PROTOCOL: SHP640-302

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 Placebo in the Treatment of Adenoviral Conjunctivitis
DRUG:	SHP640
IND:	75,723
EUDRACT NO:	2016-002440-16
SPONSOR:	Shire 300 Shire Way, Lexington, MA 02421 USA
PROTOCOL HISTORY:	Original Protocol: 30 June 2016 Amendment 1: 28 November 2016 Amendment 2: 15 February 2017 Amendment 3: 13 December 2017 Amendment 4: 31 May 2018

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted]	Dat[redacted]

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP640-302.

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 Placebo in the Treatment of Adenoviral Conjunctivitis

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

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

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

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

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

Investigator Name and Address: _____

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the Shire Clinical Study Serious Adverse Event and Non-serious Adverse Events (AEs) Required by the Protocol Form within 24 hours to the Shire Global Pharmacovigilance and Risk Management Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of this form must also be sent to the contract research organization (CRO)/Shire medical monitor by fax or e-mail using the details below.

Fax: [redacted]

Email: [redacted]

For protocol- or safety-related issues in the US and North American region, the investigator must contact the Shire medical monitor:

[redacted]

[redacted]

Primary telephone number : [redacted]
Fax: [redacted]
Alternate number: [redacted]

For protocol- or safety-related issues in regions other than North America, the investigator must contact the Quintiles 24/7 Emergency Contact center:

Primary telephone number: [redacted]
Alternate number: [redacted]

SUMMARY OF CHANGES FROM PREVIOUS VERSION

An overview of the updates incorporated into Amendment 4 is provided in the table below.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **4**	**Amendment Date** **31 May 2018**	**Global**
Description of Change		**Section(s) Affected by Change**
Updated Inclusion Criterion 4 to state that subjects must meet at least 1 of the 2 criteria below: a. Have a positive AdenoPlus® test at Visit 1 in at least 1 eye. b. Have at least 2 of the following 5 criteria, based upon medical history and examination: i. Symptoms within the past 7 days consistent with acute upper respiratory tract infection (eg, sore throat, cough, rhinorrhea, etc) ii. Contact within the past 7 days with family members or other individuals with recent onset of symptoms consistent with conjunctivitis iii. Acute onset within the past 4 days of 1 or more of the following ocular symptoms: burning/irritation, foreign body sensation, light sensitivity iv. Enlarged periauricular lymph node(s) v. Presence of follicles on tarsal conjunctiva Note: If the subject only meets Inclusion Criterion 4a (a positive AdenoPlus test in at least 1 eye), then the same eye must meet Inclusion Criterion 5.		Synopsis Section 4.1 Section 7.2.1.3
Updated the approximate number of sites.		Synopsis

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.

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

Origin of Product Quality Complaint	E-mail Address
North and South America	[redacted]
European Union and Rest of World	[redacted]

Telephone numbers (provided for reference if needed):

Shire, Lexington, MA (USA)

[redacted]

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ABBREVIATIONS

AE	adverse event
BCVA	Best Corrected Visual Acuity
CC-IFA	cell culture-immunofluorescence assay
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
eCRF	electronic case report form
EC	ethics committee
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HSV	Herpes Simplex Virus
ICH	International Conference on Harmonisation
IOP	intraocular pressure
IRB	Institutional Review Board
IRT	interactive response technology
ITT	Intent to Treat
mITT	Modified Intent to Treat
MRSA	methicillin-resistant Staphylococcus aureus
PVP-I	povidone-iodine
qPCR	quantitative polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment- emergent adverse event
US	United States

STUDY SYNOPSIS

Protocol number: SHP640-302	**Drug**: SHP640
Title of the study: 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 Placebo in the Treatment of Adenoviral Conjunctivitis	
Number of subjects (total and for each treatment arm): Total subjects: Approximately 284 SHP640 treatment arm: Approximately 142 Placebo treatment arm: Approximately 142	
Investigator(s): multicenter study	
Site(s) and Region(s): The study will be conducted in approximately 68 sites across North America, South America, Asia/Pacific, Europe, and Africa.	
Study period (planned): December 2016 to May 2018	**Clinical phase:** 3

Objectives:

Primary:

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).

Secondary:

The key secondary objective of the study is to evaluate the efficacy of SHP640 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 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 2 (Day 3), 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 (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)
    - 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 of SHP640 compared to placebo in the treatment of subjects with adenoviral conjunctivitis.

Rationale:

The clinical presentation of conjunctivitis is often nonspecific and differential diagnosis of different types of conjunctivitis can be challenging. Diagnostic testing to differentiate the underlying cause of infection is rarely performed in a clinical setting; misdiagnosis can occur in up to 50% of cases, which often results in improper antibiotic treatment. Currently there is no approved medication for the treatment of adenoviral conjunctivitis. An unmet need therefore exists for a safe and efficacious treatment that addresses infectious conjunctivitis (adenoviral and bacterial).

By combining PVP-I, a potent topical antiseptic with proven antiviral and antibacterial activity, with dexamethasone, a topical steroid, SHP640 will enable the treatment of both the infectious and inflammatory components of adenoviral and bacterial conjunctivitis even when the cause of infection is unclear.

Investigational product, dose, and mode of administration:

The drug product is SHP640 (0.1% Dexamethasone and 0.6% PVP-I) Ophthalmic Suspension.

The placebo product is Placebo Ophthalmic Solution.

Subjects will instill 1 drop of investigational product in each eye 4 times daily (with a minimum of 2 hours between doses) for 7 days.

Methodology:

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 Visit 2 (Day 3), Visit 3 (Day 6), Visit 4 (Day 8), and Visit 5 (Day 12). The study will last up to 13 days.

Inclusion and exclusion criteria:

Inclusion Criteria:

1. An understanding, ability, and willingness to fully comply with study procedures and restrictions (by the parent(s), guardian, or legally authorized representative, if applicable).
2. Ability to voluntarily provide written, signed, and dated (personally or via a parent(s), guardian, or legally authorized representative(s) informed consent (and assent, if applicable) to participate in the study.
3. Subjects of any age at Visit 1 (Note: subjects < 3 months of age at Visit 1 must have been full-term, ie ≥37 weeks gestational age at birth).
4. Meet at least 1 of the 2 criteria below:
   a. Have a positive AdenoPlus® test at Visit 1 in at least 1 eye.
   b. Have at least 2 of the following 5 criteria, based upon medical history and examination:
      vi. Symptoms within the past 7 days consistent with acute upper respiratory tract infection (eg, sore throat, cough, rhinorrhea, etc)

vii. Contact within the past 7 days with family members or other individuals with recent onset of symptoms consistent with conjunctivitis

viii. Acute onset within the past 4 days of one or more of the following ocular symptoms: burning/irritation, foreign body sensation, light sensitivity

ix. Enlarged periauricular lymph node(s)

x. Presence of follicles on tarsal conjunctiva

Note: If the subject only meets Inclusion Criterion 4a (a positive AdenoPlus test in at least 1 eye), then the same eye must meet Inclusion Criterion 5.

5. Have a clinical diagnosis of suspected adenoviral conjunctivitis in at least 1 eye confirmed by the presence of the following minimal clinical signs and symptoms in that same eye:
   - Report presence of signs and/or symptoms of adenoviral conjunctivitis for ≤ 4 days prior to Visit 1
   - Bulbar conjunctival injection: a grade of ≥1 (mild) on a 0-4 Bulbar Conjunctival Injection Scale.
   - Watery conjunctival discharge: a grade of ≥1 (mild) on a 0-3 Watery Conjunctival Discharge Scale
6. Be willing to discontinue contact lens wear for the duration of the study.
7. Have a Best Corrected Visual Acuity (BCVA) of 0.60 logMAR or better in each eye as measured using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart. BCVA will be assessed by an age appropriate method in accordance with the AAP Policy Statement for Visual System Assessment in Infants, Children, and Young Adults by Pediatricians (Donahue and Baker 2016; American Academy of Pediatrics 2016). The policy statement recommends formal vision screening can begin at 3 years of age. VA measurements for children under the age of 3 will be done at the discretion of the investigator. If not done, child should be able to fixate on and follow a moving object, except subjects <2 months of age who have not yet developed this ability. Subjects <2 months will be enrolled at the discretion of the investigator.
8. Male, or non-pregnant, non-lactating female who agrees to comply with any applicable contraceptive requirements of the protocol or females of non-childbearing potential.

Exclusion Criteria:

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Current or recurrent disease that could affect the action, absorption, or disposition of the investigational product, or clinical or laboratory assessments, per investigator's discretion.
2. Current or relevant history of physical or psychiatric illness, any medical disorder that may make the subject unlikely to fully complete the study, or any condition that presents undue risk from the investigational product or procedures.
3. Have known or suspected intolerance or hypersensitivity to the investigational product, closely related compounds, or any of the stated ingredients.
4. Prior enrollment in a FST-100 or SHP640 clinical study.
5. Subjects who are employees, or immediate family members of employees (who are directly related to study conduct), at the investigational site.
6. Have a history of ocular surgical intervention within ≤ 6 months prior to Visit 1 or planned for the period of the study.
7. Have a preplanned overnight hospitalization during the period of the study.
8. Have presence of any intraocular, corneal, or conjunctival ocular inflammation (e.g., uveitis, iritis, ulcerative keratitis, chronic blepharoconjunctivitis), other than adenoviral conjunctivitis.
9. Have presence of corneal subepithelial infiltrates at Visit 1.

10. Have active or history of ocular herpes.
11. Have at enrollment or within ≤30 days of Visit 1, a clinical presentation more consistent with the diagnosis of non-infectious conjunctivitis (except presumed seasonal/perennial allergic conjunctivitis) or non-adenoviral ocular infection (e.g., bacterial, fungal, acanthamoebal, or other parasitic). Note: history or concomitant presence of presumed seasonal or perennial allergic conjunctivitis signs/symptoms is not exclusionary.
12. Neonates or infants (ie, subjects less than 12 months of age) who have suspected or confirmed (based on the result of any test conducted prior to screening) conjunctivitis of gonococcal, chlamydial, herpetic or chemical origin.
13. Neonates or infants (ie, subjects less than 12 months of age) whose birth mothers had any sexually transmitted disease within 1 month of delivery or any history of genital herpes.
14. Presence of nasolacrimal duct obstruction at Visit 1 (Day 1).
15. Presence of any significant ophthalmic condition (eg, retinopathy of prematurity, congenital cataract, congenital glaucoma) or other congenital disorder with ophthalmic involvement that could affect study variables.
16. Be a known intraocular pressure (IOP) steroid responder, have a known history or current diagnosis of glaucoma, or be a glaucoma suspect.
17. Have any known clinically significant optic nerve defects.
18. Have a history of recurrent corneal erosion syndrome, either idiopathic or secondary to previous corneal trauma or dry eye syndrome; presence of corneal epithelial defect or any significant corneal opacity at Visit 1.
19. Presence of significant, active condition in the posterior segment which requires invasive treatment (eg, intravitreal treatment with VEGF inhibitors or corticosteroids) and may progress during the study participation period.
20. Have used any topical ocular or systemic anti-virals or antibiotics within ≤ 7 days of enrollment.
21. Have used any topical ocular NSAIDs within ≤ 1 day of enrollment.
22. Have used any topical ophthalmic steroids in the last ≤14 days.
23. Have used any systemic corticosteroid agents within ≤ 14 days of Day 1. Stable (initiated ≥ 30 days prior to enrollment) use of inhaled and nasal corticosteroids is allowed, given no anticipated change in dose for the duration of the study. Topical dermal steroids are allowed except in the peri-ocular area.
24. Have used non-corticosteroid immunosuppressive agents within ≤ 14 days of Day 1.
25. Have used any topical ophthalmic products, including tear substitutes, and over-the-counter preparations such as lid scrubs, within 2 hours of Visit 1 and be unable to discontinue all topical ophthalmic products for the duration of the study. Use of hot or cold compresses is also not permitted during the study.
26. Have any significant ocular disease (eg, Sjogren's syndrome) or any uncontrolled systemic disease or debilitating disease (e.g., cardiovascular disease, hypertension, sexually transmitted diseases/infections, diabetes or cystic fibrosis), that may affect the study parameters, per investigator's discretion.
27. Any known history of immunodeficiency disorder or known active conditions predisposing to immunodeficiency, such as human immunodeficiency virus, hepatitis B or C, evidence of active hepatitis A (antihepatitis A virus immunoglobulin M), or organ or bone marrow transplantation.
28. Within 30 days prior to the first dose of investigational product:
    - Have used an investigational product or device, or
    - Have been enrolled in a clinical study (including vaccine studies) that, in the investigator's

opinion, may impact this Shire-sponsored study.
Maximum duration of subject involvement in the study: Subject participation will last up to 13 days. Screening, randomization and the first treatment administration will occur at Visit 1 (Day 1). Additional visits will occur on Visit 2 (Day 3), Visit 3 (Day 6), Visit 4 (Day 8), and Visit 5 (Day 12). All follow-up procedures will be conducted at Visit 5 (Day 12).
Endpoints and statistical analysis: *Primary Efficacy Endpoint:* Clinical resolution status (defined as absence of bulbar conjunctival injection and watery conjunctival discharge) in the study eye at Visit 3 (Day 6) between SHP640 and placebo. *Key Secondary Efficacy Endpoints:* Adenoviral eradication status (defined as negative cell culture-immunofluorescence assay [CC-IFA]) in the study eye at Visit 3 (Day 6). *Secondary Efficacy Endpoints:* • 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 2 (Day 3), 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 • 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 • 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 • 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 *Safety Endpoints:* • Best Corrected Visual Acuity (BCVA) • Slit Lamp Biomicroscopy • Intraocular Pressure • Non-dilated/ Dilated Fundus Examination • Urine Pregnancy Testing (for females of childbearing potential)

- Adverse Events (AEs)

Statistical Methods:

The analyses on primary, key secondary, secondary, and exploratory efficacy endpoints will be performed on the mITT population (unless specified otherwise) and will be presented by treatment group. Additional sensitivity analyses may be conducted on the ITT population. Safety analysis will be conducted on the safety population.

For both efficacy and safety analyses, baseline is defined as the assessments taken at Visit 1 (Day 1).

Analyses Populations:

The **Safety Population** will include all subjects who receive at least one dose of investigational product

The **Intent to Treat (ITT) Population** will include all randomized subjects.

The **Modified Intent to Treat (mITT)** population consists of a subset of the ITT population who receives at least one dose of investigational product and have a positive CC-IFA adenovirus test at baseline in the study eye.

Designation of Study Eye:

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 (baseline is defined as the assessments taken at Visit 1 (Day 1):

- 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 (sum of the scores for discharge and redness) 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.

Primary Efficacy Analyses:

The primary efficacy endpoint of clinical resolution will be analyzed based on the mITT population at Visit 3 (Day 6). If subjects drop out of the study before Visit 3,then the last observation will be carried forward (LOCF) for the determination of clinical resolution of the eye.

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 Solution and Placebo with the alternative of the non-zero difference in the proportion with clinical resolution between them.

The proportion of subjects with clinical resolution will be compared with two-sided Fisher's Exact test at 5% level of significance.

Sensitivity analyses will be done on the primary efficacy endpoint using additional statistical method(s) including other methods of imputation of missing data.

Key Secondary Efficacy Analyses:

In order to maintain the study-wide Type I error at 5.0%, the primary and key secondary hypotheses will be tested sequentially using two-sided Fisher's exact test.

The hypothesis test for the key secondary efficacy endpoint will not be performed unless hypothesis test for the primary efficacy endpoint is significant.

Sensitivity analyses will also be done on key secondary efficacy endpoints using similar methods as described above.

Secondary Efficacy Analyses:

All secondary efficacy analyses will be performed on the mITT and presented by treatment group. No hypothesis testing is planned for the secondary efficacy endpoints. All secondary efficacy endpoints will be summarized by treatment groups using descriptive statistics at each assessment visit. Continuous endpoints will be summarized by number of subjects (n), mean, median, standard deviation, minimum, maximum and confidence intervals. Binary endpoints will be summarized by number of subjects (n), frequencies proportions and confidence intervals. Time to event endpoint will be summarized by Kaplan-Meier survival estimates.

Safety Analyses:

Safety data will be presented for the Safety Population by treatment group and overall. Adverse events will be coded using the Medical Dictionary for Regulatory Activities. The number of subjects and percentage with a treatment-emergent adverse event (TEAE) as well as the number of TEAEs will be calculated overall, by SOC, by preferred term, and by treatment group and overall. Treatment-emergent adverse events will be further summarized by severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized and listed. Any AE that occurs after the first dose of investigational product instillation will be considered a TEAE.

Generally, TEAEs will be presented separated by whether or not the AE was an ocular or non-ocular AE.

BCVA, Slit Lamp Biomicroscopy, intraocular pressure, non-dilated/dilated fundus exam, and urine pregnancy test (for females of childbearing potential), will be descriptively summarized by treatment group and overall at each applicable visit.

Study Schedule

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[m]	X[f]	X[f]	X[f]	X[f]
Conjunctival swab for bacterial culture[g]	X		X[f,g]		X[f]
Intraocular pressure	X				X
Non-dilated/ dilated fundus examination[h]	X				X
Randomization[i]	X				
Dispense investigational product [j]	X				
Instill investigational product	X[j]	X[k]	X[k]		
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[l]	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 who 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] One swab sample from each conjunctival cul-de-sac will be collected for all bacterial testing.

[h] 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).

[i] 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).

[j] 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.

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

[l] Monitoring for adverse events will begin after informed consent is obtained.

[m] 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.

1. BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

Conjunctivitis affects all populations worldwide of all ages and social strata, irrespective of gender. Within infectious conjunctivitis, viral etiology may account for up to 80% of all cases in adults and bacterial conjunctivitis is the second most common cause of infectious conjunctivitis overall. Infectious conjunctivitis represents a serious public health issue due to a risk of highly infectious epidemics, lost productivity, significant patient discomfort, and in some cases permanent visual compromise from long-term, immune-mediated sequelae (Ford et al., 1987; Nauheim et al., 1990; Gordon et al., 1993; Pelletier et al., 2009; Capriotti et al., 2010).

Adenoviruses, unlike bacteria, are not part of the normal flora of the ocular surface and their presence is indicative of an infection (Cambon and Pollard, 1959; Willamson et al., 1975; Vastine et al., 1977; Gigliotti et al., 1981; Kaneko et al., 2008). It is the most reported cause of viral conjunctivitis in up to 75% of cases (Wilkins et al., 2011). Adenoviral conjunctivitis is typically spread through direct contact between the eye and hands that are contaminated with the virus via contact with infected eye discharge, fecal matter, or respiratory discharge (CDC, 2010). Given the highly transmittable nature of the disease, it is not surprising that it is observed to be most prevalent in densely populated, overcrowded areas, or in the presence of poor hygiene, or both (Capriotti et al., 2010).

Adenoviral conjunctivitis typically lasts 14-21 days (Wilkins et al., 2011). The onset is usually rapid and the infection often spreads from one eye to the other (AAO Cornea/External Disease PPP Panel, 2013).

Currently, there are no approved treatments for adenoviral conjunctivitis; therapeutic options are limited to supportive therapies and palliative measures such as cold compresses, artificial tears, and topical antihistamines (AAO Cornea/External Disease PPP Panel, 2013). This Phase 3 study is being conducted to evaluate the clinical efficacy and safety of SHP640 for the treatment of adenoviral conjunctivitis.

1.2 Product Background and Clinical Information

SHP640, a novel topical ophthalmic suspension, is currently under development for the treatment of infectious conjunctivitis (adenoviral and bacterial).

SHP640 contains 2 active ingredients: povidone-iodine (PVP-I) and dexamethasone. PVP-I is a multivalent broad-spectrum local antiseptic with bactericidal and fungicidal properties. The effect on vegetative cells of various bacteria and fungi is due to the liberation of free iodine from the complex. It is effective against many viruses, protozoa, yeasts, cysts, and spores (Betadine, 2004). Dexamethasone is a corticosteroid routinely used as a topical ophthalmic suspension for the treatment of ocular inflammation. It suppresses the inflammatory response to a variety of causes of inflammation (Maxidex, 2007). Both components are currently approved for use in other indications (at similar or higher concentrations) and have been shown to be safe

and efficacious for use on the ocular surface in humans. The combination of PVP-I and dexamethasone has been shown to rapidly kill common ocular pathogens, including viruses, gram-positive bacteria (including MRSA), and gram-negative bacteria (Pelletier et al., 2011).

Always refer to the latest version of the SHP640 investigator's brochure for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, efficacy and safety of SHP640.

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

The clinical presentation of conjunctivitis is often nonspecific and differential diagnosis of different types of conjunctivitis can be challenging (Azari and Barney, 2013; O'Brien et al., 2009). Diagnostic testing to differentiate the underlying cause of infection is rarely performed in a clinical setting; misdiagnosis can occur in up to 50% of cases, which often results in improper antibiotic treatment (Visscher et al., 2009). Incorrect treatment can not only increase healthcare costs from unnecessary antibiotic prescriptions and repeat office visits, but can also pose serious risks for people with certain viral and bacterial variants (eg, herpes simplex or methicillin-resistant Staphylococcus aureus [MRSA]). In addition, there is also a risk of overuse and misuse of antibiotics, which are ineffective in the treatment of viral infections (Statham et al., 2008). Currently there is no approved medication for the treatment of adenoviral conjunctivitis. An unmet medical need therefore exists for a safe and efficacious treatment that addresses both bacterial and adenoviral conjunctivitis, two of the leading causes of acute infectious conjunctivitis.

By combining PVP-I, a potent topical antiseptic with proven antiviral and antibacterial activity, with dexamethasone, a topical steroid, SHP640 will enable the treatment of both the infectious and inflammatory components of adenoviral and bacterial conjunctivitis.

2.2 Study Objectives

2.2.1 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).

2.2.2 Secondary Objectives

The key secondary objective of the study is to evaluate the efficacy of SHP640 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 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 2 (Day 3), 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 (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).
- 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 of SHP640, compared to placebo in the treatment of subjects with adenoviral conjunctivitis

2.2.3 Exploratory Objectives

The exploratory objectives of this study are as follows:

[redacted]

3. STUDY DESIGN

3.1 Study Design and Flow Chart

SHP640-302 is a global, multi-center, randomized, double-masked, parallel group, placebo controlled study designed to demonstrate the safety and efficacy of SHP640 ophthalmic suspension compared to placebo in treating adenoviral conjunctivitis.

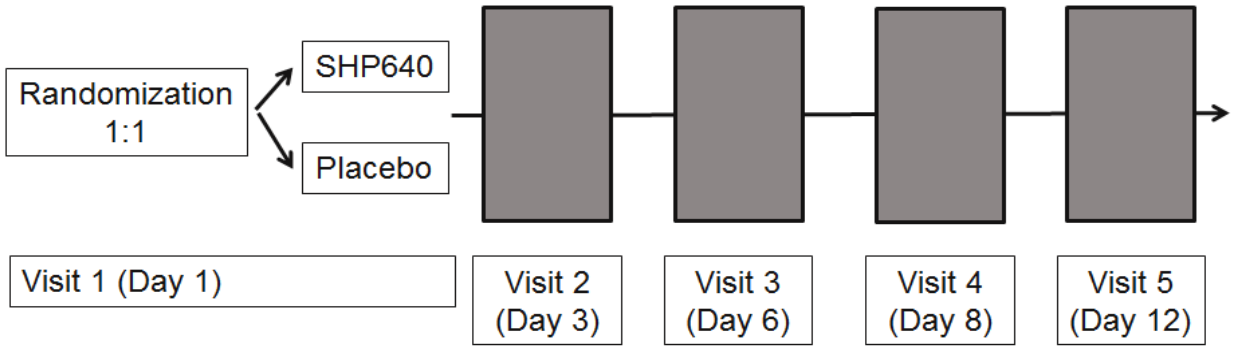
Approximately 284 subjects will be randomized into the study at Visit 1 (Day 1). Randomization will be stratified by age to maintain the randomization ratio among subjects <6 years, 6 to <18 years and subjects ≥18 years. Subjects will be randomized 1:1 to receive either SHP640 or placebo within each 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 or potential treatment unmasking. Dynamic balanced randomization will be used in this study to maintain the randomization ratio within each stratum.

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 Visit 2 (Day 3), Visit 3 (Day 6), Visit 4 (Day 8), and Visit 5 (Day 12). All follow-up procedures will be conducted at Visit 5 (Day 12). The study will last up to 13 days.

Figure 1 provides the study design.

Figure 1 SHP640-302 Study Design



3.2 Duration and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 13 days. The study will be completed in approximately 1.5 years.

The Study Completion Date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. Please note that this includes the follow-up visit (Visit 5) or contact, whichever is later. The Study Completion Date is used to ascertain timing for study results posting and reporting.

3.3 Sites and Regions

The study will be conducted in approximately 35 sites across North America, South America, Asia/Pacific, Europe, and Africa.

4. STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent before any procedures specified in the protocol are performed. If a subject is younger than the legal age of consent (per local laws), the subject's parent(s), guardian, or legally authorized representative will provide written informed consent; the subject will provide verbal or written assent as appropriate.

4.1 Inclusion Criteria

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

1. An understanding, ability, and willingness to fully comply with study procedures and restrictions (by the parent(s), guardian, or legally authorized representative, if applicable).
2. Ability to voluntarily provide written, signed, and dated (personally or via a parent(s), guardian, or legally-authorized representative(s) informed consent (and assent, if applicable) to participate in the study.
3. Subjects of any age at Visit 1 (Note: subjects < 3 months of age at Visit 1 must have been full-term, ie ≥37 weeks gestational age at birth).
4. Meet at least 1 of the 2 criteria below:
   a. Have a positive AdenoPlus® test at Visit 1 in at least 1 eye.
   b. Have at least 2 of the following 5 criteria, based upon medical history and examination:
      i. Symptoms within the past 7 days consistent with acute upper respiratory tract infection (eg, sore throat, cough, rhinorrhea, etc)
      ii. Contact within the past 7 days with family members or other individuals with recent onset of symptoms consistent with conjunctivitis
      iii. Acute onset within the past 4 days of 1 or more of the following ocular symptoms: burning/irritation, foreign body sensation, light sensitivity
      iv. Enlarged periauricular lymph node(s)
      v. Presence of follicles on tarsal conjunctiva

   Note: If the subject only meets Inclusion Criterion 4a (a positive AdenoPlus test in at least 1 eye), then the same eye must meet Inclusion Criterion 5.
5. Have a clinical diagnosis of suspected adenoviral conjunctivitis in at least 1 eye confirmed by the presence of the following minimal clinical signs and symptoms in that same eye:
   - Report presence of signs and/or symptoms of adenoviral conjunctivitis for ≤ 4 days prior to Visit 1
   - Bulbar conjunctival injection: a grade of ≥1 on 0-4 scale of Bulbar Conjunctival Injection Scale
   - Watery conjunctival discharge: a grade of ≥1 (mild) on a 0-3 Watery Conjunctival

Discharge Scale

6. Be willing to discontinue contact lens wear for the duration of the study.
7. Have a Best Corrected Visual Acuity (BCVA) of 0.60 logMAR or better in each eye as measured using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart. BCVA will be assessed by an age appropriate method in accordance with the AAP Policy Statement for Visual System Assessment in Infants, Children, and Young Adults by Pediatricians (Donahue and Baker 2016; American Academy of Pediatrics 2016). The policy statement recommends formal vision screening can begin at 3 years of age. VA measurements for children under the age of 3 will be done at the discretion of the investigator. If not done, child should be able to fixate on and follow a moving object, except subjects <2 months of age who have not yet developed this ability. Subjects <2 months will be enrolled at the discretion of the investigator.
8. Male, or non-pregnant, non-lactating female who agrees to comply with any applicable contraceptive requirements of the protocol or females of non-childbearing potential.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met.

1. Current or recurrent disease that could affect the action, absorption, or disposition of the investigational product, or clinical or laboratory assessments, per investigator's discretion.
2. Current or relevant history of physical or psychiatric illness, any medical disorder that may make the subject unlikely to fully complete the study, or any condition that presents undue risk from the investigational product or procedures.
3. Have known or suspected intolerance or hypersensitivity to the investigational product, closely related compounds, or any of the stated ingredients.
4. Prior enrollment in a FST-100 or SHP640 clinical study.
5. Subjects who are employees, or immediate family members of employees (who are directly related to study conduct), at the investigational site.
6. Have a history of ocular surgical intervention within ≤ 6 months prior to Visit 1 or planned for the period of the study.
7. Have a preplanned overnight hospitalization during the period of the study.
8. Have presence of any intraocular, corneal, or conjunctival ocular inflammation (e.g., uveitis, iritis, ulcerative keratitis, chronic blepharoconjunctivitis), other than adenoviral conjunctivitis.
9. Have presence of corneal subepithelial infiltrates at Visit 1.
10. Have active or history of ocular herpes.
11. Have at enrollment or within ≤30 days of Visit 1, a clinical presentation more consistent with the diagnosis of non-infectious conjunctivitis (except presumed seasonal/perennial allergic conjunctivitis) or non-adenoviral ocular infection (e.g., bacterial, fungal, acanthamoebal, or

other parasitic). Note: history or concomitant presence of presumed seasonal or perennial allergic conjunctivitis signs/symptoms is not exclusionary.

12. Neonates or infants (ie, subjects less than 12 months of age) who have suspected or confirmed (based on the result of any test conducted prior to screening) conjunctivitis of gonococcal, chlamydial, herpetic or chemical origin.
13. Neonates or infants (ie, subjects less than 12 months of age) whose birth mothers had any sexually transmitted disease within 1 month of delivery or any history of genital herpes.
14. Presence of nasolacrimal duct obstruction at Visit 1 (Day 1).
15. Presence of any significant ophthalmic condition (eg, retinopathy of prematurity, congenital cataract, congenital glaucoma) or other congenital disorder with ophthalmic involvement that could affect study variables.
16. Be a known intraocular pressure (IOP) steroid responder, have a known history or current diagnosis of glaucoma, or be a glaucoma suspect.
17. Have any known clinically significant optic nerve defects.
18. Have a history of recurrent corneal erosion syndrome, either idiopathic or secondary to previous corneal trauma or dry eye syndrome; presence of corneal epithelial defect or any significant corneal opacity at Visit 1.
19. Presence of significant, active condition in the posterior segment which requires invasive treatment (eg, intravitreal treatment with VEGF inhibitors or corticosteroids) and may progress during the study participation period.
20. Have used any topical ocular or systemic anti-virals or antibiotics within ≤ 7 days of enrollment.
21. Have used any topical ocular NSAIDs within ≤ 1 day of enrollment.
22. Have used any topical ophthalmic steroids in the last ≤14 days.
23. Have used any systemic corticosteroid agents within ≤ 14 days of Day 1. Stable (initiated ≥ 30 days prior to enrollment) use of inhaled and nasal corticosteroids is allowed, given no anticipated change in dose for the duration of the study. Topical dermal steroids are allowed except in the peri-ocular area.
24. Have used non-corticosteroid immunosuppressive agents within ≤ 14 days of Day 1.
25. Have used any topical ophthalmic products, including tear substitutes, and over-the-counter preparations such as lid scrubs, within 2 hours of Visit 1 and be unable to discontinue all topical ophthalmic products for the duration of the study. Use of hot or cold compresses is also not permitted during the study.
26. Have any significant ocular disease (eg, Sjogren's syndrome) or any uncontrolled systemic disease or debilitating disease (e.g., cardiovascular disease, hypertension, sexually transmitted diseases/infections, diabetes or cystic fibrosis), that may affect the study parameters, per investigator’s discretion.
27. Any known history of immunodeficiency disorder or known active conditions predisposing to immunodeficiency, such as human immunodeficiency virus, hepatitis B or C, evidence of

active hepatitis A (antihepatitis A virus immunoglobulin M), or organ or bone marrow transplantation.

28. Within 30 days prior to the first dose of investigational product:
    - Have used an investigational product or device, or
    - Have been enrolled in a clinical study (including vaccine studies) that, in the investigator's opinion, may impact this Shire-sponsored study

4.3 Reproductive Potential

4.3.1 Female Contraception

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

Female children and adolescent subjects should be either:

- Pre-menarchal and either Tanner Stage 1 or less than age 9 years, or
- Females of childbearing potential with a negative urine pregnancy test at Visit 1. Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Adult female subjects should be either:

- Postmenopausal (12 consecutive months of spontaneous amenorrhea and ≥ age 51 years)
- Surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks post-sterilization, or
- Females of childbearing potential with a negative urine pregnancy test at Visit 1 and prior to randomization. Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception are:

- Intrauterine devices plus condoms
- Intrauterine hormone-releasing systems plus condoms
- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)

Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the screening visit (Visit 1), plus condoms.

4.4 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, if in the judgment of the investigator, there is no clinical improvement or worsening to an extent that it would be in the best interest of the subject to be treated with an alternate therapy for safety reasons). The investigator is encouraged to discuss withdrawal of a subject from investigational product with the medical monitor if necessary.

If investigational product is discontinued for any reason other than a positive HSV baseline test, the evaluations listed for Visit 5 are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified follow-up (proceed to Visit 5). Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for termination and the date of stopping investigational product must be recorded in the case report form (CRF) and source documents.

Subjects who test positive for ocular HSV at baseline in either eye should have their investigational product discontinued, and should receive alternate appropriate treatment as needed based on the investigator's judgment. These subjects should be followed for the remaining duration of study at regularly scheduled visits, and all safety related assessments should be completed (AEs, BCVA, slit lamp biomicroscopy at all visits, intraocular pressure and fundus exam at Visit 5, concomitant medications at all visits, and pregnancy test [if the subject is a female of childbearing potential]).

If a subject <2 months of age has a positive CT-NG test for any one of the two Visit 1 samples, the subject will be discontinued from the study and started with alternate standard of care therapy per the investigator's clinical judgment.

Subject numbers for subjects who discontinue will not be reused.

4.4.1 Reasons for Discontinuation

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

Reasons for discontinuation include but are not limited to:

- Adverse event
- Protocol deviation
- Withdrawal by subject
- Lost to follow-up
- Lack of efficacy

- Physician decision
- Study terminated by sponsor
- Withdrawal by parent(s)/guardian/legally authorized representative (if applicable)
- Other (If "Other" is selected, the investigator must specify on the CRF)

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

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product.

5. PRIOR AND CONCOMITANT TREATMENT

All non-study treatment received within 30 days prior to the screening visit (Visit 1) (or pharmacokinetic equivalent of 5 half-lives, whichever is longer) and through the final study contact (including protocol-defined follow-up period) must be recorded on the appropriate CRF page.

5.1 Prior Treatment

Prior treatment includes all treatment received within 30 days prior to the screening visit (Visit 1) (or pharmacokinetic equivalent of 5 half-lives, whichever is longer). Prior treatment information must be recorded on the appropriate CRF page.

5.2 Concomitant Treatment

Concomitant treatment refers to all treatment other than the investigational production taken between the dates of the first dose of investigational product and the end of Visit 5 (the end of study visit), inclusive. Concomitant treatment information must be recorded on the appropriate CRF page.

The investigator may prescribe additional medications during the study, as long as the prescribed medication is not prohibited by the protocol. In the event of an emergency, any needed medications may be prescribed without prior approval, but the medical monitor must be notified of the use of any prohibited medications immediately thereafter.

5.2.1 Permitted Treatment

Medications not indicated as prohibited are permitted, including treatments for general non-excluded medical conditions.

In the event of an emergency, any needed medications may be prescribed without prior approval, but the medical monitor must be notified of the use of any prohibited medications immediately thereafter.

5.2.2 Prohibited Treatment

Table 2 details the washout period for common prior treatments that are excluded medications for this study.

Table 2 Common Excluded Treatments and Associated Washout Periods

	Minimum Time Prior to First Dose					Notes
Treatment	**30 days**	**14 days**	**7 days**	**1 day**	**2 hours**	
Topical ocular NSAIDs				X		
Topical ocular or systemic anti-virals or antibiotics			X			
Topical ophthalmic steroids		X				
Systemic corticosteroid agents		X				
Stable use of inhaled or nasal corticosteroids	X					Allowed ≥30 days if no anticipated dose changes during the study
Noncorticosteroid immunosuppressive agents		X				
Topical ophthalmic solutions, including tear substitutes, and OTC preparations (ie: lid scrubs)					X	Must be able to discontinue use for the duration of the study

Treatments not listed in Table 2 are considered permitted.

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

Three test products will be used in the clinical development program. The drug product is SHP640 (0.1% Dexamethasone and 0.6% PVP-Iodine). The placebo product is Placebo Ophthalmic Solution. Each of these test products are manufactured aseptically and filled in sterile plastic ophthalmic bottles. The placebo contains 2 additional ingredients relative to the others: Benzalkonium Chloride, USP, EP, used as a preservative, and Caramel Color, NF, included to match the dark brown color of the PVP-I active ingredient. Additional information on the two test products is provided in the current SHP640 investigator's brochure.

6.1.1 Masking the Treatment Assignment

The packaging, appearance, and labeling of the test products will match. Colorant will be added to the placebo to match the appearance of SHP640. Treatment assignment will be determined by the randomization schedule.

6.1.2 Commercially Obtained Investigational Product

Not Applicable.

6.2 Administration of Investigational Product(s)

6.2.1 Interactive Response Technology for Investigational Product Management

An Interactive Response Technology (IRT) vendor will be used for this study to manage packaged investigational medicinal product (IMP) supply, IMP shipments, receipt of IMP at clinical sites, randomization of IMP to subjects, expiry tracking, IMP returns, accountability of IMP, and emergency unmasking.

6.2.2 Allocation of Subjects to Treatment

This is a double-masked, placebo-controlled study. The actual treatment given to individual subjects 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 IRT.

Randomization will be stratified by age to maintain the randomization ratio among subjects < 6 years, 6 to <18 years and subjects ≥18 years. Subjects will be randomly assigned to receive SHP640 or placebo based on a 1:1 ratio within the randomization strata.

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 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.

6.2.3 Dosing

Subjects will be instructed to instill 1 drop of investigational product in each eye QID (with a minimum of 2 hours between doses) for 7 days.

Prior to administration of the first dose, the bottle should be removed from refrigeration and allowed to come to room temperature. The bottle will not be refrigerated before subsequent administrations. Storage requirements are discussed in Section 6.3.3.

The investigational product bottle should be shaken well prior to use at each dosing.

In-office dosing will only be performed at the first visit, and additionally if necessary.

6.2.4 Unmasking the Treatment Assignment

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 CRF. Upon breaking the mask, the subject is withdrawn from the study, but should complete Visit 5 (the end of study visit), to be followed up for safety purposes. Any code-breaks that occur must be reported to the Sponsor medical monitor.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

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

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

Space is allocated on the label so that the site representative can record the date dispensed, the subject's initials (as permitted based on local laws), and the unique subject number.

Additional labels may, on a case-by-case basis, be applied to the investigational product in order to satisfy local or institutional requirements, but must not:

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

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

6.3.2 Packaging

Investigational product is packaged in the following labeled containers:

The investigational product bottle will be labeled and then placed into a 1x labeled carton. This carton will then be secured with a tamper seal.

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

6.3.3 Storage

The investigational product must be stored at the site in a secure, refrigerated area (2ºC-8ºC) accessible only to the investigator and his/her designees. The investigational product will be administered only to subjects enrolled in the clinical study, in accordance with the conditions specified in this protocol.

Undispensed investigational product should be stored under refrigeration at 2ºC-8ºC.

Dispensed investigational product should be stored at room temperature below 30ºC. Investigational product should be protected from freezing and exposure to strong light.

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier and initials as permitted based on local laws on the investigational product bottle/carton labels as they are distributed.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that

records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

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

6.3.4 Special Handling

Not Applicable.

6.4 Drug Accountability

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

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

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All dispensed investigational product will be documented on the CRFs and/or other investigational product record.

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

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

With the written agreement of the sponsor, at the end of the study all unused stock, and empty/used investigational product packaging may be destroyed at the site or a local facility. In this case, destruction records identifying what was destroyed, when and how, must be obtained with copies provided to the sponsor. Destruction of investigational products must be in accordance with local, state, and national laws.

If a site is not approved by the sponsor to destroy IP, all used and unused stock is to be sent to a nominated contractor on behalf of the sponsor. Investigational products being returned to the sponsor's designated contractors must be counted and verified by clinical site personnel and the sponsor (or designated CRO). Validated electronic return systems (ie, IRT) may not require a shipment form. Returned investigational products must be packed in a tamper-evident manner to ensure product integrity. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

6.5 Subject Compliance

Subjects must be instructed to bring their investigational product and empty/used investigational product packaging to every visit. The pharmacist/nominated person will record details on the drug accountability form.

Subject compliance will be verified verbally during study visits. In cases of non-compliance the investigator should determine if the medical monitor must be contacted for consultation.

7. STUDY PROCEDURES

7.1 Study Schedule

The detailed study procedures/assessments to be performed throughout the study are outlined in the Schedule of Assessments (see Table 1) and must be referred to in conjunction with the instructions provided in this section. Procedures or assessments that are not completed or are performed out of order should be captured as protocol deviations.

Prior to performing any study-related procedures (including those related to screening), the investigator or his/her designee must obtain written informed consent from the subject (as per local requirements). If a subject is younger than the legal age of consent (per local laws), the subject's parent(s), guardian, or legally authorized representative will provide written informed consent; the subject will provide verbal or written assent as appropriate. There must be documentation of consent/assent (as per local requirements) indicating that the subject is aware of the investigational nature of the study and the required procedures and restrictions, prior to performing any study-related procedures.

Where applicable, all procedures will be performed in both eyes.

7.1.1 Visit 1 (Day 1)

Screening and baseline/randomization will occur at Visit 1 (Day 1 [-1 day]). Visit 1 assessments, beginning with informed consent, will be performed as outlined in Table 1.

A screen failure is a subject who has given informed consent and failed to meet the inclusion and/or met at least 1 of the exclusion criteria and has not been randomized or administered investigational product. Subjects cannot be rescreened once they have been designated as a screen failure.

A urine pregnancy test will be completed for all females of childbearing potential. The results will be read by site personnel and recorded in the source documents.

All AEs occurring after signature of informed consent must be recorded in the source documents and CRF.

Prior to randomization, the procedures should be performed in the following order (in both eyes, as appropriate):

- Informed consent (and assent, if applicable)
- Inclusion/exclusion criteria
- Medical history
- Demographics
- Concomitant medications

- Urine pregnancy test (for women of childbearing potential)
- Ocular Discomfort Scale
- Best corrected visual acuity
- Slit lamp biomicroscopy
- Bulbar conjunctival injection evaluation
- Watery conjunctival discharge evaluation
- AdenoPlus® test (if not previously conducted within 24 hours of Visit 1)

If any findings during screening exams do not meet the inclusion/exclusion criteria, the subject is not eligible to be randomized.

Eligible subjects must have a positive response in at least one eye. A positive response is defined as meeting ALL of the following criteria in the same eye:

- Report presence of signs and/or symptoms of adenoviral conjunctivitis for ≤ 4 days prior to Visit 1
- Bulbar conjunctival injection: a grade of ≥1 on 0-4 scale of Bulbar Conjunctival Injection Scale
- Watery conjunctival discharge: a grade of ≥1 (mild) on a 0-3 Watery Conjunctival Discharge Scale

Study eye will not be determined at Visit 1. All ophthalmic assessments will be conducted on both eyes. Selection of study eye for analyses will be according to the criteria outlined in Section 9.8.1.

The procedures should be performed in the following order:

- Conjunctival viral culture collection (one swab per eye)
- Conjunctival bacterial culture collection (one swab per eye)
- Intraocular pressure measurement
- Non-dilated/ dilated fundus examination
- Randomization
- Dispense and instill investigational product in both eyes by the designated site staff investigational product administrator. The investigational product bottle should be shaken well prior to use at each dosing.

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).

7.1.2 Visit 2 (Day 3), Visit 3 (Day 6), and Visit 4 (Day 8)

Visit 2 (Day 3 [+1 day]), Visit 3 (Day 6), and Visit 4 (Day 8 [+1 day]) assessments will be performed as outlined in Table 1 and as described in the Study Operations Manual. Assessments should be performed in descending order as listed.

Subject compliance will be verified verbally during study visits. In cases of non-compliance the investigator should determine if the medical monitor must be contacted for consultation.

Subjects should not instill investigational product within 12 hours of scheduled Study Visits. To ensure this, subjects should be reminded to not dose the morning of Visits 2, 3, and 4. Investigational product instillation should only be performed in-office if it is necessary, and should be done once all other assessments are completed. Subjects who instill investigational product less than 12 hours before study visits will be recorded as protocol deviations.

7.1.3 Visit 5 (End of Study or Early Termination)

Safety follow-up will be conducted at Visit 5 (the end of study visit). Visit 5 (Day 12 [+2 days]) assessments will be performed as outlined in Table 1. Assessments should be performed in descending order as listed.

Subjects who discontinue the study and proceed to Visit 5 for early termination should have investigational product collected, a compliance assessment, and drug accountability assessed at their final visit.

All AEs and SAEs that are not resolved at the time of Visit 5 or early termination will be followed to closure (see Section 8.1).

7.1.4 Additional Care of Subjects after the Study

No aftercare is planned for this study.

7.2 Study Evaluations and Procedures

7.2.1 Demographic and Other Baseline Characteristics

7.2.1.1 Demographics

Demographic information will be collected at Visit 1. Date of Birth (where permitted), Age, Sex, Race, and Ethnicity will be recorded.

7.2.1.2 Medication and Medical History

Medication History

Refer to Section 5 for full details on collection of prior treatment.

The investigator will categorize treatments as ocular (specified as left eye, right eye or both eyes) or non-ocular based on the indication for use. Prior treatment information must be recorded on the appropriate CRF page.

Medical History

The site must record all clinically or medically relevant information regardless of how much time has elapsed since the date of any diagnosis. Medical history will be classified as ocular (specified as left eye, right eye or both eyes) or non-ocular by the investigator. History should include, but is not limited to:

- History of ocular diseases/conditions.
- History of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, and any other non-ocular diseases/underlying conditions within the past year prior to the Screening Visit (Visit 1).

7.2.1.3 AdenoPlus Test

The AdenoPlus test will be performed at Visit 1 as outlined in Table 1. A positive result in at least one eye is required for enrollment in this study (unless at least 2 of the 5 criteria from Inclusion Criteria 4b, based upon medical history and examination, are met).

The AdenoPlus test is an in-office test that allows for the detection of adenoviral antigens directly from human eye fluid. A small tear sample is transferred onto the AdenoPlus test, which confirms the presence of adenovirus and the viral form of conjunctivitis.

Please refer to the Study Operations Manual for a detailed description of the AdenoPlus Test and administration.

7.2.2 Efficacy

7.2.2.1 Clinical Resolution

Clinical resolution of adenoviral conjunctivitis is defined as the absence (score = 0) of bulbar conjunctival injection and watery conjunctival discharge in the study eye. Bulbar Conjunctival Injection will be assessed based on a 0-4 scale which uses pictures from the Validated Bulbar Redness (VBR) Scale and Watery Conjunctival Discharge will be assessed based on a 0-3 scale. Details of the Bulbar Conjunctival Injection and Watery Conjunctival Discharge scales are located in the Study Operations Manual.

7.2.2.2 Adenoviral Eradication

Adenoviral eradication for an eye is defined as negative CC-IFA in that eye. CC-IFA for each eye will be conducted using conjunctival swab samples collected at each visit. See the Laboratory Manual for further details.

7.2.3 Safety

Safety assessments will be performed in both eyes.

7.2.3.1 Best Corrected Visual Acuity (BCVA)

The BCVA will be performed prior to slit lamp examination during the study as outlined in Table 1.

The complete instructions for performing the BCVA are in the Study Operations Manual. Changes in VA will be assessed for clinical significance. Clinically significant changes should be recorded in the source and on the eCRF as an AE.

For subjects who are too young to use an ETDRS chart, use an age-appropriate measurement method in accordance with the AAP Policy Statement for Visual System Assessment in Infants, Children, and Young Adults by Pediatricians (Donahue and Baker, 2016; American Academy of Pediatrics, 2016; located in the Study Operations Manual). The policy statement recommends formal vision screening can begin at 3 years of age. VA measurements for children under the age of 3 will be done at the discretion of the investigator. If not done, child should be able to fixate on and follow a moving object. This is not a requirement in subjects <2 months of age since the ability does not develop until about 2 months of age. However, if an infant <2 months of age is able to fix and follow, it should be recorded. The enrollment of subjects <2 months of age will be based on subject qualifying all other eligibility criteria and investigator discretion.

VA is to be measured using the same method at all visits in the same subject.

7.2.3.2 Slit Lamp Biomicroscopy

Slit lamp biomicroscopy (or hand held slit lamp) will be performed during the study as outlined in Table 1. Magnification of the slit lamp will be consistent with standard clinical practice. The subject will be seated.

Observations will be graded as Normal or Abnormal. Abnormal findings will be described, and clinically significant abnormalities should be recorded in the source and on the electronic CRF (eCRF) (in Medical History at Screening; any changes from the screening visit may be recorded as adverse events by the investigator). Please note the investigator may use his/her discretion to determine whether Not Clinically Significant (NCS) and disease progression should be considered AEs). The following will be examined at each visit:

- Lids
- Conjunctiva
- Cornea
- Anterior Chamber
- Iris

- Lens

For infants and young children, if the above exams cannot be performed with a slit lamp or a hand held slit lamp, an external examination is to be conducted in accordance with American Academy of Pediatrics (AAP) Policy Statement for Visual System Assessment in Infants, Children, and Young Adults by Pediatricians (Donahue and Baker, 2016; American Academy of Pediatrics, 2016; located in the Study Operations Manual). The examination of lens in these subjects should be conducted at Visit 1 and Visit 5 (or ET visit) and graded based on the external examination and red reflex exam (Section 7.2.3.4). All other structures listed above will be examined and graded at all visits based on the external examination. Observations will be graded as Normal or Abnormal. Abnormal findings will be described.

7.2.3.3 Intraocular Pressure

At Visit 1 and Visit 5 (or Early Termination visit), IOP will be assessed in both eyes using either Goldmann tonometer or a Tono-pen®. The same method of measurement must be used for each patient throughout the entire time of participation in the study. For both methods (Goldmann and Tono-Pen®), sterile disposable single-use tips must be used each time to prevent cross-contamination. Other measures as appropriate should be taken to prevent cross-contamination. For children <12 years of age, all efforts should be made to obtain IOP by an appropriate method (e.g., I-Care can be used for children <12 years of age).

7.2.3.4 Non-dilated/Dilated Fundus Examination

Fundus examination must be conducted after BCVA, Slit Lamp Biomicroscopy and conjunctival swab for adenoviral and bacterial culture has been collected.

A non-dilated fundus examination will be performed in all subjects with the exception of infants and uncooperative small children during the study as outlined in Table 1.

Observations will be graded as Normal or Abnormal. Abnormal findings will be described.

The following will be examined:

- Vitreous
- Optic Nerve
- Macula

Clinically significant changes should be recorded in the source and on the eCRF as an AE.

If a non-dilated fundus exam is attempted and is not feasible, dilated fundus exam should be conducted. The test should be conducted the same way (either dilated or non-dilated) at both Visit 1 and Visit 5 (or ET).

For infants and small children in whom a fundus examination cannot be done, a red reflex exam will be conducted in accordance with AAP Policy Statement for Visual System Assessment in Infants, Children, and Young Adults by Pediatricians (Donahue and Baker, 2016; American Academy of Pediatrics, 2016; located in the Study Operations Manual). Observations will be graded as Normal or Abnormal. Abnormal findings will be described. The red reflex should be normal (present and symmetrical for both eyes) at the screening/ baseline visit.

7.2.3.5 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). Adverse events are collected from the time informed consent is signed. (Please refer to Section 8, Adverse and Serious Adverse Events Assessment.) Any AE that occurs after the first dose of investigational product instillation will be considered a TEAE.

Adverse events may also be determined by the investigator during study examinations as mentioned in previous sections.

7.2.3.6 Microbiology Laboratory Evaluations

All laboratory assays will be performed according to the laboratory's normal procedures.

All bioanalytical assays for the study will be validated following FDA/ICH guidelines, based on the method's intended use. The lab will only receive sample ID numbers and collection dates, the lab results will then be transferred to the central lab for data analysis. The lab will not receive any information on subject treatment assignment.

The following laboratory assessments will be performed:

- Cell Culture Assay (CC-IFA): This test will be performed on samples collected at all visits to determine the presence of adenovirus.
- quantitative Polymerase Chain Reaction (qPCR): This test will be performed on all CC-IFA positive samples at all visits to determine viral count.
- Adenoviral serotyping: This test will be done at baseline only to determine what serotypes of adenovirus are present.
- qPCR: This test will be performed on samples for qualitative detection of HSV at baseline (Visit 1).

One swab sample from each eye will be taken from inferior conjunctival cul-de-sac at all study visits for adenoviral testing. For neonates and infants <2 months of age, PCR testing for qualitative detection of chlamydia and gonorrhea at baseline will also be conducted using the baseline visit sample. Qualitative PCR: This test will be performed on samples from baseline visit (Visit 1) for HSV testing.

[redacted]

7.2.3.7 Pregnancy Test

A urine pregnancy test is performed on all females of childbearing potential at Visit 1 and Visit 5, or if pregnancy is suspected. Urine pregnancy test kits will be provided by the sponsor and read on site by qualified site personnel.

7.2.3.8 Health-related Quality of Life Assessments

Ocular discomfort associated with conjunctivitis symptoms will be assessed through the Ocular Discomfort Scale. The Ocular Discomfort Scale is composed of three items: pain, itching, and foreign body sensation. All items will be evaluated using a 0-10 scale. A separate scale will be administered for children less than 8 years of age (binary ocular discomfort). Please see the Study Operations Manual for a detailed description of this assessment.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

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

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

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

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

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate CRF).

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

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

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

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

8.1.2 Relationship Categorization

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

The following additional guidance may be helpful:

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

8.1.3 Outcome Categorization

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

- Fatal
- Not recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved With Sequelae
- Recovering/Resolving
- Unknown

8.1.4 Symptoms of the Disease Under Study

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

8.1.5 Pregnancy

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

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

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

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

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

8.1.6 Abuse, Misuse, Overdose, and Medication Error

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

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

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society

- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- **Overdose** – Intentional or unintentional intake of a dose of an investigational product exceeding a pre-specified total daily dose of 4 drops per eye of the product.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

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

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

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

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

In cases of overdose the investigator should determine if the medical monitor must be contacted for consultation.

Please refer to the Study Operations Manual for further details on reporting overdose and medication errors. An AE should only be reported if any of these events meets the definition of an AE as outlined in Section 8.1.

All investigational product provided to pediatric subjects should be administered or supervised by the parent(s)/guardian/legally authorized representative/caregiver.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

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

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Pharmacovigilance and Risk Management Department and the CRO/Shire medical monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.6) unless they result in an SAE.

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

8.2.3 Serious Adverse Event Definition

A serious adverse event (SAE) is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject provides written informed consent (and assent, if applicable) until the defined follow-up period stated in Section 7.1.3 and must be reported to the Shire Global Pharmacovigilance and Risk Management Department and the CRO/Shire medical monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Global

Pharmacovigilance and Risk Management Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

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

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

8.2.6 Fatal Outcome

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

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

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The sponsor and/or the clinical CRO is responsible for notifying the relevant regulatory authorities and IRBs/ECs of related, unexpected SAEs.

In addition the sponsor and/or the clinical CRO is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP640 program.

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

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the CRF. A study monitor will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRF Completion Guidelines. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

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

9.3 Data Handling Considerations

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

9.4 Statistical Analysis Process

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

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

The SAP will be finalized prior to unmasking of the study to preserve the integrity of the statistical analysis and study conclusions.

All statistical analyses will be performed after the database is locked and unmasked.

All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC 27513) Version 9.2 or higher.

9.5 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

There is no planned interim analysis, adaptive design, or data monitoring committee (DMC) in this study.

9.6 Sample Size Calculation and Power Considerations

Subjects will be randomized 1:1 to receive either SHP640 (PVP-Iodine 0.6% /dexamethasone 0.1%) ophthalmic suspension or placebo within each stratum.

A sample size of 184 subjects (92 subjects in each treatment arm) 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 assumed proportions of subjects with clinical resolution in the 2 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 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 with post-baseline LOCF for the subjects with missing clinical resolution status at Visit 3 (Day 6). To ensure approximately 184 subjects in the mITT population, approximately 284 subjects will be randomized in this study.

9.7 Study Population

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

The **Intent to Treat (ITT) Population** will include all randomized subjects.

The **Modified Intent to Treat (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.

9.8 Efficacy Analyses

The analyses on primary, key secondary, secondary and exploratory efficacy endpoints will be performed on the mITT population (unless specified otherwise) and will be presented by treatment group.

Additional sensitivity analyses may be conducted in the ITT population.

For both efficacy and safety analyses, baseline is defined as the assessments taken at Visit 1 (Day 1).

9.8.1 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 (baseline is defined as the assessments taken at Visit 1 [Day 1]):

- 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 (sum of the scores for discharge and redness) 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.

9.8.2 Primary Efficacy Endpoint

The primary efficacy endpoint is clinical resolution status (defined as absence [ie, a score of 0] of bulbar conjunctival injection and watery conjunctival discharge) in the study eye at Visit 3 (Day 6) between SHP640 and placebo.

All efficacy analyses will be performed on the mITT and presented by treatment groups. There is a single primary comparison for the single primary endpoint. Therefore, no adjustment of multiplicity is needed for the hypothesis testing for the primary objective.

The primary efficacy endpoint of clinical resolution in the study eye at Visit 3 (Day 6) will be compared between the SHP640 and placebo group. The comparison will be based on the proportion of subjects with clinical resolution in the study eye at Visit 3 (Day 6) using Fisher's Exact test at two sided 0.05 significance level.

If subjects have missing clinical resolution status at Visit 3 (Day 6), then the last post-baseline observation will be carried forward (LOCF) for the determination of clinical resolution of the study eye.

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 Solution and Placebo with the alternative of the non-zero difference in the proportion with clinical resolution between them.

The proportion of subjects with clinical resolution will be compared with two-sided Fisher's Exact test at 5% level of significance.

Sensitivity analyses will be done on the primary efficacy endpoint using additional statistical method(s) including other methods of imputation of missing data. Sensitivity analyses may be conducted in the ITT in addition to the mITT. In addition, descriptive statistics will be generated for the primary efficacy endpoint by treatment within the overall pediatric population (ie, birth to 18 years) and within each pediatric age stratum (birth to<6 years and 6 to <18 years) in mITT. A detailed plan for primary analysis including additional sensitivity analyses will be described in the Statistical Analysis Plan (SAP).

9.8.3 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoint of this study is adenoviral eradication status (defined as negative cell culture-immunofluorescence assay [CC-IFA]) in the study eye at Visit 3 (Day 6).

In order to maintain the study-wide Type I error at 5.0%, the primary and key secondary hypotheses will be tested sequentially using two-sided Fisher's exact test.

The hypothesis test for the key secondary efficacy endpoint will not be performed unless the hypothesis test for the primary efficacy endpoint is significant.

Sensitivity analyses will also be done on key secondary efficacy endpoints using similar methods as described above. In addition, descriptive statistics will be generated for the key secondary efficacy endpoint by treatment within the overall pediatric population (ie, birth to 18 years) and within each pediatric age stratum (birth to <6 years and 6 to <18 years) in mITT. Details on the analyses will be described in the Statistical Analysis Plan (SAP).

9.8.4 Secondary Efficacy Endpoints

All secondary efficacy analyses will be performed on the mITT and presented by treatment group. No hypothesis testing is planned for the secondary efficacy endpoints. All secondary efficacy endpoint will be summarized by treatment groups using descriptive statistics at each assessment visit. Continuous endpoints will be summarized by number of subjects (n), mean, median, standard deviation, minimum, maximum and confidence intervals. Binary endpoints will be summarized by number of subjects (n), frequencies, proportions and confidence intervals. Time to event endpoint will be summarized by Kaplan-Meier survival estimates.

Secondary efficacy endpoints are defined as follows:

- Absolute and change from baseline in adenovirus viral titer as assessed by qPCR at Visits 3 (Day 6) and 4 (Day 8) in the study eye
- Adenoviral eradication status as assessed by CC-IFA at Visits 2 (Day 3), 4 (Day 8) and 5 (Day 12) in the study eye
- Clinical resolution status of adenoviral conjunctivitis at Visits 2 (Day 3), 4 (Day 8) and 5 (Day 12) in the study eye
- 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 (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
- 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
- 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
- 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

9.8.5 Exploratory Efficacy Endpoints

[redacted]

9.9 Safety Analyses

Safety data will be presented for the Safety Population by treatment group and overall.

Safety data collected at baseline (Visit 1 / Day 1) will be used as the baseline value for safety analysis.

Adverse events, including those suggestive of any local tolerability issues, will be coded using the Medical Dictionary for Regulatory Activities. The number of subjects and percentage with a treatment-emergent adverse event (TEAE) as well as the number of TEAEs will be calculated

overall, by SOC, by preferred term, and by treatment group and overall. Treatment-emergent adverse events will be further summarized by severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized and listed.

Generally, TEAEs will be presented separated by whether or not the AE was an ocular or non-ocular AE.

The following safety endpoints will be descriptively summarized by treatment group and overall at each applicable visit:

- Best Corrected Visual Acuity (BCVA)
- Slit Lamp Biomicroscopy
    - Lids
    - Conjunctiva
    - Cornea
    - Anterior Chamber
    - Iris
    - Lens
- Intraocular Pressure
- Non-dilated/ Dilated Fundus Examination
    - Vitreous
    - Optic Nerve
    - Macula
- Urine Pregnancy Testing (for females of childbearing potential)

9.10 Other Analyses

No other analyses are planned in this study.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

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

In case of substantial amendment, approval from the Competent Regulatory Authority will be sought before implementation.

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

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

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

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

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

10.1.2 Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied to CRO as necessary.

10.1.3 Public Posting of Study Information

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

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

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

10.1.5 Study Suspension, Termination, and Completion

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

The sponsor will make an end-of-study declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

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

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

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

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

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

The coordinating principal investigator will be assigned and selected based on the extent of their involvement in the study and experience in the therapeutic area.

10.2.2 Protocol Adherence and Investigator Agreement

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

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

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

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

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

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

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

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

The Clinical Research Associate (CRA)/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data. All corrections to the eCRF must indicate the reason for change. If corrections are made after the review and signature by the investigator, he or she must be made aware of the change, and his or her awareness documented by resigning the eCRF.

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

Original source data to be reviewed during this study will include, but are not limited to the: subject's medical file, scales, ocular discomfort scale, and documented results of AdenoPlus test.

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

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

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

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

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

10.2.3.3 Audit/Inspection

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

10.2.3.4 Financial Disclosure

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

10.3 Ethical Considerations

10.3.1 Informed Consent

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

Within the source documents, site personnel should document instruction of and understanding by the parent(s)/guardian/legally authorized representative/caregiver of the safe, responsible storage and administration of investigational product to the study subject.

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

10.3.2 Institutional Review Board or Ethics Committee

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

The applicant for an EC opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

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

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

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

10.4 Privacy and Confidentiality

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

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

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market SHP640; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

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

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

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2-4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

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

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

11. REFERENCES

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12. APPENDICES

APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	30 June 2016	Global
Amendment 1	28 November 2016	Global
Amendment 2	15 February 2017	Global
Amendment 3	13 December 2017	Global
Amendment 4	31 May 2018	Global

APPENDIX 2 SCALES AND ASSESSMENTS

All scales assessments referenced in the protocol, including procedural instructions for the investigator, are in the Study Operations Manual and the Laboratory Manual (provided upon request).