A PHASE 3, RANDOMIZED, MULTICENTER, DOUBLE-MASKED STUDY TO COMPARE THE OCULAR SAFETY, TOLERABILITY, AND EFFICACY OF ISV-305 (0.1% DEXAMETHASONE IN DURASITE® 2) TO DURASITE 2 VEHICLE FOR THE TREATMENT OF INFLAMMATION AND PAIN ASSOCIATED WITH CATARACT SURGERY

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Final Analysis

Statistical Analysis Plan (SAP)

STUDY NO. C-16-305-003

Protocol Title:	A PHASE 3, RANDOMIZED, MULTICENTER, DOUBLEMASKED STUDY TO COMPARE THE OCULAR SAFETY, TOLERABILITY, AND EFFICACY OF ISV-305 (0.1% DEXAMETHASONE IN DURASITE® 2) TO DURASITE 2 VEHICLE FOR THE TREATMENT OF INFLAMMATION AND PAIN ASSOCIATED WITH CATARACT SURGERY
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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-16-305-003 "A PHASE 3, RANDOMIZED, MULTICENTER, DOUBLE-MASKED STUDY TO COMPARE THE OCULAR SAFETY, TOLERABILITY, AND EFFICACY OF ISV-305 (0.1% DEXAMETHASONE IN DURASITE® 2) TO DURASITE 2 VEHICLE FOR THE TREATMENT OF INFLAMMATION AND PAIN ASSOCIATED WITH CATARACT SURGERY" dated 31st May 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, tolerability, and efficacy of topical administration of ISV-305 (0.1% dexamethasone in DuraSite 2 ophthalmic suspension) compared with DuraSite 2 Vehicle when dosed BID for 1 day prior to surgery, the day of surgery, and 14 days post cataract surgery.

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 3 phases:

- Screening/Randomization Phase (~2 weeks, Visit 1, Days −14 to −2)
- Dosing Phase (~2 weeks, Phone call Visit to Visit 4, Days -1 to 14)
- Evaluation Phase (~2 weeks, Visit 5 to Visit 7, 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.

Subjects ≥ 17 years of age scheduled to undergo uncomplicated unilateral cataract surgery and who meet all inclusion and none of the exclusion criteria will be randomized in a 2:1 ratio: 160 in the ISV- 305 group and 80 in the vehicle group. Subjects will be enrolled at approximately 15 study centers in the US.

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 (blinded) study, the study site, the study subjects (including caregiver), and sponsor/designee (other than as stated above) are masked to the identity of the IP. Dosing will be performed by the subject 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 evaluation 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.

All subjects eligible for study participation will enter from Screening/Randomization Phase (Visit 1) to the Dosing Phase. During the Dosing Phase (Day -1 to Day 14), subjects will be dosed BID for 16 days: the day before cataract surgery, the day of cataract surgery, and for 14 days after cataract surgery. Subjects will then be followed for approximately 2 weeks during the Evaluation Phase (Day 15 to Day 29). There will be 7 study visits for full study participation: 1 visit during the Screening/Randomization Phase, 3 visits (Day 0, Day 1 and Day 8) during the Dosing Phase, and 3 visits (Day 15, Day 18, and Day 29) during the Evaluation Phase.

4.0 STUDY ENDPOINTS

4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with an ACC grade of 0 at Day 15.

Anterior Chamber Cells	
Grade*	Cell Count
0	0
1	1-5
1	6-10
2	11-20
3	21-50
4	> 50

*Grade 1 includes cell count 1-5 and cell count 6-10.

4.2 Key Secondary Endpoints

The secondary efficacy endpoints are the proportion of subjects who achieve a pain score of 0 on the visual analog scale (VAS) (0-100 mm scale) for each post-surgical assessment at Days 1, 8, 15, 18, and 29.

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 in the study eye at each scheduled visit for the following ocular-specific parameters:
    - BCVA
    - IOP
    - Slit-lamp biomicroscopy
    - Ophthalmoscopy findings
    - Photophobia

5.0 ANALYSIS POPULATIONS

All efficacy endpoints will be analyzed using the modified intent-to-treat (mITT) population. The Per-Protocol (PP) population will be used for the analysis of the primary and secondary endpoints to examine the robustness of the primary analyses.

Safety and tolerability will be analyzed using the safety population.

5.1 Intention-To-Treat Population (ITT)

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

IP, if any, they receive. This population will be used in the disposition and protocol deviation summaries.

5.2 Modified Intent-To-Treat Population (mITT)

The mITT population includes randomized subjects that undergo cataract surgery, receive at least one dose of IP, and have at least one post-surgery efficacy assessment. Subjects who receive rescue medications will be included in the mITT but will be treated as failures. This population will be used in all efficacy analyses. Subjects in the mITT population will be analyzed in the treatment group to which they were assigned by the randomization scheme, regardless of which IP if any, they receive.

5.3 Per-Protocol Population (PP)

The per protocol (PP) population includes all subjects in the mITT population excluding those subjects who receive rescue medications or have major protocol violations that may compromise their efficacy data.

5.4 Safety Population (Safety)

The Safety population includes all randomized subjects who receive at least 1 dose of IP. Subjects in the safety population will be analyzed according to the IP they actually received. This population will be used in all safety analyses.

6.0 STATISTICAL CONSIDERATIONS AND ANALYSIS

6.1 Derived Variables

The below text 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

Study Day 0 represents the day of surgery. Subjects will instill doses daily, starting on Day –1 and continuing through Day 14.

Study days for the remaining visits will be based on the date of surgery and calculated as:

- (visit/assessment date – date of surgery).

Baseline

Unless stated otherwise the baseline value for a variable will be the value taken at Visit 1/Screening Visit.

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

Proportion of Subjects with ACC Grade 0 at a Given Time Point

Proportion = Number of responders at Day X /Total number of subjects in the mITT population

Notes:

1. Responders are those subjects who had ACC grade of 0 either at Day X or the last assessment prior to Day X visit (in case the Day X was not completed).
2. Those subjects who received a rescue medication between and including Day 0 and X will be considered as treatment failure or non-responder, despite a subject with zero cell count either at Day X or the last assessment prior to Day X visit (in case the Day X was not completed).

Proportion of Subjects with VAS Pain Score 0 at Each Time Point

Proportion = Number of subjects with zero score for VAS Pain /Total number of subjects in the mITT population

The VAS is a measure of overall self-rated health status. It ranges from 0 to 100 using a mark on a 100 mm line, with 0 score indicative of no pain and 100 indicative of maximum pain.

6.1.2 Definitions Relative to Safety and Tolerability Parameters

In order to assess the safety and tolerability of ISV-305 compared to Vehicle group in subjects with cataract surgery, 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 unfavorable and unintended sign, 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 preexisting 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 Last Observation Carried Forward (LOCF) method will be used to impute missing values for the primary and all secondary endpoints. In LOCF imputation, 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 first IP dose. Events with an onset date at or after the subject has signed the ICF and prior to the first IP dose 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 IP dose 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 IP date, then:

- If the full (or partial) AE end date is NOT before the first dose of IP date or AE end date is missing, then impute the AE start day as the day of first IP 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 IP year, then:

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

7.0 STATISTICAL METHODS

7.1 General Statistical Conventions

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

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. Two-sided 95% confidence intervals (CI) will be provided when relevant.

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 Visit 1, the screening visit value; all summaries 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 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 primary 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.

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, key secondary, and secondary efficacy variables. All definitions relative to efficacy endpoints are detailed in Section 4.0.

7.4.1 Analysis Methods

7.4.1.1 Analysis of Proportions Using Two-sided Z-test

The proportion of subjects with ACC grade of 0 at a given time point in the ISV-305 (PISV) and vehicle (PVEH) groups will be compared using a two-sided Z-test with continuity correction and pooled variance.

7.4.1.2 Multiplicity

Multiplicity adjustments will control the overall type I error rate at 0.05 for testing two treatment groups and multiple endpoints.

Among the primary and key secondary endpoints, the tests will be performed using a serial gatekeeping procedure based on the hierarchical order of the primary and key secondary endpoints. Therefore, the statistical tests on the key secondary endpoints across all five postsurgical time points will only be performed in case the null hypothesis for the primary endpoint is rejected.

The following multiplicity adjustment will be used to strongly control the overall type I error rate at 0.05 for the key secondary endpoints at each assessment. Multiplicity will be addressed via Hochberg's step-up method.

7.4.2 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with an ACC grade of 0 at Day 15.

The difference between treatment groups will be tested using a two-sided Z-Test with continuity correction and pooled variance using the mITT population. A subject with an ACC grade of 0 at the Day 15 visit or the last assessment prior to the Day 15 visit (in the event that Day 15 was not completed) will be considered a responder to therapy. If a subject has an ACC score of >0 at Day 15 or the last assessment prior to the Day 15 visit (in the event that Day 15 was not completed), that subject will be considered a failure (or non-responder) in the primary efficacy endpoint analysis. Additionally, any subject receiving a rescue medication between Day 0 and the Day 15 visit (inclusive) will be considered a treatment failure.

7.4.3 Analysis of Key Secondary Efficacy Endpoints

If the null hypothesis for the primary endpoint is rejected, the statistical tests on the key secondary endpoints across all five post-surgical time points will be performed using the serial gatekeeping procedure known as Hochberg's step-up method.

For the key secondary efficacy endpoint of proportion of subjects who achieve a pain score of 0 on the VAS, the difference between the treatment groups at each post-surgical assessment will be tested using a two-sided Z-Test with continuity correction and pooled variance. Missing values will be imputed using the LOCF method. Hochberg's method will be applied to the ordered p-values from these tests across the five time points. A 95% CI for the difference of the proportions at each time point will also be constructed. The effect of imputing missing values for this secondary endpoint analysis of proportions using the LOCF method will be assessed via a multiple imputations procedure.

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 population (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.

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.

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).