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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Clinical Study Protocol

STUDY NO. C-13-305-002

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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Sponsor:	InSite Vision, Inc.

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1.0 STUDY OBJECTIVE(S)

To evaluate the ocular safety, tolerability, and efficacy of topical administration of ISV-305 (0.1% dexamethasone in DuraSite® 2 ophthalmic solution) compared with DuraSite 2 Vehicle when dosed twice daily (BID) for 1 day prior to surgery, the day of surgery, and 14 days post cataract surgery.

2.0 STUDY DESIGN

This study is a Phase 3, randomized, multicenter, double-masked, vehicle-controlled, parallel-group clinical trial. Approximately 240 subjects will participate in the study and will be randomized in a 2:1 ratio to the ISV-305 group (160 subjects) and the vehicle group (80 subjects).

Written informed consent will be obtained from all subjects prior to any study-specific procedure. Subjects will be enrolled into a 16-day dosing phase, followed by a 2-week evaluation phase. There will be 7 visits scheduled during the study: a screening visit between 2 and 14 days prior to surgery; 3 visits during the dosing phase (Day 0 [Surgery Day], Day 1, and Day 8); and 3 visits during the evaluation phase (Day 15, Day 18, and Day 29). In addition, there will be a telephone call on Day -3 to remind subjects to begin dosing on Day -1, the day before surgery. Subjects will instill 3 doses prior to surgery (2 doses on Day -1, and 1 dose on Day 0 prior to surgery), 1 dose in the evening after surgery and continue dosing BID for 14 days after surgery.

Subjects will be randomized and receive instructions for dosing at home and completing a pain and dosing diary. Subjects will be cautioned to dose only for the specified amount of time. One bottle of investigational product (IP) will be dispensed to the subject, and a second bottle will remain at the site as a precaution only in the event of loss, etc., and will not be dispensed unless necessary. Throughout this protocol, the surgery eye is referred to as the study eye, and the fellow eye is referred to as the non-study eye.

All ratings and procedures should be performed by the same examiner from visit to visit whenever possible. Additional exams may be scheduled as necessary to ensure the safety of the subjects during the study period.

Subjects who terminate use of IP for any reason will be withdrawn from the study, the reason(s) clearly described on the subject's electronic Case Report Form (eCRF) and source documents, and the sponsor or designee will be notified.

If the investigator determines lack of efficacy during the dosing period, administration of a rescue medication (i.e., another medication to treat ocular inflammation and/or ocular pain in the surgery eye [study eye]) must occur after subject is withdrawn from the study, and be clearly documented on the source documents and the designated eCRF.

All adverse events (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). Ongoing AEs will be followed beyond the final study visit at the discretion of the investigator and recorded in the source documents.

3.0 STUDY POPULATION

Patients ≥ 17 years of age who are scheduled to undergo uncomplicated unilateral cataract surgery and who meet all study entry criteria. Approximately 240 subjects will be enrolled in the United States.

3.1 Inclusion Criteria

The following are inclusion criteria for prospective study subjects to be confirmed at Visit 1 (Day -14 – Day -2) prior to randomization. The sponsor will not grant any protocol eligibility waivers.

a. Are ≥ 17 years of age at Visit 1 (Day -14 – Day -2) prior to randomization, of either sex and any race, and scheduled for uncomplicated unilateral cataract surgery (phacoemulsification or extracapsular extraction) with posterior chamber intraocular lens implantation

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

c. Are willing and able to follow all instructions and attend all study visits

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

e. 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)

f. Have best corrected visual acuity (BCVA) of +1.0 log of the minimum angle of resolution (logMAR -Snellen equivalent of 20/200) or better in the fellow eye (non-study eye)

g. Able to self-instill the IP (or have a caregiver available to instill all doses of the IP, as instructed)

h. Have an intraocular pressure (IOP) of > 8 mmHg and ≤ 22 mmHg in the surgery eye (study eye)

3.2 Exclusion Criteria

The following are exclusion criteria for prospective study subjects to be confirmed at Visit 1 (Day -14 – Day -2) prior to randomization. The sponsor will not grant any protocol eligibility waivers.

a. Have a history of Fuchs' dystrophy in the study eye

b. Have a history of diabetic retinopathy (with visual impairment) and/or previous vitrectomy in the study eye within the last 2 years

c. Have any sign of iritis or scleritis in the study eye

d. Have a history of glaucoma surgery in the study eye within the last 2 years

e. Have an existing diagnosis of severe dry eye in the study eye

f. Have 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.

g. Have an acute ocular infection (bacterial, viral or fungal) or active ocular inflammation in the study eye

h. Have any extraocular/intraocular inflammation in the study eye noted prior to surgery (blepharitis is allowed if scurf only without any concurrent conjunctivitis or lid erythema/edema) or ongoing, unresolved uveitis

i. Use of the following disallowed medications within a specified amount of time before surgery:

   - topical, inhaled, or oral corticosteroids within 15 days
   - depot-corticosteroids within 45 days (triamcinolone within 90 days)
   - topical, systemic, or inhaled nonsteroidal anti-inflammatory drugs (NSAIDs) within 1 week (with the exception of low-dose aspirin)
   - ocular or systemic antihistamines, or mast cell stabilizers within 1 week
   - other analgesics and use of acetaminophen (Tylenol®) within 48 hours
   - any medication that the investigator feels may interfere with the study parameters

j. Have any active or chronic/recurrent ocular or systemic disease that is uncontrolled and likely to affect wound healing (e.g., diabetes mellitus, systemic connective tissue disease, severe atopic disease)

k. Have known blood dyscrasia or bone marrow suppression

l. Have any active corneal pathology noted in the study eye

m. Have any intraocular inflammation (cells or flare in anterior chamber) or ocular pain (greater than 0) on the pain scale in either eye

n. Have had radial keratotomy, corneal transplant, or LASIK in the study eye within the last 2 years

o. Be currently pregnant, nursing, or planning a pregnancy, or be a woman that has a positive pregnancy test

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

q. Prior participation in this study protocol

r. Prior participation in InSite Vision Protocol C-16-305-003

s. Have prior (within 30 days of beginning study treatment) or anticipated concurrent use of an investigational drug or device

t. 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

u. Contact lens wear during the dosing period on Days -1 to Day 14

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

4.0 STUDY TREATMENT AND DRUG/DOSAGE ADMINISTRATION

Subjects will be randomized in a 2:1 ratio to 1 of 2 treatment groups:

1. ISV-305 (0.1% dexamethasone in DuraSite 2) BID (160 subjects)
2. DuraSite 2 Vehicle BID (80 subjects)

One drop of IP will be self-instilled by the subject (or instilled by caregiver) BID, in the surgery eye (study eye) for 16 days: the day prior to surgery, the day of surgery and postoperatively for 14 days.

The study coordinator or investigator will instruct the subjects on the proper administration of their IP.

Subjects (and caregiver as appropriate) will be instructed to bring their pain and dosing diary to each visit for review with site staff and for collection of diary on Day 18 (Visit 6), and to return all bottles of IP on Day 15 (Visit 5) for collection.

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.

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 f.

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

	Screening/ Randomization Phase	**Dosing Phase (16 Days)**				**Evaluation Phase (15 Days)**		
Evaluation[1]	**Visit 1 Day -14 to Day -2**	**Phone Call Day -3 (±1)**	**Visit 2 Day 0 (Day of Surgery)**	**Visit 3 Day 1 (+ 1)**	**Visit 4 Day 8 (± 1)**	**Visit 5 Day 15 (+1)**	**Visit 6 Day 18 (-1/+2)**	**Visit 7 Day 29 (± 2)**
Written Informed Consent	X							
Demographics	X							
Entry Criteria	X							
Medical/Medication History	X							
Urine Pregnancy Test	X							X
Slit Lamp Biomicroscopy[2]	X			X	X	X	X	X
Visual Analog Scale	X			X	X	X	X	X
Intraocular Pressure	X			X	X	X	X	X
Best Corrected Visual Acuity	X			X[3]	X	X	X	X
Ophthalmoscopy[2]	X					X	X[5]	X[5]
Confirm and Document Subject Eligibility	X							
Randomization	X							
Dispense IP and Pain/Dosing Diary	X							
Instruct Subject on IP and Dosing/Pain Diary	X							
AE Assessment	X	X	X	X	X	X	X	X
Dosing Reminder Call		X						
Update Concomitant Medications			X	X	X	X	X	X
Review Pain/Dosing Diary			X	X	X	X	X[4]	X[5]
Collect IP						X	X[5]	X[5]
Collect Pain/Dosing Diary							X	X[5]
Exit Subject From Study								X

IP = Investigational Product; AE = adverse event; eCRF = electronic case report form
[1]All eye exams are to be conducted in the study eye only. The fellow eye (non-study eye) may be examined at the investigators' discretion.
[2]Performed by a board-certified ophthalmologist.
[3]A pinhole test may be employed at Day 1 (Visit 3).
[4]Dosing terminates on Day 14. Pain is assessed through the evening of Day 17.
[5]If not completed at previous visit.
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 7 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 in the surgery eye (study eye) at intervals specified in Table 1, The Schedule of Assessments. The fellow eye (non-study eye) may be examined at the investigators' discretion.

- **Best Corrected Visual Acuity (BCVA):** BCVA will be measured at every visit except Visit 2 (Surgery; Day 0). The Early Treatment Diabetic Retinopathy (ETDRS) log of the minimum angle of resolution (logMAR) will be used to measure BCVA.
- **Intraocular Pressure (IOP):** IOP will be measured at every visit except Visit 2 (Surgery; Day 0) in mmHg using an applanation tonometer.
- **Ophthalmoscopy**: Ophthalmoscopy will be performed at Visit 1 (Day -14 to Day -2) and Visit 5 (Day 15) by a board-certified ophthalmologist.
- **Biomicroscopy:** Slit lamp biomicroscopy, including the evaluation of ACC and anterior chamber flare (ACF), chemosis, bulbar conjunctival injection, ciliary injection, corneal edema, and keratic precipitates will be conducted by a board-certified ophthalmologist at every visit except Visit 2 (Surgery; Day 0).
- **Visual Analog Scale (VAS)**: Eye pain/discomfort and photophobia will be evaluated at every visit except Visit 2 (Surgery; Day 0) using a Visual Analog Scale (VAS), scoring from 0 to 100 using a mark on a 100 mm line (0 = absent; 100 = maximum).
- **Pain assessment via diary (Pain Diary)**: Surgery eye pain will be evaluated prior to each IP dose using a pain scale included in the pain and dosing diary that subjects complete at home.

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

Anterior chamber cell (ACC) and ACF, chemosis, bulbar conjunctival injection, ciliary injection, corneal edema, and keratic precipitates will be assessed in the study. Since the severity of these assessments will be recorded and carefully monitored during the study, worsenings do not need to be recorded as AEs unless the investigator judges it appropriate. Any treatment emergent findings (findings that were not present prior to dosing with IP, or a worsening relative to baseline [before IP dosing]) outside of these assessments should be recorded as an AE.

Ophthalmoscopy

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

VAS

Pain/discomfort and photophobia will be assessed in the study eye. Since the severity of these assessments will be recorded and carefully monitored during the study, worsenings do not need to be recorded as AEs unless the investigator judges it appropriate.

7.3 Reporting and Evaluation of AEs and SAEs

Table 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 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.

8.2 Secondary Efficacy Endpoint

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.

8.3 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 in the study eye at each scheduled visit for the following ocular-specific parameters:
    - BCVA
    - IOP

- Slit-lamp biomicroscopy
- Ophthalmoscopy findings
- Photophobia