# STATISTICAL ANALYSIS PLAN

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| **Protocol No.:** | SHP639-101 |
| **Protocol 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 |
| **Sponsor:** | Shire HGT<br>300 Shire Way, Lexington,<br>MA 02421 USA |
| **Version No. and Date** | Final Version 1.5, 30AUG2018 |

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| 1.5 | SAP Final Version 1.5 | PPD<br>PPD | 08/30/2018 |

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# ABBREVIATIONS

| | |
|---|---|
| ADA | antidrug antibody |
| AE | adverse event |
| ALT | alanine aminotransferase |
| ALP | alkaline phosphatase |
| AMD | age-related macular degeneration |
| AST | aspartate aminotransferase |
| $AUC_{0-t}$ | 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 |
| $AUEC_{0-t}$ | area under the intraocular pressure values vs time curve from time zero (predose) to the time of the last measurable intraocular pressure |
| $AUEC_{0-\tau}$ | area under the intraocular pressure values vs time curve over the dosing interval |
| $AUEC_{0-\infty}$ | area under the intraocular pressure values 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 |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| $E_{max}$ | maximum intraocular pressure reduction from baseline |
| EMA | European Medicines Agency |
| EU | European Union |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |

| | |
|---|---|
| GGT | gamma-glutamyl transferase |
| GLP | Good Laboratory Practice |
| HBsAg | hepatitis B surface antigen |
| HCV | hepatitis C virus |
| HIPAA | Health Insurance Portability and Accountability Act |
| IB | investigator's brochure |
| IP | investigational product |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IOP | intraocular pressure |
| IRB | Institutional Review Board |
| IRT | interactive response technology |
| IV | Intravenous |
| LLN | lower limit of normal |
| MDTP | multiple-dose treatment period |
| MedDRA | Medical Dictionary for Regulatory Activities |
| 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 |
| PCI | potentially clinically important |
| PD | pharmacodynamic(s) |
| PK | pharmacokinetic(s) |
| POAG | primary open-angle glaucoma |
| RBC | red blood cell |
| 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 effect (maximum intraocular pressure reduction from baseline) |
| TID | 3 times daily |
| $t_{max}$ | time to reach maximum observed concentration |
| ULN | upper limit of normal |
| US | United States |
| Vz/F | apparent volume of distribution |
| WBC | white blood cell |
| WHO-DD | World Health Organization Drug Dictionary |

# 1. INTRODUCTION

This is the full Statistical Analysis Plan (SAP) for Study SHP639-101. The SAP provides a technical and detailed elaboration of the statistical analyses of safety and PK/PD data based on the study protocol Amendment 3 (Version 4) dated 11 May 2018. Specifications for tables, figures, and listings will be provided in a separate document.

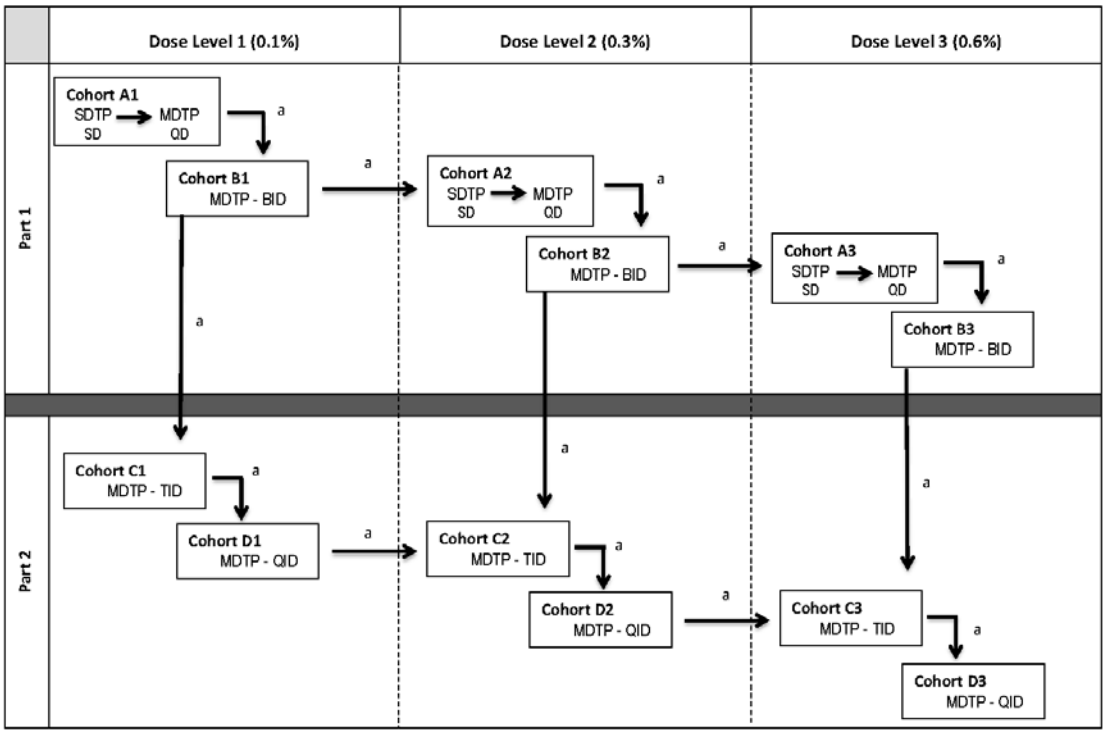
# 2. STUDY DESIGN

## 2.1 General Study Design

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 concentrations being studied for each dosing regimen are presented in the study schema in Figure 1.

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.

## Figure 1 Study Schema




Solid arrows are not drawn to scale and indicate both the flow of dosing regimens and the occurrence of a dose escalation meeting.

BID=twice daily; MDTP=multiple-dose treatment period; QD=once daily; QID=4 times daily; SD=single dose; SDTP=single-dose treatment period; TID=3 times daily

[a] Dose escalation meetings will convene when 6 out of 7 subjects have completed Day 14 in the previous cohort's multiple-dose administration. This does not include the decision to move from Cohort B to C. Decisions will include safety, tolerability, and intraocular pressure data.

## 2.2 Schedule of Assessments

### Table 1 Overall Schedule of Events

| Study Visit | Screening and WO 1[a, s] | | 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[s] | -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, s] | FU Call[g] | 88/ Fu [r,u] |
| 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[t] | | | 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 |

## Table 1 Overall Schedule of Events

| Study Visit | Screening and WO 1[a, s] | | 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[s] | -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, s] | FU Call[g] | 88/ Fu [r,u] |
| Study Day Window (Days) | -14 | ±2 | | | 0 | 0 | | | | 0 | 0 | | ±2 | | ±2 | | ±2 | | | | | 0 | ±2 | ±4 |
| Drop comfort assessment[m] | | | | | X | | | | | X | | | X | | X | | X | | | X | X | | | |
| 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 | X | X | X | X | X | | X | X | X | X | | X | | X | | X | | | X | X | X | | |
| 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 | | | | | | | | | | | | | | | | | | | | | X | | |
| IOP[v] | 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 | 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 | |
| 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 | |

## Table 1 Overall Schedule of Events

| Study Visit | Screening and WO 1[a, s] | | 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[s] | -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, s] | FU Call[g] | 88/ Fu[r,u] |
| 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 | | | |

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.

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 Protocol 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.

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

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

[t] 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.

[u] 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.

[v] 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.

## Table 2 Detailed Schedule of Events – Cohort A

| Assessment | Days Performed (Screening-D29)[f] | Predose/ Morning[a] | 0 m | 30 m | 1 h | 2 h | 3 h | 4 h | 6 h | 8 h | 12 h |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 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 | 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 and 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 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]. 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 | | | | | | | | | |

## Table 2 Detailed Schedule of Events – Cohort A

| Assessment | Days Performed (Screening-D29)[f] | Predose/ Morning[a] | 0 m | 30 m | 1 h | 2 h | 3 h | 4 h | 6 h | 8 h | 12 h |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gonioscopy[e] | SCR, D29. | X | | | | | | | | | |
| Specular microscopy, noncontact | SCR. SDTP: D-1, D2. MDTP: D-1, D14, D29. | X | | | | | | | | | |
| Corneal pachymetry | SCR. SDTP: D-1, D1, 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 | | | | | | | | | |
| Alcohol breath test | SCR (D-42), SCR (D-14). SDTP: BL (D-2), MDTP: BL (D-2 and D-1), D1, D14, D21, D26. | X | | | | | | | | | |
| Serum pregnancy test (female subjects) | SCR. SDTP: BL (D-2). MDTP: BL (D-2), D1, D26, D29. | X | | | | | | | | | |
| Biochemistry, hematology, and urinalysis | SCR. SDTP: BL (D-2), D2. MDTP: BL (D-2), D1, D7, D14, D21, D26, D27, D29. | X | | | | | | | | | |

Timings relate to dose administration or the equivalent morning assessment. Refer to Protocol 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; 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 timepoint.
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

## Table 3 Detailed Schedule of Events – Cohort B

| Assessment | Days Performed (Screening-D29)[f] | Predose/ Morning[a] | 0 m | 30 m | 1 h | 2 h | 3 h | 4 h | 6 h | 8 h | 12 h |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 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 | 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 3 Detailed Schedule of Events – Cohort B

| Assessment | Days Performed (Screening-D29)[f] | Predose/ Morning[a] | 0 m | 30 m | 1 h | 2 h | 3 h | 4 h | 6 h | 8 h | 12 h |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 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. Assessments on nondosing days (screening, baseline, and Day 29) will take place once in the morning only unless otherwise specified.

Ab=antibody; BL=baseline; 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, and 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 10:00 am ± 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 after IOP measurement but before dilation.

[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 Opcification, 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.

## Table 4 Detailed Schedule of Events – Cohort C

| Assessment | Days Performed (Screening-D29)[f] | Predose/ Morning[a] | 0 m | 30 m | 1 h | 2 h | 3 h | 4 h | 6 h | 8 h | 12 h |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 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 | 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 | | | | | | | | | |

## Table 4 Detailed Schedule of Events – Cohort C

| Assessment | Days Performed (Screening-D29)[f] | Predose/ Morning[a] | 0 m | 30 m | 1 h | 2 h | 3 h | 4 h | 6 h | 8 h | 12 h |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 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-2, D1, D7, D14, D21, D26, D27, D29. | X | | | | | | | | | |

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

Ab=antibody; BL=baseline; 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, and 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 10:00 am ± 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 after IOP measurement but before dilation.

[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 Opcification, 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.

## Table 5 Detailed Schedule of Events – Cohort D

| Assessment | Days Performed (Screening-D29)[f] | Predose/ Morning[a] | 0 m | 30 m | 1 h | 2 h | 3 h | 4 h | 6 h | 8 h | 12 h |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 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 | 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 | | | | | | | | | |

## Table 5 Detailed Schedule of Events – Cohort D

| Assessment | Days Performed (Screening-D29)[f] | Predose/ Morning[a] | 0 m | 30 m | 1 h | 2 h | 3 h | 4 h | 6 h | 8 h | 12 h |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 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-2, D1, D7, D14, D21, D26, D27, D29. | X | | | | | | | | | |

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

Ab=antibody; BL=baseline; 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, and 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 10:00 am ± 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 after IOP measurement but before dilation.

[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 Opcification, 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.

## 2.3 Determination of Sample Size

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% to 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 (SHP639) 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 to investigational product. Any cohort can be repeated to confirm findings with regard to safety or IOP response to investigational product.

## 2.4 Identification of 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 study. In Cohort A single-dose treatment period (SDTP), the investigational product will be dosed in the designated study eye only. For all subjects participating in the multiple-dose treatment period (MDTP), a designated study eye will be also identified and the investigational product will be dosed in both eyes. For Cohort A, the study eye for MDTP will be the same as the study eye in SDTP. For SDTP Cohort A and MDTP Cohorts B, C and D, 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. OBJECTIVES

SHP639 is being developed for reduction of IOP in patients with ocular hypertension and primary open angle glaucoma. 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 SHP639 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.

## 3.1 Study Objectives

### 3.1.1 Primary Objectives

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

### 3.1.2 Secondary Objectives

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

### 3.1.3 Exploratory Objectives

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

# 4. SUBJECT POPULATION SETS

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 Enrolled Set

Enrolled set consists of all subjects who have signed informed consent.

## 4.2 Randomized Set

Randomized set consists of all subjects in the enrolled set for whom a randomization number has been assigned.

## 4.3 Safety Set

The safety set will consist of all subjects in the randomized set who had administered at least 1 dose of investigational product.

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

## 4.4 Pharmacokinetic Set

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

## 4.5 Pharmacodynamic Set

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

# 5. SUBJECT DISPOSITION

Subject disposition will be summarized for the enrolled set. The disposition of subjects includes the number and percentage of subjects for the following categories: subjects who were enrolled, subjects who were randomized, subjects who were in the safety set, subjects who were in the pharmacokinetic set, subjects who were in the pharmacodynamic set, subjects who completed the study, subjects who prematurely discontinued the study treatment, and subjects who did not complete the study. Disposition data will be summarized by treatment group and overall by dosing regimen. All percentages will be based on the number of subjects randomized. Reasons for premature discontinuation from the study treatment period as recorded on the termination page of the eCRF will be summarized (number and percentage) by treatment group and overall by dosing regimen for the randomized set. The reason for study discontinuation may include any of the following: adverse event, withdrawal by subject, noncompliance with investigational product, physician decision, study terminated by sponsor, lost to follow-up, pregnancy, protocol deviation, trial screen failure and other. A by-subject listing of study completion information, including the reason for study discontinuation, where applicable, will be presented.

A listing of all Screen Failures (ie, subjects who were screened but not randomized) will be presented along with reasons for screen fail and details of any AEs.

# 6. PROTOCOL DEVIATIONS

A summary of the number and percentage of subjects in the randomized set with protocol deviations by treatment group and overall by dosing regimen will be produced.

All protocol deviation data will be listed for the subjects in the randomized set.

# 7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic variables such as age, sex, race, ethnicity, height, weight, and body mass index (BMI) at baseline will be summarized. Ocular assessments including Best Corrected Visual Acuity (BCVA) will be summarized separately for the study eye and non-study eye. Continuous variables, such as age (years), BMI, weight, height, and BCVA will be summarized using descriptive statistics for each treatment period, treatment group and overall by dosing regimen. Categorical variables such as sex, ethnicity, and race will be summarized by reporting the number and percentage of subjects in each category for each treatment group and overall by dosing regimen. Summaries will be performed using the randomized set.

Demographic data will be listed using the randomized set.

# 8. MEDICAL HISTORY

Medical history of subjects will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0. Recent ingestion of medication (received within 30 days or 5 half-lives (whichever is longer) before the date of the first dose of investigational product (see prior medications in section 10) and any ocular/non-ocular procedures performed within the 5 years before the date of the first dose of investigational product) and history of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric, and other diseases will be reviewed and recorded. The MedDRA version used for reporting the study will be documented in the summary table footnotes.

The number and percentage of subjects with medical history events in each primary system organ class (SOC) and each preferred term (PT) will be summarized by treatment group and overall by dosing regimen using the randomized set. Ocular history will be summarized for the study eye, the non-study eye, either eye if occurred in either eye, and both eyes if the event occurred in both eyes. Medical history will be counted for both eyes if a history with the same preferred term is present in both eyes regardless of the start date of history in each eye (e.g., the start date may differ between the two eyes.) Each subject's medical history will be listed by SOC and PT using the randomized set.

# 9. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

## 9.1 Exposure to Investigational product

Exposure to double-masked investigational product for the Safety set will be summarized in terms of total number of drops, and treatment duration, which is calculated as the number of days from the date of first dose of double-masked investigational product taken to the date of the last dose of double-blind investigational product taken, inclusively for the MDTP. Descriptive statistics (n, mean, standard deviation, minimum, Q1, median, Q3, and maximum) will be presented by treatment group. Additionally, the number and percentage of subjects who had at least one dose of unrefrigerated drug will be summarized.

Exposure data including the number of doses received by each subject, and treatment duration will be presented in data listings. A separate exposure listing including only subjects receiving unrefrigerated drug will also be presented.

## 9.2 Measurement of Treatment Compliance

Treatment compliance will be calculated for MDTP only and will be calculated as:

Compliance (%) = (total actual dose administered / total expected dose) × 100;

Where,

1. If the subject completed the treatment: total expected dose = x × 27 + 1 (the last dose was taken on the morning of Day 28)
2. If the subject discontinued the treatment, the date of treatment discontinuation will be used for date of expected last dose and tota expected dose will be calculated as: total expected dose = x × (date of expected last dose – date of first dose +1)

Total actual dose = number of total doses taken between scheduled clinic visits + number of total drug instillations during all clinic visits,

Number of total doses taken between scheduled clinic visits is calculated as the

Sum of [x × (the date of last dose prior to check-in at the current visit – date of last drug instillation from previous visit) – number of missed doses]

where x = 1 for Cohort A1, A2, and A3

x = 2 for Cohort B1, B2, and B3

x = 3 for Cohort C1, C2, and C3

x= 4 for Cohort D1, D2, and D3

Number of total drug instillations during all clinic visits is the sum of the numbers of drug instillation in all Study Drug Instillation CRFs of a subject.

The latest date of last dose prior to check in is the date found in Study Drug Accountability CRFs of a subject at each scheduled visit. If a subject has terminated the study early, the date of early termination on the Study Completion 1 CRF will be used. Number of missed doses is the numbers of missed doses in Study Drug Accountability CRFs of a subject at each visit. Descriptive statistics for investigational product compliance during the MDTP will be presented by treatment group for the Safety set. Individual subject compliance information will be listed with treatment group indicated.

# 10. PRIOR AND CONCOMITANT MEDICATION

World Health Organization-Drug Dictionary (WHODRUG) version March 2017 will be used to classify prior and concomitant medications by therapeutic class. Prior medication 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 5 years before the date of the first dose of investigational product. Concomitant treatment refers to all treatment and ocular procedures received between the dates of the first dose of investigational product and the end of the follow-up period, inclusive.

Both prior and concomitant medication usage will be summarized by the number and proportion of subjects in each treatment group and overall by dosing regimen receiving each medication within each preferred term for the safety set. Medications can be counted both as prior and concomitant medication. Multiple medication usage by a subject in the same category will be counted only once. Ocular medications will be summarized for the study eye, the non-study eye, either eye if received in either eye, and both eyes if received in both eyes. For a medication to be counted for both eyes, the medication start date must be the same in both eyes for a given preferred term.

All prior and concomitant medication will be listed using the safety set.

# 11. SAFETY ANALYSES

The safety analysis will be performed using the Safety set. Safety and tolerability will be assessed by monitoring AEs, vital sign measurements, clinical laboratory test values, ECG readings, antidrug antibodies, drop comfort assessment, and ophthalmologic examinations. SDTP and MDTP outputs will be summarized separately. For SDTP, data will be summarized for two periods:

a. Dosing period only: Day 1 SDTP – Day 2 SDTP

b. Dosing period and washout period: Day 1 SDTP up to First Dose MDTP

For SDTP, ocular summaries will be presented for the study eye and the non-study eye. For MDTP, all ocular summaries will be presented for the study eye, the non-study eye, and for either eye. For summarization by either eye, the eye with the less favorable response at the given timepoint will be summarized which may result in different eyes being summarized at different visits. Adverse events and selected ocular assessments summaries will also be presented for both eyes. For summarization by both eyes, subjects with events or assessments occurring in both eyes will be included. In the MDTP, ocular summaries will be presented first by dose regimen then by dose level and placebo subjects will be pooled by dosing regimen. (eg, QD placebo subjects will be pooled together, BID placebo subjects will be pooled together, TID placebo subjects will be pooled together, and QID placebo subjects will be pooled together.) All subjects in the Safety set (including placebo-treated subjects) within a regimen will also be presented. (For example, all active QD doses and QD placebo patients will be combined for the QD dosing regimen summaries.)

## 11.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Ocular and non-ocular AEs will be summarized separately. Ocular summaries will be presented separately for the study eye, the non-study eye, either eye if the event occurred in either eye, and both eyes if the event occurred in both eyes. For an event to be counted for both eyes, the event start date must be the same in both eyes for a given preferred term.

The number of events, incidence, and percentage of treatment-emergent AEs (TEAE) will be calculated overall, by system organ class and preferred term by treatment group and overall by dosing regimen. AEs leading to drug withdrawal, Serious AEs (SAE), and AEs leading to death will be similarly summarized/listed. All information obtained on AEs will be displayed in a listing by treatment group, 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. If more than 1 AE with the same preferred term is reported before the date of the first dose of double-blind investigational product, then the AE with the greatest severity will be used as the benchmark for comparison to the AEs occurring during the Double-blind Evaluation Phase under the preferred term.

Treatment-emergent AEs will be further summarized by severity and relationship to investigational product. An AE (classified by preferred term) that occurs during the Double-masked Evaluation Phase will be considered a TEAE if it has a start date and time on or after the date and time of first dose of double-blind investigational product or if it has a start date and time before the date and time of the first dose of double-blind investigational product, but increases in severity on or after the date and time of the first dose of double-blind investigational product. An AE that occurs more than 7 days after the date of the last dose of double-blind investigational product will not be counted as a TEAE.

The overall number of subjects having any type of TEAEs will be summarized by treatment group. The number and percentage of subjects reporting TEAEs will be tabulated by system organ class (SOC) and preferred term (PT) by treatment group; TEAEs by severity will be tabulated by SOC, and maximum severity by treatment group. TEAEs considered related to investigational product will also be summarized by SOC and preferred term. If more than 1 AE occurs with the same PT for the same subject, then the subject will be counted only once for that PT using the most severe and most related occurrence for the summarization by severity and by relationship to investigational product. For both eyes summaries of related TEAEs, the events in both eyes must be considered related to investigational product. For both eyes summaries of TEAEs by severity, the events with same preferred term starting on the same date will be counted by the greater severity of the events in the two eyes (eg, the eyes will not be required to have same severity of the event to be counted.)

## 11.2 Clinical Laboratory Variables

Biochemistry, hematology, and urinalysis 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. Baseline for clinical laboratory for SDTP is defined as the last non-missing scheduled assessment made prior to dosing in SDTP and baseline for MDTP is defined as the last non-missing scheduled assessment made prior to dosing in MDTP. Descriptive statistics for clinical laboratory values (in SI units) and changes from baseline at each assessment time point for quantitative variables will be presented by treatment group for the following clinical laboratory variables.

**Hematology** Hematocrit, hemoglobin, red blood cells (RBC), platelet count, white blood cell count (WBC) – total and differential: total neutrophils (absolute), lymphocytes (absolute), monocytes (absolute), eosinophils (absolute), basophils (absolute)

**Biochemistry** Sodium, potassium, glucose, creatinine, blood urea nitrogen (BUN), calcium, chloride, phosphorus, total $CO_2$ (bicarbonate), albumin, total protein, ALT, AST, gamma- glutamyltransferase (GGT), ALP, total bilirubin, uric acid, β-hCG (females only).

**Urinalysis** pH, specific gravity, blood, WBC, glucose, protein, ketones, bilirubin, nitrite, and leukocyte esterase.

Clinical laboratory test values are potentially clinically important (PCI) if they meet either the low or high PCI criteria listed in Table 6. The number and percentage of subjects with postbaseline PCI values will be tabulated by treatment group. The percentages will be calculated relative to the number of subjects with available baseline values and at least 1 postbaseline assessment. The numerator is the total number of subjects with at least 1 postbaseline PCI value. A supportive listing of subjects with postbaseline PCI values will be provided including the subject number, site, baseline, and postbaseline values.

**Table 6 Criteria Potentially Clinically Important Laboratory Tests**

| Parameter | Lower Limit | Higher Limit |
|---|---|---|
| **Hematology** | | |
| Hemoglobin | < 0.6 × LLN OR Decrease of ≥ 6% from baseline value | > 1.3 × ULN |
| Hematocrit | < 0.6 × LLN | > 1.3 × ULN |
| Leukocytes (WBC) | < 0.5 × LLN | > 2 × ULN |
| Neutrophils | < 0.5 × LLN OR < 40% | NA OR > 70% |
| Eosinophils | NA | > 4 × ULN OR >10% |
| Plateletes | < 0.4 × ULN | > 2 × ULN |
| **Blood Chemistry** | | |
| Albumin | < 0.6 × LLN | NA |
| Total Protein | < 50g/ L | > 90 g/ L |
| ALT/ SGPT | NA | > 3 × ULN |
| AST/SGOT | NA | > 3 × ULN |
| ALP | NA | > 3 × ULN |
| Total bilirubin | NA | > 1.5 × ULN |
| Sodium | < 0.9 × LLN | > 1.1 × ULN |
| Potassium | < 0.85 × LLN | > 1.2 × ULN |
| Creatinine | NA | > 1.5 × ULN |
| BUN | NA | > 3 × ULN |
| Bicarbonate | < 0.5 × LLN | > 1.3 × ULN |
| Glucose | 0.6 × LLN | > 3.5 × ULN |
| Calcium | < 0.7 × LLN | > 1.3 × ULN |
| Phosphorus | < 0.3229 mmol/L | > 1.6145 mmol/L |
| Chloride | < 0.8 × LLN | > 1.2 × ULN |
| **URINALYSIS** | | |
| pH | < 4.5 | > 7.2 |

| | | |
|---|---|---|
| Specific Gravity | < 0.9 × LLN | > 1.1 × ULN |
| Blood | | > 5 |
| WBC | | > 5 |
| Glucose | | ≥ 100 mg/dL |
| Protein | | > 20 mg/dL |
| Bilirubine | | Other than negative |
| Nitrite | | Other than negative |
| Ketones | | Other than negative |
| Leukocyte esterase | | Small, moderate and large (eg other than negative OR trace) |

## 11.3 Vital Signs

Blood pressure, pulse rate and 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. Baseline for vital signs for SDTP is defined as the last non-missing scheduled assessment made prior to dosing in SDTP and baseline for MDTP is defined as the last non-missing scheduled assessment made prior to dosing in MDTP. 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.

Descriptive statistics for vital signs (systolic and diastolic blood pressure, pulse rate, and body weight) and their changes from baseline at each postbaseline visit and at the end of study will be presented by treatment group. Vital sign results wil be listed by individual subject.

Vital sign values will be considered PCI if they meet both the observed value criteria and the change from baseline criteria listed in Table 7. The number and percentage of subjects with PCI postbaseline values will be tabulated by treatment group and overall by dosing regimen in the Safety set. Percentages will be calculated relative to the number of subjects with baseline and at least 1 postbaseline assessment. The numerator is the total number of subjects with at least 1 PCI postbaseline vital sign value. A supportive listing of subjects with postbaseline PCI values will be provided including the subject number, site, baseline, and postbaseline PCI values.

**Table 7 Criteria for Potentially Clinically Important Vital Signs**

| Vital Sign Parameter | Flag | Criteria[a] | |
|---|---|---|---|
| | | Observed Value | Change from Baseline |
| Systolic blood pressure (mmHg) | High | ≥ 160 | Increase of ≥ 20 |
| | Low | ≤ 90 | Decrease of ≥ 20 |
| Diastolic blood pressure (mmHg) | High | ≥ 105 | Increase of ≥ 15 |
| | Low | ≤ 50 | Decrease of ≥ 15 |
| Pulse rate (beats per minute) | High | ≥ 100 | Increase of ≥ 15 |
| | Low | ≤ 40 | Decrease of ≥ 15 |
| Weight (kg) | High | - | Increase of ≥ 7% |
| | Low | - | Decrease of ≥ 7% |

[a] A postbaseline value is considered as a PCI value if its meets both criteria for observed value and change from baseline.

## 11.4 Electrocardiogram (ECG)

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. Descriptive statistics for ECG variables (heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc interval) and their changes from baseline at each assessment time point will be presented by treatment group and overall by dosing regimen in the Safety set. Baseline for ECG for SDTP is defined as the last non-missing scheduled assessment made prior to dosing in SDTP and baseline for MDTP is defined as the last non-missing scheduled assessment made prior to dosing in MDTP. QTc interval will be calculated using both Bazett ($QTcB=QT/(RR)^{1/2}$) and Fridericia ($QTcF=QT/(RR)^{1/3}$) corrections. ECG interpretation will be summarized by visit and cohort. ECG results and interpretation will be listed by individual subject.

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).

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.

Electrocardiogram variable values will be considered PCI if they meet or exceed the upper limit values listed in Table 8. The number and percentage of subjects with postbaseline PCI values will be tabulated by treatment group and overall by dosing regimen in the Safety set. The percentages will be calculated relative to the number of subjects with available non-PCI baseline and at least 1 postbaseline assessment. The numerator is the total number of subjects with at least 1 PCI postbaseline ECG value. A listing of all subjects with postbaseline PCI value will be provided including the subject number, site, baseline, and postbaseline PCI values.

**Table 8 Criteria for Potentially Clinically Important ECG Values**

| ECG Parameter (unit) | Flag | Criteria | |
|---|---|---|---|
| | | **Observed Value** | **Change from Baseline** |
| Heart rate (bpm) | HIGH | ≥ 100 | Increase of ≥ 15 |
| | LOW | ≤ 40 | Decrease of ≥ 15 |
| QRS Interval (msec) | HIGH | > 200 | |
| | LOW | < 120 | |
| PR Interval (msec) | HIGH | > 220 | Increase of > 20 |
| | LOW | < 100 | |
| QTc Interval (msec) | MEN HIGH | > 430 | Increase of > 30 |
| | WOMEN HIGH | > 450 | Increase of > 30 |
| | MEN LOW | < 330 | |
| | WOMEN LOW | < 340 | |

## 11.5 Antidrug Antibody Testing

A blood sample of approximately 6 mL will be collected to test for antidrug antibodies (ADA) in serum at the visits specified in Table 1. On dosing days, samples will be collected before the first dose of the day. Any subject with newly developed antidrug antibodies at the Day 60 assessment may require follow-up. Results of ADA testing will be listed by individual subject. The summarization format will be based on the data result type.

## 11.6 Other Safety Variables

### 11.6.1 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 assessment

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.

The drop comfort assessment will be performed for each eye (study eye, non-study eye, and either eye) except for Cohort A during the SDTP, when only the study eye will be assessed. For either eye summaries, the assessment denoting the most discomfort (e.g., greater value) will be summarized. 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.

Descriptive statistics for drop comfort scores at each assessment time point during the SDTP will be presented for study eye by treatment group. Descriptive statistics for drop comfort scores at each assessment time point during the MDTP will be presented by eye (study eye, non-study eye, either eye) and by treatment group . The score of drop comfort at each assessment visit and time point will be listed by individual subject.

### 11.6.2 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. Ophthalmologic examination results will be summarized for the study eye, the non-study eye, and either eye. Summaries for either eye will be presented for MDTP only.

#### 11.6.2.1 Manifest Refraction

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

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

The manifest refraction will be repeated if the BCVA has decreased by 10 or more letters.

The status of manifest refraction assessment, and the date and time of the assessment will be listed by individual subject. No summarization of refraction data will be performed.

#### 11.6.2.2 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): baseline (Days -2 and -1) and Days 1 and 2
- MDTP (all cohorts): baseline (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.

For each treatment period, the baseline assessments are measured on Day -2 and -1 at predose/morning, +1 and +12 hours. Baseline BCVA is defined as the mean of the non-missing assessments at these 6 time points. 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 or more 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.

Descriptive statistics for BCVA letter score and changes from baseline at each assessment time point will be presented by eye (study eye, non-study eye, and either eye (MDTP only)) and treatment. Additionally, the number and percentage of subjects with BCVA changes in following categories by treatment group will be presented:

- < 6 letter decrease
- 6 to 9 letter decrease
- >=10 letter decrease

The percentages will be calculated relative to the number of subjects with available baseline BCVA and at the postbaseline assessment for the given timepoint. The complete results of BCVA will be listed by individual subject.

For either eye summaries, at baseline the eye with the lower baseline BCVA score will be summarized. For post baseline timepoints, the eye with the smaller increase from baseline will be summarized. If both eyes have the same change from baseline, the eye with the lower BCVA score at the given visit will be summarized.

#### 11.6.2.3 Slit Lamp Biomicroscopy

Slit lamp biomicroscopy will be performed at the following visits:

- Screening
- Midwashout assessment
- SDTP (Cohort A only): baseline (Days -2 and -1) and Days 1 and 2
- MDTP (all cohorts): baseline (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.

Slit lamp assessments will be performed before IOP measurement and pachymetry. Ungraded slit lamp assessments will be made before graded assessments.

The following anterior structures will be evaluated as normal or abnormal. If abnormal, the findings should be described and recorded as either CS or NCS for the overall slit lamp biomicroscopy examination. 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 (at Screening and Day 29 during dilated exams only)

The findings of overall slit lamp biomicroscopy examination will be summarized for the study eye, the non-study eye, and if observed in either eye (MDTP only) at each visit by treatment . The number and percentage of subects with clinically significant abnormal results, and non-clinically significant abnormal results for overall slit lamp biomicroscopy examination will be also summarized at each visit by treatment. For either eye summaries, a subject will be counted as normal only if both eyes are normal and as abnormal if either eye is abnormal. The percentage of subjects with each findings by ocular location will be calculated relative to the number of subjects with available finding at specific eye and visit. Additionally the number and percentage of subjects with at least one postbaseline abnormal finding for each ocular location will be summarized. Results of slit lamp biomicroscopy will be listed by individual subject and a separate listing of clinically significant findings will also be presented.

### 11.6.2.4 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).

For each treatment period, the baseline assessments are measured on Day -2 and -1 at predose/morning, +1, +3, +6, and +12 hours. Baseline conjunctival redness score is defined as

the single assessment at Day -1. A separate baseline will be derived for each scheduled time point. Change from baseline will be calculated comparing post treatment values to their respective baseline (e.g., on treatment predose assessments will be compared to baseline predose asessments, on treatment 1 hours assessments will be compared to baseline 1 hour assessments, on treatment 3 hours assessments will be compared to baseline 3 hour assessments, on treatment 6 hours assessments will be compared to baseline 6 hour assessments and on treatment 12 hours assessments will be compared to baseline 12 hour assessments).

The number and percentage of subjects in each score category at each time point will be summarized by eye (study eye, non-study eye, and either eye (MDTP only)), and treatment. For either eye assessments, the eye with the greater score will be summariezed. The denominator of the percentage is the number of subjects who have the assessment for the specified eye and visit. In addition, the number and percentage of subjects with clinically significant results, and non-clinically significant results will be summarized by treatment group. Results of conjunctival redness score assessment will be listed by individual subject.

Additionally, the number and percentage of subjects with conjunctival redness score changes from baseline in the following categories by eye (study eye, non-study eye, and either eye (MDTP only)) and treatment group will be presented:

- -4 (4 points decreased from baseline)
- -3 (3 points decreased from baseline)
- -2 (2 points decreased from baseline)
- -1 (1 point decreased from baseline)
- 0 (no change from baseline)
- 1 (1 point increased from baseline)
- 2 (2 point increased from baseline)
- 3 (3 point increased from baseline)
- 4 (4 point increased from baseline)

The percentages will be calculated relative to the number of subjects with available baseline conjunctival redness score and at the postbaseline assessment for the given timepoint. For either eye summaries, at baseline, the eye with the higher baseline redness score will be summarized. For post baseline timepoints, the eye with the smaller decrease from baseline will be summarized. If both eyes have the same change from baseline, the eye with the higher redness score at the given visit will be summarized.

#### 11.6.2.5 Corneal Haze

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.

The number and percentage of subjects for each category of corneal haze grade will be summarized by eye (study eye, non-study eye, and either eye (MDTP only)) and treatment group at each visit and time point. For either eye assessments, the eye with the greater score

will be summarized. The denominator of the percentage is the number of subjects who have the assessment for the specified eye and visit. In addition, the number and percentage of subjects with clinically significant results, and non-clinically significant results will be summarized by treatment group. Results of corneal haze assessment including corneal haze grade, epithelial edema, stromal thickening/haze, and Descemet's folds will be listed by individual subject and a separate listing of clinically significant findings will also be presented.

### 11.6.2.6 Corneal Epithelial Integrity by Fluorescein Stain

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 instillation of topical anesthetic for measurement of IOP.

For each subject at each visit and timepoint, a total score of three components from corneal epithelium integrity will be calculated by adding scores across three regions: inferior, central, and superior for each eye. The total scores will be summarized. For each treatment period, the baseline assessments are measured on Day -2 and -1 at predose/morning, +2, +4, +8, and +12 hours. Baseline corneal epithelial integrity is defined as the single assessment at Day -1 at each scheduled time point. Change from baseline will be calculated comparing post treatment values to their respective baseline (e.g., on treatment predose assessments will be compared to baseline predose asessments, on treatment 2 hours assessments will be compared to baseline 2 hour assessments, on treatment 4 hours assessments will be compared to baseline 4 hour assessments, on treatment 8 hours assessments will be compared to baseline 8 hour assessments and on treatment 12 hours assessments will be compared to baseline 12 hour assessments).

Descriptive statistics for corneal epithelial integrity total scores and change from baseline at each assessment time point will be presented by eye (study eye, non-study eye, and either eye (MDTP only)) and treatment group . For either eye summaries, at baseline the eye with the greater staining total score will be summarized. For post baseline timepoints, the eye with the greater increase from baseline will be summarized. If both eyes have the same change from baseline, the eye with the greater staining total score at the given visit will be summarized. In addition, the number and percentage of subjects with clinically significant results, and non-clinically significant results will be summarized by treatment group. Results of corneal epithelium integrity assessment including individual region scores will be listed by individual subject and clinically significant findings will also be presented.

### 11.6.2.7 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.

The number and percentage of subjects for each anterior chamber cells grade and anterior chamber flare grade will be summarized by eye (study eye,non-study eye, and either eye (MDTP only)) and treatment group. For either eye summaries, the eye with the greater score will be

summarized.The denominator of the percentage is the number of subjects who have the assessment at the specified eye and visit. In addition, the number and percentage of subjects with clinically significant results, and non-clinically significant results will be summarized by treatment group. Results of anterior chamber cell and flare assessment will be listed by individual subject and clinically significant findings will also be presented.

### 11.6.2.8 Lens Opacification

Lens opacification will be assessed with the slit lamp during dilated examination. Phakic eyes will be graded in the nuclear, cortical, and posterior 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. Pseudophakic eyes without posterior capsulotomy will be graded in the posterior subcapsular layer only. Pseudophakic eyes with posterior capsulotomy will not be graded.

The number and percentage of subjects that are phakic, the number and percentage of subjects that are psuedophakic, including number and percentage of subjects with and without a posterior capsulotomy, and the number and percentage of subjects for each category of nuclear color/opalescence, cortical, and posterior subcapsular will be summarized by eye (study eye and non-study eye) and treatment group at each visit and time point. The denominator of the percentage is the number of subjects who have the assessment for the specified eye and visit. In addition, the number and percentage of subjects with clinically significant results, and non-clinically significant results will be summarized by treatment group. Results of lens opacification will be listed by individual subject and clinically significant findings will also be presented.

### 11.6.2.9 Intraocular Pressure

Intraocular pressure will be measured at the following visits:

- Screening
- Midwashout assessment
- SDTP (Cohort A only): baseline (Days -2 and -1), Days 1and 2
- MDTP (all cohorts): baseline (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. Two consecutive IOP measurements, to the nearest mmHg, will be made in the designated study eye; if the 2 measurements differ by more than 2 mmHg, then a third measurement will be performed. The procedure will be repeated in the nonstudy eye. All measurements will be recorded in the source document and eCRF and the mean of the (2 or 3) readings for each eye will be used to determine the mean IOP at the given time point for each eye. These mean IOP values will be used for all IOP analyses.

The baseline IOP is defined as the average of the mean IOP measurements at Day -1 and Day -2. A separate baseline will be derived for each scheduled timepoint. Descriptive statistics for IOP, the change from baseline, and the percentage change from baseline at each assessment time point

will be presented by eye (study eye vs. non-study eye) and treatment. Change from baseline will be calculated comparing post-treatment values to their respective baselines (e.g., on treatment pre-dose assessments will be compared to baseline pre-dose assessments, on treatment 1 hour assessments will be compared to baseline 1 hour assessments and on treatment 12 hour assessments will be compared to baseline 12 hour assessments). Line plots displaying mean IOP, change from baseline, and percent change from baseline at each visit and each scheduled timepoint will be presented by eye (study eye, non-study eye) and treatment for SDTP and MDTP. Line plots displaying mean IOP, at selected visits (baseline, Day 14 and Day 28) and selected scheduled timepoints (predose, +2h, +4h, +8h) during MDTP will be presented for study eye by treatment. Spaghetti plots showing the IOP values at each visit and each timepoint for all subjects in the Safety set will be presented by eye (study eye, non-study eye) and treatment for SDTP and MDTP.

Diurnal fluctuation in IOP will be summarized as below:

- The baseline diurnal IOP (schedule 1) is defined as the average of all IOP meansurements across three time points (predose, +2 h, +8 h) at Day -1 and Day -2. Postbaseline diurnal IOP is defined as the average of all IOP measurements across three time points (predose, +2 h, + 8h) at each visit. Change from baseline will be calculated as the difference between postbaseline diurnal IOP and baseline diurnal IOP. Descriptive statistics for diurnal IOP, the change from baseline, and the percentage change from baseline at each visit will be presented by eye (study eye, non-study eye) and treatment.
- The baseline diurnal IOP (schedule 2) is defined as the average of all IOP meansurements across three time points (predose, +4 h, +8 h) at Day -1 and Day -2. Postbaseline diurnal IOP is defined as the average of all IOP measurements across three time points (predose, +4 h, + 8h) at each visit. Change from baseline will be calculated as the difference between postbaseline diurnal IOP and baseline diurnal IOP. Descriptive statistics for diurnal IOP, the change from baseline, and the percentage change from baseline at each visit will be presented by eye (study eye, non-study eye) and treatment.

Results of intraocular pressure will be listed by individual subject.

#### 11.6.2.10 Posterior Segment Examination

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

- Screening – dilated
- SDTP baseline (Cohort A only) – nondilated (Day -2)
- MDTP baseline – 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
- Retinal, outside of arches, including periphery
- Choroid

The number and percentage of subjects who have normal results and abnormal results for vitreous, disc, macula, retinal vasculature, retina, and choroid will be summarized by eye (study eye, non-study eye, and either eye (MDTP only)), treatment group and time point. For either eye summaries, a subject will be counted as normal only if both eyes are normal and as abnormal if either eye is abnormal. The denominator of the percentage is the number of subjects who have assessment for the specified eye and visit. In addition, the number and percentage of subjects with clinically significant abnormal results, and non-clinically significant abnormal results will be summarized by treatment. Also, the number and percentage of subjects with at least one postbaseline abnormal finding and at least one post baseline clinically significant abnormal finding for each assessment type will be summarized

Descriptive statistics for the horizontal and vertical cup to disc ratios and their changes from baseline at each assessment time point will be presented by eye (study eye, non-study eye, and either eye (MDTP only)) and treatment. Baseline disc ratio is defined as the Day -2 screening assessment. For either eye summaries, the eye with the greater disc ratio will be summarized at baseline. For post baseline assessment, the eye with the greater increase from baseline will be summarized. If both eyes have the same change from baseline, the eye with the greater value will be summarized.

The number and percentage of subjects who have no notch at baseline and a notch present at any time during post baseline period will be summarized by eye (study eye, non-study eye, and either eye (MDTP only)) and treatment. Only subjects who have no notch at baseline will be included in this summary. Baseline notch presence is defined as the Day -2 baseline assessment. For either eye summaries, a subject will be counted as notch absent if both eyes have no notch and as notch present if either eye has a notch. The percentages will be calculated relative to the number of subjects with available baseline notch assessment and at the postbaseline assessment for the given timepoint.

In addition, the number and percentage of subjects with changes in number of notches from baseline in the following categories by treatment group will be presented:

- 0 (no change)
- 1+ (increase by 1 notch)
- 2+ (increase by 2 notches)

- 3+ (increase by 3 notches)
- 4+ (increase by 4 notches)

The percentage will be calculated relative to the number of subjects with available baseline notch assessment and at the postbaseline assessment for the given timepoint. For either eye summaries, the eye with greatest increase in number of notches will be summarized.

Results of posterior segment examination will be listed by individual subject and a separate listing of clinically significant findings will also be presented.

### 11.6.2.11 Gonioscopy

Gonioscopy to assess the iridocorneal angles will be performed at SDTP baseline (Day -2; Cohort A only), MDTP baseline (Day -2; Cohorts B, C, and D), 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 number and percentage of subjects by Shaffer grading system at position 12:00 to 3:00, 3:00 to 6:00, 6:00 to 9:00, and 9:00 to 12:00 will be summarized by eye (study eye,. non-study eye, and either eye (MDTP only)) and treatment group at each visit and time point. For either eye summaries, the eye with the lower Shaffer grade will be summarized. The denominator of the percentage is the number of subjects who have the assessment for thespecified eye and visit. Results of gonioscopy will be listed by individual subject.

### 11.6.2.12 Noncontact Specular Microscopy

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

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

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

For each eye and timepoint assessed, three meaurements of central endothelial cell density (cells/mm2) will be made. All measurements will be recorded in the source document and eCRF and the mean of the 3 readings for each eye will be used to determine the mean cell density at the given time point for each eye. These mean density values will be used for all specular microscopy analyses of cell dentisty..

Baseline specular microscopy cell density is defined as the mean of the 3 readings on Day -1. Descriptive statistics for the mean central endothelial cell density and changes from baseline at each assessment time point will be presented by eye (study eye, non-study eye, and either eye (MDTP only)) and treatment group. For either eye summaries, the eye with the smaller cell density will be summarized at baseline. For post baseline assessment, the eye with the greater

decrease from baseline will be summarized. If both eyes have the same change from baseline, the eye with the smaller value will be summarized. Results of noncontact specular microscopy will be listed by individual subject.

### 11.6.2.13 Corneal Pachymetry

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

- Screening
- SDTP (Cohort A only): baseline (Day -1) and Days 1 and 2
- MDTP (all cohorts): baseline (Day -1) and Days 1, 2, 7, 14, 28, and 29.

If the range of the measurements is 15 microns or less, the set of readings is acceptable; if not, all measurements are discarded and repeated until an acceptable set of 3 measurements is obtained. The set of all 3 measures are recorded in the source document. The mean of the 3 measurements made at each timepoint are the values that will be used for analysis.

See Table 2, Table 3, Table 4, and Table 5 for detailed timings by cohort. Baseline corneal thickness is defined as the average of the mean of measures at 5 time points (pre-dose, and hours 1, 2, 4, 12) on Day -1. Descriptive statistics for the mean central corneal thickness and change from baseline at each assessment time point will be presented by eye (study eye, non-study eye, and either eye (MDTP only)) and treatment group. In addition, descriptive statistics for the percentage change from baseline at each assessment time point will be presented by eye (study eye, non-study eye, and either eye) and treatment group for MDTP only. For either eye summaries, the eye with the smaller corneal thickness will be summarized at baseline. For post baseline assessment, the eye with the greater decrease from baseline will be summarized. If both eyes have the same change from baseline, the eye with the smaller value will be summarized. Results of corneal pachymetry will be listed by individual subject.

# 12. CLINICAL PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

## 12.1 Pharmacokinetics Population and Pharmacodynamic Population

Pharmacokinetic Set

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

Pharmacodynamic Set

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

## 12.2 Pharmacokinetic Methods

All summaries and analyses of the PK data will be based on the Pharmacokinetic Set.

### 12.2.1 Concentration Data

Serial blood samples will be collected from each subject during this study to allow for the determination of the PK of SHP639 administered as SHP639 ophthalmic solution. Blood samples for PK analysis of SHP639 will be drawn according to the following schedule:

SDTP (Cohort A only): Day 1 - Predose, 30 min, 1, 2, 3, and 6 h

MDTP (all cohorts): For Days 1 and 27 - Predose, 30 min, 1, 2, 3, and 6 h

Plasma samples will be analyzed to determine the concentrations of SHP639 using a validated bioanalytical method based on liquid chromatography with mass spectrometry.

Individual plasma concentrations and time deviation data will be presented in a data listing. Plasma concentration data will be summarized by scheduled time-point using the following descriptive statistics: number of observations (n), arithmetic mean, standard deviation (SD), median, geometric mean, coefficient of variation (CV), minimum, and maximum.

The individual and mean plasma SHP639 concentration versus time profiles will be presented in figures on both linear and semi-logarithmic scales. Mean plasma concentration versus time profiles will be presented using nominal time and individual plasma concentration versus time profiles will be presented using actual time.

### 12.2.2 Handling Below the Limit of QuantificationValues

All plasma concentration values below the limit of quantification (BLQ) will be set to zero when calculating summary statistics.

For the calculation of PK parameters all plasma concentrations that are BLQ prior to the first measurable concentration will be set to zero. The BLQ values that are between measurable concentrations will be set to missing. The BLQ values following the last quantifiable time-points will be set to missing. No concentration estimates will be imputed for missing sample values. Any sample with a missing value will be treated as if the sample had not been scheduled for collection and will be ignored when calculating mean concentrations or PK parameters.

### 12.2.3 Pharmacokinetic Parameters

The following plasma PK parameters will be calculated for SHP639 on Day 1 for SDTP (Cohort A only) and on Day 1 and Day 27 for MDTP (all cohorts) by non-compartmental method using Phoenix® WinNonlin® version 6.4 or higher (Certara USA, Inc., Princeton, NJ).

| Parameter | Definition |
|---|---|
| $C_{max}$ | Maximum observed plasma concentration |
| $T_{max}$ | Time to reach maximum observed plasma concentration |
| $AUC_{0-\infty}$ | Area under the plasma-concentration time curve from time 0 extrapolated to infinity, calculated using the linear up/ log down trapezoidal rule |
| $AUC_{0-t}$ | Area under the plasma-concentration time curve from time 0 to the last measurable concentration, calculated using the linear up/ log down trapezoidal rule |
| $AUC_{0-\tau}$ | Area under the plasma-concentration time curve over a dosing interval for each multiple-dose regimen, calculated using the linear up/log down trapezoidal rule (Day 1 and Day 27 for MDTP of all cohorts) |
| $t_{1/2}$ | Apparent first-order terminal elimination half-life, calculated as $t_{1/2} = \ln 2/ Kel$ |
| Kel | Elimination rate constant estimated from the linear regression of the natural log-transformed concentration over time at the terminal phase. |
| $\%AUC_{ex}$ | Percentage of the area extrapolated for calculation of $AUC_{0-\infty}$ |
| CL/F | Apparent clearance, calculated as Dose/ $AUC_{0-\infty}$ for Day 1 for SDTP (Cohort A only) and Dose/ $AUC_{0-\tau}$ for Day 27 for MDTP (all cohorts) |
| Vz/F | Volume of distribution, calculated as $Vz/F = (CL/F)/\lambda z$ |
| $R_{ac(Cmax)}$ | Accumulation ratio based on $C_{max}$ for each multiple-dose regimen, calculated as $C_{max}$ (Day 27)/$C_{max}$ (Day 1) |
| $R_{ac(AUC)}$ | Accumulation ratio based on AUC for each multiple-dose regimen, calculated as $AUC_{0-\tau}$ (Day 27)/ $AUC_{0-\tau}$ (Day 1) |

All calculations for PK analysis will be based on actual sampling times. All PK analyses will be conducted by the Department of Clinical Pharmacology, PPD, Inc, Richmond, VA, USA.

All PK parameters will be presented in data listings and summarized in tables by dose, cohort, treatment, and study day, using descriptive statistics (n, mean, SD, median, maximum, minimum, geometric mean, and CV%. Geometric means will be reported for AUCs and $C_{max}$ only.

## 12.3 Statistical Analysis of Pharmacokinetic Data

For each of SD, QD, BID, TID and QID dosing regimens, if sufficient data are available across dose groups, dose proportionality of plasma SHP639 PK variables $AUC_{0-\infty}$, $AUC_{0-t}$, $AUC_{0-\tau}$, and $C_{max}$ over the dose ranges tested will be investigated. For Days 1 and 27 for MDTP of all cohorts, the following power model will be used to assess dose proportionality. The model is defined as:

ln(PK parameter) = a + b* ln(dose),

where 'a' is the intercept and 'b' is the slope of the line. The 95% confidence interval (CI) of the estimate of parameter 'b' will be presented. A 95% CI of the slope that includes 1.0 will be interpreted as the absence of significant evidence of non-proportionality.

For statistical analysis of accumulation of SHP639, a linear mixed-effect model with day, dose, and day and dose interaction term as fixed effects and subject as random effect will be fitted to the natural log-transformed $C_{max}$ and $AUC_{0-\tau}$ to construct 95% CIs for Day 27 compared with Day 1 for each of QD, BID, TID, and QID dosing regimens separately. Statistical analysis to assess dose proportionality and accumulation of SHP639 will be conducted using SAS for Windows® (Version 9.3 or higher).

## 12.4 Pharmacodynamic Methods

All the PD analyses will be performed using the Pharmacodynamic set. Intraocular pressure (IOP; mmHg), a PD biomarker, will be measured using Goldmann applanation tonometry.

Intraocular pressure will be measured according to the following schedule:

SDTP (Cohort A only): baseline (Days -2 and -1), Days 1 and 2, at Predose, 0.5, 1, 2, 3, 4, 6, 8, and 12 h

MDTP (Cohort A only): (all cohorts): baseline (Days -2 and -1), Days 1, 2, 27, and 28, at Predose, 0.5, 1, 2, 3, 4, 6, 8, and 12 h

MDTP (all cohorts): Days 7, 14, and 21 at Predose, 2, 4, 8, and 12 h

The individual and mean absolute IOP, IOP reduction from baseline and percentage of IOP reduction from baseline versus time profiles will be presented in figures. Mean plots will be presented using nominal time and individual plots will be presented using actual time.

In addition, the relationship of percentage of IOP reduction from baseline and dose of SHP639 will be presented in a Box-and-Whiskers plot.

Percentage of IOP reduction from baseline measurements data versus time will be used to estimate the PD parameters using Phoenix® WinNonlin® version 6.4 (Certara USA, Inc., Princeton, NJ) for each individual in each treatment by eye (study eye and non-study eye). Baseline is defined as the arthimetic mean of the time-matched IOP measurements on Days -2

and -1 for that particular subject. Potential effect of diurnal change on variation in IOP is accounted for by factoring time-matched baseline in the calculations of percent of IOP reduction from baseline measurements.

| Parameter | Definition |
|---|---|
| IOP reduction from baseline | IOP reduction from baseline is calculated as follows: Baseline IOP – IOP after treatment |
| % of IOP reduction from Baseline | Percentage of IOP reduction from baseline is calculated as follows: (Baseline IOP - IOP after treatment/ Baseline IOP) × 100 |
| $E_{max}$ | Maximum percent IOP reduction from baseline |
| $TE_{max}$ | Time of $E_{max}$ |
| $AUEC_{0-t}$ | Area under the effect curve for the percentage of IOP reduction from baseline versus time profile from time zero (predose) to the time of the last measurable percentage of IOP reduction from baseline, calculated using the linear up/log down interpolation rule. |
| $AUEC_{0-\tau}$ | Area under the effect curve for the percentage of IOP reduction from baseline versus time profile over a dosing interval, calculated using the linear up/log down interpolation rule. |
| $AUEC_{0-\infty}$ | Area under the effect curve for the percentage of IOP reduction from baseline versus time profile from time zero (predose) extrapolated to infinity, calculated using the linear up/log down interpolation rule. |

## 12.5 Statistical Analysis of Pharmacodynamic Data

Absolute IOP, IOP reduction from baseline, and percentage of IOP reduction from baseline will be listed by dose, cohort, subject, treatment period (single dose or multiple dose; Cohort A only), eye (study eye and non-study eye), study day and sample nominal time point. Descriptive summary statistics for absolute IOP, IOP reduction from baseline, percentage of IOP reduction from baseline, $E_{max}$, $TE_{max}$, $AUEC_{0-t}$, $AUEC_{0-\tau}$, and $AUEC_{0-\infty}$ (n, arithmetic mean, SD, 95% CI, median, maximum, minimum, geometric mean and geometric CV%) will be calculated by dose, cohort, treatment period, eye (study eye and non-study eye), study day, and sample nominal time point (for days with multiple assessments per day).

## 12.6 Analyses of Pharmacokinetic/Pharmacodynamic Relationships

If data permit, a potential relationship between concentrations of SHP639 ophthalmic solution and percentage of IOP reduction from baseline will be explored graphically using box plots; the

relationship between the PK and PD parameters for percentage of IOP reduction from baseline measurement will be presented graphically using scatter plots with regression line and the corresponding $R^2$ values.

# 13. INTERIM ANALYSIS

Shire's Dose Escalation Committee will be convened consisting of the coordinating principal investigator 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 interim analysis is planned for November, 2017. The safety and efficacy summaries for Part 1 of the study will be created using clean data, for the purpose of regulatory filing in Janurary 2018. Shire and PPD teams will be unmasked to treatments for subjects in Cohorts A and B as of the interim analysis, but will remain masked to treatments for subjects in Cohorts C and D until study completion

The interim analysis will consist of non period specific outputs (including but not limited to disposition, demographics, protocol violations, concomitant medications) and all MDTP outputs. Outputs to be generated for the interim analysis are denoted in the list of outputs in Section 16.

Following changes introduced in protocol amendment 3, all cohorts conducted after B3 (eg 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. Interim analysis of data from the repeat of Cohort B3 was conducted in June, 2018. Outputs for this interim analysis are denoted in the list of outputs in Section 16.

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

# 14. COMPUTER METHODS

All statistical analyses will be performed using SAS® Version 9.3 or higher (SAS Institute, Cary, NC 27513) on a suitably qualified environment.

# 15. DATA HANDLING CONVENTIONS

## 15.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, standard deviation, minimum, maximum. Categorical and count variables will be summarized by the number of subjects (n) and the percent of subjects in each category. Percentages will be presented as whole numbers.

## 15.2 Missing Date of Investigational Product

When the date of the last dose of investigational product is missing for a subject in the Safety set, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last visit date when investigational product was returned will be used in the calculation of treatment duration.

## 15.3 Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, including rescue medications, incomplete (ie, partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

### 15.3.1 Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

**Missing day and month**

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.

**Missing month only**

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

**Missing day only**

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day

- If either the year is before the year of the date of the first dose of investigational product or if both years are the same but the month is before the month of the date of the first dose of investigational product, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the date of the first dose of investigational product or if both years are the same but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.

### 15.3.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of investigational product is missing, then replace it with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

**Missing day and month**

- If the year of the incomplete stop date is the same as the year as of the date of the last dose of investigational product, then the day and month of the date of the last dose of investigational product will be assigned to the missing fields
- If the year of the incomplete stop date is before the year of the date of the last dose of investigational product, then 31 December will be assigned to the missing fields
- If the year of the incomplete stop date is after the year of the date of the last dose of investigational product, then 01 January will be assigned to the missing fields.

**Missing month only**

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

**Missing day only**

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of investigational product, then the day of the date of the last dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the last dose of investigational product or if both years are the same but the month is before the month of the date of the last dose of investigational product, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the last dose of investigational product or if both years are the same but the month is after the month of the date of the last dose of investigational product, then the first day of the month will be assigned to the missing day.

## 15.4 Missing Date Information for Adverse Events

For AEs, the default is to only impute incomplete (eg, partially missing) start dates. Incomplete stop dates may also be imputed when calculation of the duration of an AE is required per the protocol. If imputation of an incomplete stop date is required, and both the start date and the stop date are incomplete for a subject, impute the start date first.

### 15.4.1 Incomplete Start Date

Follow same rules as in Section 15.3.1.

### 15.4.2 Incomplete Stop Date

When required per the protocol, follow the same rules as in 15.3.2.

### 15.4.3 Incomplete Start/Stop Time

There is no imputation for missing start/stop time for AEs. In such cases, only the date part will be used to compare with the dosing date. If an AE start date is before the first dose of MDTP, it will be summarized in the SDTP outputs; if an AE start date is on or after the first dose of MDTP, it will be summarized in the MDTP outputs.

## 15.5 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of investigational product, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of investigational product, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

## 15.6 Missing Relationship to Investigation Product for Adverse Events

If the relationship to investigational product is missing for an AE starting on or after the date of the first dose of investigational product, a causality of "Related" will be assigned. The imputed values for relationship to double-blind investigational product will be used for incidence summaries, while the actual values will be presented in data listings.

## 15.7 Character Values of Clinical Laboratory Variables

If the reported value of a clinical laboratory variable cannot be used in a statistical analysis due to, for example, that a character string is reported for a numerical variable. The appropriately determined coded value will be used in the statistical analysis. The following rules will be followed to determine the coded value: if the reported values contain character strings of "<" or "≤", then coded value will be half of the original values. For example, if reported value is <5 then coded value will be 2.5. If the reported value contain character strings of ">" or "≥", then coded value will be twice of the original values. For example, if reported value is >5 then coded value will be 10. However, the actual values as reported in the database will be presented in data listings.

**Table 9 Examples for Coding of Special Character Values for Clinical Laboratory Variables**

| Clinical Laboratory Test | Possible Results (in SI units) | Coded Value for Analysis |
|---|---|---|
| Chemistry: ALT | < 5 | 2.5 |
| Chemistry: AST | < 5 | 2.5 |
| Chemistry: Total Bilirubin | < 2 | 1 |
| Urinalysis: Glucose | ≥ 55 | 110 |
| | ≤ 0 | 0 |
| Urinalysis: pH | > 8.0 | 16 |

## 15.8 Time Ranges for Analysis of Time Points

Subjects do not always adhere strictly to the visit schedule timing in the protocol. Mutually exclusive relative visit and time windows are defined below to provide the derived visits and time points that correspond to scheduled visits and time points. Assessments will be mapped to the corresponding visits and time points based on the visit and time window. Designation of visits and time points for assessments is tabulated below. If more than one assessment falls into a given visit and time window, the assessment closest to the planned visit and time will be used for analysis. If both assessments are equal distant from the planned assessment visit and timepoint, the earlier assessment will be used for analysis.

**Table 10 Visit and Time Ranges for Assessment at Every Schedule Visit and Time Point**

| Protocol Scheduled Visits | Visit Windows (Days) |
|---|---|
| Screening | ≥ -42 - ≤ -3 |
| Day -2 | -2 |
| Day -1 | -1 |
| Day 1 | 1 |
| Day 2 | 2 |
| Day 7 | ≥ 3 - ≤ 10 |
| Day 14 | ≥ 11 - ≤ 17 |
| Day 21 | ≥ 18 - ≤ 25 |
| Day 26 | 26 |
| Day 27 | 27 |
| Day 28 | 28 |

| | |
|---|---|
| Day 29 | 29 |
| Follow-up | > 29 |

For SDTP non-dosing days including Day -2, Day -1 and Day 2, the derived timepoints will be the same as the scheduled timepoints. For MDTP non-dosing days including Day -2, Day -1 and Day 29, the derived timepoints will also be the same as the scheduled time points. For both SDTP and MDTP dosing days, designation of timepoints for post-dosing assessments is tabulated below.

| **Protocol Scheduled TImepoints** | **Time Windows** |
|---|---|
| Predose | Predose |
| 0 m | > 0 m - ≤ 15 m |
| 30 m | > 15 m - ≤ 45 m |
| 1 h | > 45 m - ≤ 90 m |
| 2 h | > 90 m - ≤ 150 m |
| 3 h | > 150 m - ≤ 210 m |
| 4 h | > 210 m - ≤ 300 m |
| 6 h | > 300 m - ≤ 420 m |
| 8 h | > 420 m - ≤ 600 m |
| 12 h | > 600 m - ≤ 1440 m |

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|---|---|---|---|
| 14.3.2.1.1 | Ocular Treatment-emergent Adverse Events by Maximum Severity, System Organ Class, Preferred Term and Treatment Group – SDTP Dosing Period (Safety set) | Y | N |
| 14.3.2.1.2 | Ocular Treatment-emergent Adverse Events by Maximum Severity, System Organ Class, Preferred Term and Treatment Group – SDTP Dosing/Washout Period (Safety set) | Y | N |
| 14.3.2.1.3 | Nonocular Treatment-emergent Adverse Events by Maximum Severity, System Organ Class, Preferred Term and Treatment Group – SDTP Dosing Period (Safety set) | Y | N |
| 14.3.2.1.4 | Nonocular Treatment-emergent Adverse Events by Maximum Severity, System Organ Class, Preferred Term and Treatment Group – SDTP Dosing/Washout Period (Safety set) | Y | N |
| 14.3.2.1.5 | Ocular Treatment-emergent Adverse Events by Maximum Severity, System Organ Class, Preferred Term and Treatment Group – MDTP (Safety set) | Y | Y |
| 14.3.2.1.6 | Nonocular Treatment-emergent Adverse Events by Maximum Severity, System Organ Class, Preferred Term and Treatment Group – MDTP (Safety set) | Y | Y |
| 14.3.2.2.1 | Ocular Treatment-emergent Adverse Events Considered Related to Investigational Product by System Organ Class, Preferred Term and Treatment Group – SDTP Dosing Period (Safety set) | Y | N |
| 14.3.2.2.2 | Ocular Treatment-emergent Adverse Events Considered Related to Investigational Product by System Organ Class, Preferred Term and Treatment Group – SDTP Dosing/Washout Period (Safety set) | Y | N |
| 14.3.2.2.3 | Nonocular Treatment-emergent Adverse Events Considered Related to Investigational Product by System Organ Class, Preferred Term and Treatment Group – SDTP Dosing Period (Safety set) | Y | N |
| 14.3.2.2.4 | Nonocular Treatment-emergent Adverse Events Considered Related to Investigational Product by System Organ Class, Preferred Term and Treatment Group – SDTP Dosing/Washout Period (Safety set) | Y | N |

| Table | Title | Shire Std | Interim |
|---|---|---|---|
| 14.3.2.2.5 | Ocular Treatment-emergent Adverse Events Considered Related to Investigational Product by System Organ Class, Preferred Term and Treatment Group – MDTP (Safety set) | Y | N |
| 14.3.2.2.6 | Nonocular Treatment-emergent Adverse Events Considered Related to Investigational Product by System Organ Class, Preferred Term and Treatment Group – MDTP (Safety set) | Y | N |
| 14.3.3.1.1 | Ocular Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term and Treatment Group – SDTP Dosing Period (Safety set) | Y | N |
| 14.3.3.1.2 | Ocular Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term and Treatment Group – SDTP Dosing/Washout Period (Safety set) | Y | N |
| 14.3.3.1.3 | Nonocular Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term and Treatment Group – SDTP Dosing Period (Safety set) | Y | N |
| 14.3.3.1.4 | Nonocular Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term and Treatment Group – SDTP Dosing/Washout Period (Safety set) | Y | N |
| 14.3.3.1.5 | Ocular Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term and Treatment Group – MDTP (Safety set) | Y | N |
| 14.3.3.1.6 | Nonocular Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term and Treatment Group – MDTP (Safety set) | Y | N |
| 14.3.3.2.1 | Ocular Treatment-Emergent Adverse Events Leading to Withdrawal by System Organ Class and Preferred Term and Treatment Group – SDTP Dosing Period (Safety set) | Y | N |
| 14.3.3.2.2 | Ocular Treatment-Emergent Adverse Events Leading to Withdrawal by System Organ Class and Preferred Term and Treatment Group – SDTP Dosing/Washout Period (Safety set) | Y | N |

| Table | Title | Shire Std | Interim |
|---|---|---|---|
| 14.3.3.2.3 | Nonocular Treatment-Emergent Adverse Events Leading to Withdrawal by System Organ Class and Preferred Term and Treatment Group – SDTP Dosing Period (Safety set) | Y | N |
| 14.3.3.2.4 | Nonocular Treatment-Emergent Adverse Events Leading to Withdrawal by System Organ Class and Preferred Term and Treatment Group – SDTP Dosing/Washout Period (Safety set) | Y | N |
| 14.3.3.2.5 | Ocular Treatment-Emergent Adverse Events Leading to Withdrawal by System Organ Class and Preferred Term and Treatment Group – MDTP (Safety set) | Y | N |
| 14.3.3.2.6 | Nonocular Treatment-Emergent Adverse Events Leading to Withdrawal by System Organ Class and Preferred Term and Treatment Group – MDTP (Safety set) | Y | N |
| 14.3.3.4.1 | Ocular Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term and Treatment Group – SDTP Dosing Period (Safety set) | Y | N |
| 14.3.3.4.2 | Ocular Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term and Treatment Group – SDTP Dosing/Washout Period (Safety set) | Y | N |
| 14.3.3.4.3 | Nonocular Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term and Treatment Group – SDTP Dosing Period (Safety set) | Y | N |
| 14.3.3.4.4 | Nonocular Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term and Treatment Group – SDTP Dosing/Washout Period (Safety set) | Y | N |
| 14.3.3.4.5 | Ocular Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term and Treatment Group – MDTP (Safety set) | Y | N |
| 14.3.3.4.6 | Nonocular Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term and Treatment Group – MDTP (Safety set) | Y | N |
| 14.3.4.1.1 | Quantitative Clinical Laboratory Results by Visit and Treatment Group during SDTP Period: Hematology (Safety set) | Y | N |

| Table | Title | Shire Std | Interim |
|---|---|---|---|
| 14.3.4.1.2 | Quantitative Clinical Laboratory Results by Visit and Treatment Group during MDTP Period: Hematology (Safety set) | Y | Y |
| 14.3.4.1.3 | Quantitative Clinical Laboratory Results by Visit and Treatment Group during SDTP Period: Biochemistry (Safety set) | Y | N |
| 14.3.4.1.4 | Quantitative Clinical Laboratory Results by Visit and Treatment Group during MDTP Period: Biochemistry (Safety set) | Y | Y |
| 14.3.4.1.5 | Qualitative Clinical Laboratory Results by Visit and Treatment Group during SDTP Period: Urinalysis (Safety set) | Y | N |
| 14.3.4.1.6 | Qualitative Clinical Laboratory Results by Visit and Treatment Group during MDTP Period: Urinalysis (Safety set) | Y | Y |
| 14.3.4.2.1 | Potentially Clinically Important (PCI) Laboratory Results by Treatment Group in SDTP Period: Hematology (Safety set) | Y | N |
| 14.3.4.2.2 | Potentially Clinically Important (PCI) Laboratory Results by Treatment Group in MDTP Period: Hematology (Safety set) | Y | Y |
| 14.3.4.2.3 | Potentially Clinically Important (PCI) Laboratory Results by Treatment Group in SDTP Period: Biochemistry (Safety set) | Y | N |
| 14.3.4.2.4 | Potentially Clinically Important (PCI) Laboratory Results by Treatment Group in MDTP Period: Biochemistry (Safety set) | Y | Y |
| 14.3.4.2.5 | Potentially Clinically Important (PCI) Laboratory Results by Treatment Group in SDTP Period: Urinalysis (Safety set) | Y | N |
| 14.3.4.2.6 | Potentially Clinically Important (PCI) Laboratory Results by Treatment Group in MDTP Period: Urinalysis (Safety set) | Y | Y |
| 14.3.5.1.1 | Actual Values and Change from Baseline in Vital Signs by Visit and by Treatment Group – SDTP (Safety set) | Y | N |
| 14.3.5.1.2 | Actual Values and Change from Baseline in Vital Signs by Visit and by Treatment Group – MDTP (Safety set) | Y | Y |
| 14.3.5.2.1 | Potentially Clinically Important (PCI) Vital Signs Results by Treatment Group – SDTP (Safety set) | Y | N |

| Table | Title | Shire Std | Interim |
|---|---|---|---|
| 14.3.5.2.2 | Potentially Clinically Important (PCI) Vital Signs Results by Treatment Group – MDTP (Safety set) | Y | N |
| 14.3.6.1.1 | Actual Values and Change from Baseline in ECG by Visit and Treatment Group - SDTP (Safety set) | Y | N |
| 14.3.6.1.2 | Actual Values and Change from Baseline in ECG by Visit and Treatment Group - MDTP (Safety set) | Y | Y |
| 14.3.6.2.1 | ECG Interpretation by Visit and Treatment Group – SDTP (Safety set) | Y | N |
| 14.3.6.2.2 | ECG Interpretation by Visit and Treatment Group – MDTP (Safety set) | Y | Y |
| 14.3.6.3.1 | Potentially Clinically Important (PCI) ECG Results by Treatment Group - SDTP (Safety set) | Y | N |
| 14.3.6.3.2 | Potentially Clinically Important (PCI) ECG Results by Treatment Group – MDTP (Safety set) | Y | Y |
| 14.3.7.1.1 | Drop comfort Assessment Results by Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.1.2 | Drop comfort Assessment Results by Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.2.1 | Actual Values and Change from Baseline in Best-Corrected Visual Acuity (BCVA) by Visit and Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.2.2 | Actual Values and Change from Baseline in Best-Corrected Visual Acuity (BCVA) by Visit and Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.2.3 | BCVA Categorical Change from Baseline by Visit and Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.2.4 | BCVA Categorical Change from Baseline by Visit and Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.3.1 | Slit Lamp Biomicroscopy Findings by Visit and Treatment Group – SDTP (Safety set) | N | N |

| Table | Title | Shire Std | Interim |
|---|---|---|---|
| 14.3.7.3.2 | Slit Lamp Biomicroscopy Findings by Visit and Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.3.3 | Slit Lamp Examination Interpretation by Visit and Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.3.4 | Slit Lamp Examination Interpretation by Visit and Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.4.1 | Conjunctival Redness Results by Visit and Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.4.2 | Conjunctival Redness Results by Visit and Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.4.3 | Conjunctival Redness Interpretation by Visit and Treatment Group - SDTP (Safety set) | N | N |
| 14.3.7.4.4 | Conjunctival Redness Interpretation by Visit and Treatment Group - MDTP (Safety set) | N | Y |
| 14.3.7.4.5 | Conjunctival Redness Categorical Change from Baseline by Visit and Treatment Group - SDTP (Safety set) | N | Y |
| 14.3.7.4.6 | Conjunctival Redness Categorical Change from Baseline by Visit and Treatment Group - MDTP (Safety set) | N | Y |
| 14.3.7.5.1 | Corneal Haze Results by Visit and Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.5.2 | Corneal Haze Results by Visit and Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.5.3 | Corneal Haze Assessment Interpretation by Visit and Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.5.4 | Corneal Haze Assessment Interpretation by Visit and Treatment Group – MDTP (Safety set) | N | Y |

| Table | Title | Shire Std | Interim |
|---|---|---|---|
| 14.3.7.6.1 | Actual Values and Change from Baseline in Corneal Epithelial Integrity Total Scores by Visit and Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.6.2 | Actual Values and Change from Baseline in Corneal Epithelial Integrity Total Scores by Visit and Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.6.3 | Corneal Epithelium Integrity (Fluorescein Staining) Interpretation by Visit and Treatment Group - SDTP (Safety set) | N | N |
| 14.3.7.6.4 | Corneal Epithelium Integrity (Fluorescein Staining) Interpretation by Visit and Treatment Group - MDTP (Safety set) | N | Y |
| 14.3.7.7.1 | Anterior Chamber Cell and Flare Results by Visit and Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.7.2 | Anterior Chamber Cell and Flare Results by Visit and Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.7.3 | Anterior Chamber Cell and Flare Interpretation by Visit and Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.7.4 | Anterior Chamber Cell and Flare Interpretation by Visit and Treatment Group – MDTP (Safety set) | N | N |
| 14.3.7.8.1 | Lens Opacification Results by Visit and Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.8.2 | Lens Opacification Results by Visit and Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.8.3 | Lens Opacification Interpretation by Visit and Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.8.4 | Lens Opacification Interpretation by Visit and Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.9.1 | Actual Values and Change from Baseline in Intraocular Pressure (mmHg) by Treatment Group – SDTP (Safety set) | N | N |

| Table | Title | Shire Std | Interim |
|---|---|---|---|
| 14.3.7.9.2 | Actual Values and Percentage Change from Baseline in Intraocular Pressure (mmHg) by Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.9.3 | Actual Values and Change from Baseline in Diurnal (Schedule 1) Intraocular Pressure (mmHg) by Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.9.4 | Actual Values and Percentage Change from Baseline in Diurnal (Schedule 1) Intraocular Pressure (mmHg) by Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.9.5 | Actual Values and Change from Baseline in Diurnal (Schedule 2) Intraocular Pressure (mmHg) by Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.9.6 | Actual Values and Percentage Change from Baseline in Diurnal (Schedule 2) Intraocular Pressure (mmHg) by Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.9.7 | Actual Values and Change from Baseline in Intraocular Pressure (mmHg) by Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.9.8 | Actual Values and Percentage Change from Baseline in Intraocular Pressure (mmHg) by Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.9.9 | Actual Values and Change from Baseline in Diurnal (Schedule 1) Intraocular Pressure (mmHg) by Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.9.10 | Actual Values and Percentage Change from Baseline in Diurnal (Schedule 1) Intraocular Pressure (mmHg) by Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.9.11 | Actual Values and Change from Baseline in Diurnal (Schedule 2) Intraocular Pressure (mmHg) by Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.9.12 | Actual Values and Percentage Change from Baseline in Diurnal (Schedule 2) Intraocular Pressure (mmHg) by Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.10.1 | Posterior Segment Examination Results by Visit and Treatment Group – SDTP (Safety set) | N | N |

| Table | Title | Shire Std | Interim |
|---|---|---|---|
| 14.3.7.10.2 | Posterior Segment Examination Results by Visit and Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.10.3 | Actual Values and Change from Baseline Cup to Disc Ratios by Visit and Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.10.4 | Actual Values and Change from Baseline Cup to Disc Ratios by Visit and Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.10.5 | Posterior Segment Examination Notch Assessment by Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.10.6 | Posterior Segment Examination Notch Assessment by Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.10.8 | Categorical Change in Number of Notches by Treatment Group – MDTP (Safety set) | N | N |
| 14.3.7.11.1 | Gonioscopy Results by Visit and Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.11.2 | Gonioscopy Results by Visit and Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.12.1 | Actual Values and Change from Baseline in Noncontact Specular Microscopy (cells/mm^2) by Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.12.2 | Actual Values and Change from Baseline in Noncontact Specular Microscopy (cells/mm^2) by Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.13.1 | Actual Values and Change from Baseline in Corneal Pachymetry (um) by Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.13.2 | Actual Values and Change from Baseline in Corneal Pachymetry (um) by Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.13.3 | Actual Values and Percentage Change from Baseline in Corneal Pachymetry (um) by Treatment Group – MDTP (Safety set) | N | Y |

| Figure | Title | Shire Std | Interim |
|---|---|---|---|

| Figure | Title | Shire Std | Interim |
|---|---|---|---|
| 14.2.3.1.1 | Mean (+SD) Plasma Concentrations of SHP639 versus Time (Linear and Semilogarithmic Scales) (Pharmacokinetic Set) | Y | N |
| 14.2.3.1.2 | Individual Plasma Concentrations of SHP639 versus Time by Treatment (Linear and Semilogarithmic Scales) (Pharmacokinetic Set) | Y | N |
| 14.2.3.2.1 | Mean (+SD) Absolute IOP versus Time by Treatment (Pharmacodynamic Set) | Y | N |
| 14.2.3.2.2 | Mean (+SD) IOP Reduction from Baseline versus Time by Treatment (Pharmacodynamic Set) | Y | N |
| 14.2.3.2.3 | Mean (+SD) Percentage of IOP Reduction from Baseline versus Time by Treatment (Pharmacodynamic Set) | Y | N |
| 14.2.3.2.4 | Individual Absolute IOP versus Time by Treatment (Pharmacodynamic Set) | Y | N |
| 14.2.3.2.5 | Individual IOP Reduction from Baseline versus Time by Treatment (Pharmacodynamic Set) | Y | N |
| 14.2.3.2.6 | Individual Percentage of IOP Reduction from Baseline versus Time by Treatment (Pharmacodynamic Set) | Y | N |
| 14.2.3.2.7 | Relationship of Percentage of IOP Reduction from Baseline and Dose of SHP639 (Pharmacodynamic Set) | N | N |
| 14.2.3.2.8 | Relationship between Emax of Percentage of IOP Reduction from Baseline and Cmax for SHP639 (Pharmacokinetic and Pharmacodynamic Set) | N | N |
| 14.3.7.9.13 | Line Plots of Mean Intraocular Pressure (mmHg) by Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.9.14 | Line Plots of Change from Baseline in Intraocular Pressure (mmHg) by Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.9.15 | Line Plots of Percentage Change from Baseline in Intraocular Pressure (mmHg) by Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.9.16 | Line Plots of Mean Intraocular Pressure (mmHg) by Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.9.17 | Line Plots of Change from Baseline in Intraocular Pressure (mmHg) by Treatment Group – MDTP (Safety set) | N | Y |

| Figure | Title | Shire Std | Interim |
|---|---|---|---|
| 14.3.7.9.18 | Line Plots of Percentage Change from Baseline in Intraocular Pressure (mmHg) by Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.9.19 | Line Plots of Mean Intraocular Pressure (mmHg) for Study Eye by Treatment Group – MDTP (Safety set) | N | Y |
| 14.3.7.9.20 | Spaghetti Plots of Intraocular Pressure (mmHg) by Treatment Group – SDTP (Safety set) | N | N |
| 14.3.7.9.21 | Spaghetti Plots of Intraocular Pressure (mmHg) by Treatment Group – MDTP (Safety set) | N | Y |

| Listing | Title | Shire Std | Interim |
|---|---|---|---|
| 16.2.1.1.1 | Subject Disposition (Enrolled Set) | Y | Y |
| 16.2.1.1.2 | Screen Failure Subject Disposition (Enrolled Set) | Y | Y |
| 16.2.2.2 | Protocol Deviations (Randomized Set) | Y | Y |
| 16.2.4.1 | Subject Demographics (Randomized Set) | Y | Y |
| 16.2.4.3 | Medical History (Randomized Set) | Y | Y |
| 16.2.4.4.1 | Prior Medications (Safety set) | Y | Y |
| 16.2.4.4.2 | Concomitant Medications (Safety set) | Y | Y |
| 16.2.5.2.1 | Treatment Exposure (Safety set) | N | Y |
| 16.2.5.2.2 | Treatment Exposure – Subjects Who Received Unrefrigerated Drug Only (Safety set) | N | Y |
| 16.2.5.3.1 | Individual Plasma Concentrations (unit) of SHP639 (Safety set) | Y | N |
| 16.2.5.3.2 | Individual Plasma Pharmacokinetic Parameters of SHP639 (Pharmacokinetic Set) | Y | N |
| 16.2.5.3.3 | Listing of Absolute IOP, IOP Reduction from Baseline, and Percentage of IOP Reduction from Baseline (Safety set) | Y | N |

| Listing | Title | Shire Std | Interim |
|---|---|---|---|
| 16.2.5.3.4 | Listing of Pharmacodynamic Parameters of Percentage of IOP Reduction from Baseline (Pharmacodynamic Set) | Y | N |
| 16.2.6.1 | Drop Comfort Assessment Results (Safety set) | N | Y |
| 16.2.6.2 | Manifest Refraction Results (Safety set) | N | Y |
| 16.2.6.3 | Best Corrected Visual Acuity (BCVA) Results (Safety set) | N | Y |
| 16.2.6.4 | Slit Lamp Biomicroscopy Results (Safety set) | N | Y |
| 16.2.6.5 | Clinically Significant Slit Lamp Biomicroscopy Results (Safety set) | N | Y |
| 16.2.6.6 | Conjunctival Redness Score Assessment Results and Interpretation (Safety set) | N | Y |
| 16.2.6.7 | Corneal Haze Score Assessment Results and Interpretation (Safety set) | N | Y |
| 16.2.6.8 | Corneal Epithelium Integrity Results and Interpretation (Safety set) | N | Y |
| 16.2.6.9 | Anterior Chamber Cell and Flare Results and Interpretation (Safety set) | N | Y |
| 16.2.6.10 | Lens Opacification Results and Interpretation (Safety set) | N | Y |
| 16.2.6.11 | Intraocular Pressure Results and Interpreation (Safety set) | N | Y |
| 16.2.6.12 | Posterior Segment Examination Results and Interpretation (Safety set) | N | Y |
| 16.2.6.13 | Gonioscopy Results and Interpretation (Safety set) | N | Y |
| 16.2.6.14 | Noncontact Specular Microscopy Results and Interpretation (Safety set) | N | Y |
| 16.2.6.15 | Corneal Pachymetry Results and Interpreation (Safety set) | N | Y |
| 16.2.7.1 | Adverse Events (Safety set) | Y | Y |
| 16.2.7.2 | Serious Adverse Events (SAE) (Safety set) | Y | Y |
| 16.2.7.3 | Adverse Events Leading to Withdrawal (Safety set) | Y | Y |
| 16.2.7.5 | Adverse Events Leading to Death (Safety set) | Y | Y |

| Listing | Title | Shire Std | Interim |
|---|---|---|---|
| 16.2.8.1.2 | Clinical Laboratory Test Results (Safety set) | Y | Y |
| 16.2.8.1.3 | Subjects with Potentially Clinically Important Laboratory Test Results (Safety set) | Y | Y |
| 16.2.8.1.4 | Listing of Antidrug Antibody Results (Safety set) | N | N |
| 16.2.8.2.1 | Vital Signs (Safety set) | Y | Y |
| 16.2.8.2.2 | Subjects with Potentially Clinically Important Vital Signs (Safety set) | Y | Y |
| 16.2.8.3.1 | Lead ECG Results and Interpretation by Central Reader (Safety set) | Y | Y |
| 16.2.8.3.2 | Subjects with Potentially Clinically Important ECG Results (Safety set) | Y | Y |