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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Clinical Study Protocol

STUDY NO. C-12-305-001

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

Original Protocol Date:	January 31, 2012
Amendment Number:	Amendment 1
Date of Amendment:	June 22, 2017
Sponsor:	InSite Vision, Inc.

1.0 TABLE OF CONTENTS

1.0 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.

2.0 OVERALL STUDY DESIGN

This study is a Phase 3, randomized, multicenter, double-masked, vehicle-controlled, parallel-group clinical study. Patients ≥ 1 year of age diagnosed with active, symptomatic blepharitis (e.g., flare-up) will be enrolled.

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.

Once informed consent has been obtained, the subjects will be questioned regarding their medical history to determine whether or not they are in satisfactory health to enter the study and to determine if they meet the specific entry criteria.

Clinically-diagnosed, active, symptomatic blepharitis (e.g., flare-up) is defined by a minimum combined score of 6 for the following signs and symptom in at least one eye, with a minimum score of 2 for eyelid redness, and a minimum score of 1 for eyelid irritation.

1) Eyelid redness
2) Eyelid swelling
3) Eyelid debris
4) Eyelid irritation

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).

Approximately 550 evaluable subjects with blepharitis will be randomized into the study in a 2:1 ratio: ISV-305: approximately 366 subjects and vehicle: approximately 184 subjects.

Some subjects may have both eyes qualify for the study. In these cases, data from the eye with the highest combined clinical signs and symptoms score on Day 1 will be designated by the investigator as the study eye and analyzed for efficacy.

Subjects (or parent or caregiver for subjects too young or otherwise unable to self-apply the IP) will be instructed to self-apply their first dose of IP at the study site on Day 1, and will receive instructions for dosing at home and completing a dosing diary, to be used as a memory aid.

Subject safety will be evaluated throughout the study. The safety parameters to be assessed are the incidence of AEs and SAEs, discontinuations due to AEs, changes in best corrected visual acuity (BCVA) and IOP, and biomicroscopic and ophthalmoscopic findings.

Efficacy will be assessed by biomicroscopic measurement of the clinical improvement in signs of eyelid swelling, eyelid redness, eyelid debris, and subject-reported symptom of eyelid irritation. Improvement is defined as a reduction in baseline signs and symptoms score by at least 2 units by Day 15 with no worsening of any sign or symptom. Other secondary efficacy analyses will be performed as outlined in the statistical analysis plan (SAP).

3.0 SELECTION AND WITHDRAWAL OF SUBJECTS

3.1 Number of Study Subjects

The study will enroll approximately 550 subjects ≥ 1 year of age with active, symptomatic blepharitis (e.g., flare-up). Subjects will be enrolled in the US.

3.2 Inclusion Criteria

The following are inclusion criteria for prospective study subjects to be confirmed at the Screening Visit 1 (Day -10 – Day -7) and reconfirmed prior to randomization at Visit 2 (Day 1). The sponsor will not grant any protocol eligibility waivers.

a. Have a clinical diagnosis of active, symptomatic blepharitis (e.g., flare-up) defined by a minimum combined score of 6 for the following signs and/or symptoms in at least one eye, with a minimum score of 2 for eyelid redness, and a minimum score of 1 for eyelid irritation:
    1) Eyelid redness
    2) Eyelid swelling
    3) Eyelid debris
    4) Eyelid irritation

b. Are ≥ 1 year of age at Screening Visit (-10 to Day -7, Visit 1) of either sex and any race.

c. Signature of the subject or parent(s) or legally authorized representative on the ICF, and when appropriate the minor's assent in accordance with local regulations.

d. Are willing and able to follow all instructions and attend all study visits. This applies to parent or caregiver for subjects too young or otherwise unable to self-apply the IP.

e. Are willing to avoid disallowed medication for the duration of the study.

f. If female is of childbearing potential, agree to and submit a urine sample for pregnancy testing (prior to enrollment and at the end of the study), and use effective contraception for the duration of the study.

   Male subjects whose female partners are not post-menopausal must agree to one of the following: 1) completely abstain from sexual intercourse, 2) use a barrier method (condoms) with spermicide during sexual intercourse for the duration of the study, 3) provide documentation for having had a vasectomy (with documented infertility).

g. Have an intraocular pressure (IOP) > 8 mmHg and ≤ 22 mmHg in either eye.

h. Have used non-prescription lid scrubs for at least 7 days prior to Day 1 (Visit 2) and willing to continue lid scrub use throughout the duration of the study. Prescription lid scrubs are disallowed.

3.3 Exclusion Criteria

The following are exclusion criteria for prospective study subjects to be confirmed at the Screening Visit 1 (Day -10 – Day -7) and reconfirmed prior to randomization at Visit 2 (Day 1). The sponsor will not grant any protocol eligibility waivers.

a. Have known sensitivity or poor tolerance to any component of the IP.

b. Have had eyelid surgery in the study eye within twelve (12) months prior to the Screening visit (Day -10 to -7, Visit 1) or plan to have eyelid surgery during the study that, in the investigator's opinion, would interfere with the study parameters.

c. Have an acute ocular infection (bacterial, viral or fungal) or active ocular inflammation other than blepharitis in the study eye.

d. Are currently suffering from moderate or severe Dry Eye in the study eye.

e. Have used prescription medication lid scrubs within 4 weeks prior to dosing and/or plan to use them throughout the 14-day dosing period of the study.

f. Have used topical medications on the eyelids or topical ophthalmic corticosteroid medications or systemic use of a corticosteroid medication within 14 days prior to dosing and/or plan to use them throughout the duration of the study. Stable use (greater than one month prior to dosing of an unchanged dose) of inhaled or nasal corticosteroids, topical

dermal corticosteroid or antibiotic medication (except on the eyelids), or glaucoma eye medication is allowed.

g. Have used tear substitutes (e.g., artificial tears) within 2 hours prior to dosing and/or plan to use them throughout the 14-day dosing period of the study.

h. Use of any eye make-up (including lid skin, lid margins, and lashes) during the 2-week dosing period of the study.

i. Have had a micropigmentation (permanent eye makeup) procedure on the eyelid skin within 4 weeks prior to dosing, or plan to have such a procedure during the study.

j. Be currently pregnant, nursing, or planning a pregnancy, or be a woman who has a positive pregnancy test.

k. Have any uncontrolled systemic disease or debilitating disease (e.g., cardiovascular disease, hypertension, diabetes, or cystic fibrosis).

l. Have any clinically significant cardiovascular disorders (e.g., unstable angina, myocardial infarction or cerebrovascular accident within the past six months, Class III or IV congestive heart failure, ventricular arrhythmias).

m. Have any history of liver or kidney disease resulting in persisting dysfunction that, in the investigator's opinion, would interfere with the study parameters.

n. Have clinically significant lash or lid abnormality other than blepharitis (e.g. trichiasis, entropion or ectropion) in the study eye.

o. Are currently suffering from alcohol and/or drug abuse.

p. Have prior (within 30 days prior to dosing) or anticipated concurrent use of an investigational drug or device.

q. Have a condition or a situation which, in the investigator's opinion, may put the subject at increased risk, confound study data, or interfere significantly with the subject's study participation.

r. Use of any medication the investigator feels may interfere with the study parameters.

4.0 STUDY TREATMENTS

4.1 Investigational Product

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.

4.2 Instructions for Use and Administration

Subjects will be randomly assigned to receive either ISV-305 or vehicle which will be administered BID to the closed study eyelid and if needed to the closed non-study eyelid along the eyelash line as a topical ophthalmic: 1 drop per eye in the morning and 1 drop per eye in the evening for 14 days. Subjects (including parent and/or caregiver) will be instructed to smear 1 drop of IP to the closed study eyelid along the eyelash line on Day 1 at the study site upon randomization and 1 drop in the evening, and to continue dosing BID at approximately 12-hour intervals for a total of 14 days. Subjects will then be followed for an additional 15 days. Subjects will be given a dosing diary to record IP application times, and will be questioned to determine if they have followed the dosing schedule.

5.0 CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

Contraindications, warning and precautions for ophthalmic dexamethasone as described in the labeling of the approved product Maxidex (0.1% dexamethasone) are presented below.

Use of ophthalmic dexamethasone is contraindicated in epithelial herpes simplex (dendritic keratitis), vaccinia, varicella, and most other viral diseases of the cornea and conjunctiva, tuberculosis of the eye and fungal disease of ocular structures.

Class warnings for corticosteroids such as dexamethasone are well known and state that prolonged use may result in ocular hypertension and/or glaucoma, with damage to the optic nerve, defects in VA and fields of vision, and posterior subcapsular cataract formation. Prolonged use may also suppress the host response and thus increase the hazard of secondary ocular infections. In diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical corticosteroids. In acute purulent conditions of the eye, corticosteroids may mask infection or enhance existing infection. It is recommended that if corticosteroids are used for 10 days or longer, intraocular pressure should be routinely monitored even though it may be difficult in children and uncooperative patients.

The possibility of persistent fungal infections of the cornea should be considered after prolonged corticosteroid dosing.

Subjects are excluded from participating in the study if there is known hypersensitivity or poor tolerance to any component of the IP or any of the procedural medications such as anesthetic and/or fluorescein drops, dilating drops, etc. See Exclusion Criterion a.

6.0 CLINICAL ASSESSMENTS/PROCEDURES

6.1 Schedule of Assessments

The procedures and measurements to be evaluated at each study visit are shown in Table 1, Schedule of Assessments.

Table 1: Schedule of Assessments:

		Dosing Phase (14 Days)		Follow-Up Phase (15 Days)	
Evaluation[1]	**Visit 1 Day -10 to Day -7**	**Visit 2 Day 1**	**Visit 3 Day 7 (+/- 1)**	**Visit 4 Day 15 (+ 1)**	**Visit 5 Day 29 (+/- 2)**
Written Informed Consent	X				
Demographics	X				
Entry Criteria	X	X			
Medical/Medication History	X	X			
Urine Pregnancy Test		X			X
Slit Lamp Biomicroscopy[2]	X	X	X	X	X
Clinical Signs Evaluation	X	X	X	X	X
Subject-Reported Eyelid Irritation	X	X	X	X	X
Intraocular Pressure	X	X	X	X	X
Best Corrected Visual Acuity	X	X	X	X	X
Ophthalmoscopy[2]	X			X	X[3]
Confirm non-prescription Lid Scrub Use[4]	X	X	X	X	X
Confirm and Document Subject Eligibility	X	X			
AE Assessment	X	X	X	X	X
Randomization		X			
Dispense IP and Dosing Diary		X			
Instruct Subject on IP and Dosing Diary		X			
Update Concomitant Medications		X	X	X	X
Review IP and Dosing Diary		X	X	X	X[3]
Collect IP and Dosing Diary				X	X[3]
Exit Subject From Study					X

AE = Adverse Event; BSIQ= Blepharitis Symptoms and Impacts Questionnaire; eCRF = electronic case report form; IP = Investigational Product.
[1]Some procedures are completed for both eyes, study eye only, or eye(s) dosed with IP, depending on the visit.
[2]Performed by a board-certified ophthalmologist
[3]If not completed at previous visit
[4] Use of non-prescription lid scrubs is required for at least 7 days prior to Visit 2 and throughout the study period (prescription lid scrubs are prohibited)
Note: Unscheduled visits may occur during the study period. All assessments will be recorded on the eCRF for unscheduled visits, but it is up to the investigator which assessments to conduct. If the subject exits early, all Visit 5 assessments should be conducted, including ophthalmoscopy if not obtained at Day 15 (Visit 5).

6.2 Examination Procedures

The following ophthalmic examinations will be conducted at intervals specified in Table 1 Schedule of Assessments.

- **Clinical Signs and Symptom**: 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.
- **Best Corrected Visual Acuity (BCVA):** BCVA will be measured at every visit. The Early Treatment Diabetic Retinopathy Study (ETDRS) log of the minimum angle of resolution (logMAR) will be used to measure BCVA. As appropriate, Lea Symbols® will be used in children.
- **Intraocular Pressure (IOP)** IOP will be measured in mmHg using an applanation tonometer at every visit. IOP is to be measured in all subjects.
- **Ophthalmoscopy**: Ophthalmoscopy will be performed by a board-certified ophthalmologist at Day -10 to -7 (Visit 1) and Day 15 (Visit 4) or Day 29 (Visit 5) if not completed at Visit 4.
- **Biomicroscopy:** Slit lamp biomicroscopy will be performed at every visit during the study to observe the overall health of the eye, including the lid/lashes, conjunctiva, cornea anterior chamber, iris, and lens. Any observations at the screening visit should be recorded as ocular medical history, and any new or worsened observations may be recorded as AEs. Slit lamp biomicroscopy will be conducted by a board-certified ophthalmologist at every visit.

7.0 EVALUATION, RECORDING AND REPORTING OF ADVERSE EVENTS

All AEs either observed by the investigator or study site staff or reported by the subject spontaneously or in response to a direct question regarding the subject's health by the investigator will be recorded in the source document and AE eCRF.

Events reported before signing the consent form should be recorded as medical history; once the ICF is signed new conditions or worsening of existing conditions or episodes that increase in frequency should be recorded as AEs in the source document and AE eCRF.

To standardize the collection of AEs during a study, subjects should be asked a standard question to elicit AEs: "Have you had any problems since your last visit or telephone call?" and "What is the status of [list previously reported unresolved AEs]?" Subjects will also be instructed to contact the investigator immediately if they note any unusual systemic or ocular AEs between visits.

Throughout the course of the study, the investigator must remain alert to possible adverse experiences or untoward findings. If adverse experiences occur, the first concern will be the safety of the subject. Appropriate medical intervention will be provided by the investigator.

The collection, review and management of safety data (AEs and SAEs) will be conducted in compliance with the requirements of the FDA as well as the local IRB/Independent Ethics Committee (IEC).

7.1 Definitions

Adverse Event

An AE is 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 (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.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE-reporting period should be reported as the AE and the resulting appendectomy noted according to the eCRF completion guideline.

Adverse Event Reporting Period

The AE reporting period for this study begins upon signing the consent form and ends at the completion of the subjects' final visit exam. All AEs that occur in study subjects during the AE-reporting period must be reported in the source documents and on the AE eCRF, whether or not the event is considered related to the IP. In addition, any known untoward event that occurs subsequent to the AE reporting period that the investigator assesses as possibly related to the IP should be recorded in the source documents and reported to the sponsor or designee.

Serious Adverse Event (SAE)

An SAE is 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

In this study, a pre-existing condition is 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 should not be reported as an AE unless the condition worsens or episodes increase in frequency during the AE-reporting period.

7.2 Adverse Events Associated with Study Procedures

Visual Acuity

A worsening of BCVA of 3 lines or more in logMAR score should be captured in the source documents and the appropriate AE eCRF.

IOP

An increase in IOP of ≥ 10 mmHg from Visit 1 or any subsequent visit should be captured as an AE in the source documents and on the AE eCRF.

Biomicroscopy

Slit lamp biomicroscopy will be performed during the study to observe the overall health of the eye, including the lid/lashes, conjunctiva, cornea, anterior chamber, iris, and lens. Any observations prior to signing the ICF should be recorded as ocular medical history. Any new or worsened observations after signing the ICF may be recorded as an AE.

Ophthalmoscopy

A new finding or a significant worsening (2 units or more) from Visit 1 should be recorded as an AE.

7.3 Reporting and Evaluation of AEs and SAEs

Table 2Table 2 presents the reporting guidelines for AEs and SAEs. It is important that the investigator comply with the SAE reporting timelines in order to assure that safety reporting timelines of IRB/IEC and regulatory authorities such as the FDA can be met.

Table 2: Requirements for Reporting Adverse Events and Serious Adverse Events to Sponsor

Type	Reporting Time	Type of Report
Serious	Within 24 hours	Adverse Event Report (AE eCRF) Serious Adverse Event Report Form
Non-serious	Per eCRF submission procedure	Adverse Event Report (AE eCRF)

All information relevant to the SAE must be recorded on the appropriate SAE Report Form, and the form submitted immediately (within 24 hours of learning of the event) to the sponsor Medical Monitor or designee.

The investigator must also provide sponsor or designee a copy of all pertinent medical records such as source documents, hospitalization records, death certificates etc. that are de-identified and contain only the study subject number and the subject initials. The investigator should maintain a copy of these medical records in his/her files, as well as any information and medical judgments from colleagues or other medical personnel who assisted in the treatment and follow-up of the subject.

The investigator should ensure that the subject receives appropriate medical treatment and follow-up. Subjects should receive follow-up until the SAE resolves or resolves with sequelae (as judged by the investigator).

Institutional Review Board or Independent Ethics Committee

The investigator will inform the IRB/IEC of any SAE/serious, unexpected, suspected adverse reaction according to the IRB/IEC's specific reporting guidelines.

For all serious, unexpected, suspected adverse reactions, the sponsor or designee will provide documentation to the investigator for the investigator's report to the IRB/IEC or local regulatory authorities.

The investigator must provide documentation of all such IRB/IEC notifications to the sponsor or designee. Copies of each report must be kept in the investigator's files.

7.4 Follow-up of Adverse Events and Serious Adverse Events

All AEs, regardless of severity, will be followed throughout the study to the final study visit, until they resolve or resolve with sequelae (as judged by the investigator).

At the final study visit, new AEs, as well as follow-up information for continuing AEs, will be recorded in the eCRF and source document. Non-serious ongoing AEs will be followed beyond the final study visit at the discretion of the investigator and recorded in the source documents.

If an SAE is unresolved at the final study visit, it will be followed by the investigator until it resolves or resolves with sequelae (as judged by the investigator). Follow-up data for such SAEs will be recorded in the source document and reported to the sponsor or designee.

Subjects withdrawn from the study due to an AE or SAE will be followed by the investigator until the outcome is determined (resolved or resolved with sequelae) and, where appropriate, additional written reports and documentation will be provided to the sponsor.

8.0 STATISTICAL ASSESSMENTS

8.1 Study Endpoints, Subsets, and Baseline Covariates

8.1.1 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.

8.1.2 Secondary Efficacy Endpoint

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

8.1.3 Safety Endpoints

- 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