IOP, abbreviated schedule	SCR[e], D-14[d], D7, D14, D21, D29[d]	X				X		X		X	X
IOP, full schedule	D-2, D-1, D1, D2, D27, D28.	X		X	X	X	X	X	X	X	X
Posterior segment examination	SCR (dilated), D-2; nondilated, D29 (dilated)	X									
Gonioscopy[e]	SCR, D29	X									
Specular microscopy, noncontact	SCR, D-1, D14, D29	X									
Corneal pachymetry	SCR, D-1, D1, D2, D7, D14, D29	X			X	X		X			X
Antidrug Ab blood sampling	D-2, D14, D29, D88/FU	X									
Drugs of abuse	SCR, D-14), D-2 and D-1, D1, D14, D21, D26	X									

Table 3 Detailed Schedule of Events – Cohort B

Assessment	Days Performed (Screening through D29)[f]	Predose/ Morning[a]	0 m	30 m	1 h	2 h	3 h	4 h	6 h	8 h	12 h
Assessment Window (minutes)			0	±5	±15	±15	±15	±15	±15	±15	±15
Alcohol breath test	SCR, D-14, D-2, D-1, D1, D14, D21, D26	X									
Serum pregnancy test (female subjects)	SCR, D-2 D1, D26, D29.	X									
Biochemistry, hematology, and urinalysis	SCR, D-2, D1, D7, D14, D21, D26, D27, D29.	X									

Ab=antibody; BCVA=best-corrected visual acuity; D=day; ECG=electrocardiogram; FU=follow up; h=hours; IOP=intraocular pressure; m=minutes; MDTP=multiple-dose treatment period; PK=pharmacokinetic; SCR=screening.

[a] Assessments will take place 60-30 minutes before the first dose of the day or in the morning on nondosing days.

[b] Drop comfort assessments will be obtained immediately, 1, 2, and 3 minutes after instillation of the investigational product; to be assessed at morning doses only. If the score is not ≤3 at minute 3, the drop comfort assessment should be repeated at minutes 5, 10, and 15 until the score is ≤3. If the score is >3 at minute 15, it should be recorded as an adverse event.

[c] Slit lamp examination of anterior segment will be performed only during the morning assessment on the following days: Screening, Day -14, Day -2, Day -1 and Day 29.

[d] At screening IOP may be done at any time during the day. At MWOA (D-14), IOP should be done at 10:00am ±3 hours. IOP only needs to be done at one time during screening, MWOA, and Day 29.

[e] Gonioscopy at screening can be done at any time of day. Gonioscopy on Day 29 will be performed at the morning time point.

[f] Ophthalmologic assessments on screening, MWOA (D-14), and Day 29 need to be done one time during the day only.

These assessments include: BCVA, Manifest Refraction (Screening), Slit Lamp examination of anterior segment, Conjunctival Redness, Corneal Haze, Corneal Epithelial integrity using fluorescein stain, Anterior Chamber cell and flare, Lens Opacification, IOP, Posterior Segment Examination, dilated (Screening and Day 29), Specular Microscopy, Noncontact (Screening and Day 29), Corneal Pachymetry (Screening and Day 29).

[g] Subjects will be administered the last dose of study drug on the morning of Day 28.

[h] ECG is to be performed at one time point only on Day 26 and Day 29.

Timings relate to the first dose of the day or the equivalent morning assessment. Refer to Section 7.1 for guidance on the priority order of assessments. Assessments on nondosing days (screening, baseline, and Day 29) will take place once in the morning only unless otherwise specified.

Table 4 Detailed Schedule of Events – Cohort C

Assessment	Days Performed (Screening through D29)[f]	Predose/ Morning[a]	0 m	30 m	1 h	2 h	3 h	4 h	6 h	8 h	12 h
Assessment Window (minutes)			0	±5	±15	±15	±15	±15	±15	±15	±15
Dosing	D1 through D28[g]		X						X		X
PK blood sampling	D1, D27	X		X	X	X	X		X		
Drop comfort assessment[b]	D1, D7, D14, D21, D27, D28		X								
Physical examination	SCR, D-2, D14, D26, D29	X									
Vital signs	All visits except Day 88/FU	X		X			X			X	
ECG	All visits except MWOA, Day 28, and Day 88/FU[h]	X		X			X			X	
BCVA	All visits except Day 26 and Day 88/FU	X			X						X
Manifest refraction	SCR, D-2, D29	X									
Slit lamp examination of anterior segment[c]	SCR, D-14, D-2, D-1, D1, D2, D7, D14, D21, D27, D28, D29	X			X						X
Conjunctival redness	SCR, D-14, D-2,D-1, D1, D2, D7, D14, D21, D27, D28, D29	X			X		X		X		X
Corneal haze	SCR, D-14,D-2,D-1, D1, D2, D7, D14, D21, D27, D28, D29	X			X		X		X		X
Corneal epithelial integrity using fluorescein stain	SCR, D-14, D-2,D-1, D1, D2, D7, D14, D21, D27, D28, D29	X				X		X		X	X
Anterior chamber cell and flare	SCR, D-14, D-2, D-1, D1, D2, D7, D14, D21, D27, D28, D29.	X			X						X
Lens opacification	SCR, D29	X									
IOP, abbreviated schedule	SCR[e], D-14[d], D7, D14, D21, D29[d]	X				X		X		X	X
IOP, full schedule	D-2, D-1, D1, D2, D27, D28.	X		X	X	X	X	X	X	X	X
Posterior segment examination	SCR (dilated), D-2; nondilated, D29 (dilated)	X									
Gonioscopy[e]	SCR, D29	X									
Specular microscopy, noncontact	SCR, D-1 D14, D29	X									
Corneal pachymetry	SCR, D-1 D1, D2, D7, D14, D29	X			X	X		X			X
Antidrug Ab blood sampling	D-2, D14, D29, D88/FU	X									

Table 4 Detailed Schedule of Events – Cohort C

Assessment	Days Performed (Screening through D29)[f]	Predose/ Morning[a]	0 m	30 m	1 h	2 h	3 h	4 h	6 h	8 h	12 h
Assessment Window (minutes)			0	±5	±15	±15	±15	±15	±15	±15	±15
Drugs of abuse	SCR, D-14, D-2, D-1, D1, D14, D21, D26.	X									
Alcohol breath test	SCR, D-14), D-2, D-1, D1, D14, D21, D26.	X									
Serum pregnancy test (female subjects)	SCR, D-2, D1, D26, D29.	X									
Biochemistry, hematology, and urinalysis	SCR, D-2, D1, D7, D14, D21, D26, D27, D29.	X									

Timings relate to the first dose of the day or the equivalent morning assessment. Refer to Section 7.1 for guidance on the priority order of assessments. Assessments on nondosing days (screening, baseline, and Day 29) will take place once in the morning only unless otherwise specified.

Ab=antibody; BCVA=best-corrected visual acuity; D=day; ECG=electrocardiogram; FU=follow up; h=hours; IOP=intraocular pressure; m=minutes; MDTP=multiple-dose treatment period; PK=pharmacokinetic; SCR=screening

[a] Assessments will take place 60-30 minutes before the first dose of the day or in the morning on nondosing days.

[b] Drop comfort assessments will be obtained immediately, 1, 2, and 3 minutes after instillation of the investigational product; to be assessed at morning doses only. If the score is not ≤3 at minute 3, the drop comfort assessment should be repeated at minutes 5, 10, and 15 until the score is ≤3. If the score is >3 at minute 15, it should be recorded as an adverse event.

[c] Slit lamp examination of anterior segment will be performed only during the morning assessments on the following days: Screening, Day -14, Day -2, –Day 1, and Day 29.

[d] At screening IOP may be done at any time during the day. At MWOA (D-14), IOP should be done at 10:00am ±3 hours. IOP only needs to be done at one time during screening, MWOA, and Day 29.

[e] Gonioscopy at screening can be done at any time of day. Gonioscopy on Day 29 will be performed at the morning time point.

[f] Ophthalmologic assessments on screening, MWOA (D-14), and Day 29 need to be done one time during the day only.

These assessments include: BCVA, Manifest Refraction (Screening), Slit Lamp examination of anterior segment, Conjunctival Redness, Corneal Haze, Corneal Epithelial integrity using fluorescein stain, Anterior Chamber cell and flare, Lens Opacification, IOP, Posterior Segment Examination, dilated (Screening and Day 29), Specular Microscopy, Noncontact (Screening and Day 29), Corneal Pachymetry (Screening and Day 29).

[g] Subjects will be administered the last dose of study drug on the morning of Day 28.

[h] ECG is to be performed at one time point only on Day 26 and Day 29.

Timings relate to the first dose of the day or the equivalent morning assessment. Refer to Section 7.1 for guidance on the priority order of assessments. Assessments on nondosing days (screening, baseline, and Day 29) will take place once in the morning only unless otherwise specified.

Table 5 Detailed Schedule of Events – Cohort D

Assessment	Days Performed (Screening through D29)[f]	Predose/ Morning[a]	0 m	30 m	1 h	2 h	3 h	4 h	6 h	8 h	12 h
Assessment Window (minutes)			0	±5	±15	±15	±15	±15	±15	±15	±15
Dosing	D1 through D28[g]		X					X		X	X
PK blood sampling	D1, D27	X		X	X	X	X		X		
Drop comfort assessment[b]	D1, D7, D14, D21, D27, D28		X								
Physical examination	SCR, D-2, D14, D26, D29	X									
Vital signs	All visits except Day 88/FU	X		X			X			X	
ECG	All visits except MWOA, Day 28, and Day 88/FU[h]	X		X			X		X		
BCVA	All visits except Day 26 and Day 88/FU	X			X						X
Manifest refraction	SCRD-2, D29	X									
Slit lamp examination of anterior segment[c]	SCR, D-14, D-2,D-1, D1, D2, D7, D14, D21, D27, D28, D29	X			X						X
Conjunctival redness	SCR, D-14, D-2,D-1, D1, D2, D7, D14, D21, D27, D28, D29	X			X		X		X		X
Corneal haze	SCR, D-14D-2,D-1, D-1, D1, D2, D7, D14, D21, D27, D28, D29	X			X		X		X		X
Corneal epithelial integrity using fluorescein stain	SCR, D-14, D-2,D-1, D1, D2, D7, D14, D21, D27, D28, D29	X				X		X		X	X
Anterior chamber cell and flare	SCR, D-14, D-2 and D-1, D1, D2, D7, D14, D21, D27, D28, D29.	X			X						X
Lens opacification	SCR, D29	X									
IOP, abbreviated schedule	SCR[e], D-14[d], D7, D14, D21, D29[d]	X				X		X		X	X
IOP, full schedule	D-2, D-1, D1, D2, D27, D28.	X		X	X	X	X	X	X	X	X
Posterior segment examination	SCR (dilated), D-2; nondilated, D29 (dilated)	X									
Gonioscopy[e]	SCR D29	X									
Specular microscopy, noncontact	SCR, D-1, D14, D29	X									

Table 5 Detailed Schedule of Events – Cohort D

Assessment	Days Performed (Screening through D29)[f]	Predose/ Morning[a]	0 m	30 m	1 h	2 h	3 h	4 h	6 h	8 h	12 h
Assessment Window (minutes)			0	±5	±15	±15	±15	±15	±15	±15	±15
Corneal pachymetry	SCR, D-1, D1, D2, D7, D14, D29	X			X	X		X			X
Antidrug Ab blood sampling	D-2, D14, D29, D88/FU	X									
Drugs of abuse	SCR, D-14, D-2, D-1, D1, D14, D21, D26.	X									
Alcohol breath test	SCR, D-14, D-2, D-1, D1, D14, D21, D26.	X									
Serum pregnancy test (female subjects)	SCR, D-2, D1, D26, D29.	X									
Biochemistry, hematology, and urinalysis	SCR, D-2D1, D7, D14, D21, D26, D27, D29.	X									

Ab=antibody; BCVA=best-corrected visual acuity; D=day; ECG=electrocardiogram; FU=follow up; h=hours; IOP=intraocular pressure; m=minutes; MDTP=multiple-dose treatment period; PK=pharmacokinetic; SCR=screening

[a] Assessments will take place 60-30 minutes before the first dose of the day or in the morning on nondosing days.

[b] Drop comfort assessments will be obtained immediately, 1, 2, and 3 minutes after instillation of the investigational product; to be assessed at morning doses only. If the score is not ≤3 at minute 3, the drop comfort assessment should be repeated at minutes 5, 10, and 15 until the score is ≤3. If the score is >3 at minute 15, it should be recorded as an adverse event.

[c] Slit lamp examination of anterior segment will be performed only during the morning assessment on the following days: Screening, Day -14, Day -2, Day 1, and Day 29.

[d] At screening IOP may be done at any time during the day. At MWOA (D-14), IOP should be done at 10:00am ±3 hours. IOP only needs to be done at one time during screening, MWOA, and Day 29.

[e] Gonioscopy at screening can be done at any time of day.Gonioscopy on Day 29 will be performed at the morning time point.

[f] Ophthalmologic assessments on screening, MWOA (D-14), and Day 29 need to be done one time during the day only.

These assessments include: BCVA, Manifest Refraction (Screening), Slit Lamp examination of anterior segment, Conjunctival Redness, Corneal Haze, Corneal Epithelial integrity using fluorescein stain, Anterior Chamber cell and flare, Lens Opacification, IOP, Posterior Segment Examination, dilated (Screening and Day 29), Specular Microscopy, Noncontact (Screening and Day 29), Corneal Pachymetry (Screening and Day 29)

[g] Subjects will be administered the last dose of study drug on the morning of Day 28.

[h] ECG is to be performed at one time point only on Day 26 and Day 29.

Timings relate to the first dose of the day or the equivalent morning assessment. Refer to Section 7.1 for guidance on the priority order of assessments. Assessments on nondosing days (screening, baseline, and Day 29) will take place once in the morning only unless otherwise specified.

1. BACKGROUND INFORMATION

SHP639 is a 9-amino acid, synthetic, C-type natriuretic peptide (CNP) analog that is a potent and selective agonist of natriuretic peptide receptor B (NPR-B). It is being developed by Shire for the treatment of glaucoma and ocular hypotension (OHT). Interaction of SHP639 with NPR-B would potentially have an intraocular pressure (IOP)-lowering effect with a novel mode of action that targets the primary outflow mechanism that is altered in these diseases.

Natriuretic peptides are potent activators of the cell membrane-bound guanylyl cyclases, thereby increasing the intracellular concentration of cyclic guanosine monophosphate (cGMP). C-type natriuretic peptide or CNP analog activation of NPR-B can consequently increase cGMP leading to various physiological effects (eg, smooth muscle relaxation, vasorelaxation, and vascular remodeling) including trabecular meshwork relaxation. It has been reported in several publications that compounds that increase cellular concentrations of cGMP will lower IOP by potentially increasing aqueous humor outflow through relaxation of the trabecular meshwork (Becker, 1990; Nathanson, 1988; Nathanson, 1992; Stein and Clack, 1994). Targeting the trabecular meshwork pathway, which is the dominant ocular outflow mechanism responsible for the majority of aqueous humor drainage, can potentially translate into an attractive target for treating OHT and glaucoma.

In vitro, SHP639 has shown to be highly selective towards activating NPR-B receptors (50% of maximal effective concentration [EC_{50}]=61.4±11.0nM) when compared with natriuretic peptide receptor A (NPR-A) receptors (EC_{50}=2179±335nM), ie, SHP639 is 35 times more potent for the NPR-B receptor compared with NPR-A receptor.

In vivo, a robust lowering of IOP was noted in rabbits and dogs following topical ocular instillation of SHP639. In rabbit models, a dose-dependent IOP-lowering efficacy (≥40% IOP reduction at 0.6%) was observed and the IOP-lowering effect persisted for at least 8 hours for the highest dose tested (0.6%/180 µg per eye). Single-dose administration also significantly increased outflow facility (trabecular outflow) by 2.6-fold in the same species.

Topical ocular administration of SHP639, at a concentration up to 0.6%, was well tolerated in rabbits and monkeys. The no-observed-adverse-effect level (NOAEL) following 28 days of topical administration was 0.6%, administered as 1 drop, into both eyes, 4 times daily (QID) (total daily dose of 1.51 mg/day of SHP639).

1.1 Indication and Current Treatment Options

Glaucoma is an optic neuropathy characterized by retinal ganglion cell degeneration and death, evident at the optic nerve head, and which results in visual field loss. Glaucoma can be classified by anatomy (open-angle or angle-closure glaucoma) or by etiology (primary, secondary, or congenital). Primary open-angle glaucoma (POAG) can progress asymptomatically for months or years, causing a delay in diagnosis and treatment. In contrast, OHT is a condition of elevated IOP without signs of early glaucoma but which increases the risk of developing the disease.

Glaucoma is a leading cause of irreversible vision loss worldwide (Weinreb et al., 2014; Quigley and Broman, 2006). Primary open-angle glaucoma affected approximately 58 million people in 2015; this number is projected to increase to approximately 66 million in 2020 (Kapetanakis et al., 2016). Additionally, approximately 2.71 million Americans had open-angle glaucoma in 2011, a prevalence expected to almost triple to 7.32 million by 2050 (Vajaranant et al., 2012).

Intraocular pressure is the major modifiable risk factor of glaucoma (Leske et al., 2003), including in patients with IOP in the statistically "normal" range (Collaborative Normal-Tension Glaucoma Study Group, 1998). Reduction of IOP has been demonstrated in landmark studies to protect against further damage to the optic nerve in patients with early (Heijl et al., 2002) and advanced (AGIS Investigators, 2000) glaucoma and to decrease the risk of progression to glaucoma in patients with OHT (Kass et al., 2002).

Based on data from the Early Manifest Glaucoma Trial (Heijl et al., 2002) and Collaborative Initial Glaucoma Treatment Study (Lichter et al., 2001), ophthalmologists consider a patient's clinical status, age, and lifestyle in order to decide on an initial target IOP, along with the therapeutic measures to achieve that IOP. While closely following the patient's visual fields and optic disc status, the target IOP will be reassessed periodically or if the patient demonstrates evidence of glaucoma progression.

Intraocular pressure elevation can occur because of a decrease in aqueous humor outflow through the trabecular meshwork (conventional pathway) or uveoscleral outflow (unconventional pathway) or a relative increase in aqueous humor production compared to outflow (Goel et al., 2010). Pharmacotherapy options can target any or all of these mechanisms. The main classes of topical ocular hypertensive either decrease aqueous humor production (prostaglandin analogs, α-adrenergic agonists, and cholinergic agonists) or increase aqueous humor outflow (carbonic anhydrase inhibitors, β-blockers, and α-adrenergic agonists). Orally administered carbonic anhydrase inhibitors are more effective at lowering IOP compared with topically applied medication; however, the high incidence of systemic side effects associated with an oral regimen (Weinreb and Khaw, 2004) makes it an unacceptable option for routine clinical use.

1.2 Product Background

1.2.1 Nonclinical Information

In vitro and in vivo primary pharmacology studies, in vitro secondary pharmacology studies to assess "off-target" potential, and in vivo pharmacokinetics and distribution studies were performed. Good Laboratory Practice (GLP)-compliant safety pharmacology studies using SHP639 were conducted in vitro in a human ether-à-go-go-related gene assay and in vivo by the intravenous (IV) route in rats and nonhuman primates (NHPs). Pivotal GLP-compliant 4-week toxicology studies with topical SHP639 were conducted in rabbits and NHPs, with accompanying toxicokinetics. A 4-week toxicology and toxicokinetics study with intravenously administered SHP639 was performed to assess potential systemic toxicity. Rabbits and NHPs are both pharmacologically relevant species and both are commonly used species to assess topical and systemic toxicity in ocular drug development. The topical safety studies in both species included a full assessment of potential systemic toxicity (toxicokinetics, clinical pathology, and anatomic pathology for a full list of organs), such that a single species (NHP) to assess the IV

toxicity of SHP639 was considered appropriate. The SHP639 formulation used in the pivotal topical studies is identical to the proposed clinical formulation. This formulation contains standard components typically used in topical ocular formulations. In vitro and in vivo genotoxicity studies were also GLP compliant.

The nonclinical studies demonstrated that topically administered SHP639 has robust and dose-dependent IOP-lowering efficacy in rabbits and dogs, is distributed to relevant ocular tissues with minimal systemic absorption, and is well tolerated in rabbits and NHPs when administered up to QID for 1 month of treatment at concentrations of up to 0.6% SHP639 (30 µL drop). Clinical signs of ocular discomfort were minimal, transient, and not associated with any ocular pathology or toxicity. Following topical administration, systemic exposure to SHP639 is very low to nondetectable, suggesting a low risk of producing systemic toxicities. Central nervous system, cardiovascular, respiratory, and renal safety pharmacology and systemic toxicity were characterized following IV SHP639 administration, and SHP639 was well tolerated. The nonclinical findings following IV administration were generally transient and monitorable and/or occurred at systemic exposures markedly higher than those expected clinically. SHP639 was nongenotoxic in in vitro and in vivo assays.

The nonclinical data therefore adequately support the initiation of this clinical study. Refer to the latest version of the SHP639 investigator's brochure (IB) for additional nonclinical information.

1.2.2 Clinical Information

There have been no prior clinical studies administering the topical ophthalmic solution of SHP639 that will be used for this study. Alcon, the previous sponsor of intravitreally administered SHP639 (formerly known as AL-59412C), initiated a study in adult subjects with no light perception vision in their study eye to assess the safety and efficacy of intravitreally administered SHP639. Subjects were randomized to receive either 30 µg SHP639 in a phosphate vehicle as a 50 µL intravitreal (IVT) injection or 80 ng travoprost via a 50 µL IVT injection. The SHP639 IVT formulation was a different formulation from the SHP639 topical ophthalmic solution that will be used in this study.

Four subjects were recruited for the first cohort and 3 of the 4 subjects received their IVT injection: 2 subjects randomized to SHP639 and 1 subject to travoprost. One of the 2 SHP639-treated subjects developed moderate corneal edema 10 minutes after SHP639 administration, which resolved within 8 hours (no treatment was required for the event). The other experienced a marked rise in IOP, in addition to corneal edema, immediately after SHP639 administration. The subject was treated for the events; however, the elevated IOP persisted for 2 weeks. The subject who received 80 ng travoprost did not develop any significant adverse findings; travoprost was administered by the IVT route with a different formulation to that of SHP639.

Based on the unexpected occurrence of these corneal findings in the 2 subjects who received the 50 µL IVT injection containing 30 µg SHP639, further enrollment in the study was suspended. Alcon initiated some exploratory IVT toxicity studies in rabbits to better understand the effects noted.

Always refer to the latest version of the SHP639 investigator's brochure (IB) for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, efficacy, and safety of SHP639.

1.3 Risk/Benefit and Ethical Assessment

There are no expected benefits to the subjects enrolled in this study. The safety profile of topically administered SHP639 in rabbits and NHPs shows that the compound is well tolerated with no adverse effects up to 0.6% when administered QID as 1 drop (30 µL) in both eyes.

Although, following IVT administration, corneal opacity was seen clinically, the topical ocular toxicity studies in rabbits and NHPs using an exaggerated dosing regimen of QID for 4 weeks did not demonstrate corneal adverse effects up to 0.6% (in a 30 µL drop; total daily dose of 1.51 mg).

The topical formulation used for this study is the same as that evaluated nonclinically in rabbits and NHPs, and utilizes a well-characterized and widely used vehicle, similar to the marketed MAXIDEX® vehicle. Refer to Section 3.3 of the current SHP639 IB for further details.

Considering topical administration, the safety margin for SHP639 ocular drops is calculated based on approximate conjunctival surface area. As the corneal and conjunctival surface areas in rabbits and humans are similar, the human-equivalent dose to the rabbit NOAEL is equivalent to a drop of 0.6% topical solution when administered QID in both eyes, equivalent to a dose of 1.51 mg SHP639 per eye per day.

As the anticipated toxicities for SHP639 are local ocular discomfort, as noted in the animal studies, the proposed topical concentrations to be administered clinically to both eyes (with the exception of Cohort A single-dose treatment period [SDTP], which will occur in 1 designated study eye only) will initiate as a once daily (QD) administration, and will be escalated to multiple times daily based on clinical tolerability. Frequent, serial ophthalmologic examinations, including thorough slit lamp and retinal examinations, will ensure that any corneal or other effects will be detected early, although it is considered highly unlikely that any such effects may occur. The tables below show the margins for each of the dose and dose schedule escalations proposed, based on 1) SHP639 concentrations/drop numbers, and 2) based on SHP639 µg/day, using a nonclinical NOAEL (both eyes) of 0.6% QID or 1.51 mg/eye/day.

Margins to proposed clinical concentrations, based on concentration of SHP639 and the number of drops/day, are shown in Table 6.

Table 6 Dose Margins Based on SHP639 Concentration and Dosing Regimen

Topical Concentration	Dose Margin[a] QD/Both Eyes	BID/Both Eyes	TID/Both Eyes	QID/Both Eyes
0.1% (50 µg/drop)	24-fold	12-fold	9-fold	6-fold
0.3% (150 µg/drop)	8-fold	4-fold	3-fold	2-fold
0.6% (300 µg/drop)	4-fold	2-fold	1.5-fold	1-fold

BID=twice daily; NOAEL=no-observed-adverse-effect level; QD=once daily; QID=4 times daily; TID=3 times daily

[a] Dose margin is based on concentration and number of drops per day; nonclinical single eye NOAEL/clinical dose. Rabbit NOAEL for both eyes is 0.6%, 8 drops per day (4 drops per eye).

Margins to proposed clinical doses, based on SHP639 µg/day, are shown in Table 7.

Table 7 Dose Margins Based on SHP639 Daily Dose

Topical Concentration	Dose Margin[a] QD/Both Eyes	BID/Both Eyes	TID/Both Eyes	QID/Both Eyes
0.1% per 50 µL (50 µg/drop)	15-fold	7.5-fold	5-fold	3.75-fold
0.3% per 50 µL (150 µg/drop)	7.5-fold	3.75-fold	2.5-fold	~2-fold
0.6% per 50 µL (300 µg/drop)	2.5-fold	1.3-fold	~1-fold	0.6-fold

BID=twice daily; NOAEL=no-observed-adverse-effect level; QD=once daily; QID=4 times daily; TID=3 times daily

[a] Dose margin is based on µg/day dose; nonclinical single eye NOAEL/clinical dose. The NOAEL is 0.6% = 0.6 mg/100 µL = 0.18 mg/30 µL drop; the actual drop size in the animal studies was 31.5 µL drop (equivalent to 189 µg/drop). 189 µg/drop × both eyes × QID = 1.51 mg (free-base equivalent); the clinical studies propose a maximal volume of 50 µL drop.

Always refer to the latest version of the SHP639 investigator's brochure (IB) for the overall benefit/risk assessment and the most accurate and current information regarding drug metabolism, pharmacokinetics, efficacy, and safety of SHP639

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

SHP639 is being developed for reduction of IOP in glaucoma patients. It is expected to act through a novel mode of action (NPR-B agonism) that leads to an increase in trabecular meshwork outflow, thus reducing the IOP. SHP639-101 is a first-in-human clinical study for a topical ophthalmic formulation of SHP639. Up to 3 different concentrations (0.1%, 0.3%, and 0.6%) will be explored and safety and tolerability of SHP639 ophthalmic solution will be evaluated. As a secondary objective, the study will also aim to characterize the pharmacodynamics (PD) of SHP639, using IOP as a PD biomarker. The pharmacokinetic (PK)-PD relationship will be explored if the data permit.

2.2 Study Objectives

2.2.1 Primary Objectives

The primary objective of this study is to investigate the safety and tolerability of single and multiple ascending doses of SHP639 ophthalmic solution in subjects with OHT or with POAG.

2.2.2 Secondary Objectives

The secondary objective of this study is to evaluate reduction of IOP, as a PD biomarker, following different SHP639 dosing regimens.

2.2.3 Exploratory Objectives

The exploratory objective for this study is to explore the PK-PD relationship of SHP639 in subjects with OHT or POAG.

3. STUDY DESIGN

3.1 Study Design and Flow Chart

This is a multicenter, randomized, double-masked, placebo-controlled, single- and multiple-dose escalation study. Three different SHP639 concentrations will be studied: 0.1%, 0.3%, and 0.6%. There will be up to 12 cohorts in total, 1 cohort for each dose level and different dosing regimen. Each cohort will consist of 7 subjects for a total of 84 subjects in the study. Eligible subjects will be randomized in a 5:2 ratio to receive either SHP639 or placebo, respectively. The anticipated doses being studied for each dosing regimen are presented in the dose-escalation scheme in Table 10.

A sufficient number of subjects will be screened and enrolled to ensure that at least 6 of 7 subjects complete each treatment in their assigned cohort. In the event that a sufficient number of subjects do not complete a cohort, replacement subjects may be enrolled. Each replacement subject will follow the same screening procedures and randomization sequence as the subject who is discontinued, regardless of when the subject discontinued.

3.1.1 Designated Study Eye

For the purpose of overall analysis, 1 eye will be designated as the primary eye for the duration of the subject's participation in the trial. In Cohort A SDTP, the investigational product will be dosed in the designated study eye only. For all subjects participating in the MDTP, a designated study eye will be also identified and the investigational product will be dosed in both eyes. The following procedure will be used to determine the designated study eye:

- For each subject, the mean baseline IOP at a time point will be the mean of the IOPs on days -2 and -1 at that time point.
- The designated study eye will be the eye with the highest mean baseline IOP at the predose time point.
- If both eyes have equal mean baseline IOPs, the eye with the highest mean IOP at the +2-hour time point will be the designated study eye.
- If both eyes have equal mean IOPs at the +2-hour time point, the eye with the highest mean IOP at the +4-hour time point will be the designated study eye.
- If both eyes have equal mean IOPs at the +4-hour time point, the eye with the highest mean IOP at the +8-hour time point will be the designated study eye.
- If both eyes have equal mean IOPs at the +8-hour time point, the right eye will be the designated study eye.

3.1.2 Screening Period

For all cohorts, the maximum duration of the screening period is 42 days. On the initial visit to the site, the subject will first give informed consent. This will be the date that he/she enters the screening period. After giving consent, the subject will be evaluated against the inclusion and exclusion criteria and undergo the procedures as outlined in Table 1.

During the screening period, subjects will return to the site approximately every 2 weeks for safety evaluations. Subjects requiring a washout from current medications will begin their washout period as required in Section 5.2.2 and Table 8.

Following the screening visit, subjects who continue to meet the protocol-specific inclusion and exclusion criteria will return to the site on either Day -3 or Day -2, to reconfirm eligibility criteria for participation and undergo the predose safety and ophthalmologic assessments as outlined in Table 1.

3.1.3 Study Parts

The study will consist of 2 parts, Part 1 and Part 2.

- Part 1 consists of Cohorts A1, A2, and A3, each of which is a single-dose and QD multiple-dose cohort (1 cohort for each of the 3 dose levels), followed by Cohorts B1, B2, and B3, each of which is a twice daily (BID) multiple-dose cohort (1 cohort for each dose level).
- Part 2 consists of Cohorts C1, C2, and C3, each of which is a 3 times daily (TID) multiple-dose cohort (1 cohort for each dose level), followed by Cohorts D1, D2, and D3, each of which is a QID multiple-dose cohort (1 cohort for each dose level).

3.1.4 Cohorts A1-A3

In Cohorts A1, A2, and A3, there will be an SDTP followed by a multiple-dose treatment period (MDTP).

3.1.4.1 Cohorts A1-A3: Single-dose Treatment Period

Subjects will be randomized prior to administration of investigational product on Day 1 after all entry criteria have been confirmed.

One drop of investigational product will be administered topically to a designated eye. The first 3 of 7 subjects will be dosed with a minimum of 1-hour intervals between the subjects for safety purposes. The subject will then undergo assessments at the time points outlined in Table 1 and Table 2.

Subjects will be observed for the next 24 hours with appropriate medical oversight. An ophthalmologist will be on call to assess ophthalmic-related medical issues. If no adverse events (AEs) occur that are consistent with the predefined stopping criteria, the rest of the subjects in the cohort can be administered investigational product in 1 designated eye.

3.1.4.2 Cohorts A1-A3: Multiple-dose Treatment Period

After completion of the assessments scheduled for Day 2 of the SDTP, subjects will enter a washout period. The duration of the washout period will last between 3 and 14 days. A dose escalation meeting will occur prior to the advancement to each cohort (refer to Section 6.2.3.2 for additional details). For each cohort, following a decision to commence the MDTP, subjects will attend the site on Days -2 and -1 to undergo the scheduled safety and ophthalmic assessments. In Cohorts A1, A2, and A3 MDTP, all subjects will be administered investigational product in both eyes. The same dose concentration that was administered during the SDTP of the relevant cohort (A1, A2, or A3) will be administered during the MDTP QD for the next 28 days. Subjects are to place 1 drop in each eye at approximately the same time each day. Refer to Table 1 and Section 6.2.3 for additional details.

Subjects will be admitted to the site on Day 1 and will be discharged after completion of all Day 2 assessments. On Days 7, 14, and 21, subjects will return to the site as described in Table 1. On Day 26, subjects will be readmitted to the site. On Day 27, subjects will continue to self-administer investigational product while undergoing the scheduled assessments. The last dose will be administered on the morning of Day 28. After completion of the assessments scheduled for Day 29, subjects will then be discharged from the site.

Subjects will receive a follow-up telephone call approximately 7 days after being discharged from the site. They will return to the site to undergo antidrug antibody (ADA) sampling approximately 60 days after the last dose of investigational product (Day 88).

3.1.5 Cohorts B1-B3, C1-C3, and D1-D3

Authorization from the sponsor to proceed from 1 cohort to the next is to be received before subjects enter the screening period for Cohorts B, C, and D. Once authorization has been received from the sponsor, subjects are to be admitted to the screening period of the appropriate cohort as previously described in this section.

Subjects will undergo the scheduled safety and ophthalmic assessments on Day -2 and Day -1 (refer to Table 1). Subjects will then be administered investigational product per the sponsor's authorization to proceed to that cohort. In Cohorts B, C, and D, subjects will be administered investigational product in both eyes. Refer to Section 6.2.3 for additional details.

Subjects will continue to self-administer investigational product as instructed for the duration of the MDTP. Subjects will be admitted to the site on Day 1 and will be discharged after completion of all Day 2 assessments. On Days 7, 14, and 21 (±2 days, each), subjects will return to the site as described in Table 1. On Day 26, subjects will be readmitted to the site. On Day 27, subjects will continue to self-administer investigational product while undergoing the scheduled assessments. The last dose will be administered on the morning of Day 28. After completion of the assessments scheduled for Day 29, subjects will then be discharged from the site.

Subjects will receive a follow-up telephone call approximately 7 days after being discharged from the site. They will return to the site to undergo ADA sampling approximately 60 days after the last dose of investigational product (Day 88).

3.2 Duration and Study Completion Definition

The subjects' maximum duration of participation in the study is expected to be 146 days or approximately 5 months (Cohort A1, A2, and A3). The subjects' maximum duration of participation in the study for Cohorts B, C, and D is expected to be 130 days or approximately 4.5 months.

- Maximum planned duration of screening and Washout 1: 42 days
- Planned duration of treatment period: 2 days for SDTP (Cohort A only) and 29 days for MDTP (all cohorts)
- Planned duration of Washout 2 (Cohort A only): 3-14 days
- Planned duration of follow-up: until Day 88±4 days (final assessment visit and anticipated Study Completion Date for each subject)

The study will be completed in approximately 56 weeks.

The Study Completion Date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. Please note that this includes the follow-up visit or contact, whichever is later. The Study Completion Date is used to ascertain timing for study results posting and reporting.

3.3 Sites and Regions

SHP639-101 will be a multicenter study conducted in the United States. Approximately 7 sites will participate in the study.

4. STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent/assent before any procedures specified in the protocol are performed.

4.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below.

Subjects cannot be enrolled or randomized before all inclusion criteria (including test results) are confirmed.

1. Subjects must provide written, signed and dated informed consent to participate in the study in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guideline E6 and applicable regulations, before completing any study-related procedures.
2. Subjects must be aged from 18 through 90 at the time of consent. This inclusion criterion will only be assessed at the screening visit.
3. Subjects must have OHT or stable early POAG in both eyes with acceptable Humphrey visual fields (HVF). Early POAG for this protocol is defined as healthy appearing anterior chamber angles (Shaffer classification system grade 3 or 4) and focal and/or generalized thinning of the optic disc rim characteristic of glaucomatous disease. An acceptable HVF must have been performed within approximately one year of screening, have a false-positive rate of 25% maximum, false-negative rate of 25% maximum, and fixation loss rate of 33% maximum, and mean deviation of no worse than -6.00 dB.
4. On Day -1, subjects must have a mean IOP of ≥24 mmHg at 8:00 AM and a mean IOP of ≥22 mmHg at 10:00 AM in at least 1 eye, with an IOP difference of <4 mmHg between eyes at both of these time points. If only 1 eye meets this criterion, then it will be the designated study eye for pharmacodynamic analysis; this eye will also be used for dosing in Cohort A SDTP (designated study eye criteria are detailed in Section 3.1.1).
5. Subjects must have a best-corrected visual acuity (BCVA) in both eyes of 65 letters on the Early Treatment Diabetic Retinopathy Study chart (Snellen equivalent ~20/60) or better at the screening and baseline assessments.
6. Subjects must be males or females who are nonpregnant and nonlactating at screening (negative serum beta-human chorionic gonadotropin [β-hCG]); if sexually active during the study, they must agree to comply with the applicable contraceptive requirements (refer to Section 4.4) throughout the study period and for 60 days following the last dose of investigational product.
7. Subjects must have a satisfactory medical assessment with no clinically significant or relevant abnormalities as determined by medical history, physical examination, and clinical and laboratory evaluation (hematology, biochemistry, urinalysis) as assessed by the investigator.

8. Subject must understand and be able, willing, and likely to fully comply with study procedures and restrictions.
9. Subjects must be nonsmokers or have had stable use of tobacco or nicotine-containing products for a 3-month period before signing the informed consent form (ICF).
10. Subjects who drink alcohol must have had stable use of alcohol for a 3-month period before signing the ICF.

4.2 Exclusion Criteria

The subject will be excluded from the study if any of the following exclusion criteria are met:

1. Subject has an anatomically narrow angle, synechiae or evidence of prior inflammation, angle closure glaucoma, normal tension glaucoma, pseudoexfoliation syndrome or pigmentary dispersion syndrome with or without glaucoma, or secondary glaucoma.
2. Subject has corneal endothelial cell counts of less than 2000 cells/mm^2 (measured by noncontact specular microscopy) at the screening or baseline assessments.
3. Subject has central corneal thickness less than 500 µm or greater than 620 µm at the screening or baseline assessments.
4. Subject has IOP greater than 32 mmHg in either eye before randomization.
5. Subject has used topical ocular hypotensive medications as follows: prostaglandin analogs, β-adrenoceptor antagonists, α-adrenergic agonists, or epinephrine-related medications within 4 weeks before the first dose of investigational product; or pilocarpine or carbonic anhydrase inhibitors within 7 days before the first dose of investigational product.
6. Subject has a history of angle closure, ocular surgery, microinvasive glaucoma surgery device insertion, or laser surgery, except for the following procedures, which are allowed: uncomplicated cataract surgery, laser peripheral iridotomy with resultant angle of Shaffer grade 3 or 4, and postcataract neodymium-doped yttrium-aluminum-garnet (Nd:YAG) laser posterior capsulotomy. Cataract surgery and other procedures must have occurred a minimum of 3 months before randomization.
7. Subject has a history of significant ocular trauma or ocular disease including but not limited to moderate to severe dry eye disease that requires chronic treatment or punctal plugs.
8. Subject has evidence of ocular infection, inflammation, degeneration, or dystrophy at the screening or baseline assessments, including but not limited to moderate to severe blepharitis (mild blepharitis is allowed), conjunctivitis (allergic or infectious), corneal dystrophy (epithelial, stromal, or endothelial), corneal haze of grade 1 or greater based on the Hwang Grading Scale of Corneal Haze, corneal opacities, keratitis, uveitis, or vitritis.
9. Subject has retinal disease including but not limited to: moderate or severe nonproliferative diabetic retinopathy (NPDR) (early NPDR is allowed), proliferative diabetic retinopathy, intermediate or advanced dry age-related macular degeneration (AMD) (early dry AMD is allowed), all geographic atrophy, or all wet AMD.
10. Subject has any nonglaucomatous optic neuropathy or other significant nonglaucomatous ocular disease that is likely to affect visual function.

11. Subject has any corneal or ocular surface pathology in either eye that prevents proper IOP measurement, pachymetry, or other study data collection procedures.
12. Subject has had changes to their existing prescription medication regimen for chronic disease, including those medicines that affect IOP, within 14 days or 5 half-lives before screening, whichever is longer.
13. Subject has started any new prescription drug medication for chronic disease, including those medicines that affect IOP, within 14 days or 5 half-lives before screening, whichever is longer.
14. Subject has a history of corticosteroid use within 3 months before randomization, except for nonperiocular dermatologic use, which is allowed.
15. Subject has used belladonna alkaloids (scopolamine, hyoscyamine, atropine) within 7 days prior to randomization, cannabinoids or opioids within 28 days before randomization, or B-type natriuretic peptides within the past year before randomization; or a subject has an anticipated need for any of the aforementioned drugs/drug categories during the study.
16. Subject has used amantadine within 28 days before randomization.
17. Subject is unable to discontinue contact lens use during and for 60 minutes following instillation of study medication, during ophthalmologic examinations, and during study visits.
18. Subject has a current or relevant history of any physical, medical, mental, or psychiatric illness, disorder, or condition that may require treatment during the study and/or that may interfere with the subject complying with the study rules and procedures or completing the study.
19. Subject has any condition that presents undue risk from use of the investigational product, assessment tools, or procedures.
20. Subject is a woman who is pregnant (positive serum β-hCG pregnancy test at the time of screening), lactating, or less than 90 days post partum at randomization.
21. Subject has donated blood within 60 days before first dose of investigational product.
22. Subject has donated plasma within 28 days before first dose of investigational product.
23. Subject has used another investigational product within 30 days before the first dose of investigational product or is actively enrolled in a drug or vaccine clinical study.
24. Subject has a positive human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) antibodies screen.
25. Subject has a positive drugs of abuse screen or alcohol breathalyzer test.
26. Subject has been previously enrolled in this study.
27. Subject has known hypersensitivity or allergy to any of the ingredients of the investigational product.

28. Subject consumes more than 21 units of alcohol per week or is unable to refrain from alcohol consumption within 48 hours before a scheduled visit. (1 alcohol unit=1 beer or 1 wine [5 oz/150 mL] or 1 liquor [1.5 oz/40 mL] or 0.75 oz alcohol.)
29. Subject is unable to refrain from tobacco or any products containing nicotine within 8 hours before a scheduled visit.

4.3 Restrictions

1. Subjects should refrain from strenuous physical exercise from 48 hours before admission to the site and during the visit.
2. Subjects must refrain from alcohol from 48 hours before admission to the site and during the visit.
3. Subjects should refrain from foods or beverages containing caffeine/xanthine from 48 hours before admission to the site and during the visit.
4. During washout periods, subjects should attempt to limit the use of alcohol and tobacco or nicotine-containing products.
5. Subjects must avoid using tobacco and other nicotine-containing products (smoking, chewing, patch, etc.) from 8 hours before admission to the site and during the visit.
6. Subjects must adhere to the restrictions on use of artificial tears as detailed in Section 5.2.2.

4.4 Reproductive Potential

4.4.1 Female Contraception

Sexually active females of childbearing potential must use an acceptable form of contraception throughout the study period and for 60 days following the last dose of investigational product. If hormonal contraceptives are used, they should be administered according to the package insert. Females of childbearing potential who are not currently sexually active must agree to use acceptable contraception, as defined below, if they become sexually active during the period of the study and 60 days following the last dose of investigational product.

Female subjects should be one of the following:

- Postmenopausal (12 consecutive months of spontaneous amenorrhea and age ≥51 years)
- Surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy, or bilateral salpingectomy) and at least 6 weeks after sterilization, or
- A female of childbearing potential with a negative serum β-hCG pregnancy test at the screening visit and before randomization. Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception are:

- Intrauterine devices plus condoms
- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)
- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days before the first dose of investigational product, plus condoms. Note: If subject becomes sexually active during the study, they should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

4.4.2 Male Contraception

Male subjects will be required to use a condom in conjunction with spermicidal gel, foam, cream, film, or suppository from the time of first dosing until 60 days after the last dose of investigational product.

Childbearing female partners of male study participants will be required to follow the acceptable methods of contraception for this study (described in Section 4.4.1) from the time of first dosing until 60 days after the last dose of investigational product.

Male subjects must not donate sperm for 3 months after the last dose of investigational product.

4.5 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from investigational product with the medical monitor when possible.

If investigational product is discontinued, regardless of the reason, the early withdrawal evaluations listed in Table 1 are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified follow-up. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for termination and date of stopping investigational product must be recorded in the electronic case report form (eCRF) and source documents.

Randomized subjects who discontinue from the study may be replaced at the sponsor's discretion to ensure that at least 6 out 7 subjects complete a dosing regimen cohort. Replacement subjects will be assigned to the same treatment group as the subject they are replacing.

4.5.1 Subject Withdrawal Criteria

At any time in the study, subjects will be discontinued from the study if the IOP measurement in either eye reaches a reading greater than 36 mmHg or a reading less than 8 mmHg. If the subject falls outside the above measurements, rescue treatment will be started by the investigator as per the current standard of care.

If subjects experience corneal hazing of grade 3 or greater on the Hwang Grading Scale of Corneal Haze, they will be discontinued from the study and standard of care will be initiated.

The early termination evaluations listed in Table 1 are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified follow-up.

4.5.2 Reasons for Discontinuation

The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record and on the eCRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the eCRF.

Reasons for discontinuation include but are not limited to:

- Completed
- Adverse event
- Withdrawal by subject
- Noncompliance with investigational product
- Physician decision
- Study terminated by sponsor
- Lost to follow-up
- Pregnancy
- Protocol deviation
- Screen failure
- Other

4.5.3 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point before the last scheduled contact (office visit or telephone contact). At least one of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product.

4.5.4 Stopping Criteria for Dose Escalation

1. Progressing from a dosing regimen cohort to the next or from a study part to the next will not occur in the presence of moderate or severe drug-related ocular AEs in 2 or more SHP639-treated subjects in a given cohort.
2. If 1 or more subjects experience corneal hazing of grade 3 or greater on the Hwang Grading Scale of Corneal Haze, they will be discontinued from the study. At that time, the study will stop for further evaluation by the Shire's Dose Escalation Committee.

3. If 2 or more subjects in a given cohort receiving active drug have a severe AE in the same organ or body system, no further subjects will be enrolled or dosed until further evaluation of the available data is made by the medical monitor and investigator to determine whether to stop or proceed with the study. Following a safety review of the event, study enrollment or dosing of currently enrolled subjects may be restarted if the medical monitor and the investigator determine that it is safe to proceed with the study.
4. If any other drug-related event occurs in subjects receiving active drug and is deemed to pose an unacceptable risk to subjects by the investigator or medical monitor after further evaluation, no further subjects will be enrolled or dosed until further evaluation of the available data is made by the medical monitor and investigator to determine whether to stop or proceed with the study. Following a safety review of the event, study enrollment or dosing of currently enrolled subjects may be restarted if the medical monitor and the investigator determine that it is safe to proceed with the study.

5. PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Treatment

Prior treatment includes all treatments (including but not limited to prescription treatments, investigational products, vitamins, herbal treatments, and nondrug therapies) received within 30 days or 5 half-lives (whichever is longer) before the date of the first dose of investigational product and any procedures performed within the 5 years before the date of the first dose of investigational product. Prior treatment information must be recorded on the appropriate eCRF page.

5.2 Concomitant Treatment

Concomitant treatment refers to all treatment and ocular procedure received between the dates of the first dose of investigational product and the end of the follow-up period, inclusive. Concomitant treatment information must be recorded on the appropriate eCRF page.

5.2.1 Permitted Treatment

Subjects should refrain from taking any medications (excluding those medications listed below) during the course of the study, until after discharge from the site on Day 29 of the MDTP; refer to Section 5.2.2 for details. Any medication that is considered necessary for the subject's safety and well-being may be given at the discretion of the investigator. The administration of all medications (including investigational products) must be listed on the appropriate eCRF page.

The following medications are permitted during the study:

- A stable dose (defined as at least 4 weeks) of prescription medication for chronic use (with the exception of those medications listed in Section 5.2.2, Table 8), including but not limited to:
  - Hormonal contraceptives for females of childbearing potential administered according to the package insert (see Section 4.4.1)
  - Hormone replacement therapy
  - Antihypertensive medication if the subject is on a stable dose for at least 4 weeks
  - A stable dose (defined as at least 4 weeks) of medication that can substantially alter IOP (with the exception of those medications listed in Table 8)
- Occasional use of acetaminophen (paracetamol) and ibuprofen

Refer to Section 5.2.2 for information on use of artificial tears.

5.2.2 Prohibited Treatment

Table 8 details the washout period (relative to randomization) for common prior medications that are excluded for this study. Refer to Section 7.1.1.3 for details of the washout period for prohibited medications. Subjects must not take these medications until after discharge from the site on Day 29 of the MDTP, at which time they may resume taking their usual medication.

Table 8 Common Excluded Medications and Associated Washout Period

Medication	Minimum Time Before Randomization				
	7 days	14 days	28 days	3 months	1 year
Steroids (except for nonperiocular dermatologic use)				X	
Belladonna alkaloids (scopolamine, hyoscyamine, atropine)	X				
B-type natriuretic peptides (eg, nesiritide)					X
Prostaglandins			X		
β-adrenoceptor antagonists (eye drops)			X		
α-adrenergic agonists (eye drops)			X		
Epinephrine-related medications (eye drops)			X		
Carbonic anhydrase inhibitors (eye drops)	X				
Pilocarpine (all drops)	X				
Carbachol (eye drops)			X		
Echothiophate (eye drops)			X		
Glycerol	X				
Mannitol	X				
Theophylline		X			
Amantadine			X		

The use of all preserved artificial tears and any ocular gels and other lubricants is **prohibited** at all times during the study.

The use of **nonpreserved** artificial tears is **prohibited** during the following intervals, which include study visits:

- Cohort A, SDTP: Day -2 to Day 2, after final assessment
- Cohort A, MDTP: Day -2 to Day 29, after final assessment
- Cohorts B, C, and D: Day -2 to Day 29, after final assessment

The use of **nonpreserved** artificial tears is **allowed only during washout periods**, according to the schedule below.

- Cohort A, SDTP, Washout 1: Start of screening until the evening of Day -2, SDTP
- Cohort A, Washout 2: Day 2 after last assessment until the evening of Day -2, MDTP
- Cohorts B, C, and D, Washout 1: Start of screening until the evening of Day -2

Refer to Section 4.3 for restrictions on the use of alcohol, tobacco, caffeine, and xanthine.

Other medications not listed in Table 8 may be considered allowable; see Section 5.2.1 for further details.

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The test product is SHP639 ophthalmic solution, which will be provided as an ophthalmic solution packaged in 7.5 mL (filled to 5 mL) multiuse eye drop bottles. SHP639 ophthalmic solution is a sterile, colorless topical solution containing 0.1%, 0.3%, or 0.6% SRD006086 (as free-base equivalent). The SHP639 ophthalmic solution is preserved with benzalkonium chloride and will be supplied in a multiuse low-density polyethylene eye drop bottle. Additional information is provided in the current SHP639 IB.

The quantities of SHP639 drug substance per drop of SHP639 ophthalmic solution are shown in Table 9.

Table 9 SHP639 Drug Substance per Drop of SHP639 Ophthalmic Solution

Topical Concentration (% weight/volume)	Quantity of SH639 Drug Substance per Drop (µg)
0.1	35
0.3	104
0.6	208

Quantities of drug substance per drop were calculated using a drop volume of 34.7 µL, which was the mean volume obtained at various temperatures, bottle orientations, and concentrations. Values have been rounded to the nearest microgram.

The reference product is placebo, which will be provided as an ophthalmic solution packaged in 7.5 mL (filled to 5 mL) multiuse eye drop bottles identical to those used for the SHP639 ophthalmic solution. The placebo solution will contain the same excipients as the SHP639 ophthalmic solution but will not contain SHP639.

6.1.1 Masking the Treatment Assignment

This is a double-masked, placebo-controlled study. The packaging, appearance, and labeling of the investigational products will match.

6.2 Administration of Investigational Products

6.2.1 Interactive Response Technology for Investigational Product Management

The actual treatment given to individual subjects is determined by a randomization schedule. The associated treatment assignments giving details of individual subject treatment are in the form of a randomization schedule created by the interactive response technology (IRT) vendor.

Each bottle/carton of SHP639 ophthalmic solution or matching placebo will be assigned a unique packaging identification number corresponding to the investigational product allocated to the subject, once eligibility has been determined. When a bottle/carton of SHP639 ophthalmic solution or matching placebo is assigned to a subject, the packaging identification number will be recorded in the eCRF and in the drug accountability records. Once assigned, it is important that the bottle/carton remains with the same subject throughout the study.

6.2.2 Allocation of Subjects to Treatment

This is a double-masked, placebo-controlled study.

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation. This will be a 4-digit number starting at 0001.

For screen failures, the screening number will be the identifying number used throughout the eCRF.

The actual treatment given to individual subjects is determined by a randomization schedule.

The randomization number represents a unique number corresponding to investigational product allocated to the subject and will be allocated before dosing after eligibility has been determined.

A randomization number is allocated before dosing once eligibility has been determined. Once a randomization number has been assigned, that number must not be used again, if for example, a subject is withdrawn from the study. If a randomization number is allocated incorrectly, the study monitor must be notified as soon as the error is discovered.

Replacement subjects are to be assigned the same treatment as subjects they are replacing.

Individual subject treatment is automatically assigned by the IRT.

Investigational product packaging identification numbers, separate from randomization numbers/unique identifiers, may also be assigned to subjects for specific treatment assignment as dictated by the study. In these cases, the same investigational product packing identification number may not be assigned to more than 1 subject.

6.2.3 Dosing

6.2.3.1 Dosing Procedures

After satisfying all screening and entry criteria for the study before dosing on Day 1 of each cohort, subjects will be randomized to receive either SHP639 ophthalmic solution or placebo, respectively. Investigational product (SHP639 ophthalmic solution or placebo) will be administered topically in 1 designated eye (Cohort A, SDTP only) or in both eyes (Cohort A, MDTP only, and Cohorts B, C, and D) at the time points specified in Table 1.

Subjects will receive their assigned dose as dispensed by the pharmacist or designee at each site. Investigational product will be administered by the principal ophthalmologist or trained designee at each site while subjects are on site, and will then be self-administered by each subject for the remainder of the treatment period.

Subjects should receive the single dose or first dose if multiple daily dosing (depending on cohort assignment) each day between 7:00am and 9:00am. This is particularly important for cohorts C and D as these subjects will receive 3 and 4 doses daily.

In Cohort A only, there will be a SDTP and an MDTP. The 2 treatment periods will be separated by a washout period of 3-14 days. In Cohort A, single-dose administration of the corresponding dose level (concentration) will occur first, followed by the multiple-dose administration of the same dose level (concentration) QD. The dosing regimens for Cohorts B, C, and D will consist of multiple-dose administration of the appropriate dose level concentration BID, TID, or QID, respectively. For all cohorts, the final dose during the MDTP will be administered on the morning of Day 28.

In Cohort A only, as a safety measure, the first 3 subjects in the SDTP will be dosed with a minimum of 1-hour intervals between subjects. Subjects will then be observed overnight and until the next day (24 hours after dosing) with an ophthalmologist on call. If no AEs occur that are consistent with the predefined stopping criteria, dosing the rest of the cohort (Cohort A, single dose) will proceed as previously outlined. Designated study eye criteria are detailed in Section 3.1.1.

6.2.3.2 Dose Escalation

Throughout the study, dose escalation meetings will commence at regular time points to review safety data and authorize progression into the next cohort. The anticipated dose escalation scheme is presented in Table 10.

- Single-dose cohorts: a dose escalation meeting may convene after a minimum of 6 subjects have completed the 24-hour assessments for the SDTP. At the dose escalation meeting, a preselected Dose Escalation Committee will determine whether it is safe to continue to the anticipated cohort at either the next dose level or the next dosing regimen.
- Multiple-dose cohorts: a dose escalation meeting may convene after a minimum of 6 subjects have completed the Day 14 assessments for the MDTP. At the dose escalation meeting, a preselected Dose Escalation Committee will determine whether it is safe to continue to the anticipated cohort at either the next dose level or the next dosing regimen. If the dose escalation meeting was held prior to the completion of the cohort, the remainder of the treatment period will be completed following the dose escalation meeting.

Table 10 Anticipated Dose-escalation Scheme

Dose Authorized by Committee			Enabling Required Dose-escalation Activity					
			Before Switch from Single to Multiple Dose - BID, TID, or QID			Before Increasing Dose Level		
Cohort	**Dose**	**Regimen**	**Cohort**	**Dose**	**Regimen**	**Cohort**	**Dose**	**Regimen**
A1	**0.1%**/Placebo	SD	NA	–	–	NA	–	–
A1	**0.1%**/Placebo	QD	A1	**0.1%**/Placebo	SD	NA	–	–
A2	**0.3%**/Placebo	SD	NA	–	–	A1	**0.1%**/Placebo	SD
A2	**0.3%**/Placebo	QD	A2	**0.3%**/Placebo	SD	A1	**0.1%**/Placebo	QD
A3	**0.6%**/Placebo	SD	NA	–	–	A2	**0.3%**/Placebo	SD
A3	**0.6%**/Placebo	QD	A3	**0.6%**/Placebo	SD	A2	**0.3%**/Placebo	QD
B1	**0.1%**/Placebo	BID	A1	**0.1%**/Placebo	QD	NA	/–	–
B2	**0.3%**/Placebo	BID	A2	**0.3%**/Placebo	QD	B1	**0.1%**/Placebo	BID
B3	**0.6%**/Placebo	BID	A3	**0.6%**/Placebo	QD	B2	**0.3%**/Placebo	BID
C1	**0.1%**/Placebo	TID	B1	**0.1%**/Placebo	BID	NA	/–	–
C2	**0.3%**/Placebo	TID	B2	**0.3%**/Placebo	BID	C1	**0.1%**/Placebo	TID
C3	**0.6%**/Placebo	TID	B3	**0.6%**/Placebo	BID	C2	**0.3%**/Placebo	TID
D1[a]	**0.1%**/Placebo	QID	C1	**0.1%**/Placebo	TID	NA	–/	–
D2	**0.3%**/Placebo	QID	C2	**0.3%**/Placebo	TID	D1	**0.1%**/Placebo	QID
D3	**0.6%**/Placebo	QID	C3	**0.6%**/Placebo	TID	D2	**0.3%**/Placebo	QID

BID=twice daily; NA= not applicable; QD=once daily; QID=4 times daily; SD=single dose; TID=3 times daily.

[a] Cohort D1 is not to be enrolled as it was decided that the resulting data would not contribute to the understanding of the safety of SHP639.

Shire's Dose Escalation Committee will consist of, at a minimum, the coordinating principal ophthalmologist, the Shire medical monitor, and the Shire ophthalmic study physician. Additional team members may be included as needed.

At any time during the course of the study, subjects will be discontinued from the study if their IOP measurement reaches a reading of greater than 36 mmHg or a reading of less than 8 mmHg. Additionally, if subjects experience corneal hazing of grade 3 or greater on the Hwang Grading Scale of Corneal Haze, then they will be discontinued from the study. Should an event occur that requires a subject's discontinuation from the study, the study will be halted for further evaluation by Shire's Dose Escalation Committee.

The Dose Escalation Committee may authorize progression from 1 cohort to the next after the completion of the previous treatment regimen cohort and completion of the previous dose level cohort, as appropriate. Additionally, more than 1 cohort of safety data may be reviewed at a dose escalation meeting depending on scheduling and study progress. A minimum of 6 subjects should have completed the previous cohort(s) without clinically significant adverse changes; this includes findings on the ophthalmologic examination. Additionally, progression will not occur in the presence of moderate or severe drug-related ocular AEs in 2 or more subjects.

If, in the judgment of the coordinating principal ophthalmologist, the Shire medical monitor, and the Shire ophthalmic study physician, it is unclear whether there is a potential safety concern or whether dose escalation should occur, a dose level may be reduced, modified, or repeated depending on the outcome of the safety data review between doses or treatments. Further, based on the findings from the dose escalation review meetings, a cohort (or cohorts) may be determined to not be necessary to determine the safety of SHP639. Finally, upon completion of all dose cohorts, additional doses may be studied based on emergent safety, PD, and PK data following the necessary protocol amendment and Institutional Review Board (IRB) reviews.

6.2.4 Unmasking the Treatment Assignment

The treatment assignment code must not be broken during the study except in emergency situations where the identification of the investigational product is required for further treatment of the subject. The investigator should contact the medical monitor as soon as possible after the investigator has been unmasked.

In the event that the treatment assignment code is broken and the date and signature of the person who broke the code are recorded in the IRT and the source documents. The reason for breaking the code will be captured in the clinical database. Upon breaking the code, the subject is withdrawn from the study but should be followed up for safety purposes. Any code breaks that occur must be reported to the contract research organization (CRO) and sponsor. Code-break information is held by the pharmacist/designated person at the site.

6.3 Labeling, Packaging, Storage, and Handling

SHP639 ophthalmic solution will be supplied in a multiuse low-density polyethylene eye drop bottle containing 5 mL of ophthalmic solution. Each labeled bottle will be placed into a single labeled carton. Bottles must be stored at refrigerated temperatures (2-8°C) at all times.

6.3.1 Labeling

Labels containing study information and pack identification are applied to the investigational product(s) container.

All investigational product is labeled with a minimum of the following: protocol number, medication identification number, dose form, directions for use, storage conditions, expiry date (if applicable), batch number and/or packaging reference number, the statements, "For clinical trial use only" and/or "CAUTION: New Drug – Limited by Federal (or US) Law to Investigational Use," and the sponsor's name and address. Any additional labeling requirements for participating countries and/or controlled substances will also be included on the label, if necessary.

Additional labels (eg, those used when dispensing marketed product) may, on a case-by-case basis, be applied to the investigational product in order to satisfy local or institutional requirements, but must not:

- Contradict the clinical study label
- Obscure the clinical study label
- Identify the study subject by name

Additional labels may not be added without the sponsor's prior full agreement.

6.3.2 Packaging

Investigational product is packaged in the following labeled containers:

The investigational product bottles will be labeled and then each bottle will be placed into an individual labeled carton. This carton will then be secured with a tamper-evident seal.

Changes to sponsor-supplied packaging before dosing may not occur without full agreement in advance by the sponsor.

6.3.3 Storage

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Investigational products are distributed by the pharmacy or nominated member of the study team (eg, site pharmacist or principal ophthalmologist).

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

Such a device (ie, certified minimum/maximum thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

6.3.4 Special Handling

Not applicable.

6.4 Drug Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed-upon number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content, and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for administering/dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will administer and dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment with instructions as how to administer and store the product. All administered and dispensed medication will be documented in the eCRFs and/or other investigational product record. The investigator is responsible for assuring the retrieval of all study supplies from subjects. Due to the health/safety concerns with returning the investigational product container, the investigator must request that subjects keep the empty investigational product packaging after use and return it to the site for drug accountability purposes.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records provided the masking of the study is not compromised.

With the written agreement of the sponsor, at the end of the study, all used and unused stock are to be sent to a nominated contractor on behalf of the sponsor. In this case, destruction records identifying what was destroyed, when and how, must be obtained with copies provided to the sponsor. Destruction of investigational products must be in accordance with local, state, and national laws. Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

6.5 Subject Compliance

Compliance must be assessed by observation of dosing by the investigator or designee during site visits. In addition, the site personnel should witness the ophthalmic drop administration by the subject during these visits to ensure proper technique of drop administration. The investigator/nominated person will record details on the drug accountability log(s) and/or source documents. In addition, in-clinic dosing details (time, date, dose level, dosing regimen) will be captured on the appropriate eCRF page.

Subjects must be instructed to bring their unused investigational product and empty/used investigational product packaging to every visit. Drug accountability must be assessed at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (eg, bottles, trays, vials) or at the individual count level for opened containers/packaging. The pharmacist/nominated person will record details on the drug accountability form.

6.6 Retention of Bioavailability and Bioequivalence Testing Samples

Not applicable.

7. STUDY PROCEDURES

7.1 Study Schedule

See Table 1 for the visits at which each assessment and procedure will be performed. See Table 2, Table 3, Table 4, and Table 5 for the time points at which assessments and procedures will be performed for Cohorts A, B, C, and D, respectively.

Visit windows for the MDTP are as follows:

- Start of screening: For all subjects, the maximum duration of the screening period is 42 days.
- Days 7, 14, and 21: ±2 days
- Follow-up telephone call: 7±2 days after the final dose administration
- Day 88 follow-up visit: ±4 days

The following is a suggested "priority order" when more than 1 procedure or assessment is required at a particular time point. The actual order of procedures will be dictated by the clinical setting. Departure from the priority order below will not be considered a protocol deviation.

- Spontaneous or solicited AE reporting
- Vital signs
- Electrocardiogram (ECG)
- Physical examination
- Clinical laboratory tests
- Dosing
- Drop comfort assessment (must not be performed within 30 minutes after instillation of topical anesthetic)
- Ophthalmologic examination
- Intraocular pressure measurement
- Pharmacokinetic blood sampling

NOTE: Blood sampling for PK evaluation must be performed at the precise protocol-scheduled time. Actual sampling time(s) must be accurately recorded in the source document and on the appropriate eCRF page.

7.1.1 Screening Period

For all subjects, the maximum duration of the screening period is 42 days. All screening assessments and procedures are to be performed by the principal ophthalmologist or a qualified designee. See Table 1 for details of the screening procedures to be performed.

Written, signed, and dated informed consent before the performance of any study-related procedures must be obtained by the principal ophthalmologist or a designee. A copy of the signed ICF must be given to the subject for their records.

7.1.1.1 Screening Failure

A screen failure is a subject who has given informed consent and failed to meet the inclusion and/or met at least one of the exclusion criteria and has not been enrolled/randomized or administered investigational product.

For the purposes of data collection, subjects who give consent to the study but are not enrolled and/or randomized will be reported with a study discontinuation reason of "sponsor decision" in the eCRF if they were otherwise fully eligible for the study (for example, alternates/reserve subjects).

7.1.1.2 Rescreening of Subjects

Subjects who fail to meet all inclusion/exclusion criteria will not be permitted to be rescreened for the study at any point. Any subject who is qualified but not dosed (ie, an alternate subject) may be rescreened at a later date for the study.

Eligible subjects who meet all inclusion/exclusion criteria but are unable to participate in the study due to scheduling conflicts/timing may be rescreened based on investigator discretion and sponsor approval should their availability to participate fall outside the screening window. In these cases, a new screening number must be assigned for each subject who is rescreened and a new ICF must be signed.

7.1.1.3 Washout Period 1

A washout period (Washout 1) of up to 28 days is required for certain predefined prescription medication as detailed in Section 5.2.2, Table 8. The washout will take place during the screening period and may start from Day -28 onwards depending on the length of washout required. Subjects will continue not to take prohibited medications until discharge from the site on Day 29 of the MDTP.

A midwashout ophthalmic assessment (MWOA) will be performed on both eyes 14±2 days after a subject either starts the washout period or undergoes a previous MWOA. Ophthalmic and safety assessments will be performed during the MWOA at the visits specified in Table 1**;** the time points during each visit are specified in Table 2, Table 3, Table 4, and Table 5 for Cohorts A, B, C, and D, respectively.

7.1.2 Treatment Period

Investigational product will be administered by study staff when subjects are present at the site during study visits.

7.1.2.1 Day -2 Through Day 2, Single-dose Treatment Period (Cohort A Only)

Following screening and Washout 1, eligible subjects in Cohort A will be admitted to the site for the SDTP, either on Day -3 (optional early check-in to unit if more convenient for the subject) or

on the morning of Day -2. Subjects will undergo baseline assessments on Day -2 and Day -1 as specified in Table 1.

On Day 1 of the SDTP, before dosing, subjects who continue to be eligible will be randomized to SHP639 ophthalmic solution or placebo, as described in Section 6.2.2. In each treatment period, subjects will receive a single dose of investigational product in 1 eye, according to the treatment to which they are assigned.

On Day 1 of the SDTP, subjects will undergo assessments and procedures as specified by visit in Table 1 and by time point during each visit in Table 2.

Subjects will be discharged from the site on Day 2 after completion of the evening assessments. After subject checkout on Day 2 of the SDTP, subjects will have a washout period (Washout 2) of 3-14 days and then return for the MDTP.

7.1.2.2 Day -2 Through Day 29, Multiple-dose Treatment Period (All Cohorts)

Subjects will attend the site daily on Day -2 and Day -1 for MDTP baseline procedures, as specified in Table 1.

Time points of ophthalmic assessments performed on Day -2 and Day -1 should be carried forward to assessments on Day 1. This ensures that the baseline IOP time points established before dosing begins are time-matched to the IOP assessments performed during dosing days for the duration of the study.

On the morning of Day 1 of the MDTP, subjects will be admitted to the site. Before dosing, subjects in Cohorts B, C, and D who continue to be eligible will be randomized to SHP639 ophthalmic solution or placebo, as described in Section 6.2.2. Subjects will receive doses of investigational product according to the treatment to which they are assigned. (Subjects in Cohort A will continue to receive SHP639 ophthalmic solution or placebo according to the treatment assigned on Day 1 of the SDTP.) All subjects in the MDTP cohorts will receive investigational product in both eyes.

On Day 1 of the MDTP, subjects will receive dose(s) during the day depending on their cohort assignment (Cohort A, B, C, or D). They will undergo assessments and procedures as specified by visit in Table 1 and by time point during each visit in Table 2, Table 3, Table 4, and Table 5 for Cohorts A, B, C, and D, respectively.

Subjects will be discharged on Day 2 following study procedures and the dispensing of SHP639 ophthalmic solution for subject use on an outpatient basis. Subjects will be trained on SHP639 ophthalmic solution administration and will be provided with diaries to record dosing times.

On Days 3-26, subjects will be responsible for their outpatient dosing and for recording dosing in their diaries.

On each of Days 7, 14, and 21, subjects will attend the site for assessments and procedures as specified by visit in Table 1 and by time point during each visit in Table 2, Table 3, Table 4, and Table 5 for Cohorts A, B, C, and D, respectively.

Subjects will be readmitted to the site on the evening of Day 26. Subjects will continue to receive their assigned doses, with the final dose being administered on the morning of Day 28. Subjects will undergo assessments and procedures as specified by visit in Table 1 and by time point during each visit in Table 2, Table 3, Table 4, and Table 5, for Cohorts A, B, C, and D, respectively. They will be discharged from the site after completion of the morning assessments on Day 29.

Subjects who are prematurely discontinued from the study will complete the Day 29 assessments as fully as possible.

7.1.3 Follow-up

A follow-up telephone call will take place 7±2 days after the final dose (Day 28 of the MDTP). Site staff will query subjects for serious AEs (SAEs), AEs, and concomitant treatments. In the event that a subject is prematurely discontinued from the study, every attempt should be made to complete the follow-up assessments.

On Day 88±4 days, subjects will attend the site for ADA blood sample collection. Site staff will query subjects for serious AEs (SAEs), and AEs. Adverse events that occur from Day 33 to Day 88 should be captured on the AE eCRF page. Concomitant medications during this period will also be captured. All AEs and SAEs that are not resolved at the time of this contact will be followed for an additional 30 days (see Section 8.1).

7.1.4 Additional Care of Subjects after the Study

No aftercare is planned for this study.

7.2 Study Evaluations and Procedures

7.2.1 Demographic and Other Baseline Characteristics

7.2.2 Safety

The name and address of each third-party vendor (eg, clinical laboratory) used in this study will be maintained in the investigator's and sponsor's files.

Actual safety assessment times will be monitored and recorded. The sponsor's expectation is that the investigator will ensure that every effort is made to perform all assessments at the precise protocol-scheduled time. Any safety assessment that deviates from the scheduled assessment time set forth in the protocol by more than ±15 minutes will be considered a protocol deviation.

Ophthalmic assessments are considered safety assessments. If an ophthalmic assessment deviates from the scheduled assessment time set forth in the protocol by more than ±15 minutes (or 5 minutes for the 15-minute and 30-minute time points), it will be considered a protocol deviation.

All AEs, prior medication use, and concomitant medication use will be assessed and monitored from the time the subject signs the ICF to completion of the study (including to time of screen failure or drop out/discontinuation); see Sections 7.2.2.4 and 8.1 for further details. The AEs will include nontreatment-emergent AEs (ie, those occurring from the time of informed consent

signature to the first dose of investigational product) and treatment-emergent AEs (ie, AEs occurring after the first dose). While housed at the site, subject safety will also be closely monitored through study procedures and physician oversight.

7.2.2.1 Medical and Medication History

A complete medical and medication history, as well as demographic information, will be collected at the screening visit by a qualified licensed physician, physician's assistant, or a nurse practitioner. The medical history will be reviewed and recorded, including:

- Date of birth
- Sex
- Race and ethnicity
- Recent ingestion of medication (Section 5.1)
- History of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric, and other diseases

7.2.2.2 Physical Examination (Including Height and Weight)

A complete physical examination will be performed at the visits specified in Table 1 by a qualified licensed physician, physician's assistant, or nurse practitioner.

The physical examination will include a review of the following body systems:

- General appearance
- Skin
- Head, eyes, ears, nose, and throat
- Spine/neck/thyroid
- Musculoskeletal
- Respiratory
- Cardiovascular
- Neurological
- Abdomen (including liver and kidneys)

Abnormalities identified at the screening visit will be documented in the subject's source documents and on the medical history eCRF page. Clinically significant changes after the screening visit will be captured as AEs on the AE eCRF page, as deemed by the investigator.

Height and weight will be recorded at screening only.

7.2.2.3 Ophthalmologic Examination

Ophthalmologic examinations of both eyes will be performed at the visits specified in Table 1; the time points during each visit are specified in Table 2, Table 3, Table 4, and Table 5 for Cohorts A, B, C, and D, respectively. Both eyes will be assessed at each examination unless otherwise specified.

Manifest Refraction

Manifest refraction will be determined at the following visits in order to assess BCVA:

- Screening
- SDTP (Cohort A only): Day -2
- MDTP (all cohorts): Day -2 and Day 29

The manifest refraction will be repeated if the BCVA has decreased by 10 or more letters. Full instructions for performing the manifest refraction are included in the ophthalmology procedures manual.

Best-Corrected Visual Acuity

Using the manifest refraction, the BCVA will be assessed at distance before slit lamp examination at the following visits:

- Screening
- Midwashout assessment
- SDTP (Cohort A only): Days -2 and -1 and Days 1 and 2
- MDTP (all cohorts): Days -2 and -1 and Days 1, 2, 7, 14, 21, 27, 28, and 29

See Table 2, Table 3, Table 4, and Table 5 for detailed timings by cohort.

Full instructions for measuring BCVA are provided in the ophthalmology procedures manual.

A decrease in BCVA by 6 or more letters may be considered clinically significant (CS) or not clinically significant (NCS) and requires a dilated posterior segment examination. A 10-letter loss in BCVA is considered CS and requires a repeat manifest refraction and dilated posterior segment examination. Clinically significant changes should be recorded as AEs in the source document and eCRF.

Slit Lamp Biomicroscopy

Slit lamp biomicroscopy will be performed at the following visits:

- Screening
- Midwashout assessment

- SDTP (Cohort A only): Days -2 and -1 and Days 1 and 2
- MDTP (all cohorts): Days -2 and -1 and Days 1, 2, 7, 14, 21, 27, 28, and 29

See Table 2, Table 3, Table 4, and Table 5 for detailed timings by cohort.

The anterior segment will be examined through the slit lamp before performing IOP measurements, pachymetry, or graded assessments. The following structures will be evaluated as normal or abnormal. If abnormal, the findings should be described and recorded as either CS or NCS. Any CS findings should be recorded as AEs; the investigator may use his/her discretion to determine whether a finding considered NCS is reported as an AE. Findings and assessment of clinical significance should be recorded in the source documents and eCRF.

The following will be examined at each visit:

- Lids/lashes/lacrimal
- Conjunctiva
- Cornea
- Anterior chamber
- Iris
- Lens

Anterior Segment Graded Assessments

Anterior segment graded assessments will be performed at the following visits:

- Screening
- Midwashout assessment
- SDTP (Cohort A only): Days -2 and -1 and Days 1 and 2
- MDTP (all cohorts): Days -2 and -1 and Days 1, 2, 7, 14, 21, 27, 28, and 29

See Table 2, Table 3, Table 4, and Table 5 for detailed timings by cohort.

Anterior segment graded assessments should be performed during the slit lamp examination but before IOP measurement. The following assessments will be performed:

- Conjunctival redness score assessment
- Corneal haze assessment
- Corneal epithelial integrity assessment by fluorescein staining
- Anterior chamber cell and flare
- Lens opacification (performed during dilated examination only)

The procedures are outlined in Appendix 2; full instructions are provided in the ophthalmology procedures manual.

Any abnormal findings should be described and recorded as either CS or NCS. Any CS findings should be recorded as AEs; the investigator may use his/her discretion to determine whether a finding considered NCS is reported as an AE. Findings and assessment of clinical significance should be recorded in the source document and eCRF.

Intraocular Pressure

Intraocular pressure will be measured at the following visits:

- Screening
- Midwashout assessment
- SDTP (Cohort A only): Days -2 and -1, Days 1 and 2
- MDTP (all cohorts): Days -2 and -1 and Days 1, 2, 7, 14, 21, 27, 28, and 29

See Table 2, Table 3, Table 4, and Table 5 for detailed timings by cohort.

Predose morning IOP assessments must be completed at least 30 minutes before dosing to allow the anesthetic to wear off.

Intraocular pressure will be measured at the slit lamp using Goldmann applanation tonometry. The procedure for measuring IOP is outlined in the ophthalmology procedures manual. Special care must be taken to avoid placing pressure on the globe with the fingers when moving the eyelids to fully expose the cornea.

Intraocular pressure must be measured after assessing the corneal epithelium for fluorescein staining and before pachymetry, gonioscopy, or dilation for posterior segment examination (if being performed).

Two consecutive IOP measurements, to the nearest mmHg, will be made in the designated study eye (designated study eye criteria are detailed in Section 3.1.1); if the 2 measurements differ by more than 2 mmHg, then a third measurement will be performed. All (2 or 3) readings will be used to determine the mean IOP at the given time point. The procedure will be repeated in the nonstudy eye. All measurements will be recorded in the source document and eCRF.

Every effort should be made to obtain an accurate IOP measurement. If the mires are irregular and/or an IOP reading is not obtainable, this should be noted in the source document and eCRF.

Posterior Segment Examination

The posterior segment will be visualized by a fundus examination at the following visits:

- Screening – dilated
- SDTP– nondilated Day -2

- MDTP– nondilated Day -2
- Day 29 – dilated

A dilated posterior segment examination of both eyes should also be performed if the BCVA in either eye decreases by 6 or more letters.

The following structures will be assessed (suggested technique):

- Vitreous (binocular indirect examination)
- Optic nerve head (slit lamp biomicroscopy)
- Cup-to-disc ratio (slit lamp biomicroscopy)
- Macula (slit lamp biomicroscopy)
- Retina vasculature
- Retina, outside of arcades, including periphery
- Choroid

Observations will be described and/or will be graded as normal or abnormal. Abnormal findings will be described. Clinically significant abnormalities will be recorded as AEs; NCS findings will be recorded as AEs at the investigator's discretion. Further details will be specified in the ophthalmology procedures manual.

Gonioscopy

Gonioscopy to assess the iridocorneal angles will be performed at screening and on Day 29. Gonioscopy should be performed after the corneal epithelium has been evaluated for defects with fluorescein and after IOP has been measured but before dilated posterior segment examination (Day 29). The angle of each eye should be graded in all 4 quadrants using the Shaffer grading system.

Noncontact Specular Microscopy

Noncontact specular microscopy will be performed to assess endothelial cell count at the following visits:

- Screening
- SDTP (Cohort A only): Day -1 and Day 2
- MDTP (all cohorts): Day -1 and Days 14 and 29

Details of the procedure will be found in the ophthalmology procedures manual.

Corneal Pachymetry

Corneal pachymetry to assess central corneal thickness will be performed after the predose examination and at 1, 2, 4, and 12 hours after dosing. With the pachymeter set to perform a single measurement, take and record 3 consecutive measurements at each applicable time point at the following visits:

- Screening
- SDTP (Cohort A only): Day -1 and Days 1 and 2
- MDTP (all cohorts): Day -1 and Days 1, 2, 7, 14, and 29

If the range of the measurements is 15 microns or less, the set of readings is acceptable; if not, discard all measurements and repeat until an acceptable set of 3 measurements is obtained. Record all 3 measures in the source document and the eCRF.

See Table 2, Table 3, Table 4, and Table 5 for detailed timings by cohort.

Full details of the procedure are provided in the ophthalmology procedures manual.

Drop Comfort Assessment

Drop comfort assessment should be performed immediately after instillation of investigational product and before IOP assessment (which requires topical anesthetic).

Drop comfort assessments will be performed for the first dose of the day as follows:

- SDTP (Cohort A only): Day 1
- MDTP (all cohorts): Days 1, 7, 14, 21, 27, and 28

Drop comfort assessment will not be captured in the subject's daily journal.

The drop comfort assessment will be performed for each eye except for Cohort A during the SDTP, when only the study eye will be assessed. The assessment will be performed immediately and 1, 2, and 3 minutes after instillation of the investigational product. The subject will be asked to rate drop comfort on a scale of 0-10, where 0=very comfortable and 10=very uncomfortable.

If the score is not ≤3 at minute 3, the drop comfort assessment should be repeated at 5, 10, and 15 minutes after dosing until the score is ≤3. If the score is >3 at 15 minutes after dosing, it should be recorded as an AE.

7.2.2.4 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, “Have you had any health problems since your last visit?”). Adverse events are collected from the time informed consent is signed until Day 88/FU (refer to Section 8). Adverse events that occur after Day 33 to Day 88/FU should be captured on the AE eCRF page.

7.2.2.5 Vital Signs

Blood Pressure and Pulse Rate

Blood pressure and pulse rate will be measured at the visits specified in Table 1**;** the time points during each visit are specified in Table 2, Table 3, Table 4, and Table 5 for Cohorts A, B, C, and D, respectively. Additional blood pressure and pulse rate measurements may be performed, as determined by the investigator, in order to ensure appropriate monitoring of subject safety and accurate recording of vital sign measurements. Any changes from baseline that are deemed clinically significant by the investigator are to be recorded as an AE.

The same method for obtaining blood pressure measurement (auscultatory or oscillometric) should be used throughout the study for all subjects (and documented). In addition, the conditions of vital sign measurements should be controlled and as consistent as possible during the study, in order to minimize external variability of the readings. It is advised that measurements be collected at a comfortable room temperature with little to no background noise, using the same (appropriately sized) cuff placed at the same location of the same arm during the study. The bladder deflation rate should be deflated (calibrated for oscillometric method or manually by auscultatory method) at a rate of 2-3 mmHg/s (and the first and last audible sounds recorded as systolic and diastolic pressure) after at least 5 minutes of rest in the assumed position.

The cuff should have a bladder length that is 80% and a width that is at least 40% of arm circumference (a length-to-width ratio of 2:1).

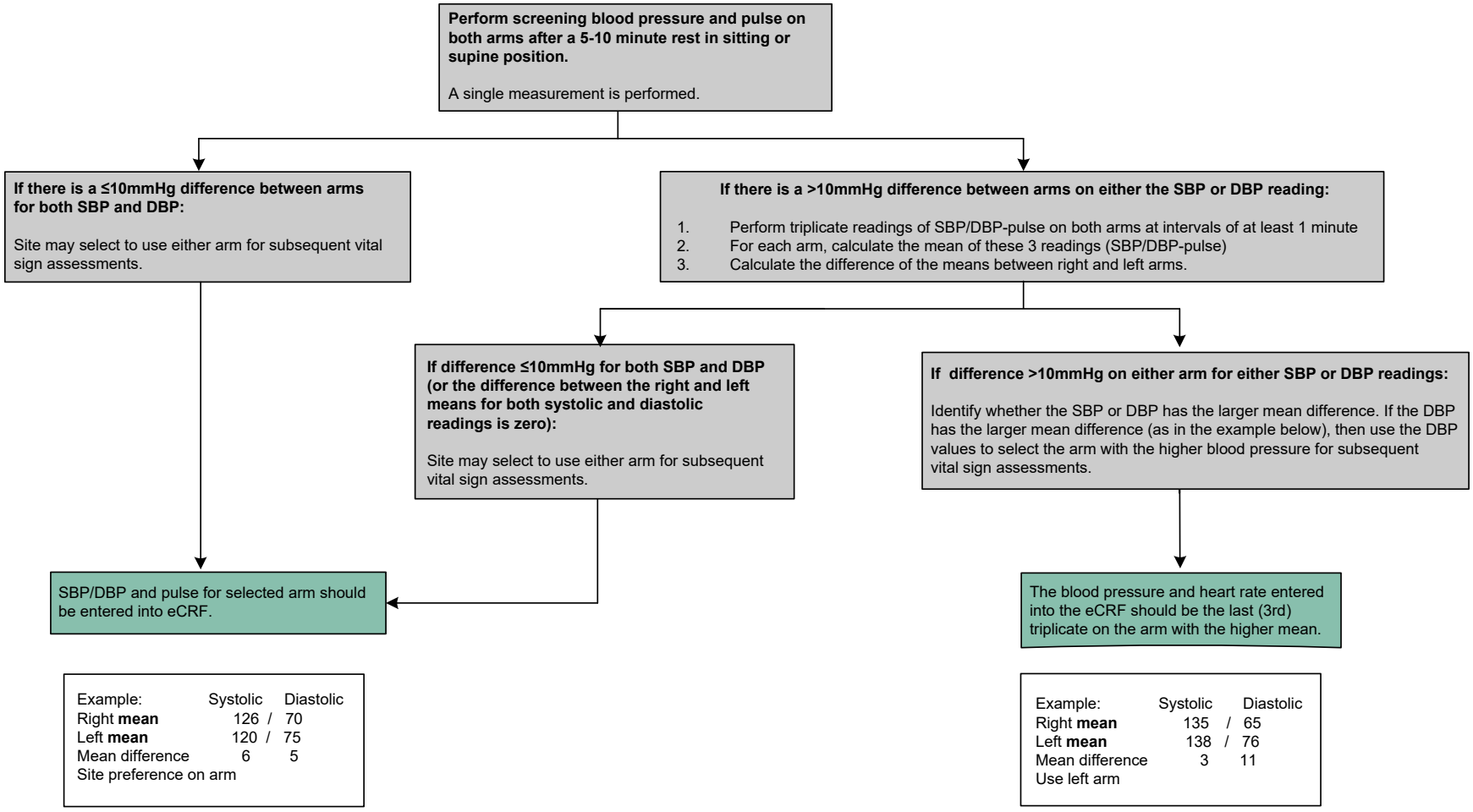
The subject should be asked to remove all clothing that covers the location of cuff placement. The subject should be instructed to relax as much as possible for at least 5 minutes before collection. The subject should remain quiet during this time and through the measurement.

The subject should be comfortably seated, with the legs uncrossed, with feet flat on the floor, and the back and arm supported, such that the middle of the cuff on the upper arm is at the level of the right atrium (the midpoint of the sternum).

At the screening visit, blood pressure should be compared between both arms. When there is a consistent interarm difference confirmed over 3 consecutive measurements (>10 mmHg), the arm with the higher blood pressure should be used for inclusion at screening and the last measurement recorded in the eCRF. The same (right or left) arm with the higher blood pressure will be used throughout the study.

For details on blood pressure and pulse procedures, see Figure 1.

Figure 1 Procedures for Screening Vital Signs (Blood Pressure – Pulse)



DBP=diastolic blood pressure; eCRF=electronic case report form; SBP=systolic blood pressure

One reading (seated systolic blood pressure/diastolic blood pressure and pulse rate) should be taken.

The use of automated devices for measuring pulse rate is acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, blood pressure and pulse rate should be obtained before the nominal time of the blood collection.

Body Temperature

Body temperature will be measured at the visits specified in Table 1**;** the time points during each visit are specified in Table 2, Table 3, Table 4, and Table 5 for Cohorts A, B, C, and D, respectively.

Oral temperature should be taken by placing a digital thermometer under the tongue for at least 30 seconds. Tympanic temperature may also be used.

7.2.2.6 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the laboratory's normal procedures. Reference ranges are to be supplied by the laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved. Any laboratory results that are determined to be clinically significant or indicative of an AE, as determined by the investigator, will be captured in the clinical database.

The following clinical laboratory assessments will be performed:

Biochemistry

Blood samples (8.5 mL) for serum biochemistry will be collected into a gel separator tube at the visits specified in Table 1. The following parameters will be assessed:

Sodium	Total CO_2 (Bicarbonate)
Potassium	Albumin
Glucose	Aspartate aminotransferase
Blood urea nitrogen	Alanine aminotransferase
Creatinine	Gamma-glutamyltransferase
Calcium	Alkaline phosphatase
Chloride	Total bilirubin

Phosphorus	Uric acid
Total protein	β-hCG[a]

[a] Females only. Only females of child-bearing potential ie, not postmenopausal or surgically sterile, as defined in Section 4.4.1, will be required to have β-hCG evaluated. Reported values of β-hCG that are >1.0 and <6.0 mIU/mL are less than the upper range for non-pregnant, post-menopausal female (7.0-8.3 mIU/mL) and are considered negative.

Hematology

Blood samples (4 mL) for hematology will be collected into an ethylenediaminetetraacetic acid tube at the visits specified in Table 1. The following parameters will be assessed:

Hemoglobin	Total neutrophils (absolute)
Hematocrit	Eosinophils (absolute)
Red blood cells	Monocytes (absolute)
Platelet count	Basophils (absolute)
White blood cell count (total and differential)	Lymphocytes (absolute)

Urinalysis

A urine sample for urinalysis will be collected at the visits specified in Table 1. The following parameters will be assessed:

pH	Blood	Nitrites
Glucose	Ketones	Leukocyte esterase
Protein	Bilirubin	Specific gravity

Microscopic examination will be conducted if protein and/or blood is/are detected during urinalysis. At a minimum, the microscopic examination will consist of red blood cells, white blood cells, casts, and bacteria.

7.2.2.7 Pregnancy Test

For all female subjects (regardless of reproductive potential status), a serum pregnancy test will be performed at the visits specified in Table 1; or if pregnancy is suspected; or on withdrawal of the subject from the study. Pregnancy test results must be confirmed as negative before proceeding in the study.

7.2.2.8 Drug and Alcohol Screen

A urine screen for drugs of abuse and a urine screen or breathalyzer test for alcohol will be performed at the visits specified in Table 1. Additional drug and alcohol screens may be performed at the investigator's discretion.

Urine samples are to be tested for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, opiate metabolite, and phencyclidine. Additional drugs of abuse, eg, methamphetamines and tricyclic anti-depressants, which are included in currently marketed products for drugs of abuse screening, will also be tested in these samples.

Results of drug and alcohol screens will be reviewed and verified by the study monitor but will not be collected in the eCRF database.

Any positive result for drugs of abuse or alcohol at screening or on Day -1 will exclude the subject from further participation in the study.

7.2.2.9 Serology Screen

At the screening visit, a blood sample of approximately 8 mL will be collected into a serum separator tube to test for the presence of HIV, HBsAg, and HCV antibody.

The test results must be confirmed negative before randomization. If a test result is positive, the subject will be excluded from entering the study. Results of the virology screen will be reviewed and verified by the study monitor but will not be collected in the eCRF database.

7.2.2.10 Antidrug Antibody Testing

A blood sample of approximately 6 mL will be collected to test for antidrug antibodies in serum at the visits specified in Table 1. On dosing days, samples will be collected before the first dose of the day. A full description of the ADA sample collection, handling, storage, and shipping is provided in the laboratory manual.

Any subject with newly developed antidrug antibodies at the Day 60 (Day 88/FU) assessment, which is 60 days after dosing, may require follow-up. This will be discussed as necessary by the principal ophthalmologist and medical monitor on a case-by-case basis.

7.2.2.11 Electrocardiogram

Twelve-lead ECGs will be performed at the visits specified in Table 1**;** the time points during each visit are specified in Table 2, Table 3, Table 4, and Table 5 for Cohorts A, B, C, and D, respectively.

The following parameters will be recorded on the appropriate eCRF page: heart rate, PR, RR, QRS, and QT intervals. The QT interval corrected for heart rate using the Bazett formula (QTcB) and QT interval corrected for heart rate using the Fridericia formula (QTcF) will be derived from the data in the database. The investigator's assessment of the ECG tracing as normal or abnormal must be documented, and if abnormal, his/her determination of whether the abnormality is clinically significant or not will be documented on the tracing and recorded in the eCRF.

The subject should be asked to remove all clothing that covers the location of lead placement. The subject must be resting in the supine position for at least 5 minutes before collecting the ECG.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings.

One complete recording, including a 10-second rhythm strip, should be taken at each time point. It should be immediately assessed as a valid recording and, if not valid, it should be repeated. Invalid recordings will not be entered in the eCRF.

The ECG collected before dosing on Day 1 will serve as the subject's baseline ECG.

To ensure the safety of the subjects, a qualified individual at the investigator site will make comparisons to baseline measurements.

If the QTcF interval (calculated online on site) is increased by >45 msec from the baseline or an absolute QTcF value is >500 msec for any scheduled ECG, then 2 additional ECGs will be collected, approximately 2-4 minutes apart, to confirm the original measurement. If either of the QTcF values from these repeated ECGs remains above the threshold value (>45 msec from the baseline; or is >500 msec), then a single ECG must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement. When triplicate ECGs are collected, the mean of the triplicate measurements should be used to trigger the decision to collect follow-up ECGs.

If QTcF values remain above 500 msec (or >45 msec from the baseline) for >4 hours (or sooner at the discretion of the investigator) or QTcF intervals get progressively longer, the subject should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF intervals do not return to <500 msec (or to <45 msec above the baseline) after 8 hours of monitoring (or sooner at the discretion of the investigator). The parameters from the continuous ECG monitoring will be recorded in the source documents.

If a machine-read QTcF/QTcB value is prolonged, as defined above, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTcF/QTcB values are in the acceptable range.

7.2.3 Pharmacokinetic Procedures

The name and address of the bioanalytical laboratory(ies) for this study will be maintained in the investigator's files at each site and in the Trial Master File at the CRO. A laboratory manual fully describing the schedule and method of sample handling will be provided.

Actual PK blood (for plasma) sample collection times versus time of dosing will be monitored. The sponsor's expectation is that the investigator will ensure that every effort is made to collect all PK samples at the precise protocol scheduled time. Pharmacokinetic sample collection must not deviate from the nominal collection time set forth in the protocol by more than ±5 minutes from samples collected within 4 hours after dosing or by more than ±15 minutes for samples collected beyond 4 hours after dosing. Samples collected outside these parameters will be considered protocol deviations.

7.2.3.1 Pharmacokinetic Sample Collection and Handling Procedures

Blood samples will be collected for determination of plasma concentrations of SHP639 at the visits specified in Table 1**;** the time points during each visit are specified in Table 2, Table 3, Table 4, and Table 5 for Cohorts A, B, C, and D, respectively. Potential metabolites may also be determined as appropriate.

A full description of the PK blood sample collection, handling, storage, and shipping is provided in the laboratory manual.

Polypropylene plasma sample tubes for bioanalysis must be freezer-safe and identified with freezer-safe labels provided by the central laboratory. The labels will contain the following information:

- Study number (SHP639-101)
- Subject identifier
- Cohort (eg, A1, A2, A3)
- Treatment period (single dose or multiple dose; Cohort A only)
- Nominal day
- Nominal time
- Matrix identifier (plasma)
- Split (primary or back-up)

7.2.3.2 Shipment of Pharmacokinetic Samples

All PK samples should be double-bagged to contain leaks and packed with a sufficient quantity of dry ice to ensure that they remain frozen for at least 72 hours to allow for delays in shipment. Primary and back-up samples must be shipped separately. A courier that will track shipments and replenish dry ice if necessary should be used. All applicable shipping regulations must be followed. Shipments should be scheduled so that no samples arrive on the weekend and should be shipped Monday-Wednesday only. Samples should be transported to ensure that they arrive at the bioanalytical laboratory between the hours of 9:00 AM and 4:00 PM. The recipient and primary Shire contact must be notified by telephone or email when the samples are shipped and they must be provided with the shipment tracking number.

All PK samples, along with the corresponding documentation, should be shipped according to the instructions provided in the laboratory manual.

Pharmacokinetic samples will be stored nominally at -70^{o}C before and after analysis at the laboratory until their disposal is authorized by Shire.

7.2.3.3 Plasma Drug Assay Methodology

Plasma sample analysis will be performed according to the laboratory standard operating procedures.

Plasma concentrations will be measured using a validated bioanalytical method based on liquid chromatography with mass spectrometry. In addition, selected plasma samples may be used to investigate incurred sample reproducibility (full details will be described in the bioanalytical study plan). The presence of other metabolites or artifacts may be monitored or quantified as appropriate. Raw data will be stored in the archive of the designated bioanalytical contract laboratory.

7.2.4 Pharmacodynamic Assessments

Intraocular pressure (in mmHg) will be measured using Goldmann applanation tonometry at the visits specified in Table 1; the time points during each visit are specified in Table 2, Table 3, Table 4, and Table 5 for Cohorts A, B, C, and D, respectively. Refer to Section 7.2.2.3 for details.

7.2.5 Volume of Blood to Be Collected from Each Subject

For Cohort A, it is expected that approximately 241.5 mL of blood will be collected from all subjects, regardless of sex (Table 11).

For Cohorts B, C, and D, it is expected that approximately 192.5 mL of blood will be collected from all subjects, regardless of sex (Table 12).

Table 11 Volume of Blood to Be Collected from Each Subject in Each Treatment Regimen: Cohort A

Assessment		Sample Volume (mL)	Number of Samples	Total Volume (mL)
Pharmacokinetic samples		4	18	72
HBsAg, HIV, HCV		8	1	8
Safety	Biochemistry and β-hCG[a]	8.5	11	93.5
	Hematology	4	11	44
Antidrug antibody		6	4	24
Total				**241.5**

β-hCG=beta-human chorionic gonadotropin; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus

[a] β-hCG testing for females only. β-hCG will be assessed in 6 of the 11 samples collected for biochemistry assessments (screening, SDTP [Day -2], MDTP [Day -2, Day 1, Day 26, and Day 29])

Cohort A: Single-dose treatment followed by multiple-dose treatment once daily.

Table 12 Volume of Blood to Be Collected from Each Subject in Each Treatment Regimen: Cohorts B, C, and D

Assessment		Sample Volume (mL)	Number of Samples	Total Volume (mL)
Pharmacokinetic samples		4	12	48
HBsAg, HIV, HCV		8	1	8
Safety	Biochemistry and β-hCG[a]	8.5	9	76.5
	Hematology	4	9	36
Antidrug antibody		6	4	24
Total				**192.5**

β-hCG=beta-human chorionic gonadotropin; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus

[a] β-hCG testing for females only. β-hCG will be assessed in 5 of the 9 samples collected for biochemistry assessments (screening and MDTP [Day -2, Day 1, Day 26, and Day 29])

Cohort B: Multiple-dose treatment twice daily; Cohort C: Multiple-dose treatment 3 times daily; Cohort D: Multiple-dose treatment 4 times daily.

Note: The amount of blood to be collected for each assessment is an estimate. The amount of blood to be collected may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments may be combined.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An **AE** is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guideline E2A 1995).

All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the eCRF and in source documents. Adverse events that occur from Day 33 to Day 88/FU should be captured on the AE eCRF page. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE eCRF page.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that worsens in severity should be captured as a new event. Worsening of pretreatment events, after initiation of investigational product, or a pre-existing medical history with worsening severity, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia before dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate eCRF page). If an AE is a recurrence, even if at a lower severity, it should be captured as a new AE.

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his/her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related." Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related." The causality assessment must be documented in the source document and the eCRF.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the eCRF. Outcomes are as follows:

- Fatal
- Not recovered/not resolved
- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Unknown.

8.1.4 Ocular and Nonocular Categorization

The investigator will categorize AEs as ocular (specified as left eye, right eye, or both eyes) or nonocular.

8.1.5 Symptoms of the Disease under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE.

8.1.6 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory, vital sign, or ECG assessment can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory, vital sign, or ECG values that were not present at the pretreatment value observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory, vital sign, or ECG parameter is clinically significant and therefore represents an AE.

8.1.7 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.1.3.

Any report of pregnancy for any female study participant or the partner of a male study participant must be reported within 24 hours to the Shire Global Drug Safety Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Shire medical monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days post partum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Study Serious Adverse Event and Nonserious AEs Required by the Protocol Form. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Study Serious Adverse Event and Nonserious AEs Required by the Protocol Form as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-hCG test or ultrasound result will determine the pregnancy onset date.

8.1.8 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not it results in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a nonmedical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- **Overdose** – Intentional or unintentional intake of a dose of investigational product higher than the protocol-prescribed dose
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of the unassigned treatment is/are always reportable as a medication error.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the IB, which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Drug Safety Department and the CRO/Shire medical monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.8) unless they result in an SAE.

The investigator must complete, sign, and date the Shire Clinical Study Serious Adverse Event and Nonserious AEs Required by the Protocol Form, verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested), and fax or email the form to the Shire Global Drug Safety Department. A copy of the Shire Clinical Study Serious Adverse Event and Nonserious AEs Required by the Protocol Form (and any applicable follow-up reports) must also be sent to the CRO/Shire medical monitor using the details specified in the emergency contact information section of the protocol.

Email address for reporting SAEs: PPD

8.2.3 Serious Adverse Event Definition

An **SAE** is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death.
- Is life-threatening. Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations that are the result of elective or previously scheduled surgery for pre-existing conditions and have not worsened after initiation of treatment should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity.
- Is a congenital abnormality/birth defect.
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon

appropriate medical judgment, they 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 inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.3 and must be reported to the Shire Global Drug Safety Department and the CRO/Shire medical monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Global Drug Safety Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the ICF, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (ie, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of withdrawn should not be selected solely as a result of the subject's death.

8.2.7 Regulatory Agency, Institutional Review Board, and Site Reporting

The sponsor is responsible for notifying the relevant regulatory authorities/United States *(*US) central IRBs of related, unexpected SAEs.

In addition the sponsor is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP639 program.

The investigator is responsible for notifying the local IRB or the relevant local regulatory authority of all SAEs that occur at his/her site as required.

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the eCRF. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is randomly assigned, it is expected that site personnel will complete the eCRF entry within approximately 3 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRO's data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Data Handling Considerations

Data that may potentially unmask the treatment assignment (ie, investigational product blood concentrations, antidrug antibody, treatment allocation, and investigational product preparation/accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, before unmasking, any data that may unmask study team personnel will be presented as masked information or otherwise will not be made available. If applicable, unmasked data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

9.4 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent**.**

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the PK, PD, and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized before database lock.

All statistical analyses will be performed using SAS® software (SAS Institute, Inc, Cary, NC 27513).

9.5 Planned Interim Analysis, Adaptive Design, and Dose Escalation Committee

Shire's Dose Escalation Committee will be convened consisting of the coordinating principal ophthalmologist and Shire medical monitor. Ad hoc study team members can be included such as biostatistics, pharmacokinetics, drug safety, and clinical operations if needed. The committee will review collective safety data for Cohort A and Cohort B to decide whether Part 2 in the same dose level and Part 1 in the next dose level (concentration) can commence.

An unmasked interim analysis (IA) will be performed after cohorts A1, A2, A3, B1, B2, and B3 have completed through Day 29 of the B3 cohort. Data from sites will be entered into the database, queried, and discrepancies resolved. There is no intention to stop early based on data from the IA. The intent of this IA is to determine if the escalated doses have identified a pharmacodynamically significant safe and tolerable dose(s) for further clinical evaluation.

Team members reviewing the interim analysis will be reviewing unmasked data from cohorts A1, A2, A3, B1, B2, and B3. The SAP will be finalized before data are frozen for this interim analysis.

All cohorts conducted after B3 (ie Part 1 of the study) may be unmasked following completion of Day 29 to permit review of safety, tolerability and the pharmacodynamics effects of each cohort to better inform planning for additional cohorts and further clinical development options for SHP639.

A final unmasked analysis will be conducted when all subjects of the remaining cohorts have completed through Day 29. The Day 88/FU visit is the planned study completion for each subject.

9.6 Sample Size Calculation and Power Considerations

A sufficient number of subjects will be screened to ensure the enrollment and completion of 84 subjects.

The number of subjects in this study is not based on statistical power considerations because the statistical analyses are primarily descriptive in nature. However, if at least 7 subjects complete each cohort, then there will be at least 65% to 85% probability of observing at least 1 occurrence of any AE with a true incidence rate for a given dose group of at least 15-25%, respectively.

It is estimated that dose escalation will occur for up to 3 dose levels (4 cohorts within each dose level). Each cohort will include 5 subjects randomized to active drug and 2 subjects randomized to placebo for an estimated total of at least 84 subjects.

For each cohort, the number of subjects will be increased as needed based on safety and IOP response. Any cohort can be repeated to confirm findings with regard to safety or IOP response.

9.7 Study Population

The **safety set** will consist of all subjects who have been randomized and who have received at least 1 dose of investigational product.

The **PK set** will consist of all subjects in the safety set for whom the primary PK data are considered sufficient and interpretable.

The **PD set** will consist of all subjects in the safety set for whom the primary PD data are evaluable.

9.8 Pharmacokinetic and Pharmacodynamic Analyses

9.8.1 Pharmacokinetic Analysis

All PK analyses will be performed using the PK set.

Plasma concentrations of SHP639 will be measured using a fully validated bioanalytical method. If data permit, PK parameters for SHP639 will be calculated based on plasma concentration-time data using a noncompartmental approach (Phoenix® WinNonlin® version 6.4 or higher, Certara USA, Inc, Princeton, NJ, 08540).

9.8.1.1 Pharmacokinetic Endpoints

If data permit, PK parameters will be estimated as appropriate and may include, but are not limited to, the following:

- Maximum observed concentration (C_{max})
- Time to reach C_{max} (t_{max})
- Area under the observed concentration vs time curve:
  - From time zero (predose) to the time of the last measurable concentration (AUC_{0-t})
  - Over the dosing interval ($AUC_{0-\tau}$) for each multiple-dose regimen including QD, BID, TID, and QID
  - From time zero (predose) extrapolated to infinity ($AUC_{0-\infty}$) for QD dosing
- Apparent terminal phase elimination half-life ($t_{½}$)
- Apparent clearance (CL/F)
- Apparent volume of distribution (Vz/F)
- Accumulation ratio based on AUC for each multiple-dose regimen, calculated as $AUC_{0-\tau}$ (Day 27)/$AUC_{0-\tau}$ (Day 1) ($R_{ac[AUC]}$)
- Accumulation ratio based on C_{max} for each multiple-dose regimen, calculated as C_{max} (Day 27)/C_{max} (Day 1) ($R_{ac[Cmax]}$)

9.8.1.2 Statistical Analysis of Pharmacokinetic Parameters

Summary statistics (number of observations, mean, standard deviation [SD], coefficient of variation, median, maximum [max], minimum [min], and geometric mean) will be determined

for all plasma PK parameters and will be presented by dose, cohort, treatment period (single dose or multiple dose; Cohort A only), and study day. Plasma concentrations at each nominal sampling time will also be summarized using descriptive statistics.

For accumulation ratios, the 95% confidence interval (CI) for the arithmetic mean of the difference (for example, $AUC_{0-\tau}$ [Day 28] - $AUC_{0-\tau}$ [Day 1]) on the logarithmic scale (natural base) will be calculated. The results will be back-transformed to give the ratio of geometric means together with the corresponding 95% CI.

Before statistical comparisons, dose-dependent parameters (C_{max}, AUC_{0-t}, $AUC_{0-\tau}$, and $AUC_{0-\infty}$) will be normalized to a common dose, assuming linearity. Additionally, the linear dose proportionality will be evaluated for C_{max}, $AUC_{0-\tau}$, AUC_{0-t}, and $AUC_{0-\infty}$ using the power function model (eg, $C_{max}=\alpha \cdot Dose^{\beta}$ or equivalently $\log[C_{max}]=\log[\alpha]+\beta \cdot \log[Dose]$, where C_{max} is considered to increase linearly proportional to dose if β is not significantly different from 1.0) (Gough et al., 1995).

9.8.2 Pharmacodynamic Analysis

All the PD analyses will be performed using the PD set. Intraocular pressure (mmHg) will be measured using Goldmann applanation tonometry.

9.8.2.1 Pharmacodynamic Endpoints

Pharmacodynamic parameters will be estimated as appropriate and may include, but are not limited to, the following:

- Change from baseline in IOP
- Time to the maximum change from baseline in IOP
- Proportion of subjects maintaining IOP reduction after specified days of treatment

Specific endpoints in order to understand the effect of SHP639 on IOP will be defined in the SAP.

9.8.2.2 Statistical Analysis of Pharmacodynamic Parameters

Descriptive summary statistics for IOP (number of subjects, mean, SD, median, min, and max) will be calculated by dose, cohort, treatment period (single dose or multiple dose; Cohort A only), study day, and time point (for days with multiple assessments per day). Additionally, 95% CIs for each estimate and summary statistics of change from baseline and percentage change from baseline, along with 95% CIs, will be calculated. Pharmacodynamic parameters will be calculated and summarized by dose, cohort, treatment period (single dose or multiple dose; Cohort A only), and study day as applicable.

All IOP data will be listed by dose, cohort, subject, treatment period (single dose or multiple dose; Cohort A only), and study day.

9.8.3 Pharmacokinetic and Pharmacodynamic Analysis

The relationship between dose of SHP639 ophthalmic solution, plasma PK parameters, and changes in IOP may be explored using graphical and/or regression methods if the data permit.

Further details of PK, PD, and PK-PD analyses will be presented in the SAP.

9.9 Safety Analyses

9.9.1 Safety Endpoints

Safety and tolerability will be assessed by monitoring AEs, vital sign measurements, clinical laboratory assays, ECGs, ADA, drop comfort assessment, and ophthalmologic examinations.

9.9.2 Statistical Analysis of Safety Data

The placebo subjects will be pooled together as a pooled placebo group.

All vital sign, clinical laboratory, ECG, ADA, drop comfort assessment, and ophthalmologic examination data (per schedule of events) will be listed by dose, cohort, subject, treatment period (single dose or multiple dose; Cohort A only), visit, day, and time point (for days with multiple assessments per day). If the ranges are available then abnormalities will be flagged. Summary statistics with number of subjects, mean, SD, median, minimum, and maximum will be provided by dose, cohort, treatment period (single dose or multiple dose; Cohort A only), visit, day, and time point (for days with multiple assessments per day).

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. The number of events, incidence, and percentage of treatment-emergent AEs will be calculated overall and by system organ class and preferred term by dose and cohort. Treatment-emergent AEs will be further summarized by severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed. All information obtained on AEs will be displayed by dose, cohort, subject, treatment period (single dose or multiple dose; Cohort A only), visit, and day. A subject with multiple AEs within a body system will be counted only once.

9.10 Other Analyses

No other analyses are planned in this study.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations including ICH E6, EU Directive 2001/20/EC, and all updates, as well as local ethical and legal requirements.

Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki

The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations and ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and eCRFs in accordance with current GCP and the respective local and international/national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required before release of investigational product for shipment to the site.

10.1.2 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.3 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the community guideline on GCP. This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for nonpediatric studies as per guidance.

10.1.4 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies, and IRBs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site before commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curricula vitae for investigators and subinvestigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal ophthalmologist is appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the coordinating principal ophthalmologist, in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guideline E3 (1995).

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB, and regulatory agency with final reports and summaries as required by international/national regulations.

Communication with local IRBs to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or, for multicenter studies, the coordinating principal ophthalmologist, according to national provisions, and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

Electronic case report forms are supplied by the CRO and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded into the eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Electronic case report forms must be completed by the investigator or designee as stated in the site delegation log.

All data will have separate source documentation; no data will be recorded directly into the eCRF.

All data sent to the sponsor must be endorsed by the investigator.

The clinical research associate/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, subject diaries, and original clinical laboratory reports.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The clinical research associate/study monitor (and auditors, IRB, or regulatory inspectors) may check the eCRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or IRB, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, and X-rays). Non-study site personnel will not disclose any personal information or personal medical information.

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US Food and Drug Administration [FDA], European Medicines Agency (EMA), United Kingdom Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 Code of Federal Regulations 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent from all study subjects before any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally authorized representative, as applicable, is requested to sign and date the subject ICF or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal ophthalmologist provides the sponsor with a copy of the consent form that was reviewed by the IRB and received their favorable opinion/approval. A copy of the IRB's written favorable opinion/approval of these documents must be provided to the sponsor before the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) before study start that another party (ie, sponsor or coordinating principal ophthalmologist) is responsible for this action. Additionally, if the IRB requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB for review, and all must be approved before site initiation.

For multicenter studies, the applicant can be the coordinating principal ophthalmologist or sponsor, according to national provisions.

Responsibility for coordinating with IRBs is defined in the clinical trial agreement.

Before implementing changes in the study, the sponsor and the IRB must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor or CRO has received written IRB approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; for multicenter studies, this can be done by the coordinating principal ophthalmologist, according to national provisions. The investigator must also keep the local IRB informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with Health Insurance Portability and Accountability Act (HIPAA) of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the CRO or sponsor.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives' reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market SHP639; national or local regulatory authorities; and the IRB(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (eg, to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results/Publication Policy

The term "Publication" shall mean any paper, article, manuscript, report, poster, internet posting, presentation slides, abstract, outline, video, instructional material, presentation (in the form of a written summary), or other public disclosure of the study results, in printed, electronic, oral, or other form. The parties understand and agree that participation in the study may involve a commitment to publish the data from all sites participating in the study in a cooperative publication with other investigators prior to publication or oral presentations of the study results on an individual basis. The site agrees not to publish or present the site's study results until such time as either the aggregate multi-site study results are published in a cooperative publication or for a period of one (1) year after termination or completion of the study at all participating sites, whichever shall first occur. After that time, the site may publish the site's study results in scientific journals or present the study results at symposia or other professional meetings in accordance with the following provisions:

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single site data being presented.

At least sixty (60) days prior to submitting an abstract, manuscript, or other document for publication, a copy of the proposed publication will be provided to the sponsor by the site for review. Upon the sponsor's request, the site agrees to remove any and all confidential information (expressly excluding study results) identified in the publication and to delay such submission or presentation for an additional sixty (60) day period in order to allow the sponsor time to file any patent application(s). All publications of the study results shall appropriately reference the multi-site study publication, if any, or the fact that the study results are a subset of data resulting from a larger multi-site study.

Shire is committed to transparent dissemination of all scientific, technical and medical manuscripts generated from Shire-supported research. Therefore, after January 1, 2018, Shire will require the submission of all Shire-supported research manuscripts to journals that offer public availability via Open Access (including publisher platforms/repositories and self-

archiving). Open Access refers to the free at point of entry, online availability of published research output with, where available, rights of re-use according to an End User License.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) Recommendation for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical journals. Participation as an investigator does not confer any rights to authorship of publications.

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12. APPENDICES

APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol (Version 1)	12 Dec 2016	Global
Original Protocol (Version 2)	15 Feb 2017	Global
Amendment #1 (Version 2.1)	16 May 2017	Global
Amendment #2 (Version 3)	04 Oct 2017	Global
Amendment #3 (Version 4)	11 May 2018	Global

<table>
<tr><th colspan="3">Protocol Amendments</th></tr>
<tr><th colspan="3">Summary of Change(s) Since Last Version of Approved Protocol</th></tr>
<tr><th>Amendment Number
2</th><th>Amendment Date
4 Oct 17</th><th>Global/Country/Site Specific
Global</th></tr>
<tr><th colspan="2">Description of Change</th><th>Section(s) Affected by Change</th></tr>
<tr><td colspan="2">Clarification that there would be one e-mail for product quality complaints

Please use the information below as applicable to report the Product Quality Complaint:

<table><tr><th>Origin of Product Quality Complaint</th><th>Email Address</th></tr><tr><td>North and South America</td><td>PPD</td></tr><tr><td><s>European Union and Rest of World</s></td><td>PPD</td></tr></table></td><td>Product Quality Complaints</td></tr>
<tr><td colspan="2">Removal of Figure 1 showing dose escalation.</td><td>Synopsis
Section 3.1</td></tr>
<tr><td colspan="2">Clarification in table that gonioscopy will be performed at screening.</td><td>Table 1</td></tr>
<tr><td colspan="2">Clarification that the washout period (Washout 2) prior to the MDTP is to be of 3-14 days duration.</td><td>Table 1
Section 7.1.2.1</td></tr>
<tr><td colspan="2">Addition of footnote r to table 1 to clarify that slit lamp exam at screening and Day 29 should not repeat assessments done repeat opacification assessment.
Lens opacification is graded at screening and Day 29, during the scheduled dilated exam. The lens assessment that is part of the slit lamp exam on those days should not report graded opacification findings, but should report other lens-related findings that are visible during the non-dilated exam</td><td>Table 1</td></tr>
<tr><td colspan="2">A window (in minutes) was added for assessments.</td><td>Table 2, Table 3, Table 4, Table 5</td></tr>
<tr><td colspan="2">ECG was removed from MWOA, Day 28, and Day 88/Follow-up visits.</td><td>Table 2, Table 3, Table 4, Table 5</td></tr>
<tr><td colspan="2">Table 5 corrected to indicate that anti-drug antibody blood sampling will not occur at screening for cohort D.</td><td>Table 5</td></tr>
<tr><td colspan="2">Clarification that Day 88 is the anticipated Study Completion Date for each subject
Day 88±4 days (final assessment visit and anticipated Study Completion Date for each subject)</td><td>Section 3.2</td></tr>
</table>

Clarification that all procedures, not only ocular procedures, performed within the 5 years before the first dose, should be recorded any ~~**ocular**~~ procedures performed within the 5 years before the date of the first dose of investigational product. Prior treatment information must be recorded on the appropriate eCRF page.	Section 5.1
Clarification that subjects should receive the single or first dose on the same time each day. **Subjects should receive the single or first dose (depending on cohort assignment) each day between 7:00am and 9:00am. This is particularly important for cohorts C and D as these subjects will receive 3 and 4 doses daily**	Section 6.2.3.1
Documentation that decision was made not to enroll cohort D1. Footnote: **Cohort D1 is not to be enrolled as it was decided that the resulting data would not contribute to the understanding of the safety of SHP639.**	Table 10
Addition of language to support not enrolling a proposed dose cohort if dose escalation meeting findings indicate that information from that dose cohort would not increase understanding of the safety of SHP639. If, in the judgment of the coordinating principal ophthalmologist, the Shire medical monitor, and the Shire ophthalmic study physician, it is unclear whether there is a potential safety ~~**signal**~~ **concern** or whether dose escalation should occur, a dose level may be reduced, modified, or repeated depending on the outcome of the safety data review between doses or treatments. **Further, based on the findings from the dose escalation review meetings a cohort (or cohorts) may be determined to not be necessary to determine the safety of SHP639.** Finally, upon completion of all dose cohorts, additional doses may be studied based on emergent safety, PD, and PK data following the necessary protocol amendment and Institutional Review Board (IRB) reviews.	Section 6.2.3.2
Clarification that the time points of ophthalmic assessments performed on Day -2 and Day -1 are to be carried forward to assessments on Day 1. **Time points of ophthalmic assessments performed on Day -2 and Day -1 should be carried forward to assessments on Day 1. This ensures that the baseline IOP time points established before dosing begins are time-matched to the IOP assessments performed during dosing days for the duration of the study.**	Section 7.1.2.2
Clarification that ophthalmic assessments are considered safety assessments, and therefore, if their timing deviates from the scheduled time (and window), this will be considered a protocol deviation.	Section 7.2.2
Clarification that pregnancy testing by β-hCG is only required for females of childbearing potential, as defined in Section 4.4.1. Interpretation of β-hCG results performed for post-menopausal subjects also added.	Biochemistry table in Section 7.2.2.6
Clarification that urine drug screen will include drugs of abuse included in marketed screening products. **Additional drugs of abuse, eg, methamphetamines and tricyclic anti-depressants, which are included in currently marketed products for drugs of abuse screening, will also be tested in these samples.**	Section 7.2.2.8

Clarification that Day 60 (60 days after dosing), which is the day of antidrug antibody blood sampling, is also study Day 88/FU.	Section 7.2.2.10
Addition of adverse event collection at the Day 88/FU visit	Section 7.1.3, Section 7.2.2.4, Section 8.1
Clarification that only AEs that worsen in severity (as opposed to all changes in severity) are to be captured as a new AE.	Section 8.1.1
Correction of the address for reporting SAEs. Email address for reporting SAEs: PPD	Section 8.2.2
Addition of an unmasked interim analysis when cohorts A1, A2, A3, B1, B2, and B3 have reached Day 29. Addition of a second unmasked analysis when all subjects in the remaining cohorts have reached Day 29.	Section 9.5

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **16 May 2017**	**Global/Country/Site Specific** **Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Inclusion criteria #3 text updated ~~"Subjects must have OHT or stable early POAG in both eyes. Early POAG for this protocol is defined as healthy appearing anterior chamber angles (Shaffer classification system grade 3 or 4), maximum C/D ratio of 0.4, focal thinning of the optic disc rim and a Humphrey visual field preformed within 6 months of screening that meets the following criteria: false positive of 25% maximum; false negative of 25% maximum; fixation losses of 33% maximum and mean deviation (MD) within 0 to -6.00 dB."~~ "Subjects must have OHT or stable early POAG in both eyes with acceptable Humphrey visual fields (HVF). Early POAG for this protocol is defined as healthy appearing anterior chamber angles (Shaffer classification system grade 3 or 4), and focal and/or generalized thinning of the optic disc rim characteristic of glaucomatous disease. An acceptable HVF must have been performed within approximately one year of screening, have a false positive rate of 25% maximum, false-negative rate of 25% maximum, fixation loss rate of 33% maximum, and mean deviation of no worse than -6.00 dB.		Synopsis Section 4.1
Inclusion criteria # 6 text updated " Subjects must be males or females who are nonpregnant and nonlactating at screening (negative serum beta-human chorionic gonadotropin [β-hCG]); if sexually active during the study, they must agree to comply with the applicable contraceptive requirements (refer to Section 4.4) throughout the study period and for ~~30 days~~ **60 days** following the last dose of investigational product. Section 4.4.1 will be updated to state " Sexually active females of		Synopsis Section 4.1 Section 4.4.1 Section 4.4.2

childbearing potential must use an acceptable form of contraception throughout the study period and for ~~30 days~~ **60 days** following the last dose of investigational product. If hormonal contraceptives are used, they should be administered according to the package insert. Females of childbearing potential who are not currently sexually active must agree to use acceptable contraception, as defined below, if they become sexually active during the period of the study and ~~30 days~~ **60 days** following the last dose of investigational product. Section 4.4.2 will be updated to state "Male subjects will be required to use a condom in conjunction with spermicidal gel, foam, cream, film, or suppository from the time of first dosing until ~~30 days~~ **60 days** after the last dose of investigational product. Childbearing female partners of male study participants will be required to follow the acceptable methods of contraception for this study (described in Section 4.4.1) from the time of first dosing until ~~30 days~~ **60 days** after the last dose of investigational product. Male subjects must not donate sperm for at least ~~30 days~~ **3 months** after the last dose of investigational product.	
Exclusion criteria #15 updated to remove restriction on the use of anticholinergic medication. "Subject has used belladonna alkaloids (scopolamine, hyoscyamine, atropine) within 7 days before randomization, cannabinoids or, opioids, ~~or anticholinergic drugs~~ within 28 days before randomization, or B-type natriuretic peptides within the past year before randomization; or subject has anticipated need for any of the aforementioned drugs/drug categories during the study.	Synopsis Section 4.2 Table 8
Ophthalmologic assessments on screening and midwashout ophthalmic assessments (MWOA) need to be done one time during the day only. Ophthalmic assessments include: BCVA, Manifest Refraction (Screening), Slit Lamp examination of anterior segment, Conjunctival Redness, Corneal Haze, Corneal Epithelial integrity using fluorescein stain, Anterior Chamber cell and flare, Lens Opacification, IOP, Posterior Segment Examination, dilated (Screening and Day 29), Specular Microscopy (Day 29), Noncontact (Screening and Day 29), Corneal Pachymetry (Screening and Day 29)	Table 1, Table 2, Table 3, Table 4, Table 5
IOP assessments on Screening and MWOA (D-14) need to be done one time during the day only. At screening: IOP may be measured at any time during the day. At MWOA (D-14) IOP will be measured in the morning at 10:00am (+3 hours). Additional assessments other than the "morning assessments" at screening and MWOA (D-14) do not need to be conducted.	Table 1, Table 2, Table 3, Table 4, Table 5
Clarification of last study drug dose: Subjects will be administered the last dose of study drug on the morning of Day 28. Add a footnote to tables 2, 3, 4, and 5.	Table 2, Table 3, Table 4, Table 5

Clarification of Corneal Pachymetry Timing: The timing of IOP and Corneal Pachymetry will be more closely aligned to allow for procedure scheduling at sites: Corneal Pachymetry will be performed at the following time points for all applicable visit days: Predose/Morning, 1 hour post dose, 2 hours post dose, 4 hours post dose, and 12 hours post dose.	Table 2, Table 3, Table 4, Table 5 Section 7.2.2.3
Clarification of Baseline: The Baseline "BL" Column will be removed from Tables 2, 3, 4, and 5. All reference to "BL" will be removed from the column titles "Days Performed" and all reference to visits will be done by day number. Removed all reference to "Baseline" in Section 7.2.2.3	Table 2, Table 3, Table 4, Table 5 Section 7.2.2.3
Clarification of Antidrug antibody (Ab) sampling in Table 1: remove "X" from Day 26 as no sample will be collected at Day 26. Clarification of Antidrug Ab sampling in Tables 2, 3, 4, 5. The column titled "Days Performed" incorrectly identifies Antidrug Ab blood sampling to be collected at the screening visit. No ADA samples will be taken at screening. Clarification of Antidrug Ab sampling at Day 26: No ADA samples will be taken at Day 26. In Table 2 only: Antidrug Ab blood sampling time point was added to Table 2 at the predose/morning time point. Site personnel should collect the Antidrug Ab blood sample at the predose/morning time point.	Table 1, Table 2, Table 3, Table 4, Table 5
The volume of blood to be drawn per subject has changed due to the removal of an ADA sample at the Screening visit for all subjects.	Table 11 and Table 12 Section 7.2.5
Clarification of Full and Abbreviated IOP exam time points: The schedule for abbreviated IOP exams is to be followed on Days 7, 14, and 21. In tables 3, 4, and 5 update IOP, full schedule: Removed D7, D14, D21 from "Days performed" column.	Table 3, Table 4, Table 5 on Days 7, 14, and 21.
Clarification of artificial tears use: When subjects are at a study visit artificial tears are not to be used. "The use of non-preserved artificial tears is prohibited during the following intervals, **which include study visits:** • Cohort A, SDTP: Day -2 -1 to Day 2, after final assessment • Cohort A, MDTP: Day -2 -1 to Day 29, after final assessment • Cohorts B, C, and D: Day -2 -1 to Day 29, after final assessment."	Section 5.2.2
Gonioscopy Time points: Gonioscopy will be done at screening at any time during the day.	Table 2, Table 3, Table 4, Table 5 Section 7.2.2.3

Gonioscopy will not be done at D-2 or D-1. Gonioscopy will be performed at the morning time point on Day 29. Gonioscopy will not be performed at the 6 hour time point on Day 29.	
Conjunctival redness assessments will be done at the following time points: Predose, 1 hour, 3 hours, 6 hours, and 12 hours	Table 2, Table 3, Table 4, Table 5
Footnote added to column headings of Screening, MWOA, and Day 29 to clarify that only one round of ophthalmic assessments will be done in the morning.	Table 1
Clarify that only the following will be done at check-in: Physical exam Drugs of abuse screening Alcohol breathalyzer Vital signs Hematology, Chemistry, Urinalysis One ECG	Table 1
A footnote was added to refer the reader to tables 2, 3, 4, and 5 for specific details on assessment timing for study days.	Table 1
Clarification on re-screening: Any subject who is qualified but not dosed (ie, an alternate subject) may be re-screened at a later date for the study. A subject who does not meet all eligibility criteria during screening cannot re-screen.	Section 7.1.1.2
Clarify the study day for screening and clarify the study day window (days): Screening study day will become -28 and the study day window will be +14. This does not change the duration of screening (up to 42 days total).	Table 1
Remove all reference to "SDTP" in tables 3, 4, 5. There is no SDTP in Cohorts B, C, and D.	Table 3, Table 4, Table 5
Clarification of IOP on Day 29: Day 29 only a single IOP. Day 29 removed from the full IOP schedule.	Table 3, Table 4, Table 5
Clarification of the Day 60 visit and total subject duration of participation: ADA sampling will be collected approximately 60 days post last dose (Day 28). This is accurate in the synopsis, Section 3.1.4.2, and Section 3.1.5. The synopsis and Section 3.2 will now state: The subjects' maximum duration of participation in the study is expected to be **146** ~~122~~ days or approximately 5 4 months (Cohort A1, A2, and A3). The subjects' maximum duration of participation in the study for Cohorts B, C, and D is expected to be 130 days or approximately 4.5 months. • Maximum planned duration of screening and Washout 1: 42 days • Planned duration of treatment period: 2 days for SDTP (Cohort A only) and 29 days for MDTP (all cohorts) • Planned duration of Washout 2 (Cohort A only): 3 14 days Planned duration of follow-up: until Day **88** ~~60±4~~ days	Synopsis Section 3.2 Section 7.1 Section 7.1.1 Section 7.1.3 Table 1

The Table 1 column header titled Day 60/FU will be renamed **Day 88/FU** and footnoted. Section 7.1.3 was re-worded to ensure it is clear that the sample is to be drawn approximately 60 days post last dose (Day 28).	
Clarify Vitals will not be done on Day 88: Change "all visits" in Days Performed to "All visits except Day 88/FU"	Table 2, Table 3, Table 4, Table 5
Clarify BCVA time points: Change "all visits" in Days Performed to "All visits except Day 26 and Day 88/FU"	Table 2, Table 3, Table 4, Table 5
Clarification of the follow-up phone call timing: The synopsis, Section 3.1.4.2, and Section 3.1.5 state that the follow up phone call will be 7 days post discharge. Table 1 footnote "g" incorrectly states that the follow up phone call will be 7 days post last dose of study drug. Footnote "g" was corrected.	Table 1
Removed: If unavailable, please contact: PPD PPD ~~Telephone:~~ PPD ~~(24-hour coverage)~~ Replaced with: If unavailable please contact: PPD PPD **Telephone:** PPD **(24-hour coverage)**	Additional Contact Information

APPENDIX 2 ANTERIOR SEGMENT GRADED ASSESSMENTS

Corneal Haze Assessment

Corneal haze assessments will be performed as part of the slit lamp examination at the time points outlined in Table 1 (all cohorts) and specified in Table 2, Table 3, Table 4, and Table 5 for Cohorts A, B, C, and D, respectively.

Corneal haze assessments will be based on the Hwang Grading Scale of Corneal Haze developed by PPD . Refer to the ophthalmology procedures manual for the scale and full instructions for performing the assessment.

Conjunctival Redness Score Assessment

The Efron scale/conjunctival redness assessment (Efron et al., 2001) is a clinically validated, image-based scale that will be used to evaluate bulbar conjunctival redness during all ophthalmologic examinations, as outlined in Table 1 (all cohorts) and specified in Table 2, Table 3, Table 4, and Table 5 for Cohorts A, B, C, and D, respectively. The scale contains 5 categories ranging from 0 (normal) to 4 (severe).

At the slit lamp, under standard magnification, the investigator will compare the bulbar conjunctiva of 1 eye with the Efron scale images and select the image that most closely matches the level of redness.

Refer to the ophthalmology procedures manual for the image-based scale and full instructions for performing the assessment.

Corneal Epithelial Integrity Assessment by Fluorescein Staining

The integrity of the corneal epithelium will be assessed using topically applied fluorescein at the time points outlined in Table 1 (all cohorts) and specified in Table 2, Table 3, Table 4, and Table 5 for Cohorts A, B, C, and D, respectively. It is important to perform the assessment **before** installation of topical anesthetic for measurement of IOP.

Sodium fluorescein is a dye that fluoresces when viewed under cobalt light. When applied topically to the ocular surface, fluorescein admixes with the tear film and diffuses into intercellular spaces in areas of corneal epithelial disruption. At the slit lamp, under standard magnification and a cobalt filter, a defect in the corneal epithelium appears as a bright green glow.

Corneal epithelial integrity will be graded based on the pattern and intensity of fluorescein staining (Lemp, 1995; Shimmura et al., 1995).

Refer to the ophthalmology procedures manual for instructions for performing the assessment.

Anterior Chamber Cell and Flare

Anterior chamber cell and flare will be assessed and graded using the Standardization of Uveitis Nomenclature grading scale at the time points outlined in Table 1 (all cohorts) and specified in Table 2, Table 3, Table 4, and Table 5 for Cohorts A, B, C, and D, respectively.

Lens Opacification

Lens opacification will be assessed with the slit lamp during dilated examination and graded in the nuclear, cortical, and subcapsular layers using the Lens Opacities Classification System III grading scale at the time points outlined in Table 1 (all cohorts) and specified in Table 2, Table 3, Table 4, and Table 5, for Cohorts A, B, C, and D, respectively. The presence and placement of an intraocular lens and the presence of a posterior capsulotomy will be recorded.