STATISTICAL ANALYSIS PLAN

Protocol No.:	SHP640-303
Protocol Title:	A Phase 3, Multi-center, Randomized, Double-Masked Study to Evaluate the Clinical Efficacy and Safety of SHP640 (PVP-Iodine 0.6% and Dexamethasone 0.1%) Ophthalmic Suspension Compared to Placebo in the Treatment of Bacterial Conjunctivitis
Drug:	SHP640
Sponsor:	Shire 300 Shire Way, Lexington, MA 02421 USA
Version No. and Date	Protocol Amendment 3: Dec 13, 2017

Version No:	Document History Description of Update	Author(s)	Effective Date
Version 1.0	Final Version	[redacted]	June 22, 2018
Amendment 1.0	In Section 6, PD categories were updated according to CTMS classifications. In Section 8.2, derivation rule for total number of expected doses was updated. In Section 10, how to handle subjects with no post baseline efficacy assessment in the analyses were clarified. In Section 11.2, change from baseline BCVA has been added. In Section 18.4, LOCF and WOCF derivation was clarified.	[redacted]	Nov 8, 2018

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ABBREVIATIONS

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

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy and safety data as described in the final study protocol amendment 3.0 dated Dec 13, 2017. Specifications for tables, figures, and listings are contained in a separate document.

2. STUDY DESIGN

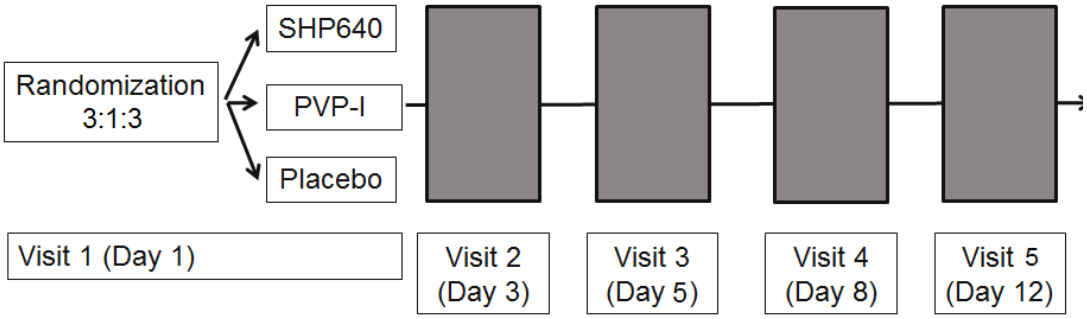
2.1 General Study Design

SHP640-303 is a global, multicenter, randomized, double-masked, parallel-group, placebo-controlled study designed to demonstrate the safety and efficacy of SHP640 ophthalmic suspension compared to placebo in treating bacterial conjunctivitis. In addition, an exploratory arm of povidone-iodine (PVP-I) 0.6% ophthalmic solution will be included.

Once screening and baseline assessments are complete and subjects are confirmed eligible to enroll in the study, subjects will be randomized, and investigational product (IP) 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 Days 3 (Visit 2), 5 (Visit 3), 8 (Visit 4), and 12 (Visit 5). 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: SHP640-303 Study Design



2.2 Randomization

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

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

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

Approximately 721 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 3:1:3 to receive either SHP640, PVP-I, or placebo within each stratum.

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

2.3 Masking

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

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

In the event that the treatment assignment is broken, the date and person who broke the code will be recorded by the interactive response technology (IRT), and the reason for breaking will be recorded on the electronic case report form (eCRF). Upon breaking the mask, the subject will be 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's medical monitor.

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

2.4 Schedule of Assessments

Table 1 below presents the schedule of assessments.

Table 1 Schedule of Assessments

Procedure (All ocular assessments and procedures performed bilaterally)	**Visit 1 Screening[a] and Baseline (Day 1) -1 Day**	**Visit 2 (Day 3) +1 Day**	**Visit 3 (Day 5)**	**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
Ocular conjunctival discharge evaluation	X	X	X	X	X
AdenoPlus® test	X[d]				
Conjunctival swab for bacterial culture[e]	X	X[f]	X[f]	X[f]	X
Conjunctival swab to test for HSV, and chlamydia and gonorrhea[l]	X				
Non-dilated/dilated fundus examination[k]	X				X
Randomization[g]	X				
Dispense investigational product[h]	X				
Instill investigational product	X[h]	X[i]	X[i]		
Collect investigational product				X	X[b]
Compliance assessment		X	X	X	X[b]
Drug accountability				X	X[b]
Adverse events	X[j]	X	X	X	X
Study completion					X

ET=early termination;

[a] Informed consent and confirmation of inclusion/exclusion criteria can be conducted on Day -1; these criteria must be reconfirmed 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 bacterial testing.

[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] All assessments, randomization, and investigational product instillation on Day 1 must take place with sufficient time to allow

Table 1 Schedule of Assessments

Procedure (All ocular assessments and procedures performed bilaterally)	Visit 1 Screening[a] and Baseline (Day 1) -1 Day	Visit 2 (Day 3) +1 Day	Visit 3 (Day 5)	Visit 4 (Day 8) +1 Day	Visit 5[b] (Day 12) +2 Days

all 4 Day 1 doses (with a minimum of 2 hours between doses).

[h] 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.

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

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

[k] 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 Visits 1 and 5 (or ET).

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

2.5 Determination of Sample Size

The sample size was estimated for the primary comparison of SHP640 versus placebo on clinical resolution in the treatment of subjects with bacterial conjunctivitis in the study eye at Visit 3 (Day 5) using nQuery Advisor 7.0. Subjects will be randomized 3:1:3 to receive either SHP640, PVP-I, or placebo within each age stratum.

The primary efficacy endpoint is clinical resolution status (defined as absence [ie, a score of 0] of bulbar conjunctival injection and ocular conjunctival discharge) in the study eye at Visit 3 (Day 5) between SHP640 and placebo. The null hypothesis to be tested is that there is no difference in proportion of subjects with clinical resolution in the study eye between SHP640 ophthalmic suspension and placebo with the alternative of the non-zero difference in the proportion with clinical resolution between them.

A sample size of 504 subjects (216 subjects in each of the SHP640 and placebo groups, 72 in PVP-I group) will ensure ~90% power to compare the SHP640 and placebo treatment groups assuming 61% and 45% subjects with clinical resolution, respectively, using Fisher's Exact test at 2-sided 5% level of significance.

All efficacy analyses will be based on the modified Intent-to-Treat (mITT) population (refer to Section 4.4 for the definition of mITT) with post-baseline last observation carried forward (LOCF) for the subjects with missing clinical resolution status at Visit 3 (Day 5). To ensure 504 subjects in the mITT population, approximately 721 subjects will be randomized in this study (approximately 309 subjects in each of SHP640 and placebo groups; approximately 103 subjects in PVP-I group).

2.6 Multiplicity Adjustments for Type I Error Control

An unmasked interim analysis (IA) will be performed after ~50% subjects exit the trial in the mITT population for possible sample size increase. The final sample size will be calculated in the unmasked IA based on the conditional power for the primary comparison of SHP640 versus placebo on clinical resolution in the treatment of subjects with bacterial conjunctivitis in the

study eye at Visit 3 (Day 5). There is no inflation of type I error from this IA because the sole purpose of the IA is to adjust the sample size by using the conditional power approach, and the sample size will be changed only under certain conditions (Mehta and Pocock, 2011). However, for conservativeness, two sided 0.0001 alpha will be spent for the proposed IA and a two sided alpha of 0.0499 will be used for final analyses.

Formal hypothesis testing will be conducted on the primary efficacy endpoint and key secondary efficacy endpoint with a total of 2 pairwise comparisons. The comparison on the primary efficacy endpoint will be based on clinical resolution in the study eye at Visit 3 (Day 5) between SHP640 and placebo in the mITT population. The comparison on the key secondary efficacy endpoint will be based on bacterial eradication in the study eye at Visit 3 (Day 5) between SHP640 and placebo in the mITT population.

A fixed sequence procedure will be used to maintain the study-wide Type I error at 4.99% for final analyses with the primary efficacy endpoint being tested first and the key secondary efficacy endpoint being tested second. Both the primary and key secondary hypothesis tests will be conducted at the two-sided 0.0499 significance level following the pre-specified order. The hypothesis test for the key secondary efficacy endpoint will not be performed unless the hypothesis test for the primary efficacy endpoint is statistically significant.

3. OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of SHP640 based on clinical resolution (defined as absence of bulbar conjunctival injection and ocular conjunctival discharge) compared with placebo in the treatment of subjects with bacterial conjunctivitis in the study eye at Visit 3 (Day 5).

3.2 Secondary Objective

The key secondary objective is to evaluate the efficacy of SHP640 based on bacterial eradication (defined as absence of all bacterial species present at or above pathological threshold at baseline) compared with placebo in the treatment of subjects with bacterial conjunctivitis in the study eye at Visit 3 (Day 5).

Other secondary objectives of this study are as follows:

- To evaluate the effect of treatment in the study eye, for the following endpoints:
  - Clinical resolution of bacterial conjunctivitis at Visits 2 (Day 3), 4 (Day 8), and 5 (Day 12)
  - Bacterial eradication at Visits 2 (Day 3), 4 (Day 8), and 5 (Day 12)
  - Absolute and change from baseline of the individual clinical signs (bulbar conjunctival injection and ocular conjunctival discharge) at Visits 2 (Day 3), 3 (Day 5), 4 (Day 8), and 5 (Day 12)
  - The global clinical score (sum of bulbar conjunctival injection and ocular conjunctival discharge) and change from baseline in the global clinical score at Visits 2 (Day 3), 3 (Day 5), 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 5), 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 5), 4 (Day 8), and 5 (Day 12)
  - Time to clinical resolution based upon assessments at Visits 2 (Day 3), 3 (Day 5), 4 (Day 8), and 5 (Day 12)
- To evaluate the safety and tolerability of SHP640, compared to PVP-I and placebo in the treatment of subjects with bacterial conjunctivitis
- Use of rescue medication

3.3 Exploratory Objective

The exploratory objective of this study is as follows:

- To evaluate ocular discomfort due to conjunctivitis symptoms in subjects receiving SHP640 compared to PVP-I and placebo at Visits 2 (Day 3), 3 (Day 5), 4 (Day 8), and 5 (Day 12)

4. SUBJECT POPULATION SETS

4.1 Screened Population

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

4.2 Safety Population

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

4.3 Intent to Treat (ITT) Population

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

4.4 Modified Intent to Treat (mITT) population

The mITT Population consists of a subset of the ITT population who receive at least one dose of investigational product and have a positive bacterial culture (presence of one or more bacterial species at or above pathological threshold) at baseline (i.e. Visit 1) in the study eye.

Pathological threshold for individual bacterial species will be based on colony forming unit (CFU)/ml threshold levels established by Cagle and modified by Leibowitz (Leibowitz, 1991) for different ocular bacterial species found in the specimens collected from each subject as specified in Appendix 20.1.

5. SUBJECT DISPOSITION

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

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

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

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

6. PROTOCOL DEVIATIONS

Protocol deviations will be recorded by the site monitors separately from the clinical database. Protocol deviations will be listed and summarized for subjects in the ITT Population for each treatment group by country and overall. Summary tables will be presented with the following Clinical Trial Management System (CTMS) categories:

- Informed Consent
- Eligibility and Entry Criteria
- Concomitant Medication Criteria
- Laboratory Assessment Criteria
- Study Procedures Criteria
- Serious Adverse Event Criteria
- Randomization Criteria
- Visit Schedule Criteria
- IP Compliance
- Efficacy Criteria
- Administrative Criteria
- Source Document Criteria
- Regulatory or Ethics Approvals Criteria
- Other Criteria

In addition to the 14 CTMS categories, number of subjects in the ITT population for each treatment group by country and overall will also be summarized for subjects coming to visits who did not have 12 hours since their last dose, which could be mapped to multiple CTMS categories.

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

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

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

A listing will be generated for demographic and baseline characteristics for the ITT Population.

Ocular and non-ocular medical history will be descriptively summarized based on the system organ class (SOC) and preferred term coded terms (Medical Dictionary for Regulatory Activities [MedDRA] version 19.1) by treatment group and overall for the Safety Population. Data summaries will be sorted by the overall frequency of reporting within SOC.

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

8. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

8.1 Exposure to Investigational product

Exposure to double-masked investigational product for the Safety Population will be summarized in terms of treatment duration, which is calculated as the number of days from the date of first dose of double-masked investigational product taken to the date of the last dose of double-masked investigational product taken, inclusively, and irrespective of any investigational product interruption(s). Descriptive statistics will be presented by treatment group and overall.

A listing of investigational product exposure will be provided for all subjects in the Safety Population.

8.2 Measurement of Treatment Compliance

Investigational product dosing compliance for the double masked treatment period is defined as the total number of doses actually taken by a subject during that period divided by the number of doses expected to be taken during the same period multiplied by 100.

For completers (i.e. subjects who completed all 7 days of dosing), the total number of expected doses is 28 (i.e. 4 doses per day for 7 days). For subjects who early terminated dosing on Day 1, the total number of expected doses is set to be 1. For the rest of subjects who terminated dosing before 7 days, the total number of expected doses is the number of full dosing day multiplied by 4. For example, if a subject early terminates on Day 4, his/her total number of expected doses is 3 (full dosing day) x 4 (doses per day) = 12.

At each visit, the number of missed doses or extra doses since last visit will be recorded on the CRF. The total number of missed doses will be derived as the sum of the number of missed doses since last visit across all visits. The total number of extra doses will be derived as the sum of the number of extra doses since last visit across all visits. The total number of doses actually taken will be derived as the total number of expected doses plus the total number of extra doses minus the total number of missed doses.

Descriptive statistics [number of subjects (n), mean, median, standard deviation (SD), minimum, maximum] for investigational product compliance will be presented by treatment group and overall for the whole double-masked evaluation phase for the Safety Population. Number of subjects (percentage) who completed 4 days of dosing by Visit 3 with no extra or missed dose will also be presented by treatment group and overall for the Safety Population.

A listing of treatment compliance will be provided for all subjects in the Safety Population.

9. PRIOR AND CONCOMITANT MEDICATION

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

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

Concomitant medication/therapy is defined as any medication/therapy with a start date prior to the date of the first dose of investigational product and continuing after the first dose of investigational product or with a start date between the dates of the first and last doses of investigational product, inclusively. Concomitant procedure is defined as any procedure with a start date between the dates of the first and last doses of investigational product, inclusively. Any medication/therapy/procedure with a start date after the date of the last dose of investigational product will not be considered a concomitant medication/therapy/procedure.

Both prior and concomitant medication usage will be summarized by the number and proportion of subjects receiving each medication within each ATC and each preferred term by treatment group and overall for the Safety Population. Medications can be counted both as prior and concomitant medication. Multiple medication usage by a subject in the same category will be counted only once.

Ocular and non-ocular medications will be summarized separately.

All prior and concomitant medication will be listed. Prior and concomitant therapy/procedure will not be summarized, but will be listed. Imputed dates (see Section 18.6 for imputation rules) will be marked in the listings.

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

10. EFFICACY ANALYSES

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

All statistical tests will be 2-sided hypothesis tests performed at the 4.99% level of significance for main effects. All confidence intervals (CIs) will be 2-sided 95% CI, unless stated otherwise.

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

Multiplicity adjustments will be done on the primary and key secondary efficacy endpoints testing as described in Section 2.6.

Missing post-baseline efficacy assessments will be imputed using LOCF from post-baseline values and all efficacy statistical inference will be made based on analyses using LOCF, unless stated otherwise. If a subject has no post-baseline efficacy assessment then no LOCF will be done for that efficacy assessment for the subject. In other words, the subject's Visit 3 (Day 5) data will remain missing which means the subject will be excluded from the primary analysis in mITT and sensitivity analysis in ITT for that efficacy assessment.

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

10.1 Study Eye Designation

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

- For subjects with both eyes eligible and both with a positive bacterial culture (presence of 1 or more bacterial species at or above pathological threshold) at baseline or both eyes eligible and both with a non-positive bacterial culture (absence of any bacterial species at or above pathological threshold) at baseline, the study eye will be the eye with the highest global clinical score (refer to Section 3.2) at baseline. If both eyes have the same global clinical score at baseline, then the study eye will be the right eye.
- For subjects with both eyes eligible with a positive bacterial culture in 1 eye at baseline, the baseline bacterial culture positive eye will be the study eye.
- For subjects with only 1 eligible eye, the eligible eye will be the study eye irrespective of its baseline bacterial culture result.

The study eye designation is summarized in the table below:

Eligible Eye(s)	Bacterial Culture Results	Study Eye
Both eyes	Both eyes positive	Highest global clinical score at Visit 1 (or right eye if scores are the same)
Both eyes	Both eyes negative	Highest global clinical score at Visit 1 (or right eye if scores are the same)
Both eyes	One eye positive	The bacterial culture positive eye at Visit 1
One eye	Positive or negative for either eye	The eligible eye

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

10.2 Primary Efficacy Endpoint and Analysis

The primary efficacy endpoint is clinical resolution status (defined as absence [ie, a score of 0] of bulbar conjunctival injection and ocular conjunctival discharge) in the study eye at Visit 3 (Day 5) between SHP640 and placebo.

The null hypothesis to be tested is that there is no difference in proportion of subjects with clinical resolution in the study eye between SHP640 ophthalmic suspension and placebo with the alternative of the non-zero difference in the proportion with clinical resolution between them. The proportion of subjects with clinical resolution will be compared between SHP640 and placebo groups using two-sided Fisher's Exact test at two-sided 4.99% level of significance. Missing data will be imputed based on post baseline LOCF for the determination of clinical resolution in the study eye at Visit 3 (Day 5). The primary basis of inference for this comparison will be based on the analysis conducted in mITT. Frequency and percent of subjects who reached/did not reach clinical resolution in the study eye at Visit 3 (Day 5) will be reported by treatment group along with the two-sided Fisher's Exact test p value for comparison between SHP640 and placebo. The two-sided 95% CI for response rate (exact CI for binominal proportion) in each treatment group as well as the estimated difference in response rates and corresponding two-sided 95% asymptotic CI for the difference will also be reported.

Example SAS code for conducting Fisher's exact test and generating the CIs is in Appendix 20.2.1.

10.3 Sensitivity Analyses for the Primary Efficacy Endpoint

ITT Population Analysis

A sensitivity analysis will be conducted by repeating the primary analysis using the ITT Population. Frequency and percent of subjects who reached/did not reach clinical resolution in the study eye at Visit 3 (Day 5) will be reported by treatment group along with the two-sided Fisher's Exact test p value for comparison between SHP640 and placebo. The two-sided 95% CI for response rate (exact CI for binominal proportion) in each treatment group as well as the estimated difference in response rates and corresponding two-sided 95% asymptotic CI for the difference will also be reported.

Missing Data Imputation

Method 1: Modified Worst Observation Carry Forward (WOCF)

The between-treatment group comparison (SHP640 versus placebo) for the primary efficacy endpoint will be performed using Fisher's Exact test on the mITT data set. Missing data will be imputed based on post baseline WOCF for the determination of clinical resolution in the study eye at Visit 3 (Day 5). For clinical resolution status, not reaching clinical resolution is considered worse than reaching clinical resolution. If a subject has no post-baseline efficacy assessment up to Visit 3 (Day 5), then his/her baseline efficacy assessment will be carried forward as the Visit 3 (Day 5) assessment.

Frequency and percent of subjects who reached/did not reach clinical resolution in the study eye at Visit 3 (Day 5) in the imputed data set will be reported by treatment group along with the two-sided Fisher's Exact test p value for comparison between SHP640 and placebo. The two-sided 95% CI for response rate (exact CI for binominal proportion) in each treatment group as well as the estimated difference in response rates and corresponding two-sided 95% asymptotic CI for the difference will also be reported.

Method 2: Multiple imputations

Multiple imputation (MI) methods will utilize the SAS procedures PROC MI and PROC

MIANALYZE in mITT. The MI procedure will first impute the global clinical score (GCS) at Visit 3 based on a regression model with treatment, age strata (< 6 years, 6 to <18 years and ≥18 years) as categorical independent variables and baseline GCS and GCS at Visit 2 as continuous independent variable assuming monotone missing pattern. In case the missing pattern is not monotone, Markov Chain Monte Carlo (MCMC) multiple imputation will be conducted first to impute enough data to produce a monotone missing data pattern. The MI procedure will generate 10 datasets with missing data imputed. The imputed GCS data will be rounded to integers and bounded to 0 to 7 during imputation so that the imputed values match the format of the observed values as well as existing range. Once the missing values are imputed and each dataset is created, clinical resolution status at Visit 3 will be derived based on the GCS scores at Visit 3. Binomial proportion for clinical resolution at Visit 3 in each treatment group, corresponding standard error (SE), the difference in the proportions between SHP640 and placebo and SE of the difference will be generated in each imputed data set and then appropriately pooled across the multiply imputed data sets using PROC MIANALYZE. The pooled binominal proportion point estimate in each treatment arm, the two-sided 95% CI for pooled proportion point estimate, the pooled point estimate of the difference between proportions in SHP640 and placebo, the corresponding p value and two-sided 95% CI will be reported.

Appendix 20.2.2 shows example SAS code for MI analysis.

10.4 Exploratory Analyses for the Primary Efficacy Endpoint

Adjusted Chi-square Test

Since all subjects from the same household will be assigned to the same treatment group, an exploratory analysis will be conducted on the primary efficacy endpoint in mITT based on an adjusted Chi-square test to account for clustering of the data (Jung et al., 2001). The proportion of subjects with clinical resolution in the study eye will be compared between SHP640 ophthalmic suspension and placebo with missing data imputed with post baseline LOCF for the determination of clinical resolution in the study eye at Visit 3 (Day 5). Adjusted Chi-square test statistics and corresponding p value will be presented.

Appendix 20.2.3 shows example SAS code for the adjusted chi-square test.

Analysis Based on CRF Visits

Analysis visits in the primary analysis will be derived based on rules specified in Section 18.2 of this SAP. An exploratory analysis will be conducted repeating the primary analysis on the primary efficacy endpoint of clinical resolution in the study eye at Visit 3 (Day 5) in mITT based on CRF recorded Visit 3 data. Frequency and percent of subjects who reached/did not reach clinical resolution in the study eye at Visit 3 will be reported by treatment group along with the two-sided Fisher's Exact test p value for comparison between SHP640 and placebo. The two-sided 95% CI for response rate (exact CI for binominal proportion) in each treatment group as well as the estimated difference in response rates and corresponding two-sided 95% asymptotic CI for the difference will also be reported.

10.5 Key Secondary Efficacy Endpoints and Analysis

The key secondary efficacy endpoint of this study is bacterial eradication status (defined as absence of all bacterial species present at or above pathological threshold at baseline) in the study eye at Visit 3 (Day 5) between SHP640 and placebo.

The null hypothesis to be tested is that there is no difference in proportion of subjects reaching bacterial eradication in the study eye at Visit 3 (Day 5) between SHP640 and placebo with the alternative hypothesis of non-zero difference in the proportion of responders between the two treatment groups.

In order to maintain the study-wide Type I error at 5% (two sided alpha of 0.0001 at IA and two sided alpha of 0.0499 at final analyses), the primary and key secondary hypotheses will be tested sequentially using two-sided Fisher's exact test with the primary efficacy endpoint being tested first and the key secondary efficacy endpoint being tested second. The hypothesis test for the key secondary efficacy endpoint will not be performed unless the hypothesis test for the primary efficacy endpoint is statistically significant.

Missing data will be imputed based on the post baseline LOCF for the determination of bacterial eradication status in the study eye at Visit 3 (Day 5). The primary basis of inference for the key secondary comparison will be based on the analysis conducted in mITT. Frequency and percent

of responders in the study eye at Visit 3 (Day 5) will be reported by treatment group along with the two-sided Fisher's Exact test p value for comparison between the two treatment groups. The two-sided 95% CI for response rate (exact CI for binominal proportion) in each treatment group as well as the estimated difference in response rates and corresponding two-sided 95% asymptotic CI for the difference will also be reported.

Sensitivity and exploratory analyses will also be conducted on key secondary efficacy endpoint using the same methods as described in Section 10.3 and 10.4 (i.e. modified WOCF imputation and multiple imputation as sensitivity analyses; adjusted Chi-square test and analysis based on CRF visits as exploratory analyses) except for the ITT population sensitivity analysis, which will not be conducted for bacterial eradication key secondary endpoint.

In addition, a subgroup analysis will be conducted by repeating the Fisher's exact test with post baseline LOCF for the determination of bacterial eradication status in the study eye at Visit 3 (Day 5) in the mITT excluding bacterial eradication data obtained from swabs where the last dose of study medication was instilled within 12 hours of the swab (i.e. swab occurred <12 hours after last dose of investigational product). Frequency and percent of responders in the study eye at Visit 3 (Day 5) will be reported by treatment group along with the two-sided Fisher's Exact test p value for comparison between the two treatment groups. The two-sided 95% CI for response rate (exact CI for binominal proportion) in each treatment group as well as the estimated difference in response rates and corresponding two-sided 95% asymptotic CI for the difference will also be reported. This subgroup analysis is not statistically powered.

10.6 Other Secondary Efficacy Endpoints and Analysis

Secondary efficacy endpoints are defined as follows:

- Clinical resolution status of bacterial conjunctivitis at Visits 2 (Day 3), 4 (Day 8), and 5 (Day 12) in the study eye
- Bacterial eradication status (defined as absence of all bacterial species present at or above pathological threshold at baseline) as assessed by bacterial culture at Visits 2 (Day 3), 4 (Day 8), and 5 (Day 12) in the study eye
- Absolute and change from baseline of the individual clinical signs score (bulbar conjunctival injection and ocular conjunctival discharge) at Visits 2 (Day 3), 3 (Day 5), 4 (Day 8), and 5 (Day 12) in the study eye
- The global clinical score (defined as the sum of bulbar conjunctival injection and ocular conjunctival discharge) and change from baseline in the global clinical score at Visits 2 (Day 3), 3 (Day 5), 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 5), 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 5), 4 (Day 8), and 5 (Day 12) in the study eye

- Time to clinical resolution based upon assessments at Visits 2 (Day 3), 3 (Day 5), 4 (Day 8), and 5 (Day 12) in the study eye
- Use of rescue medication

All secondary efficacy analyses will be performed on the mITT and presented by treatment group. No hypothesis testing will be conducted for the secondary efficacy endpoints. All secondary efficacy endpoints will be summarized by treatment group using descriptive statistics at each assessment visit. Continuous endpoints will be summarized by number of subjects (n), mean, median, SD, minimum, maximum and two-sided 95% CI. Binary endpoints will be summarized by number of subjects (n), frequency, proportion and two-sided 95% CI (exact CI for binominal proportion). Time to event endpoint will be summarized by Kaplan-Meier survival estimates (number of events, number at risk, survival function at each assessment visit, median survival time and 95% CI). Survival plot by treatment group will also be generated.

Appendix 20.2.4 shows example SAS code for generating descriptive statistics.

10.7 Exploratory Efficacy Endpoints and Analyses

Ocular discomfort associated with conjunctivitis symptoms will be assessed through the Ocular Discomfort Scale. The Ocular Discomfort Scale is composed of three items: eye pain, itching, and foreign body sensation. The subject will be asked three questions about his/her experience with pink eye over the past 24 hours: how bad was your eye pain (for example, a hurting, burning, or stinging feeling in your eye) at its worst; how bad was the felling that something was in your eye (like an eyelash or dirt) from your pink eye at its worst; how bad was the itching from your pink eye at its worst. All questions will be evaluated using a 0-10 scale with 0 indicating no symptom and higher score indicating more severe symptom. A separate scale will be administered for children less than 8 years of age, which has a single question for the parent about whether his/her child experienced eye pain or discomfort because of pink eye over the past 24 hours (child rubbing his/her eyes, crying or tearing up, and/or telling parent that he/she is having pain or discomfort) with a Yes/No answer.

The ocular discomfort endpoints will be collected at Visit 2 (Day 3), Visit 3 (Day 5), Visit 4 (Day 8), and Visit 5 (Day 12). For the ocular discomfort endpoints obtained from the scale for adults and children 8 years and older (individual scores and total score), absolute and change from baseline of ocular discomfort scores due to conjunctivitis symptoms will be summarized by treatment group at each visit in mITT and ITT population.

The binary ocular discomfort endpoint obtained from children less than 8 years of age will also be summarized by treatment group at each visit in mITT and ITT population.

No hypothesis testing will be conducted for the exploratory efficacy endpoints. Similar to secondary efficacy endpoints, all exploratory efficacy endpoints will be summarized by treatment group using descriptive statistics at each assessment visit. Continuous endpoints will be summarized by number of subjects (n), mean, median, SD, minimum, maximum and two-sided 95% CI. Binary endpoints will be summarized by number of subjects (n), frequency, proportion and two-sided 95% CI (exact CI for binominal proportion).

11. SAFETY ANALYSES

The safety analysis will be performed using the Safety Population. Safety variables include adverse events (AEs; including local tolerability), slit lamp biomicroscopy, non-dilated/dilated fundus exam, red reflex exam, best corrected visual acuity (BCVA), and urine pregnancy testing (for females of childbearing potential) variables.

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

All safety analyses will be conducted according to the treatment the subject actually received.

11.1 Adverse Events

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

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

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

Listings of all TEAEs will be provided by subject.

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

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

11.2 Other Safety Variables

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

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

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

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

12. CLINICAL PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Not applicable.

13. OTHER ANALYSES

Subgroup analyses will be performed on the primary and key secondary efficacy endpoint. The following subgroups will be used: age stratum (< 6 years, 6 to <18 years, ≥18 years and overall pediatric group, i.e. <18 years), gender, race, ethnicity, iris color of the study eye and region. The planned regions and countries are: North America (Canada and United States including Puerto Rico), South America (Colombia, Peru), Asia-Pacific (Australia, India and Philippines), Europe (Austria, Estonia, France, Germany, Hungary, Italy, Poland, Spain and United Kingdom) and Middle East/Africa (Israel, South Africa). Descriptive statistics (number of subjects [n], frequency, proportion, two-sided 95% exact CI for binominal proportion) will be generated for the primary and key secondary efficacy endpoints by treatment group in mITT. Pairwise difference in response rates and corresponding two-sided 95% asymptotic CI for the difference will also be generated in mITT. No hypothesis testing will be conducted as the study is not powered to detect treatment effect within subgroups.

14. INTERIM ANALYSIS

An unmasked IA will be performed after ~50% subjects exit the trial in the mITT population, with data to be analyzed entered into the database, queried, and discrepancies resolved. The purpose of the IA will be to assess the adequacy of the initial sample size estimation by evaluating conditional power for the primary comparison of SHP640 versus placebo on clinical resolution in the treatment of subjects with bacterial conjunctivitis in the study eye at Visit 3 (Day 5). There is no intention to stop early for efficacy or futility based on the results from the IA.

The IA will be performed by an external unmasked independent statistician and/or unmasked programmers based on a prespecified interim SAP. The interim SAP will explicitly describe how the conditional power is to be calculated and the precise rules for altering the sample size depending on the potential results. The interim SAP will be finalized prior to IA. The interim statistical report including the results will be distributed only to a limited group of people who are not involved in the conduct of the trial. All sponsor, CRO, and site staff involved in the conduct of the trial must remain masked throughout the trial. Recommendation from the IA to increase the sample size may require an amendment to the study protocol. There is no inflation of type I error from this IA because the sole purpose of the planned IA is to adjust the sample size by using the conditional power approach, and the sample size will be changed only under certain conditions (Mehta and Pocock, 2011). However, for conservativeness, two sided 0.0001 alpha will be spent for the proposed IA and a two sided alpha of 0.0499 will be used for final analyses.

15. DATA MONITORING/REVIEW COMMITTEE

There is no data monitoring committee for this study.

16. COMPUTER METHODS

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

17. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

Change from baseline BCVA has been added in Section 11.2, other safety variables.

18. DATA HANDLING CONVENTIONS

18.1 General Data Reporting Conventions

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

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

18.2 Study Visits and Windows

Assessments will be assigned to visits based upon the date the assessment took place regardless of the CRF page completed. Assessments will be mapped to visits as outlined in Table 2.

Should there be more than 1 assessment mapped into a given study visit, the assessment closest to the planned visit will be used for analysis (referred to as analysis visit); if equally close, choose assessment obtained on the scheduled visit or the last assessment if there is no data on the scheduled visit.

Study day will be calculated as follows:

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

  Study day = assessment date – first dosing date + 1

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

  Study day = assessment date – first dosing date

Table 2: Visit Windows (Study Day Based)

Visit	Planned Study Day	Start Day of Window	End Day of Window
Visit 1 (Screening & Baseline)	1	Date of CRF Visit 1	1
Visit 2	3	3	4
Visit 3	5	5	6
Visit 4	8	8	9
Visit 5	12	12	14

18.3 Derived Efficacy Endpoints

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

Bacterial eradication is defined as absence of all bacterial species present at or above pathological threshold at baseline (see Appendix 20.1 for pathological thresholds). Presence of at least one bacterial species that were at or above pathological threshold at baseline is considered not reaching bacterial eradication. If an eye has missing bacterial culture result at baseline, the eye will be assumed to be bacterial culture negative at baseline for determination of the study eye.

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

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

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

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

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

18.4 Repeated or Unscheduled Assessments of Safety Parameters

Assessments will be mapped to analysis visit according to rules specified in Section 18.2. Additional repeated or unscheduled assessments will not be included in the by visit summary tables, but will be included in subject listings. Assessments that were not mapped to any analysis window (including repeated or unscheduled assessments) will be included in LOCF and modified WOCF imputation and subject listings.

18.5 Missing Date of Investigational Product

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

18.6 Missing Date Information for Prior or Concomitant Medications

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

18.6.1 Incomplete Start Date

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

Missing day and month

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

Missing month only

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

Missing day only

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

18.6.2 Incomplete Stop Date

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

Missing day and month

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

Missing month only

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

Missing day only

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

18.7 Missing Date Information for Adverse Events

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

18.7.1 Incomplete Start Date

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

18.8 Missing Severity Assessment for Adverse Events

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

18.9 Missing Relationship to Investigation Product for Adverse Events

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

19. REFERENCES

Jung, S.-H., Ahn, C.and Donner, A. 2001. Evaluation of an adjusted chi-square statistic as applied to observational studies involving clustered binary data. *Statistics in Medicine,* 20, 2149-2161.

Leibowitz, H. M. 1991. Antibacterial effectiveness of ciprofloxacin 0.3% ophthalmic solution in the treatment of bacterial conjunctivitis. *American Journal of Ophthalmology,* 112, 29S-33S.

Mehta, C. R.and Pocock, S. J. 2011. Adaptive increase in sample size when interim results are promising: a practical guide with examples. *Statistics in medicine,* 30, 3267-84.

Pocock, S. J.and Simon, R. 1975. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics,* 31, 103-15.

20. APPENDIX

20.1 Threshold Criteria for Judging Culture Positive Specimens

Threshold criteria for judging culture positive specimens*

Group I – Threshold = 1 CFU/ml
Streptococcus, Group A, beta hemolytic (St. pyogenes)
St. pneumoniae
Citrobacter sp.
Enterobacter sp.
Escherichia sp.
Klebsiella sp.
Proteus/Morganella sp.
Serratia Marcescens
Other Enterobacteriaceae
N.gonorrhoeae
Other Neisseria sp.
Other Moraxella sp.
Acinetobacter sp.
Achromobacter sp.
Haemophilus sp.
Pseudomonas aeruginosa
Other Pseudomonas sp.
Group II – Threshold = 10 CFU/ml
Staphylococcus aureus
Streptococcus Group B (beta or nonhemolytic)
Streptococcus Group C (alpha, beta, or nonhemolytic)
Other Streptococcus (Groups D, G; nongrouped; viridans)
Moraxella (Branhamella) catarrhalis
Group III – Threshold = 100 CFU/ml
S. epidermidis
Other coagulase-negative Staphylococcus sp.
Micrococcus sp.
Bacillus sp.
Group IV – Threshold == 1000 CFU/ml
Corynebacterium (diphtheroids)

*An ocular specimen will be considered culture-positive if the colony count equalled or exceeded the threshold value.

Bacterial isolates *that are not specified or otherwise covered* in the table above (from Leibowitz, 1991) will be assigned threshold criteria (i.e., assigned to either of groups I to IV) as below:

1. **Phylum Actinobacteria**
   a. Gram positive bacilli or coccobacilli will be assigned to group IV.
   b. Gram positive cocci will be assigned to group III.

2. **Phylum Firmicutes**
   a. Gram positive isolates will be assigned to group III, except known pathogens which may be assigned to either group I (eg, B. anthracis) or group II (eg, clostridium perfringens)

3. **Phylum Proteobacteria**
   a. Gram negative isolates will be assigned to group I, except M. catarrhalis which is assigned to group II.

4. **Other**
   a. Gram negative isolates belonging to Phylum Bacteroidetes will be assigned to group I.

Note: All group assignments, including for any species that may not be covered by the above schemes, will be made prior to final database lock.

20.2 Example SAS Code

20.2.1 Example SAS Code for Fisher's Exact Test and the CIs

Example SAS code for conducting Fisher's Exact Test is as follows

```
proc freq data = testData_SHP640_PBO;
tables treatment*CS / chisq nocol nopercent;
run;
```

Example SAS code for generating exact CI for binominal proportion is as follows:

```
proc freq data = testData_SHP640_PBO;
tables CS / binomial (exact level='Yes') alpha=0.05;
by treatment;
run;
```

Example SAS code for generating the estimated difference in response rates and corresponding 95% asymptotic CI for the difference.

```
proc freq data = testData_SHP640_PBO;
tables treatment*CS / nocol nopercent cl riskdiff alpha=0.05;
run;
```

20.2.2 Example SAS Code for Multiple Imputation

```
*First generate enough data to produce a monotone missing data pattern;
*Only include SHP640 and placebo arm in this imputation;
*MCMC does not work with class statement. Age has been converted to an
indicator variable;
*For <6 year old, age1=0 and age2=0, for 6-18 year old, age1=1 and age2=0,
for >18 year old, age1=0 and age2=1;
*all variables are rounded to integers. Age1, age2, and trt are bounded to 0
to 1, GCS_V2 and GCS_V3 are bounded to 0 to 7;
*Since bacterial eradication is a binary endpoint, the max bound for
bacterial eradication will be 1 instead of 7;
proc mi data = testIM3 seed =188 out = impOne NIMPUTE=10 round =  1 1 1 1 1 1
min =  0 0 0 0 0 0 max =  1 1 1 7 7 7;
mcmc impute = monotone;
var trt age1 age2 GCS_BASE GCS_V2 GCS_V3;
run;

*Full imputation based on a regression model assuming monotone missing
pattern;
*All missing treatment and age should have been imputed in MCMC step;
*Use an indicator variable for age to avoid warning message;
proc mi data = impOne seed = 321 out = impFinal NIMPUTE = 1 round =  1 1 1 1
1 1 min =  0 0 0 0 0 0 max =  1 1 1 7 7 7;
var trt age1 age2 GCS_BASE GCS_V2 GCS_V3;
monotone regression (GCS_V3 = trt age1 age2 GCS_BASE GCS_V2);
run;

*Convert GCS to clinical resolution;
data impFinal1;
set impFinal;
if (GCS_V3 = 0) then CS_V3 = 'Yes';
else CS_V3 = 'No';
run;

*Generate exact binomial proportions in imputed data set;
proc freq data = impFinal1;
tables CS_V3 / binomial (exact level='Yes') alpha=0.05;
by _IMPUTATION_ TREATMENT;
ods output BINOMIALPROP=prop;
run;

*create a dataset with estimated proportion of responders in each treatment
arm and their SE;
data prop_trt;
merge prop(where=(LABEL1='Proportion') keep = _IMPUTATION_ TREATMENT NVALUE1
LABEL1 rename=(NVALUE1=proportion))
        prop(where=(LABEL1='ASE') keep = _IMPUTATION_ TREATMENT NVALUE1
LABEL1 rename=(NVALUE1=prop_se));
by  IMPUTATION_ TREATMENT;
run;

*Combine proportion estimates;
proc mianalyze data = prop_trt;
modeleffects proportion;
stderr prop_se;
```

```
by treatment;
run;

*compute estimates of the difference in proportions between SHP640 and
placebo and the corresponding SE;
data trt_diff_640_pbo;
merge prop_trt(where=(TREATMENT='SHP640') rename=(PROPORTION=prop_640
PROP_SE=prop_640_SE))
        prop_trt(where=(TREATMENT='Placebo') rename=(PROPORTION=prop_pbo
PROP_SE=prop_pbo_SE));
by  IMPUTATION_;
run;

data trt_diff_640_pbo1;
set trt_diff_640_pbo;
diff_640_pbo = prop_640 - prop_pbo;
se diff_640_pbo = sqrt(prop_640_SE*prop_640_SE + prop_pbo_SE*prop_pbo_SE);
run;


*Combine proportion difference estimates;
proc mianalyze data = trt_diff_640_pbo1;
modeleffects diff_640_pbo;
stderr se_diff_640_pbo;
run;
```

20.2.3 Example SAS Code for Adjusted Chi-square Test

```
proc freq data = CSdata1;
tables treatment*CS / nocol nopercent;
ods output CrossTabFreqs = CrossTabFreqs (drop = TABLE _TYPE_ _TABLE_
ROWPERCENT MISSING);
run;

data param (drop = TREATMENT CS);
merge CrossTabFreqs(where=(TREATMENT='640' and CS='Yes')
rename=(FREQUENCY=y_640))
        CrossTabFreqs(where=(TREATMENT='PBO' and CS='Yes')
rename=(FREQUENCY=y_pbo))
        CrossTabFreqs(where=(TREATMENT='640' and CS='')
rename=(FREQUENCY=M_640))
        CrossTabFreqs(where=(TREATMENT='PBO' and CS='')
rename=(FREQUENCY=M_pbo))
        CrossTabFreqs(where=(TREATMENT='' and CS='') rename=(FREQUENCY=M));
run;

data param1;
label y_640 = 'y_640';
label y_pbo = 'y_pbo';
label M_640 = 'M_640';
label M_pbo = 'M_pbo';
label M = 'M';
set param;
*p is the response rate across the two treatment arms;
p=(y 640+y_pbo)/M;
q=1.0-p;
*Derive X 1^2 and X 2^2;
x 640 = (y 640-M 640*p)**2/(M 640*p)+(M 640-y 640-M 640*q)**2/(M 640*q);
x_pbo = (y_pbo-M_pbo*p)**2/(M_pbo*p)+(M_pbo-y_pbo-M_pbo*q)**2/(M_pbo*q);
*Derive the response rates in the two treatment arms;
p_640 = y_640/M_640;
p_pbo = y_pbo/M_pbo;
run;

proc sort data = CSdata1;
by treatment;
run;

proc freq data = CSdata1;
tables HOUSEID*CS / nocol nopercent;
by treatment;
ods output CrossTabFreqs = CrossTabFreqs1 (drop = TABLE _TYPE_ _TABLE_
ROWPERCENT MISSING);
run;


data CrossTabFreqs2;
set CrossTabFreqs1;
if (HOUSEID >= 1 and CS='') then CS = 'All';
if (HOUSEID=.) then delete;
run;
```

```
proc sort data = CrossTabFreqs2;
by TREATMENT HOUSEID;
run;

*y_house is the number of responders in each household, m_house is the total
number of subjects in each household;
proc transpose data = CrossTabFreqs2 out = param2 (rename=(YES=y_house
ALL=m_house));
var FREQUENCY;
id CS;
by TREATMENT HOUSEID;
run;

proc sort data = CSdata1 out = CSdata2 nodupkey;
by HOUSEID;
run;

proc freq data = CSdata2;
tables treatment;
ods output OneWayFreqs = OneWayFreqs (keep = TREATMENT FREQUENCY);
run;

*n_640 is the total number of household in 640 arm;
*n_pbo is the total number of household in Placebo arm;
*n is the total number of household across the two arms;
data param3 (drop = treatment);
merge param1
        OneWayFreqs(where=(TREATMENT='640') rename=(FREQUENCY=n_640))
        OneWayFreqs(where=(TREATMENT='PBO') rename=(FREQUENCY=n_pbo));
n = n_640 + n_pbo;
run;

data param4;
set param3;
do houseid = 1 to n;
      output;
end;
run;

proc sort data = param2;
by houseid;
run;

proc sort data = param4;
by houseid;
run;

data combined (drop = _NAME_ _LABEL_ NO);
merge param2 param4;
by houseid;
run;

data combined1;
set combined;
*p_house is p_ki in the paper, which is the response rate within household i
in treatment k;
```

```
p_house = Y_HOUSE/M_HOUSE;
*Derive MSC within each household;
if (TREATMENT = '640') then MSC = M_HOUSE*((p_house-p_640)**2)/(n-2.0);
else if (TREATMENT = 'PBO') then MSC = M_HOUSE*((p_house-p_pbo)**2)/(n-2.0);
*Derive MSE within each household;
MSE = Y_house*(1.0-p_house)/(M-n);
*Derive M k^-1*m ki^2;
if (TREATMENT = '640') then m tilda temp = (m house**2)/M 640;
else if (TREATMENT = 'PBO') then m_tilda_temp = (m_house**2)/M_pbo;
run;

proc means data = combined1 sum;
var MSC MSE m_tilda_temp;
ods output summary = stats;
run;

data stats1 (drop = VNAME_MSC VNAME_MSE VNAME_M_TILDA_TEMP);
label MSC_SUM = 'MSC_SUM';
label MSE_SUM = 'MSE_SUM';
label M_TILDA_TEMP_SUM = 'M_TILDA_TEMP_SUM';
set stats;
run;

proc sort data = combined1;
by treatment;
run;

*Need to sum up m_ki^2/M_k separately within treatment k;
proc means data = combined1 sum;
var m_tilda_temp;
by treatment;
output out = stats2 (drop = _TYPE_ _FREQ_) sum = sum;
run;

proc transpose data = stats2 out = stats3;
var SUM;
id TREATMENT;
run;

data stats4 (rename =(_640=C_temp_640 PBO = C_temp_pbo));
set stats3;
drop _NAME_;
run;

data finalStats;
merge param3 stats1 stats4;
run;

data finalStats1;
set finalStats;
m_tilda = (M - M_TILDA_TEMP_SUM)/(n-2.0);
rho = (MSC_SUM - MSE_SUM)/(MSC_SUM+(m_tilda-1.0)*MSE_SUM);
C_640 = 1.0 + (C_temp_640-1.0)*rho;
C_pbo = 1.0 + (C_temp_pbo-1.0)*rho;
adj_chi_square = X_640/C_640 + X_PBO/C_pbo;
```

```
*The adjusted chi square statistic follows a Chi-Square distribution with
df=1;
p_value = 1.0-probchi(adj_chi_square, 1);
run;

proc print data = finalStats1;
var adj_chi_square p_value;
title 'Adjusted Chi Square Restult';
run;
```

20.2.4 Example SAS Code for Generating Descriptive Statistics

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

*For continuous endpoint;
proc means data = testData alpha = 0.05 n mean median std min max clm;
var continuous_endpoint;
by visit treatment;
run;

*For time to event endpoint;
proc lifetest data= testData atrisk plots=survival(atrisk);
time timeToCS*censor(0);
strata treatment;
run;
```

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