A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, PARALLEL-GROUP, COMPARATIVE STUDY TO EVALUATE THE CLINICAL EFFICACY AND SAFETY OF ISV-305 (0.1% DEXAMETHASONE) COMPARED TO VEHICLE IN THE TREATMENT OF SUBJECTS WITH BLEPHARITIS

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Final Analysis

Statistical Analysis Plan (SAP)

STUDY NO. C-12-305-001

Protocol Title:	A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, PARALLEL GROUP, COMPARATIVE STUDY TO EVALUATE THE CLINICAL EFFICACY AND SAFETY OF ISV-305 (0.1% DEXAMETHASONE) COMPARED TO VEHICLE IN THE TREATMENT OF SUBJECTS WITH BLEPHARITIS
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1.0 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the statistical methods, data derivations and data displays for study protocol C-12-305-001 Amendment 01 "A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-MASKED, PARALLEL GROUP, COMPARATIVE STUDY TO EVALUATE THE CLINICAL EFFICACY AND SAFETY OF ISV-305 (0.1% DEXAMETHASONE) COMPARED TO VEHICLE IN THE TREATMENT OF SUBJECTS WITH BLEPHARITIS" dated 22nd June 2017 for final analysis. The table of contents and templates for the tables, figures, and listings (TFLs) will be produced in a separate document.

Any deviations from this SAP will be described and justified in the Clinical Study Report (CSR).

The preparation of this SAP has been based on International Conference on Harmonisation (ICH) E3 and E9.

All data analyses and generation of TFLs will be performed using Statistical Analysis System (SAS®) 9.4 or higher version.

2.0 STUDY OBJECTIVES

To evaluate the ocular safety and efficacy of topical administration of ISV-305 (0.1% dexamethasone in DuraSite 2) compared to vehicle when dosed BID for 14 days in subjects diagnosed with blepharitis.

3.0 STUDY DESIGN

3.1 General study design

This study is a Phase 3, randomized, multicenter, double-masked, vehicle-controlled, parallel-group clinical trial, with total study duration of 29 days, consisting of 2 phases:

- Dosing Phase (2 weeks, Visit 2 and Visit 3, Days 1 to 14)
- Follow-up Phase (~2 weeks, Visit 4 and Visit 5, Days 15 to 29)

Prior to enrollment, the study will be discussed with prospective subjects and those wishing to

enter will be asked to give written informed consent. For subjects who, according to local regulations, have not yet reached the age of majority, the subject's parent(s) or legally authorized representative must sign the Informed Consent Form (ICF) and the minor's written assent will be obtained according to the local requirements.

Subject's ≥ 1 year of age with active, symptomatic blepharitis (e.g., flare-up) subjects will be enrolled at study centers in the US. Approximately 550 evaluable subjects will be randomized into the study in a 2:1 ratio: approximately 366 subjects in the ISV-305 group and approximately 184 subjects in the vehicle group.

3.2 Randomization and Masking

In this double-masked trial, subject randomization is managed in accordance with InSite Vision's Standard Operating Procedure (SOP). The randomization is generated by a statistician that is not affiliated with the study. Once the randomization plan is generated it is provided to the Head of Quality Assurance (QA) only.

The central randomization plan contains the coded treatment assignments for each randomization number. The randomization plan is shared with Manufacturing to allow for proper packaging and labeling of study supplies. Once the packaging of the IP is complete and the product released, all records are sealed and secured in a locked area of Document Control. The randomization plan remains under the confidential control of the InSite Vision QA Department or designee until the study is completed.

Eligible subjects will be randomly assigned to the ISV-305 and vehicle groups in a 2:1 ratio according to the central randomization plan. At each site, subjects will be randomized sequentially to the appropriate treatment group by assigning the number corresponding to the lowest numbered drug kit available at the site.

In this double-masked study, the study site, the study subjects (including parent[s] and/or caregiver), and sponsor/designee are masked to the identity of the study drug. Dosing will be performed by the subject (parent and/or caregiver) and not by study site personnel.

Unmasking of the randomization code prior to study completion due to a medical emergency or suspected AE is also managed in accordance with InSite Vision's SOP.

The randomization is not unmasked until the study is complete and the database is locked.

3.3 Study treatments and assessments

The maximum study duration from screening to end of the follow-up phase is 29 (± 2) days.

There will be two treatment groups in this study.

- ISV-305 group
- Vehicle group

ISV-305 is a topical ophthalmic formulation of 0.1% dexamethasone in DuraSite 2. The vehicle utilized in this study is the same formulation as ISV-305 (i.e., DuraSite 2) without dexamethasone.

Subjects meeting all entry requirements will be asked to use lid scrubs for at least 7 days prior to Day 1, and will then be reassessed for eligibility prior to being randomized into the study. Subjects still meeting the entry criteria will be randomized into the study and begin a 14-day dosing phase (Day 1 – Day 14) followed for approximately 2 weeks during the follow-up phase (Day 15 – Day 29). Five visits will be required for full study participation: Screening Visit (Day -10 to Day -7), Rescreening/Randomization/Dosing visit (Day 1), Dosing visit (Day 7), and the Follow-up visits (Day 15 and Day 29).

4.0 STUDY ENDPOINTS

4.1 Primary efficacy endpoint

The primary efficacy endpoint is the reduction in the Day 1 (baseline) total clinical sign and symptom score (eyelid swelling, eyelid redness, eyelid debris, and eyelid irritation) by at least 2 units at Day 15 with no worsening of any sign or symptom.

4.2 Secondary efficacy endpoint

The secondary efficacy endpoint is complete resolution of eyelid irritation at Day 15.

4.3 Safety endpoints

The safety endpoints of this study are:

- Incidence of ocular adverse events and serious adverse events
- Incidence of non-ocular adverse events and serious adverse events
- Measurement/evaluation and change from baseline at each scheduled visit for the following ocular-specific parameters:
    - best corrected visual acuity (BCVA)
    - Intraocular pressure (IOP)
    - Slit-lamp biomicroscopy
    - Ophthalmoscopy findings

5.0 ANALYSIS POPULATIONS

All efficacy endpoints will be analyzed using the Intent-to-Treat (ITT) analysis set. The Per Protocol (PP) analysis set will be used for the sensitivity analysis of the efficacy endpoints to examine the robustness of the ITT analyses.

Safety will be analyzed using the safety set.

5.1 Intention-to-Treat (ITT) Analysis Set

The ITT analysis dataset includes all randomized subjects regardless of whether post-baseline measures are collected or IP is received. Subjects in the ITT dataset will be analyzed in the treatment group to which they were assigned by the randomization scheme, regardless of which IP, if any, they receive.

5.2 Per-Protocol (PP) Analysis Set

The PP analysis dataset includes all randomized subjects in who received at least one dose of IP and had no significant protocol deviations. Subjects in the PP dataset will be analyzed in the treatment group to which they were assigned by the randomization scheme, regardless of which IP they receive.

5.3 Safety Set

The Safety analysis dataset includes all randomized subjects who received at least one dose of IP. Subjects in the Safety dataset will be analyzed according to the IP they actually received. If both treatments were received, the subject will be included within the active treatment group for analysis.

6.0 STATISTICAL CONSIDERATIONS AND ANALYSIS

6.1 Derived Variables

The below table provides the list of derived variables for demographic and baseline characteristics, various duration derivations, drug compliance, baseline derivations and other important derivations applicable for this study.

Study days

Subjects will be dosed BID for 14 days, starting on Day 1 and continuing through Day 14. Study days for the given visit will be based on the date of first dose of study drug and calculated as:

- (visit/assessment date – date of first dose of IP) + 1.

Baseline

Unless stated otherwise the baseline value for a variable will be the last measurement taken on or before Day 1 (Visit 2).

Change from baseline

Change from baseline value at each post baseline assessment (scheduled and unscheduled assessments) will be calculated as post baseline value - baseline value for each post baseline time point.

Definitions relative to demographic and other baseline characteristics - Age

Age at informed consent will be calculated as:

Age (years) = (date of informed consent - date of birth + 1) / 365.25

6.1.1 Definitions relative to efficacy parameters

Individual/Total clinical sign and symptoms score

The clinical signs of blepharitis: eyelid redness, eyelid swelling and eyelid debris will be evaluated at every visit and will be scored by the investigator using a 0-3 grading scale. The subject symptom of eyelid irritation will also be evaluated at every visit and graded by the subject using a 0-3 grading scale. The total score is obtained by adding each of the item scores in a given domain.

6.1.2 Definitions relative to safety parameters

In order to assess the safety of ISV-305 compared to Vehicle group in subjects with blepharitis, adverse events will be observed throughout the entire study.

Adverse Event (AE)

An AE is defined as any untoward medical occurrence associated with the use of an IP in humans, whether or not considered related to the IP. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an IP, without any judgment about causality. An AE can arise from any use of the IP (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation or dose, including overdose.

Medical conditions or diseases present before a subject starts study treatment are only considered AEs if they worsen after the subject signs informed consent.

Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is defined as an event that, in the view of either the investigator or sponsor, results in any of the following outcomes:

- death
- a life-threatening AE or sight-threatening AE, where ophthalmics are involved
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening/sight-

threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The criterion of inpatient hospitalization is met if the subject is admitted to the hospital as the result of an AE, even if the subject is released on the same day. An emergency room visit does not qualify as "inpatient hospitalization" unless the subject is admitted to the hospital during the visit; however, the reason for the emergency room visit may qualify as an SAE based on another SAE criteria (e.g., life threatening or medically significant event).

Pre-existing Conditions

Pre-existing condition is defined as a disorder/disease present before the AE-reporting period starts (i.e., prior to the subject signing the ICF) and noted on the Medical History eCRF. A pre-existing condition will not be reported as an AE unless the condition worsens or episodes increase in frequency during the AE-reporting period.

Duration of AEs

The duration of an AE will be calculated as the resolution date minus the date of onset plus 1. In the case of an AE still continuing at the end of the study, the duration will be considered as unknown.

6.2 Handling of missing data and/or invalid data and outliers

6.2.1 Missing data analysis methods for efficacy data

The sensitivity analyses of the primary and/or secondary efficacy endpoints will be performed using Last Observation Carried Forward (LOCF) will be assessed.

In LOCF, missing Day X values will be imputed using the last non-missing observation prior to Day X.

6.2.2 Handling of missing or incomplete dates

Definition of treatment-emergent AEs and handling of missing or incomplete dates

A Treatment-Emergent AE (TEAE) is defined as an AE occurring or worsening on or after the receipt of the first dose of study drug. Events with an onset date at or after the subject has signed the ICF and prior to the first dose of study drug will be classified as pre-treatment AEs.

In the event of an incomplete onset date, the event will be considered to be treatment-emergent unless the partial onset date information or complete or partial end date confirms onset or end prior to the first dose of study drug date (worst case approach).

For AEs listings, dates will be presented as they have been recorded (missing and partial dates will not be replaced).

Imputation rules for missing or partial AE start dates

If only Day of AE start date is missing:

If the AE start year and month are the same as that for the first dose of study drug date, then:

- If the full (or partial) AE end date is NOT before the first dose of study drug date or AE end date is missing, then impute the AE start day as the day of first study drug date.
- Otherwise, impute the AE start day as 1.

If Day and Month of AE start date are missing:

If AE start year = first dose of study drug year, then:

- If the full (or partial) AE end date is NOT before the first dose of study drug date or AE end date is missing, then impute the AE start Month and Day as the Month and Day of first dose of study drug date.
- Otherwise, impute the AE start MONTH as January and the DAY as 1.

If Year of AE start date is missing:

If the year of AE start is missing or AE start date is completely missing then query site with no imputation. Also compare the full (or partial) AE end date to the first dose of study drug date. If the AE end date is before the first dose of study drug date then the AE should be considered as a pre-treatment AE. Otherwise, the AE will be considered as TEAE.

7.0 STATISTICAL METHODS

7.1 General statistical conventions

All statistical procedures will be completed using SAS version 9.4 or higher.

Continuous variables will be summarized using descriptive statistics, including number of subjects with non-missing value (n), mean, median, standard deviation (SD), minimum (min) and maximum (max).

For categorical variables, summaries will include counts of subjects (frequencies) and percentages. Percentages will be rounded to one decimal place.

For summary purposes, baseline will be defined as the last measurement taken before the first dose of IP on Day 1 (Visit 2).

Unless otherwise specified, all statistical hypothesis testing for the primary and secondary efficacy endpoints will be two-sided and will be performed using a significance (alpha) level of 0.05, and missing data imputed using the last observation carried forward (LOCF) approach. Two-sided 95% confidence intervals (CI) will be provided when relevant.

For the safety endpoints, no hypothesis will be tested, and missing data will not be imputed.

All summaries and analyses will be presented by treatment group, unless otherwise specified.

7.2 Subject disposition

All subjects who provided informed consent will be included in a summary of subject accountability. The number of subjects screened, the number of screen failures, the number and percent of subjects randomized, and the number and percent of subjects will be summarized.

Subject disposition information will be summarized by treatment group and overall. The number of subjects completing and withdrawing from the study will be tabulated in the study disposition table which will also include the reason for withdrawal of the subject as reported on the eCRF.

7.3 Demographics and baseline characteristics

No formal comparison between treatment groups for demographic or baseline characteristics will be done. All demographic and baseline characteristics data will be listed.

7.3.1 Demographics

Age and other continuous demographic variables at baseline will be summarized descriptively.

7.4 Efficacy analyses

This section addresses separately the analyses to be conducted on the primary and secondary efficacy variables. All definitions relative to efficacy endpoints are detailed in Section 4.0.

7.4.1 Analysis methods

Fisher's exact test: Distribution of categorical variables (such as response [yes/no]) in the efficacy tables will be compared using Fisher's exact test. Exact unconditional 95% confidence intervals will also be provided.

7.4.2 Analysis of primary efficacy endpoint

The primary efficacy endpoint is whether or not a subject's Day 15 total clinical sign and symptom score has decreased by at least 2 units from baseline with no increase in any sign and symptom score. The primary analysis method for this endpoint is Fisher's exact test conducted on the ITT analysis set. The point estimate of treatment effect (ISV-305 compared with vehicle), its 95% confidence interval (CI), and the corresponding p-value will be reported.

7.4.3 Analysis of secondary efficacy endpoints

Complete resolution of eyelid irritation at Day 15 will be analyzed using the same approach as in the analysis of the primary efficacy endpoint, i.e., Fisher's exact test conducted in the ITT analysis set with missing score imputed using LOCF.

7.5 Safety analyses

All definitions relative to safety endpoints are detailed in Section 6.1.2.

All the safety analyses will be based on the Safety set (treated subjects) and will be

performed for all safety variables specified below.

All safety data will be summarized by treatment group. No statistical test will be performed.

7.5.1 Adverse events

All Adverse events (AEs) will be coded by Primary System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA®) Version 20.0 or higher.

In summaries by SOC and PT, adverse events will be sorted by decreasing frequency within each SOC and PT according to the alphabetically order of ISV-305 treatment group.

All AEs will be listed. However, only treatment-emergent AEs (TEAEs) will be summarized. An AE will be considered a TEAE if it occurs or worsens on or after receipt of the first dose of study drug. AEs will be presented by subject.

Details for imputing missing or partial start dates of adverse events are described in Section 6.2.2. AE summary tables will be presented for TEAEs only and will include the following:

- All TEAEs
- Serious AEs/TEAEs
- TEAEs leading to death

All TEAEs will be summarized by SOC, PT and treatment group using frequency counts and percentages (i.e., number and percentage of subjects with an event).