STATISTICAL ANALYSIS PLAN

Protocol No.:	SHP640-301
Protocol Title:	A Phase 3, Multi-center, Randomized, Double-Masked Study to Evaluate the Clinical Efficacy and Safety of SHP640 (PVP-Iodine 0.6% and Dexamethasone 0.1%) Ophthalmic Suspension Compared to PVP-Iodine and Placebo in the Treatment of Adenoviral Conjunctivitis
Drug:	SHP640
Sponsor:	Shire 300 Shire Way, Lexington, MA 02421 USA
Version No. and Date	Protocol Amendment 3: 13 December, 2017

Version No:	Document History Description of Update	Author(s)	Effective Date
Version 1.0	Final Version	[redacted]	24 June, 2019

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ABBREVIATIONS

AE	adverse event
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
CC-IFA	cell culture-immunofluorescence assay
CFU	colony forming unit
CI	confidence interval
CRF	case report form
eCRF	electronic case report form
GCS	Global clinical score
HSV	Herpes Simplex Virus
IRT	interactive response technology
ITT	Intent To Treat
LOCF	last observation carried forward
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent To Treat
PT	Preferred Term
PVP-I	povidone-iodine
qPCR	quantitative polymerase chain reaction
RPS	Rapid Pathogen Screening, Inc.
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SE	standard error
TEAE	treatment-emergent adverse event
VBR	Validated Bulbar Redness
WHO-DD	World Health Organization – Drug Dictionary
WOCF	worst observation carried forward

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy and safety data as described in the final study protocol amendment 4.0 dated April 5, 2019. Specifications for tables, figures, and listings are contained in a separate document.

2. STUDY DESIGN

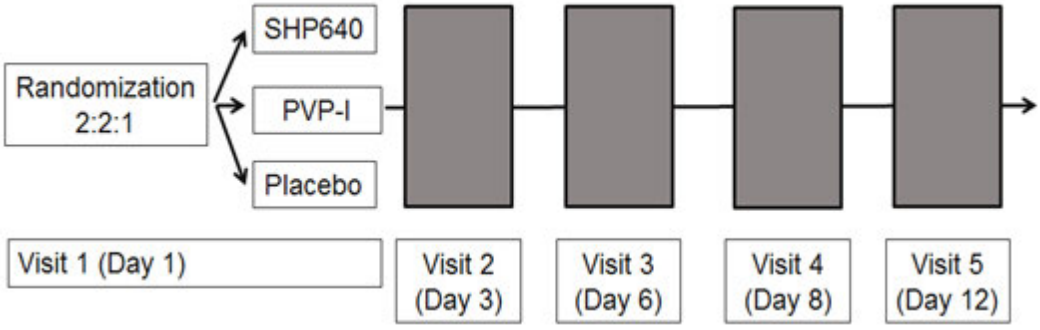
2.1 General Study Design

SHP640-301 is a global, multi-center, randomized, double-masked, parallel group, placebo controlled study designed to demonstrate the safety and efficacy of SHP640 (povidone-iodine [PVP-I] 0.6% and dexamethasone 0.1%) ophthalmic suspension compared to PVP-I 0.6% ophthalmic solution and to placebo in treating adenoviral conjunctivitis.

Once screening and baseline assessments are complete and subjects are confirmed eligible to enroll in the study, subjects will be randomized, and investigational product will be administered on the same day (Day 1). The first dose will be administered by site staff on Day 1, and thereafter subjects will administer 1 drop in each eye 4 times a day (QID) for 7 days. Additional visits will occur on Day 3 (Visit 2), Day 6 (Visit 3), Day 8 (Visit 4), and Day 12 (Visit 5). All follow-up procedures will be conducted at Visit 5 (Day 12). The study will last up to 15 days.

Figure 1 provides the study design.

Figure 1: SHP640-301 Study Design



2.2 Randomization

This is a double-masked, placebo-controlled study. The actual treatment given to individual subject is determined by a randomization schedule.

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

The randomization number represents a unique number corresponding to investigational product allocated to the subject, once eligibility has been determined. Individual subject treatment is automatically assigned by the interactive response technology (IRT).

Approximately 540 subjects will be randomized into the study at Visit 1 (Day 1). Randomization will be stratified by age strata: subjects < 6 years, 6 to <18 years and ≥18 years. Subjects will be randomized 2:2:1 to receive either SHP640, PVP-I, or placebo within each stratum.

Multiple subjects from the same household will be eligible to participate in the study. Subjects from the same household will be assigned to the same treatment group to which the first enrolled subject in the household was randomized in order to prevent treatment administration errors (switching of the assigned treatment) or potential treatment unmasking. Dynamic balanced randomization (Pocock and Simon, 1975) will be used in this study to maintain the randomization ratio within each stratum. The randomization will be done centrally.

2.3 Masking

This is a double-masked study. The packaging, appearance, and labeling of the test products will match. Colorant will be added to the placebo to match the appearance of SHP640 ophthalmic suspension and the PVP-I ophthalmic solution.

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

In the event that the treatment assignment is broken, the date and person who broke the code will be recorded by the IRT and the reason for breaking will be recorded on the electronic case report form (eCRF). Upon breaking the mask, the subject is withdrawn from the study, but should complete Visit 5 (the end of study visit) assessments for safety purposes. Any code-breaks that occur must be reported to the Sponsor medical monitor.

The final unmasking of the data will occur after all the data has been received, appropriately reviewed and checked, and the database has been locked per Shire's SOPs. Final analyses will be performed after the official database release using the unmasked data.

2.4 Schedule of Assessments

below presents a schematic of the study design.

Table 1 Schedule of Assessments

Procedure (All ocular assessments and procedures performed bilaterally)	**Visit 1 Screening[a] & Baseline (Day 1) -1 Day**	**Visit 2 (Day 3) +1 Day**	**Visit 3 (Day 6)**	**Visit 4 (Day 8) +1 Day**	**Visit 5[b] (Day 12) +2 Days**
Informed consent/assent[a]	X				
Inclusion/exclusion criteria[a]	X				
Medical history	X				
Demographics	X				
Concomitant medications	X	X	X	X	X
Urine pregnancy test	X[c]				X[c]
Ocular Discomfort Scale	X	X	X	X	X
Best corrected visual acuity	X	X	X	X	X
Slit lamp biomicroscopy	X	X	X	X	X
Bulbar conjunctival injection evaluation	X	X	X	X	X
Watery conjunctival discharge evaluation	X	X	X	X	X
AdenoPlus® test	X[d]				
Conjunctival swab for viral culture[e]	X[l]	X[f]	X[f]	X[f]	X[f]
Non-dilated/ dilated fundus examination[g]	X				X
Randomization[h]	X				
Dispense investigational product[i]	X				
Instill investigational product	X[j]	X[j]	X[j]		
Collect investigational product				X	X[b]
Compliance assessment		X	X	X	X[b]
Drug accountability				X	X[b]

Table 1 Schedule of Assessments

Procedure (All ocular assessments and procedures performed bilaterally)	Visit 1 Screening[a] & Baseline (Day 1) -1 Day	Visit 2 (Day 3) +1 Day	Visit 3 (Day 6)	Visit 4 (Day 8) +1 Day	Visit 5[b] (Day 12) +2 Days
Adverse events	X[k]	X	X	X	X
Study completion					X

CC-IFA= cell culture-immunofluorescence assay; HSV= herpes simplex virus; qPCR= quantitative polymerase chain reaction;

[a] Informed consent and confirmation of inclusion/exclusion criteria can be conducted on Day -1; Inclusion/Exclusion must be re-confirmed on Day 1.

[b] If investigational product is discontinued, regardless of the reason, all discontinued subjects should proceed to Visit 5 whenever possible. Subjects that discontinue the study and proceed to Visit 5 should perform all Visit 5 assessments as well as drug return, compliance and accountability.

[c] Women of childbearing potential, prior to enrollment and at exit from the study.

[d] If not previously conducted within 24 hours of Visit 1 (Day 1).

[e] One swab sample from inferior conjunctival cul-de-sac of each eye will be collected for all viral testing. If the CC-IFA test is positive, qPCR will be performed. Adenoviral serotyping will be conducted at baseline only.

[f] Conjunctival swab samples MUST be taken at least 12 hours after the last dose of investigational product at Visits 2, 3, 4 and ET, if applicable.

[g] If a non-dilated fundus exam is not feasible, a dilated examination should be conducted. For each subject, the exam should be conducted the same way (either non-dilated or dilated) at both Visit 1 and Visit 5 (or ET).
[h] All assessments, randomization, and investigational product instillation on Day 1 must take place with sufficient time to allow all 4 Day 1 doses (with a minimum of 2 hours between doses)

[i] The investigational product bottle should be shaken well prior to use at each dosing. The first dose will be administered by site staff on Day 1, and thereafter subjects will administer 1 drop in each eye 4 times a day for 7 days.

[j] Investigational product instillation should only be performed in-office if it is necessary.

[k] Monitoring for adverse events will begin after informed consent is obtained. Information about unresolved AEs at the time of study exit (eg, resolution status, resolution date, treatment received for AE) and related information (eg, data from any assessments conducted to follow up on the status of unresolved AE) for a period of up to 14 days after subject exit may be collected by the Sponsor. Corneal AEs that are ongoing at the end of study visit should be followed up by the site until resolution or stabilization and all related information should be collected in the CRF.

[l] This sample will be used for baseline HSV testing for all subjects. For subjects <2 months of age, testing will also be conducted using the same sample for chlamydia and gonorrhea detection.

2.5 Determination of Sample Size

The sample size was estimated for the primary comparison and key secondary comparisons of SHP640 ophthalmic suspension to placebo and to PVP-I, respectively, by using nQuery Advisor 7.0. Subjects will be randomized in a 2:2:1 ratio to receive either SHP640 ophthalmic suspension, PVP-I, or placebo within each stratum.

The primary efficacy endpoint is clinical resolution (defined as absence of bulbar conjunctival injection and watery conjunctival discharge) in the study eye at Visit 3 (Day 6). The null hypothesis to be tested is that there is no difference in proportion of subjects with clinical resolution in the study eye between SHP640 ophthalmic suspension and placebo with the alternative of the non-zero difference in the proportion with clinical resolution between them.

A sample size of 350 subjects (140 subjects in each of SHP640 and PVP-I groups, 70 subjects in placebo) will ensure 90% power to compare the SHP640 and placebo treatment groups assuming 31% and 11% subjects with clinical resolution respectively using Fisher's Exact test at two-sided 5% level of significance.

The first key secondary efficacy comparison is to compare the proportion of subjects achieving at least 2 points reduction from baseline in global clinical score (GCS) at Visit 3 (Day 6) between SHP640 and PVP-I. The null hypothesis to be tested is that there is no difference in proportion of subjects with at least 2 points reduction from baseline in GCS in the study eye between SHP640 ophthalmic suspension and PVP-I with the alternative of the non-zero difference in the proportion with at least 2 points reduction from baseline in GCS between them.

A sample size of 350 subjects (140 subjects in each of SHP640 and PVP-I groups, 70 subjects in placebo) will also ensure 98% power to compare SHP640 and PVP-I treatment groups assuming 90% and 70% subjects with at least 2 points reduction from baseline in global clinical score at Visit 3 (Day 6) respectively using Fisher's Exact test at two-sided 5% level of significance.

The assumed proportions of subjects with clinical resolution in the three treatment arms are based on response rates observed in FST100-AVC-004 with a dropout rate of approximately 6% prior to Visit 3 in FST100-AVC-004 modified Intent-to-Treat (mITT) population which excluded subjects with no post baseline data. The dropout rate would become approximately 8% if FST100-AVC-004 mITT population included subjects with no post baseline data.

All efficacy analyses will be based on the mITT population (refer to Section 4.4 for the definition of mITT). Assuming a 35% reduction from randomized to the mITT, approximately 540 subjects (i.e. approximately 216 in each of SHP640 and PVP-I group and approximately 108 in placebo group) will be randomized in this study.

2.6 Multiplicity Adjustments for Type I Error Control

Multiplicity adjustment is not applicable and no hypothesis testing will be conducted for any efficacy endpoints since the study was terminated early.

3. OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of SHP640 based on clinical resolution (defined as absence of bulbar conjunctival injection and watery conjunctival discharge) compared with placebo in the treatment of subjects with adenoviral conjunctivitis in the study eye at Visit 3 (Day 6).

3.2 Secondary Objective

Key secondary objectives of this study are as follows:

- To evaluate the efficacy of SHP640 based on ≥2 point reduction from baseline on the global clinical score compared with PVP-I in the treatment of subjects with adenoviral conjunctivitis in the study eye at Visit 3 (Day 6).
- To evaluate the efficacy of PVP-I based on adenoviral eradication (defined as negative cell culture-immunofluorescence assay [CC-IFA]) compared with placebo in the treatment of subjects with adenoviral conjunctivitis in the study eye at Visit 2 (Day 3).
- To evaluate the efficacy of SHP640 based on adenoviral eradication compared with placebo in the treatment of subjects with adenoviral conjunctivitis in the study eye at Visit 3 (Day 6).
- To evaluate the efficacy of SHP640 based on adenoviral eradication compared with PVP-I in the treatment of subjects with adenoviral conjunctivitis in the study eye at Visit 3 (Day 6).
- To evaluate the efficacy of PVP-I based on ≥2 point reduction from baseline on global clinical score compared with placebo in the treatment of subjects with adenoviral conjunctivitis in the study eye at Visit 3 (Day 6).

Secondary objectives of this study are as follows:

- To evaluate the effect of treatment in the study eye, for the following endpoints:
    - Adenovirus viral titer assessed by quantitative polymerase chain reaction (qPCR) at Visit 3 (Day 6) and 4 (Day 8)
    - Adenoviral eradication as assessed by CC-IFA at Visits 4 (Day 8) and 5 (Day 12)
    - Clinical resolution of adenoviral conjunctivitis at Visits 2 (Day 3), 4 (Day 8) and 5 (Day 12)

  - Individual clinical signs (bulbar conjunctival injection and watery conjunctival discharge) at Visits 2 (Day 3), 3 (Day 6), 4 (Day 8) and 5 (Day 12)
  - The global clinical score (GCS) (sum of bulbar conjunctival injection and watery conjunctival discharge) and change from baseline in the global clinical score at Visits 2 (Day 3), 3 (Day 6), 4 (Day 8) and 5 (Day 12)
  - At least 2 point reduction from baseline on global clinical score at Visits 2 (Day 3), 4 (Day 8) and 5 (Day 12)
  - Modified clinical resolution, defined as a global clinical score of 0 or 1, at Visits 2 (Day 3), 3 (Day 6), 4 (Day 8) and 5 (Day 12)
  - Expanded clinical resolution, defined as a global clinical score of 0, 1, or 2 with neither injection nor discharge having a score of 2, at Visits 2 (Day 3), 3 (Day 6), 4 (Day 8) and 5 (Day 12)
  - Time to clinical resolution based upon assessments at Visits 2 (Day 3), 3 (Day 6), 4 (Day 8), and 5 (Day 12)
- To assess the status of cross-over infection (as assessed by CC-IFA) to a subject's fellow eye at Visits 2 (Day 3), 3 (Day 6), 4 (Day 8) and 5 (Day 12) for subjects with only 1 infected eye at baseline.
- To evaluate the safety and tolerability (including local tolerability) of SHP640 compared to PVP-I and placebo in the treatment of subjects with adenoviral conjunctivitis.

3.3 Exploratory Objective

The exploratory objectives of this study are as follows:

- [redacted]

4. SUBJECT POPULATION SETS

4.1 Screened Population

The Screened Population will consist of all subjects who have provided written informed consent.

4.2 Safety Population

The Safety Population will consist of all subjects who receive at least one dose of investigational product.

4.3 Intent to Treat (ITT) Population

The ITT Population will include all randomized subjects.

4.4 Modified Intent to Treat (mITT) population

The mITT Population consists of a subset of the ITT population who receive at least one dose of investigational product and have a positive CC-IFA adenovirus test at baseline in the study eye.

Analyses conducted using the ITT and mITT will be based upon the treatment assigned while analyses conducted using the Safety Analysis Set will be based upon the treatment received.

5. SUBJECT DISPOSITION

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

The number of subjects included in each subject population (ie, Screened, Safety, ITT and mITT) will be summarized by randomized treatment group, age strata and overall except for the Screened Set, which will be summarized for all subjects only.

The number and percentage of subjects who completed and prematurely discontinued during the Double-masked Evaluation Phase will be presented for each treatment group, age strata and overall. Reasons for premature discontinuation from the Double-masked Evaluation Phase as recorded on the termination page of the eCRF will be summarized (number and percentage) by treatment group, age strata and overall. All percentages will be based on the number of subjects in the ITT Population.

A listing of disposition will be provided for all subjects. All subjects who prematurely discontinued during the Double-masked Evaluation Phase will be listed by discontinuation reason.

6. PROTOCOL DEVIATIONS

Protocol deviations will be recorded by the site monitors separately from the clinical database. Protocol deviations will be listed for subjects in the ITT Population.

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive summaries of demographic and baseline characteristics will be presented by treatment group and overall for Safety population, ITT population and mITT population.

The following demographic characteristics will be summarized in the following order in the tables: age, age strata (< 6 years [0-27 days], 6 to <18 years and ≥18 years), sex, ethnicity and race. In addition, iris color in the study eye will be summarized.

Percentages will be based on the total number of subjects in each treatment group.

A listing will be generated for demographic and baseline characteristics for the ITT Population with flags indicating whether the subject is in the Safety Population and mITT population.

A listing of ocular and non-ocular medical history will be provided for the Safety Population.

8. EXTENT OF EXPOSURE

Exposure to double-masked investigational product for the Safety Population will be summarized in terms of 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-masked investigational product taken, inclusively, and irrespective of any investigational product interruption(s). Descriptive statistics will be presented by treatment group and overall.

Listings of investigational product exposure and study drug withheld will be provided for all subjects in the Safety Population.

9. PRIOR AND CONCOMITANT MEDICATION

All medications will be coded using the World Health Organization – Drug Dictionary (WHO-DD) Version 01SEP2016 categorized by anatomical therapeutic class (ATC) and preferred term. Medications/therapies/procedures will be further categorized as ocular or non-ocular by the investigator based on the indication for which the medication/therapy/procedure was used.

Prior medication/therapy/procedure is defined as any medication/therapy/procedure with a start date prior to the date of the first dose of investigational product.

Concomitant medication/therapy is defined as any medication/therapy with a start date prior to the date of the first dose of investigational product and continuing after the first dose of investigational product or with a start date between the dates of the first and last doses of investigational product, inclusively. Concomitant procedure is defined as any procedure with a start date between the dates of the first and last doses of investigational product, inclusively. Any medication/therapy/procedure with a start date after the date of the last dose of investigational product will not be considered a concomitant medication/therapy/procedure. Medications/therapy/procedure will be further categorized as ocular or non-ocular by the investigator based on the indication for which the medication/therapy/procedure was used.

Medications can be considered both as prior and concomitant medication.

All prior and concomitant medication will be listed. Prior and concomitant therapy/procedure will also be listed. Imputed dates (see Section 18.6 for imputation rules) will be marked in the listings.

Medication/therapy/procedure with a start date after the date of the last dose of investigational product will also be listed.

10. EFFICACY ANALYSES

All efficacy summaries will be based on the mITT unless stated otherwise. Baseline for all efficacy analyses is defined as the value for the efficacy assessment at Visit 1.

All confidence intervals (CIs) will be 2-sided 95% CIs.

All efficacy analyses will be conducted according to the treatment assigned.

All efficacy endpoints will be listed in the ITT Population. The listing will include a flag to indicate whether the subject is in mITT.

10.1 Study Eye Designation

The study eye for analyses will be defined as follows, where an eligible eye is an eye with a score of at least 1 for both watery conjunctival discharge and bulbar conjunctival redness at baseline:

- For subjects with both eyes eligible and both with a positive CC-IFA result at baseline or both eyes eligible and both with a negative CC-IFA result at baseline, the study eye will be the eye with the highest global clinical score (refer to Section 3.2) at baseline. If both eyes have the same global clinical score at baseline, then the study eye will be the right eye.
- For subjects with both eyes eligible with a positive CC-IFA result in one eye at baseline, the baseline CC-IFA positive eye will be the study eye.
- For subjects with only one eligible eye, the eligible eye will be the study eye irrespective of its baseline CC-IFA status.

The eye other than the study eye is considered the fellow eye in all safety and efficacy analyses.

10.2 Primary, Key Secondary and Secondary Efficacy Endpoints and Analysis

Primary efficacy Endpoint:

- The clinical resolution status of adenoviral conjunctivitis at Visits 3 (Day 6) in the study eye

Key secondary efficacy endpoint:

- ≥2 point reduction from baseline on GCS at Visit 3 (Day 6) in the study eye
- Adenoviral eradication status (defined as negative cell culture-immunofluorescence assay [CC-IFA]) at Visits 2 (Day 3) and 3 (Day 6) in the study eye

Secondary efficacy endpoints are defined as follows:

- Absolute and change from baseline in adenovirus viral titer as assessed by qPCR at Visit 3 (Day 6) and 4 (Day 8) in the study eye
- Adenoviral eradication status as assessed by CC-IFA at Visits 4 (Day 8) and 5 (Day 12) in the study eye
- The clinical resolution status of adenoviral conjunctivitis at Visits 2 (Day 3), 4 (Day 8) and 5 (Day 12) in the study eye
- The individual clinical signs score (bulbar conjunctival injection and watery conjunctival discharge) and change from baseline at Visits 2 (Day 3), 3 (Day 6), 4 (Day 8) and 5 (Day 12) in the study eye
- The global clinical score (as defined as the sum of bulbar conjunctival injection and watery conjunctival discharge) and change from baseline in the global clinical score at Visits 2 (Day 3), 3 (Day 6), 4 (Day 8) and 5 (Day 12) in the study eye
- At least 2 point reduction from baseline on global clinical score at Visits 2 (Day 3), 4 (Day 8) and 5 (Day 12) in the study eye
- Modified clinical resolution status, defined as a global clinical score of 0 or 1, at Visits 2 (Day 3), 3 (Day 6), 4 (Day 8) and 5 (Day 12) in the study eye
- Expanded clinical resolution status, defined as a global clinical score of 0, 1, or 2 with neither injection nor discharge having a score of 2, at Visits 2 (Day 3), 3 (Day 6), 4 (Day 8) and 5 (Day 12) in the study eye
- Time to clinical resolution based upon assessments at Visits 2 (Day 3), 3 (Day 6), 4 (Day 8), and 5 (Day 12) in the study eye
- The status of cross-over infection (as assessed by CC-IFA) to a subject's fellow eye at Visits 2 (Day 3), 3 (Day 6), 4 (Day 8) and 5 (Day 12) for subjects with only 1 infected eye at baseline

No hypothesis testing will be conducted for the efficacy endpoints. Clinical resolution status, ≥2 point reduction from baseline on GCS and adenoviral eradication status efficacy endpoints will be summarized by treatment group using descriptive statistics at each assessment visit in the mITT Population. Clinical resolution status will also be summarized by treatment group using descriptive statistics at each assessment visit in the ITT Population. These binary endpoints will be summarized by number of subjects (n), frequency, proportion and two-sided 95% CI (exact CI for binominal proportion). Other secondary endpoints will not be summarized by treatment group.

No hypothesis testing will be conducted for any efficacy endpoints.

All efficacy endpoints will be listed in ITT with a flag indicating whether the subject is in mITT population.

Appendix 20.1 shows example SAS code for generating descriptive statistics:

10.3 Exploratory Efficacy Endpoints and Analyses

11. SAFETY ANALYSES

The safety analysis will be performed using the Safety Population. Safety variables include adverse events (AEs, including local tolerability), slit lamp biomicroscopy, non-dilated/dilated fundus exam, red reflex exam, best corrected visual acuity (BCVA), and urine pregnancy testing (for females of childbearing potential) variables. Safety data collected at baseline (Visit 1) will be used as the baseline value for safety analysis. All safety analyses will be conducted according to the treatment the subject actually received.

11.1 Adverse Events

AEs will be coded using MedDRA version 19.1. Any AE that occurs after the first dose of investigational product instillation will be considered a treatment- emergent adverse event (TEAE).

An overall summary of the number of subjects with TEAEs will be presented, including the number and percentage of subjects with any TEAEs, ocular TEAEs, non-ocular TEAEs, TEAEs leading to death, serious TEAEs, TEAEs related to investigational product and TEAEs leading to discontinuation of investigational product as well as the total number of events in each category.

The number and percentage of subjects reporting TEAEs in each treatment group and across all subjects will be tabulated by System Organ Class (SOC) and Preferred Term (PT) as well as by SOC, PT, and maximum severity. TEAEs considered related to investigational product will also be summarized by SOC and PT. If more than 1 AE occurs with the same SOC/PT for the same subject, then the subject will be counted only once for that SOC/PT using the most severe and most related occurrence for the summarization by severity and by relationship to investigational product, respectively. The incidence of common TEAEs (≥ 5% of subjects in any treatment group) will also be summarized by SOC and PT. Serious TEAEs, TEAEs leading to discontinuation of investigational product and TEAEs leading to death, will be summarized by SOC, PT and treatment group and across all subjects. The number and percentage of subjects reporting local tolerability TEAEs (overall, related to IP and not related to IP) in each treatment group and across all subjects will also be tabulated by SOC and PT. PTs that are considered to be local tolerability AEs will be provided by global drug safety (GDS) before database lock. Separate tables will be generated for ocular TEAEs and non-ocular TEAEs. For all above tables, ocular TEAEs will be summarized at subject level and also by study eye, fellow eye and both eyes.

Listings of all TEAEs will be provided by subject.

Pre-treatment events (captured on the AE form that occurred prior to the first dose of investigational product) will be listed by subject but not tabulated.

Imputed dates, severity and relationship (see Section 18.7, 18.8 and 18.9 respectively for imputation rules) to investigational product will be marked in the listings.

11.2 Other Safety Variables

The following safety measures will be descriptively summarized by study eye and fellow eye and by treatment group and across all subjects at each visit:

- Best corrected visual acuity (BCVA, logMAR scoring) and change from baseline BCVA
- Slit lamp biomicroscopy (normal, abnormal – not clinically significant, abnormal – clinically significant) for 6 anatomic anterior segment regions: lids, conjunctiva, cornea, iris, anterior chamber and lens
- Non-dilated/ Dilated Fundus examination (normal, abnormal – not clinically significant, abnormal – clinically significant) for 3 anatomic posterior segment regions: vitreous, optic nerve and macula
- Red reflex examination (normal, abnormal– not clinically significant, abnormal – clinically significant) for infants and small children in whom a fundus examination cannot be done

Continuous endpoints will be summarized by number of subjects (n), mean, median, SD, SE, minimum and maximum. Binary endpoints will be summarized by number of subjects (n), frequency and percentage.

BCVA/change from baseline BCVA and slit lamp biomicroscopy at each visit as well as non-dilated/ dilated fundus examination (or red reflex exam for infants and small children in whom a fundus examination cannot be done) and pregnancy test results at visits 1 and 5/early termination will be provided by subject in Safety Population in data listings. A by subject listing will also be generated for chlamydia and gonorrhea results at Visit 1 in Safety Population in subjects less than 2 month of age and for Herpes Simplex Virus (HSV) at Visit 1 in Safety Population.

12. CLINICAL PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

N/A.

13. OTHER ANALYSES

There is no other analysis planned for this study.

14. INTERIM ANALYSIS

There is no interim analysis in this study.

15. DATA MONITORING/REVIEW COMMITTEE

There is no data monitoring committee for this study.

16. COMPUTER METHODS

Statistical analyses will be performed using Version 9.2 (or higher) of SAS® on a suitably qualified environment.

17. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

Since a decision has been made to early terminate the trial, an abbreviated Clinical Study Report (CSR) will be generated, which will contain a full report of information related to safety and abbreviated summary of efficacy evaluation. The majority of the efficacy analyses outlined in section 9.8, efficacy analysis section of the protocol will not be conducted. No hypothesis testing will be performed on any of the efficacy endpoint. Only descriptive statistics will be generated for clinical resolution status, ≥2 point reduction from baseline on GCS and adenoviral eradication status as outlined in section 10.2 of this SAP.

18. DATA HANDLING CONVENTIONS

18.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: number of subjects (n), mean, median, SD, minimum, maximum unless otherwise specified. Categorical and count variables will be summarized by the number of subjects (n), frequency and the percent of subjects in each category unless otherwise specified. Percentages will be presented with one decimal point.

See TFLs4Shire for rules on the number of decimal places to present data and p-values.

18.2 Study Visits and Windows

CRF visits will be used in all summary tables and listings.

Study day will be calculated as follows:

- If the assessment date is on or after the date of first instillation:

  Study day = assessment date – first dosing date + 1

- If the assessment date is before the date of first instillation:

  Study day = assessment date – first dosing date

18.3 Derived Efficacy Endpoints

Clinical resolution is defined as absence of bulbar conjunctival injection and watery conjunctival discharge. Bulbar Conjunctival Injection will be assessed based on a 0-4 scale which uses pictures from the Validated Bulbar Redness (VBR) Scale. Watery Conjunctival Discharge will be assessed based on a 0-3 scale. For both bulbar conjunctival injection and watery conjunctival discharge, 0 score indicates normal or none and a higher score indicates a higher severity of the clinical sign. A 0 sum of bulbar conjunctival injection score and watery conjunctival discharge score represents reaching clinical resolution. Any non 0 sum means not reaching clinical resolution. If either individual score is missing, clinical resolution status will be set to missing.

Adenoviral eradication is defined as negative CC-IFA (indeterminate CC-IFA result is considered negative CC-IFA). Positive CC-IFA is considered not reaching adenoviral eradication. If an eye has missing CC-IFA result at baseline, the eye will be assumed to be CC-IFA negative at baseline for determination of the study eye.

Global clinical score is defined as the sum of bulbar conjunctival injection score and watery conjunctival discharge score. If either individual score is missing, global clinical score will be set to missing.

Modified clinical resolution is defined as a global clinical score of 0 or 1. All other scores are considered not reaching modified clinical resolution. If either individual score is missing, modified clinical resolution status will be set to missing.

Expanded clinical resolution is defined as a global clinical score of 0, 1, or 2 with neither bulbar conjunctival injection score nor watery conjunctival discharge score having a score of 2. Otherwise, the subject is considered not reaching expanded clinical resolution. If either individual score is missing, expanded clinical resolution status will be set to missing.

Time to clinical resolution will be derived based upon assessments at Visits 2 (Day 3), 3 (Day 6), 4 (Day 8), and 5 (Day 12) in the study eye. Time to clinical resolution will equal to the study day corresponding to the visit when the subject first reaches clinical resolution in the study eye.

Cross over infection status will be assessed by CC-IFA results as follows:

Scenario		Cross-over Infection Status at Post Baseline Visit
Both eyes CC-IFA positive at baseline		Not applicable
Only one eye CC-IFA positive at baseline	The other eye CC-IFA positive at post baseline visit	Yes
	The other eye CC-IFA negative at post baseline visit	No
Both eyes CC-IFA negative at baseline		Not applicable

Ocular discomfort total score (in the version for adult and older children) is defined as the sum of eye pain score, the feeling that something was in your eye score and itching score. If any individual score is missing, then ocular discomfort total score will be set to missing.

18.4 Repeated or Unscheduled Assessments of Safety Parameters

Assessments obtained on the scheduled CRF visits will be included in summary tables. Additional repeated or unscheduled assessments will not be included in the by visit summary tables, but will be included in subject listings.

18.5 Missing Date of Investigational Product

When the date of the last dose of investigational product is missing for a subject in the Safety Population, 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.

18.6 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.

18.6.1 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.

18.6.2 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.

18.7 Missing Date Information for Adverse Events

For AEs, incomplete (i.e. partially missing) start dates will be imputed if the subject is missing whether the event occurred prior to the first study drug dose. Incomplete stop dates will not be imputed.

18.7.1 Incomplete Start Date

If incomplete state date needs to be imputed, then follow same rules as in Section 18.6.1.

18.8 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 after 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 both the actual and imputed values will be used in data listings.

18.9 Missing Relationship to Investigation Product for Adverse Events

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

19. REFERENCES

1. Pocock SJ, Simon R 1975. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics; 31: 103-15.

20. APPENDIX

20.1 Example SAS Code for Generating Descriptive Statistics

```
*For binary endpoint;
proc freq data = testData;
tables binary_endpoint / binomial (exact level='Yes') alpha=0.05;
by visit treatment;
run;
```

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