Compound Name:	CLS-TA, triamcinolone acetonide injectable suspension
Protocol Number:	CLS1001-302
IND Number:	115683
NCT Number:	NCT03097315
Protocol Title	AZALEA: Open-label Safety Study of Suprachoroidal Triamcinolone Acetonide Injectable Suspension in Patients with Non-Infectious Uveitis
Sponsor:	Clearside Biomedical, Inc. 900 North Point Parkway, Suite 200 Alpharetta, GA 30005
Issue Date: **Protocol Amendment 1 Date:**	16 January 2017 27 April 2017

CLEARSIDE BIOMEDICAL

Clinical Protocol CLS1001-302

Project:	1001
Compound Number/Name:	CLS-TA, triamcinolone acetonide injectable suspension
Protocol Number:	CLS1001-302
Phase:	3
IND Number:	115683
Protocol Title:	**AZALEA**: Open-label Safety Study of Suprachoroidal Triamcinolone Acetonide Injectable Suspension in Patients with Non-Infectious Uveitis
Sponsor:	Clearside Biomedical, Inc. 900 North Point Parkway, Suite 200 Alpharetta, GA 30005, USA
Medical Monitor:	Peter Nicholas, MD, PhD
Original Protocol Issue Date:	16 JAN 2017
Amendment #1 Issue Date:	27 APR 2017

Jennifer M. Kissner, Ph.D.
Vice President, Clinical Development
Clearside Biomedical, Inc.

27 APR 2017
Date

CONFIDENTIAL

This protocol contains confidential information about a product provided by Clearside Biomedical, Inc. This information is provided for the exclusive use of the Investigators participating in this study. Any and all confidential information contained herein may not be disclosed to any other person or party without the prior written consent of Clearside Biomedical, Inc.

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for CLS-TA. I have read the CLS1001-302 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Telephone number
Medical Monitor (24-Hour emergency contact)	Peter Nicholas, MD, PhD	919.259.9521
Sponsor Clinical Lead	Ellie Smith	678.448.4717
Principal Investigator	*The Coordinating Principal Investigator will be appointed by the Sponsor before the end of the study. As part of his or her responsibilities, the Coordinating Principal Investigator will review the final Clinical Study Report and will sign the report to confirm that it accurately describes the conduct and results of the study.*	

2. SYNOPSIS

Name of Sponsor/Company: Clearside Biomedical, Inc.	
Name of Investigational Product: CLS-TA (triamcinolone acetonide) injectable suspension	
Name of Active Ingredient: triamcinolone acetonide	
Title of Study: AZALEA: Open-label Safety Study of Suprachoroidal Triamcinolone Acetonide Injectable Suspension in Patients with Non-Infectious Uveitis	
Study center(s): Multi-center	
Protocol Number: CLS1001-302	
Studied period: 6 Month Duration Estimated date first subject enrolled: 1Q2017 Estimated date last subject completed: 2Q2018	**Phase of development:** Phase 3
Objectives: **Primary:** To evaluate the safety of suprachoroidally administered CLS-TA in subjects with non-infectious uveitis. **Secondary:** • To assess changes to signs and complications of uveitis • To collect use information on the suprachoroidal injection procedure • To determine systemic exposure to triamcinolone acetonide following suprachoroidal injection	
Number of subjects (planned): Approximately 35	
Diagnosis and main criteria for inclusion: Patients diagnosed with non-infectious uveitis for which the administration of local corticosteroid therapy would be a viable treatment option	
Investigational product, dosage and mode of administration: CLS-TA, injectable suspension, 4.0 mg in 100 µL administered via suprachoroidal injection	
Criteria for evaluation: The primary endpoint is the incidence of treatment-emergent adverse events and serious adverse events, grouped by organ system, relatedness to study medication, and severity	
Statistical methods: All data collected in the study database will be presented in the listings. Listings will include change from baseline. Baseline is Visit 2 (Day 0). The safety population will include all subjects who are administered at least one dose of CLS-TA (4 mg/100 µL). All analyses will be based on safety population. Descriptive statistics are displayed to provide an overview of the study results. Descriptive statistics include n, mean, median, minimum, and maximum values. The distribution of responses (n, %) will be tabulated for each category of response.	

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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LIST OF FIGURES

4. LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
BCVA	Best corrected visual acuity
CRC	Central reading center
CRF	Case report form
CST	Central subfield thickness
ETDRS	Early Treatment of Diabetic Retinopathy Study
FA	Fluorescein angiography/angiogram
IEC	Independent Ethics Committee
IND	Investigational New Drug
IOP	Intraocular pressure
IRB	Institutional Review Board
IVT	Intravitreal
ME	Macular edema
MedDRA	Medical Dictionary for Regulatory Activities
OCT	Optical coherence tomography
PK	Pharmacokinetics
RVO	Retinal vein occlusion
SAE	Serious adverse event
SC	Suprachoroidal
SCS	Suprachoroidal space
SD-OCT	Spectral-domain optical coherence tomography
TA	Triamcinolone acetonide
TEAEs	Treatment-emergent adverse events
US	United States
VEGF	Vascular endothelial growth factor
VA	Visual acuity

5. INTRODUCTION

Clearside Biomedical is developing a proprietary formulation of triamcinolone acetonide (CLS TA) to treat non-infectious uveitis. This multicenter, open-label study is designed to evaluate the safety of suprachoroidally injected CLS-TA in subjects with non-infectious uveitis. Suprachoroidal (SC) injection is a novel drug delivery approach that employs Clearside's proprietary suprachoroidal space (SCS™) microinjector and allows drugs to be precisely administered to the SCS via a minimally invasive injection procedure. This injection has been shown in animal models to allow distribution of drug candidates dominantly to the posterior segment ocular tissues while limiting exposure to anterior structures in the eye, thereby providing the potential for improved efficacy and safety. The purpose of this study is to expand the safety database of suprachoroidally injected CLS-TA in patients with non-infectious uveitis.

5.1. Disease Background

Uveitis is the fifth most common cause of visual loss in the developed world (Goldstein, 2009; Wood, 2011; Miserocchi, 2013). Significant vision loss can occur in up to 35% of children and adults, and uveitis accounts for 5% - 20% of legal blindness in both the United States (US) and Europe, and perhaps as much as 25% of blindness in the developing world (Rothova, 1996; Bodaghi, 2001).

There are a number of causes associated with this vision loss including cataract formation or progression, chorioretinal scarring, retinal detachment, and secondary glaucoma, but the dominant cause of vision loss within uveitis comes from chronic macular edema (ME), accounting for about one-third of visual impairment or blindness (Wood, 2011; Dick, 1994; Karim, 2013). Approximately 30% of all uveitis patients and up to 60% of intermediate- and pan-uveitis patients experience ME (Lardenoye, 2006).

5.2. Scientific Rationale

Clearside is developing CLS-TA, a proprietary TA formulation, for the treatment of non-infectious uveitis administered by SC injection. This therapy for uveitis is part of Clearside's paradigm of developing drug treatments for unmet or underserved blinding eye diseases where the pathologies dominantly originate or manifest in the choroid and the retina.

Uveitis is commonly treated with corticosteroids and other immunomodulatory agents; such treatments are either systemic or local. The challenge with systemic, frequently oral, corticosteroid treatments for ophthalmic inflammatory conditions is that these treatments are often associated with adverse events (AEs) such as peptic ulcerations, osteoporosis, necrosis of the hip, weight gain, muscle weakness, hyperglycemia, and systemic hypertension. All currently used modes of steroid administration for ophthalmic conditions, including local administrations, are associated with increases in intraocular pressure (IOP) that could result in glaucoma, progression of glaucoma, and to both the formation and the progression of cataracts (Karim, 2013).

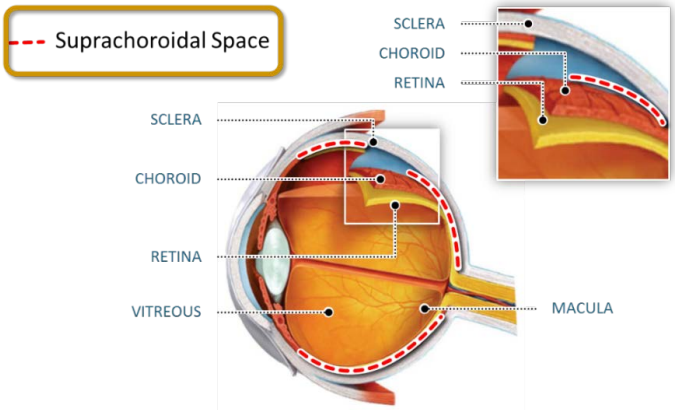
The potential advantages of using suprachoroidal administration to precisely provide local corticosteroid therapy to the affected tissues of the eye are that it can result in robust efficacy based upon data from animal models and from Phase 1/2 and Phase 2 clinical data. Further, the unique distribution of drug following suprachoroidal administration confining it to the posterior

segment and sparing anterior segment portions of the eye, along with the extremely low systemic steroid exposure to other organs in the body, can provide differentiating efficacy along with the potential for improved safety.

5.3. Description of Investigational Product

CLS-TA, triamcinolone acetonide injectable suspension, is a preservative-free, terminally sterilized, aqueous suspension, formulated for administration into the eye. It will be administered as a single SC injection of 4 mg in 100 µL. The suprachoroidal space (SCS) is the region of the eye between the sclera and the choroid (Figure 1).

Figure 1: Anatomy of the Eye



Additional information regarding CLS-TA, triamcinolone acetonide injectable suspension, is available in the Clinical Investigator's Brochure.

5.4. Summary of Clinical Experience and Justification of Dose Selection

Triamcinolone acetonide (TA) has been used safely and effectively in human ocular therapeutics to treat conditions involving inflammation for over 50 years. The initial recommended dose of the TA formulation approved by the US Food and Drug Administration for ocular indications is 4 mg in 100 µL (TRIESENCE Prescribing Information, 2007). The dose of CLS-TA administered as a single suprachoroidal injection will be similar (4 mg in 100 µL). TRIESENCE and CLS-TA contain the same active and inactive ingredients at approximately the same concentrations. Both formulations are aqueous suspensions that have been terminally sterilized and designed for ophthalmic use.

Clearside has completed 2 clinical trials in patients with non-infectious uveitis and one clinical trial in patients with retinal vein occlusion (RVO).

The completed clinical study, CLS1001-101 (NCT01789320), was a Phase 1/2, open-label, safety and tolerability study in subjects with intermediate, posterior, or pan non-infectious uveitis (Goldstein 2016). Each subject received a single SC injection of 4 mg in 100 µL TA (TRIESENCE®). Nine of the 11 subjects in the safety analysis set (82%) completed the 26-week study. All subjects had at least one AE, with a total of 37 AEs reported. One serious adverse

event (unrelated pulmonary emboli; SAE) occurred. No deaths were reported. No significant increases in IOP were reported. The most commonly reported AE, eye pain, was reported in 5 subjects. All subjects in the per-protocol (n=8) analysis set showed improvements in BCVA in this study.

The completed clinical study, CLS1001-201 (NCT02255032), was a Phase 2, randomized, masked safety and efficacy study in subjects with ME associated with non-infectious uveitis. Twenty-two subjects were assigned to receive a single SC injection of CLS-TA, either 4 mg in 100 µL or 0.8 mg in 100 µL in a 4:1 randomization. Subjects in the 4.0 mg treatment group were observed to have a mean reduction in central subfield thickness (CST) of 164 microns (p=0.002) when measured from Baseline at 2 months. One SAE (unrelated atrial fibrillation) occurred. No subjects discontinued due to an AE, and there were no Investigator-reported increases in IOP at follow-up visits.

The completed clinical study, CLS1003-201 (CT02303184), was a Phase 2, randomized, masked safety and efficacy study in subjects with ME following RVO. Forty-six subjects were randomly assigned 1:1 to either SC injection of CLS-TA administered in conjunction with an intravitreal (IVT) injection of aflibercept (ACTIVE), or an IVT injection of aflibercept alone (CONTROL). Subjects were observed to have a mean reduction in CST of 445 µm in the ACTIVE group and 342 µm in the CONTROL group when measured from Baseline at 3 months. Mean improvements in best corrected visual acuity (BCVA) were 16, 20 and 19 letters in the ACTIVE group and 11, 12 and 11 letters in the CONTROL group at Months 1, 2 and 3 respectively. Sixty percent fewer additional intravitreal aflibercept injections (p=0.013) were required in the ACTIVE group receiving the combination of suprachoroidal CLS-TA and intravitreal aflibercept compared to subjects in the CONTROL arm. No subjects discontinued due to an AE and no SAEs were reported. Two subjects in the active group reported 2 events each of ocular hypertension and IOP increase. All events were mild or moderate in intensity and considered to be related to study drug.

Safety profiles have been similar in all three studies with eye pain being the most commonly reported AE. Additional information regarding clinical experience with TA administered to the SCS is available in the Investigator's Brochure.

6. TRIAL OBJECTIVES AND PURPOSE

The purpose of this open-label study is to evaluate the safety of suprachoroidally administered CLS-TA for the treatment of non-infectious uveitis.

6.1. Primary Objective

The primary objective of this study is to evaluate the safety of suprachoroidally administered CLS-TA in subjects with non-infectious uveitis.

6.2. Secondary Objective

The secondary objectives of the study are:

- To assess changes to signs and complications of uveitis
- To collect use information on the suprachoroidal injection procedure
- To determine systemic exposure to triamcinolone acetonide after suprachoroidal injection

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a Phase 3, open-label, multi-center study to assess the safety of 4 mg of CLS-TA administered via suprachoroidal injection for the treatment of subjects with non-infectious uveitis.

The study design includes 8 clinic visits over a maximum of 29 weeks. Subject eligibility will be established at Visit 1 during the screening process (Day -30 to 0). Eligible subjects will return to the clinic for Visit 2 (Day 0). Visit 1 and Visit 2 can occur on the same day. Qualified subjects will receive two unilateral suprachoroidal injections of CLS-TA administered to the study eye, approximately 12 weeks apart (Visit 2 and Visit 5). Follow up visits will be conducted every 4 weeks up to 24 weeks (Visit 8). Subjects will have a final evaluation conducted 24 weeks (Visit 8) following Treatment #1 (Day 0). All subjects will be included in pharmacokinetic evaluations at Visits 2, 3, 5 and 8.

Subjects will be assessed via study procedures outlined in the time and events schedule.

7.2. Endpoints

7.2.1. Primary Endpoint

The primary endpoint is the incidence of treatment-emergent adverse events (TEAEs) and SAEs, grouped by organ system, relatedness to study medication, and severity.

7.2.2. Safety Endpoints

- Percentage of subjects whose IOP increases are >5 and > 10 mmHg from their own baseline measurement at each follow-up visit (except Visits 2 & 5 [post-dose])
- Percentage of subjects whose IOP increases to a reading > 30 mmHg at each follow-up visit (except Visits 2 & 5 [post-dose])
- Percentage of subjects who require 1 or more additional IOP lowering medications at any follow-up visit (except Visits 2 & 5 [post-dose])
- Percentage of subjects who experience an 11 – 20 mm, 21-30 mm, >30 mm rise in IOP 30 min post injection
- Mean change in lens grading based on standardized cataract grading system assessment

7.2.3. Additional Endpoints

- User evaluation and information pertaining to the use of the microinjector during the injection procedure
- Triamcinolone acetonide blood concentrations prior to each dose (Visits 2 and 5), 4 weeks following the first dose (Visit 3) and at 24 weeks (Visit 8)
- Percentage change in anterior chamber cells and flare, and vitreous haze
- Mean change from baseline in Early Treatment of Diabetic Retinopathy Study (ETDRS) BCVA

- Mean change from baseline in CST
- Percentage of subjects with <300 micron CST
- Percentage of subjects with a decrease in systemic concomitant uveitis medications
- Percentage of subjects in whom any additional therapy was initiated to manage uveitis

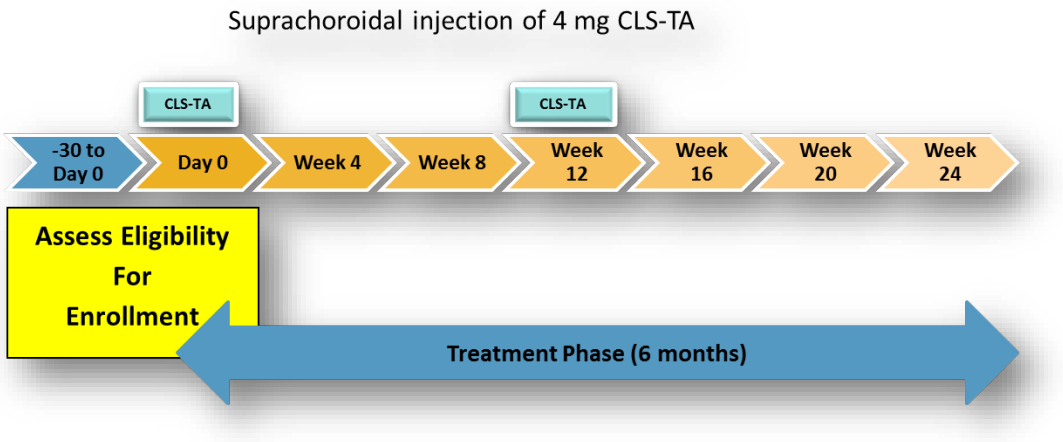
7.3. Number of Subjects

Approximately 35 subjects with non-infectious uveitis will be enrolled into the study.

7.4. Treatment Assignment

After Screening (Day -30 to Day 0) and Baseline assessments on Day 0, subjects will be assigned to the study treatment that consists of two unilateral suprachoroidal injections of 4 mg (100 µL of 40 mg/mL) CLS-TA administered to the study eye, approximately 12 weeks apart (Visit 2 and Visit 5).

Figure 2: Study Schedule



CLS-TA=Triamcinolone Acetonide Injectable Suspension

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Inclusion Criteria

Individuals are eligible for participation in this study if s/he meets all of the following criteria:

1. A diagnosis of non-infectious uveitis of any etiology for which the administration of local corticosteroid therapy would be a viable treatment option; either anterior-, intermediate-, posterior- or pan-uveitis are acceptable; both active and inactive uveitis are acceptable
2. ETDRS BCVA score of ≥ 5 letters read in the study eye
3. Understands the language of the informed consent; willing and able to provide written informed consent prior to any study procedures; willing to comply with the instructions and attend all scheduled study visits
4. At least 18 years of age

8.2. Exclusion Criteria

8.2.1. Ophthalmic Exclusion Criteria

An individual is ineligible for participation in this study if s/he meets any of the following criteria:

1. Has significant media opacity in the study eye precluding evaluation of the retina and vitreous
2. Any active ocular disease or infection in the study eye other than uveitis
3. Intraocular pressure > 22 mmHg or uncontrolled glaucoma (open angle or angle closure) in the study eye at Visit 1; subjects are not excluded if IOP is ≤ 22 mmHg in the study eye with no more than 2 IOP lowering medications
4. Has a history of severe glaucoma as defined by optic nerve damage (cup/disc ratio of ≥ 0.9 or any notching of optic nerve to the rim)
5. History of any vitreoretinal surgery (examples include but are not limited to scleral buckle, retrieval of a dropped nucleus or intraocular lens) in the study eye; prior photocoagulation and IVT injections are acceptable; prior cataract extraction, Yttrium-Aluminum-Garnet laser capsulotomy, and pars plana vitrectomy is allowed, but must have been performed at least 3 months prior to Visit 2
6. Has had cyclodestructive procedures ,filtration surgeries, or laser trabeculoplasty in the study eye in the 3 months prior to Visit 2
7. Has high myopia in the study eye defined as a spherical equivalent > -6 diopters or an axial length ≥ 26 mm
8. Has had photocoagulation or cryotherapy in the study eye within the 6 months prior to Visit 2
9. Has had any IVT injection of anti-vascular endothelial growth factor treatment (bevacizumab, aflibercept, pegaptanib or ranibizumab) in the study eye in the 30 days prior to Visit 2
10. In the study eye, any topical ocular corticosteroid in the 10 days prior to Visit 2; intraocular and periocular corticosteroid injection in the 2 months prior to Visit 2; an

Ozurdex® implant in the 6 months prior to Visit 2; Retisert®or Iluvien® implant in the 3 years prior to Visit 2

8.2.2. General Exclusion Criteria

Individuals are not eligible for participation in this study if s/he meets any of the following criteria:

11. Female subjects who are pregnant, lactating or planning a pregnancy. Females of childbearing potential must agree to submit to a pregnancy test at screening and agree to use an acceptable method of contraception throughout participation in the study. Acceptable methods of contraception include double barrier methods (condom with spermicide or diaphragm with spermicide), hormonal methods (oral contraceptives, implantable, transdermal, or injectable contraceptives), or an intrauterine contraceptive device with a documented failure rate of less than 1% per year. Abstinence may be considered an acceptable method of contraception at the discretion of the Investigator, but the subject must agree to use one of the acceptable birth control methods if she becomes sexually active.
12. Any uncontrolled systemic disease that, in the opinion of the Investigator, would preclude participation in the study (eg. unstable medical status including uncontrolled elevated blood pressure, cardiovascular disease, and glycemic control) or put the subject at risk due to study treatment or procedures
13. Likely need for hospitalization or surgery within the study period, including planned elective surgery or hospitalization that cannot be deferred
14. Hypersensitivity to any component of the CLS-TA, fluorescein, or to topical anesthetics
15. Is currently enrolled in an investigational drug or device study or has used an investigational drug or device within 30 days of Visit 2 OR was ever enrolled in a previous clinical study of CLS-TA
16. Has used acetazolamide (Diamox®) 1 week prior to Visit 2
17. Has taken systemic corticosteroids at doses greater than 20 mg per day for oral prednisone (or equivalent for other corticosteroids) in the 2 weeks prior to Visit 2; subjects on 20 mg or less per day can be enrolled; decreases and termination of dose are allowable during the study
18. Is currently using prescribed nonsteroidal anti-inflammatory drugs (excluding over-the-counter use) unless the dose has been stable for at least 2 weeks prior to Visit 2; decreases and termination of dose are allowable during the study
19. Is currently using prescribed immunomodulatory therapies, unless the dose has been stable for at least 2 weeks prior to Visit 2; decreases and termination of dose are allowable during the study

8.3. Subject Withdrawal Criteria

Subjects may withdraw from the study at any time and for any reason without obligation. Subjects may be removed from the study at the Investigator's discretion.

Subjects who withdraw prematurely from the study will be asked to complete study assessments at the Early Termination Visit. If an SAE is unresolved at the time of the subject's final study

visit, the Investigator should make every attempt to follow up until the SAE is resolved or stabilized, the subject is lost to follow-up, or there is some other resolution of the event.

8.4. Visit Procedure Descriptions

8.4.1. General Procedures

The study will consist of up to 8 study visits over a maximum of 29 weeks. Subjects are expected to attend all study visits. All ocular assessments at Visit 1 and Visit 8 will be performed on both eyes. IOP will be collected in both eyes at all visits. All other ocular assessments at all other visits (Visits 2-7) will be collected on the study eye only.

Subjects will be screened for entry at Visit 1 (Days -30 to 0) and the study eye will be identified. Each eligible subject will return to the clinic within 30 days to be treated at Visit 2 (Day 0). Visit 1 and Visit 2 can occur on the same day. After baseline assessments on Day 0, subjects will receive an active SC dose of CLS-TA in the study eye. Subjects will be assessed after injection for safety.

Additional safety follow-up visits will occur every 4 weeks for 24 weeks. Subjects will receive a second SC injection of CLS-TA at Visit 5 (Week 12). The final study visit will occur at Visit 8 (Week 24).

8.4.2. Re-screening Procedures

Subjects may be re-screened if the reason for their initial screening failure has changed. A subject who is designated as a screen failure before being randomly assigned at Visit 2 (Day 0) may be re-screened up to 2 additional times, for a total of 3 screenings, upon Sponsor approval.

Subjects who are re-screened are required to sign a new consent form. Screening assessments must be repeated if timings for the assessments fall outside of the specified study windows.

8.4.3. Visit 1 – Screening (Day -30 to 0)

At Visit 1, subjects will be screened for eligibility. Before any study-specific assessments are performed, written informed consent will be obtained for each subject. During Visit 1, the following procedures will be performed by study staff:

1. Obtain written informed consent
2. Assign subject number
3. Collect demographics, medical and ocular history
4. Review current and prior concomitant medications
5. Measure resting heart rate and blood pressure
6. Collect blood and urine for central lab tests prior to fluorescein angiography (FA)
7. Collect serum or urine for local pregnancy test on females of childbearing potential
8. Perform ophthalmic assessments on both eyes:
    a. ETDRS BCVA

b. Slit-lamp biomicroscopy, including dilated lens grading
c. IOP (Goldmann applanation tonometry)
d. Dilated indirect ophthalmoscopy
e. Fundus photography and upload images to the Central Reading Center (CRC)
f. SD-OCT and upload images to the CRC
g. FA and upload images to the CRC

9. Perform a review of systems
10. Verify subject eligibility based on Inclusion/Exclusion requirements
11. Determine study eye based upon eye specific eligibility criteria (see Section 9.2)
12. Schedule subject to return for Visit 2, Treatment, or continue on to Visit 2 procedures

8.4.4. Visit 2 –Treatment (Day 0)

Visit 2 may occur on the same day as Visit 1 (Screening) but must occur within 30 days of Visit 1 (Screening). The following procedures will be performed by study staff:

8.4.4.1. Pre-Injection Procedures

The following must be performed prior to the injection of CLS-TA (the same day as the injection). If Visit 1 and Visit 2 are performed on the same day, the pre-injection procedures in Visit 2 can be waived:

1. Assess for AEs
2. Review changes to concomitant medications
3. Review lab results for any clinically significant abnormalities that would exclude the subject from entry
4. Measure resting heart rate and blood pressure
5. Perform ophthalmic assessments on the study eye only, unless otherwise designated:
    a. ETDRS BCVA
    b. Slit-lamp biomicroscopy, including dilated lens grading
    c. IOP (Goldmann applanation tonometry), both eyes
    d. Dilated ophthalmoscopy
    e. SD-OCT and upload images to the CRC
6. Collect a blood sample for PK analysis; blood must be collected PRIOR to dosing

8.4.4.2. Injection Procedure and Immediate Post-Injection Assessments

For details on the injection procedure, please see the Investigator Site File.

1. Confirm study eye
2. Retrieve study drug kit number

3. Prepare eye for injection per the investigator's standard practice
4. The injecting investigator should administer suprachoroidal injection of CLS-TA procedure to the study eye; see Manual of Procedures for detailed instructions
5. Immediately following the injection, assess study eye by indirect ophthalmoscopy

8.4.4.3. Post-Injection Procedures

The following assessments must occur following the injection of CLS-TA:

1. Assess for AEs
2. Review changes to concomitant medications
3. Perform ophthalmic assessments on the study eye only:
    a. Perform slit-lamp biomicroscopy
    b. Perform indirect ophthalmoscopy
    c. Evaluate IOP approximately 30 minutes post-injection:
        - If IOP remains elevated, subject must remain on site until IOP is under control per investigator judgment
        - If IOP is < 30 mmHg, the subject may leave the clinic
4. Document injection procedure use information
5. Schedule subject to return for next visit

8.4.5. Follow-Up: Visit 3 – Week 4 (Day 28 ±5)

Visit 3 should be 42 ±5 days from Visit 2. The following procedures will be performed by study staff at Visit 3:

1. Assess for AEs
2. Review changes to concomitant medications
3. Perform ophthalmic assessments on the study eye only, unless otherwise designated:
    a. ETDRS BCVA
    b. Slit-lamp biomicroscopy, including dilated lens grading
    c. IOP (Goldmann applanation tonometry), both eyes
    d. Dilated indirect ophthalmoscopy
    e. SD-OCT and upload images to the CRC
4. Collect a blood sample for PK analysis
5. Schedule subject to return for next visit

8.4.6. Follow-Up: Visit 4 – Week 8 (Day 56 ±5)

Visit 4 should be 56 ±5 days from Visit 2. The following procedures will be performed by study staff at Visit 4:

1. Assess for AEs
2. Review changes to concomitant medications
3. Perform ophthalmic assessments on the study eye only, unless otherwise designated:
    a. ETDRS BCVA
    b. Slit-lamp biomicroscopy, including dilated lens grading
    c. IOP (Goldmann applanation tonometry), both eyes
    d. Dilated indirect ophthalmoscopy
    e. SD-OCT and upload images to the CRC
4. Schedule subject to return for next visit

8.4.7. Visit 5 – Week 12 – Treatment #2 (Day 84 ±5)

At Visit 5, subjects will receive their second, unilateral, suprachoroidal injection of CLS-TA. The following Visit 5 procedures will be performed by study staff:

8.4.7.1. Pre-Injection Procedures

The following must be performed prior to the injection of CLS-TA (the same day as the injection):

1. Assess for AEs
2. Review changes to concomitant medications
3. Measure resting heart rate and blood pressure
4. Confirm study eye
5. Perform ophthalmic assessments on the study eye only, unless otherwise designated:
    a. ETDRS BCVA
    b. Slit-lamp biomicroscopy, including dilated lens grading
    c. IOP (Goldmann applanation tonometry), both eyes
    d. Dilated indirect ophthalmoscopy
    e. SD-OCT and upload images to the CRC
7. Collect a blood sample for PK analysis; blood must be collected PRIOR to dosing

8.4.7.2. Injection Procedure and Immediate Post-Injection Assessments

For details on the injection procedure, please see the Investigator Site File. The Visit 5 injection procedure should be identical to the Visit 2 injection procedure.

1. Confirm study eye

2. Retrieve study drug kit number
3. Prepare eye for injection per the investigator's standard practice
4. The injecting investigator should administer a suprachoroidal injection of CLS-TA in the study eye
5. Immediately following the injection, assess study eye by indirect ophthalmoscopy

8.4.7.3. Post-Injection Procedures

The following assessments must occur following the injection:

1. Assess for AEs
2. Review changes to concomitant medications
3. Perform ophthalmic assessments on the study eye only:
    a. Perform slit-lamp biomicroscopy
    b. Perform indirect ophthalmoscopy
    c. Evaluate IOP approximately 30 minutes post-injection:
        - If IOP remains elevated, subject must remain on site until IOP is under control per investigator judgment
        - If IOP is < 30 mmHg, the subject may leave the clinic
4. Document injection procedure use information
5. Schedule subject to return for next visit

8.4.8. Follow-Up: Visit 6 – Week 16 (Day 112 ± 5) & Visit 7 – Week 20 (Day 140 ±5)

Visit 6 should be 112 ± 5 days from Visit 2. Visit 7 should be 140 ±5 from Visit 2. The following procedures will be performed by study staff:

1. Assess for AEs
2. Review changes to concomitant medications
3. Perform ophthalmic assessments on study eye only, unless otherwise designated:
    a. ETDRS BCVA
    b. Slit-lamp biomicroscopy, including dilated lens grading
    c. IOP (Goldmann applanation tonometry), both eyes
    d. Dilated indirect ophthalmoscopy
    e. SD-OCT and upload images to the CRC
4. Schedule subject to return for next visit

8.4.9. Visit 8 – Week 24 End of Study (Day 168 ± 5) or Early Termination

Visit 8 should be 168 ± 5 days from Visit 2 or at the time of early termination. The following Visit 8 procedures will be performed by study staff:

1. Assess for AEs
2. Review changes to concomitant medications
3. Measure resting heart rate and blood pressure
4. Collect blood and urine for central lab tests prior to FA (including serum pregnancy test on females of childbearing potential)
5. Collect a blood sample for PK analysis
6. Perform a review of systems
7. Perform ophthalmic assessments on both eyes, unless otherwise designated:
    a. ETDRS BCVA
    b. Slit-lamp biomicroscopy, including dilated lens grading
    c. IOP (Goldmann applanation tonometry), both eyes
    d. Dilated indirect ophthalmoscopy
    e. Fundus photography and upload images to the CRC
    f. SD-OCT and upload images to the CRC
    g. FA and upload images to the CRC

8.4.10. Unscheduled Visit

To ensure subject safety during the study, any subject who requires additional follow-up or treatment for any reason at any time during the study that does not fall on a scheduled study visit should have that visit recorded as an Unscheduled Visit.

9. TREATMENT OF SUBJECTS

9.1. Treatments to be Administered

Treatment will consist of two unilateral suprachoroidal injections of 4 mg of CLS-TA in 100 μL, administered 12 weeks apart.

Approximately 35 subjects will be enrolled. The CLS-TA injections will occur at Visit 2 (Day 0) and at Visit 5 (Day 84 ± 5).

All SC injections may only be performed by trained Investigators. Training will be documented by the Sponsor in writing. Training documentation will be maintained at the site as well as with the Sponsor.

Detailed instructions on the SC injection procedure can be found in the Investigative Site File.

9.2. Study Eye Determination

The study eye will be the eye receiving the SC CLS-TA injection. The determination of the study eye will be based on Screening/Baseline information and will be determined prior to injection.

If both eyes meet study criteria, then the right eye should be designated as the study eye. The eye that is not designated as the study eye will be denoted as the fellow eye.

9.3. Treatment of the Fellow Eye

Subjects may have bilateral disease, but only one eye will be designated the study eye and treated.

Local medications are permitted for the fellow eye during the course of this trial. The choice of local ocular therapy for the fellow eye is not subject to the requirements of this protocol. Systemic therapy for diseases of the fellow eye is subject to the list of prohibited medications below. Medications used for therapy of the fellow eye will be recorded in the subject's medical chart and the case report form (CRF).

9.4. Additional Treatment

If at any time during the study a subject is considered at immediate risk for a vision-threatening event, the Investigator should immediately follow best medical practice in the Investigator's judgment for treating the subject. All additional therapy will be recorded in the subject's medical chart and the CRF.

9.4.1. Rescue Criteria

Beginning at Week 4 (Visit 3), if any of the following criteria are met in the study eye, the use of a treatment may be introduced. The therapy implemented is left to the discretion of the Investigator.

- A decrease of 10 or more ETDRS BCVA letters read from baseline (Day 0)

- An increase in CST of ≥ 100 µm or 20%, whichever is lower, from baseline (Day 0) based on the CST measurement at the clinical site
- A ≥ 1.5-step increase from baseline (Day 0) in the level of inflammation (eg, anterior chamber cells or flare, or vitreous haze) or an increase from 3+ to 4+
- A decrease of 10 or more ETDRS BCVA letters read from the best ETDRS BCVA data observed during the study, along with an increase in other signs or complications associated with the patient's uveitis
- In the investigator's medical judgement, the uveitic complications in the study eye have not improved and the condition needs to be addressed

9.5. Concomitant Medications

The list of prohibited medications provided below is not intended to be comprehensive, but rather to help guide the Investigator's medical judgment. In cases where a subject presents with a medication not included on the following list, or should there be any question on the part of the Investigator, Investigators are encouraged to confer with the Medical Monitor for any clarification.

Use of the following medications are prohibited at any time during the study:

- Any corticosteroid implant (ie, Ozurdex®, Iluvien® or Retisert™) in the study eye
- Topical, periocular or IVT corticosteroids in the study eye
- Anti-angiogenic drugs (anti-VEGF) in the study eye or systemically (including pegaptanib sodium, bevacizumab, ranibizumab)
- Any investigational drug or device

In cases where there is anticipated need for the above listed medications during the study or if a subject presents to the Investigator having initiated treatment during the study with one of these medications or classes of medications, it is the responsibility of the Investigator to notify the Sponsor immediately. If additional therapy is necessary to treat uveitis in the study eye and normal standard of care requires these medications, they will be recorded in the subject's case report form and should follow the guidelines presented for Rescue Criteria. Subjects will not be discontinued from the study due to initiation/change in a prohibited medication.

9.6. Treatment Compliance

Study drug will only be administered by trained study investigators (Principal Investigator or Sub-Investigator) in the office at Visit 2 and Visit 5. No study drug will be dispensed to subjects; subject treatment compliance is not applicable.

9.7. Randomization and Masking

This study is neither randomized nor is the study treatment masked. Investigators, study staff, subjects and the sponsor will be aware of the investigational treatment provided to the subject.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

CLS-TA, triamcinolone acetonide injectable suspension, is a sterile, preservative-free, aqueous suspension formulated for administration into the eye. The drug product is terminally sterilized and is intended for single use. CLS-TA is supplied as a 40 mg/mL sterile suspension in a 2 mL/13 mm TopLyo® single-use vial with a rubber stopper and an aluminum seal.

Additional information regarding CLS-TA is available in the Investigator's Brochure.

10.2. Study Drug Packaging and Labeling

The study drug kits for SC injection of CLS-TA will be supplied to each site by the Sponsor (or designee) and will be labeled for "Investigational Use only".

10.3. Study Drug Storage

CLS-TA will be stored at ambient temperatures between 15°C and 25°C (59°F-77°F) in an area with limited, controlled access and temperature monitoring; do not freeze. CLS-TA should be protected from light by storing in the carton provided.

10.4. Study Drug Preparation

Shake the vial of CLS-TA vigorously for 10 seconds to ensure a uniform suspension before withdrawing the product from the vial.

10.5. Administration

CLS-TA will be administered as a single SC injection of 4 mg in 100 µL.

All CLS-TA injections may only be performed by trained Investigators. Training will be documented by the Sponsor in writing. Training documentation will be maintained at the site as well as with the Sponsor.

Detailed instructions on the CLS-TA injection procedure can be found in the Investigative Site File.

The date and time of the injection will be recorded in the subject's medical chart and the CRF. All needles used, the needle length used for injection and procedure use information will also be recorded.

10.6. Study Drug Accountability

Accountability of study drug kits will be conducted by either designated study staff and/or the study monitor. Accountability will be ascertained by performing reconciliation between the number of study drug cartons (kits and components) sent to the site and the number used and unused at the time of reconciliation.

Study drug shipment records will be verified and accountability performed by comparing the shipment inventory sheet to the actual quantity of drug and injectors received at the site. Accurate records of receipt and disposition of the study drug and injectors (eg, dates, quantity,

subject number, kits used, and kits unused) must be maintained by the Investigator or his/her designee.

10.7. Study Drug Handling and Disposal

At the end of the study and after study drug kit accountability has been verified, all study drug (used and unused vials) and unused microinjector components will be returned to the Sponsor (or designee) or destroyed at the site and documented according to the site's standard process. Any used injectors and vials of study drug involved in a product complaint must be maintained and return to the Sponsor (or designee). All study drug and injector accounting procedures must be completed before the study is considered complete.

11. ASSESSMENTS OF EFFICACY

For additional information on an assessment, see the Investigative Site File.

11.1. Best Corrected Visual Acuity

BCVA will be evaluated by ETDRS using electronic visual acuity or standardized lighting and lanes. The method of visual acuity assessment should remain consistent throughout a subject's study participation. The results will be reported as the number of letters read following refraction. Visual acuity testing should precede any examination requiring contact with the eye.

In order to provide standardization and well-controlled assessments of BCVA during the study, all BCVA assessments must be performed by trained staff who are certified on the study procedure using certified VA equipment/lanes.

11.2. Central Subfield Thickness as Measured by Spectral Domain Optical Coherence Tomography

Retinal thickness and disease characterization will be assessed via spectral domain – optical coherence tomography (SD-OCT). The SD-OCT instrument and technician must be certified before screening any subjects. The technician is encouraged to use the same certified equipment throughout the subject's study participation. All images should be taken by the same technician, whenever possible, on each subject per research site. De-identified images will be uploaded to the CRC.

11.3. Pharmacokinetics Assessments

Blood samples for measurement of CLS-TA plasma concentrations will be collected by venipuncture by qualified study personnel. A single blood sample will be obtained from each subject at the following time points: Day 0 (Visit 2) pre-dose, Week 4 (Visit 3) any time during visit, Week 12 (Visit 5) pre-dose and Week 24 (Visit 8) any time during visit. Blood samples will be processed and shipped to a central lab as outlined in the manual of procedures for the study.

12. ASSESSMENTS OF SAFETY

For additional information on an assessment, see the Investigative Site File.

12.1. Safety Parameters

12.1.1. Intraocular Pressure

Intraocular pressure will be measured by applanation tonometery and results will be recorded in mmHg. Goldmann applanation tonometry should be used at all visits. Tonopens may be used for post-injection pressure checks. A single measurement will be made at approximately the same time of day. The technician is encouraged to use the same tonometry method throughout the subject's study participation. Tonometers must be calibrated for accuracy before the first subject screening at that site and according to the manufacturer specifications during the study, until the last subject has exited the study at that site.

12.1.2. Slit-Lamp Biomicroscopy

Slit-lamp biomicroscopy, including magnification, will be performed consistent with standard clinical practice. This procedure should be conducted in the same manner for all subjects and will include an assessment of each of the following as normal or abnormal: eyelids, cornea, anterior chamber, iris and lens. All abnormal findings will be described.

12.1.3. Cataract Lens Grading

If an abnormal finding of cataract is noted during the slit-lamp exam, the cataract should be graded for nuclear opalescence, cortical opacity and posterior subcapsular opacity. Graders must verify training on the grading procedures.

12.1.4. Anterior Chamber Cells

Anterior chamber cells will be assessed clinically using a field size of 1 mm slit beam and using a standardized grading scale ranging from 0 to 4+, as defined in Table 3 (SUN, 2005).

Table 3: Anterior Chamber Cell Grading Scale

Score	Cells in Field
0	<1
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50

12.1.5. Anterior Chamber Flare

Anterior chamber flare will be assessed clinically via slit lamp using a standardized scale ranging from 0 to 4, as defined in Table 4 (SUN, 2005).

Table 4: Anterior Chamber Flare Grading Scale

Score	Description
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

12.1.6. Indirect Ophthalmoscopy

Indirect ophthalmoscopy should be performed according to the Investigator's standard procedure. This procedure should be the same for all subjects observed at the Investigator's site. The fundus will be examined thoroughly and the following variables will be assessed as normal or abnormal (including but not limited to): vitreous, retina, choroid, and optic nerve/disc, appearance of vessels, absence of neovascularization.

12.1.6.1. Vitreous Haze

Vitreous haze will be assessed clinically via indirect ophthalmoscopy using a standardized photographic scale ranging from 0 to 4, as defined in Table 5 (Nussenblatt 1985 as modified in Lowder 2011).

Table 5: Scale for Determining Degree of Vitreous Haze

Score	Description
0	no inflammation
+0.5	trace inflammation (slight blurring of the optic disc margins and/or loss of the nerve fiber layer reflex)
+1	mild blurring of the retinal vessels and optic nerve
+1.5	optic nerve head and posterior retina view obscuration greater than +1 but less than +2
+2	moderate blurring of the optic nerve head
+3	marked blurring of the optic nerve head
+4	optic nerve head not visible

12.1.7. Fluorescein Angiography

Fluorescein angiography will be performed for anatomic assessments and will include the area of fluorescein leakage, area of capillary nonperfusion, the presence of retinal vascular and optic nerve head staining, and retinal pigment epithelium abnormalities. Digital equipment will be registered and photographers certified for the imaging procedures. De-identified images will be uploaded to the CRC.

12.1.8. Fundus Photography

Color fundus photographs will be obtained. It is recommended that when both fundus photographs and FA are conducted in the same visit, the fundus photographs should be taken first. All photographs should be taken by the same photographer, whenever possible, on all subjects per research site. Digital equipment will be registered and photographers certified for the imaging procedures. De-identified images will be uploaded to the CRC.

12.1.9. Resting Heart Rate and Blood Pressure

Resting heart rate and resting blood pressure (systolic and diastolic, preferably on the same group each time) will be measured at Visits 1, 2, 5 and 8 after the subject has rested for about 5 minutes.

12.1.10. Pregnancy Test

Pregnancy tests will be performed on all females of childbearing potential. Urine or serum pregnancy tests may be performed locally.

12.1.11. Central Laboratory Tests

Non-fasting clinical laboratory tests will be performed at Visits 1 and 8. These laboratory tests include serum chemistry, hematology, and urinalysis and are to evaluate any underlying disease condition.

12.1.12. Review of Body Systems

A review of body systems will include an assessment of each of the following as normal or abnormal: skin, cardiovascular, respiratory, neurological and musculoskeletal systems. All abnormal findings will be described. This exam may be performed by any medical doctor or legally qualified personnel per local laws/regulations.

12.2. Adverse and Serious Adverse Events

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition after or during exposure to a pharmaceutical product, whether or not considered causally related to the product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

All AEs that occur after any subject has signed consent, before treatment, during treatment, or during the study participation, whether or not they are related to the study, must be recorded on the forms provided.

12.2.1.2. Serious Adverse Event

An SAE is an AE occurring during any study phase (ie, baseline, treatment, washout, or follow-up), and at any dose of the investigational product, comparator, or placebo, that fulfils one or more of the following:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

All SAEs that occur after any subject has been enrolled, before treatment, during treatment, or during study participation, whether or not they are related to the study, must be recorded.

12.2.2. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (Unrelated or Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated.” If there is any valid reason, even if

undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

12.2.3. Recording Adverse Event

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Clinically significant changes in laboratory values, blood pressure, and pulse need not be reported as AEs. However, abnormal values that constitute an SAE or lead to discontinuation of administration of study drug must be reported and recorded as an AE. Information about AEs will be collected from the signing of the consent form until the end of the study. Serious adverse event information will be collected from signing of the consent form until the end of study participation. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, seriousness outcome (if applicable), and whether or not it caused the subject to discontinue the study.

12.2.4. Intensity

The intensity of each AE will be graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.03. The criteria can be accessed at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

The term "severe" is a measure of intensity. A severe AE is not necessarily an SAE.

Grade refers to the intensity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of intensity for each AE based on this general guideline:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of the hospitalization indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 12.2.1.2. An AE of severe intensity may or may not be considered serious.

Should a pregnancy occur, it must be reported and recorded on the provided pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

12.2.5. Reporting Adverse Events

All SAEs (related and unrelated) will be recorded from the signing of the consent form until the end of study participation. Any SAEs considered related to the investigational product and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported to Clearside Biomedical, or its designee, within one business day of the first awareness of the event. The Investigator must complete, sign, and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy by fax to Clearside Biomedical, or its designee.

Additional follow-up information, if required or available, should be faxed to Clearside Biomedical, or its designee, within one business day of receipt. The information should be recorded on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the CRF and/or study file.

Clearside Biomedical is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15-Day Safety Reports) that occur during the clinical study. Each site is responsible for notifying its IRB/IEC of these additional SAEs.

12.2.6. Follow-up of AEs and SAEs

All AEs and SAEs reported during study conduct must be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or the subject is lost to follow-up. Subjects will be followed for any treatment-related SAEs reported at the end of participation until the condition stabilizes, the event is otherwise explained, the subject is lost to follow-up, or the subject withdraws consent.

> **NOTE:** "Resolution" means the subject has returned to baseline state of health, or the Investigator does not expect any further improvement in the subject's condition or does not expect worsening of the AE.

For a non-serious AE that is first identified on the last scheduled contact, the event must be recorded on the AE CRF with the current status noted, but no further follow-up needs to be performed.

Post-Study SAEs: Investigators are not obligated to actively seek SAE information in former study participants; however, any new SAE reported by the subject to the Investigator that occurs after the last scheduled contact and is determined by the Investigator to be associated with the use of study drug, should be reported to the Sponsor. The Investigator should follow related

SAEs identified after the last scheduled contact until the event has resolved or stabilized or the subject is lost to follow-up.

13. STATISTICAL CONSIDERATIONS

A detailed statistical analysis plan will be prepared for this study. Even though the endpoints in this study will only be based on descriptive statistics, the plan will contain a discussion of the statistical methods, a description of any computational algorithms and data handling conventions, and specifications for the data summaries and listings. It will be finalized before database lock. No inferential statistical analyses will be performed. All safety and efficacy endpoints will be summarized using descriptive statistics.

Pharmacokinetic analyses to determine systemic levels of triamcinolone acetonide following suprachoroidal injection will be described in a separate detailed plan.

13.1. Determination of Sample Size and Level of Significance

Approximately 35 subjects will be enrolled in this open-label safety study. Because this is a safety study, it was not powered for hypothesis testing; statistical analyses were descriptive in nature. The study sample size was not based on statistical calculations or statistical assumptions.

13.2. Subject Disposition, Demographic and Baseline Characteristics

Subject disposition, demographic, and baseline characteristics will be summarized descriptively.

13.3. Analysis Populations

13.3.1. Safety Population

The safety population will include all subjects who are administered at least one dose of CLS-TA. All analyses will be based on the Safety Population.

13.3.2. Pharmacokinetic Population

The pharmacokinetic population will include all subjects who are administered at least one dose of CLS-TA. Analyses will be conducted on all samples collected during the study.

13.4. Analysis Methods

Safety and efficacy endpoints are provided in Section 7.12.

13.4.1. Primary Safety Analysis

The primary endpoint is the incidence of treatment-emergent adverse events (TEAEs) and SAEs, grouped by organ system, relatedness to study medication, and severity.

The TEAEs and SAEs will be summarized by system organ class (SOC) and preferred term (PT) by presenting the number and percentage of subjects with each TEAE and SAE. The following AE summaries will be produced:

- TEAEs by SOC and PT
- SAEs by SOC and PT
- Treatment-related TEAEs by SOC and PT

- Treatment-related SAEs by SOC and PT
- TEAEs by SOC, PT, and maximum severity

In the summary, subjects may be counted under multiple SOCs and PTs, but for each SOC and PT, subjects are only counted once. If a subject has the same AE on multiple occasions, the highest severity (severe, moderate, mild) recorded for the event will be presented and the highest drug relationship will be presented on the respective tables. Percentages are based on the number of subjects in the Safety population.

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

13.4.2. Secondary Safety Analysis

Unless otherwise specified, all continuous variables will be summarized with descriptive statistics including: the number of observation (n), mean, standard deviation, median, minimum and maximum. All categorical/qualitative data will be presented using the number of observations (n), the frequency count and percentages by visit. The listings will be provided using the safety population. In general, the subject listings will be sorted by the subject number and assessment date (and time, if applicable).

13.4.2.1. Extent of Exposure

The extent of exposure (the number of injections and whether it was a complete or partial injection) will be listed.

13.4.2.2. Secondary Safety Endpoints

- Percentage of subjects whose IOP increases are >5 and > 10 mmHg from their own baseline measurement at each follow-up visit (except Visits 2 & 5 [post-dose])
- Percentage of subjects whose IOP increases to a reading > 30 mmHg at each follow-up visit (except Visits 2 & 5 [post-dose])
- Percentage of subjects who require 1 or more additional IOP lowering medications at any follow-up visit (except Visits 2 & 5 [post-dose])
- Percentage of subjects who experience an 11 – 20 mm, 21-30 mm, >30 mm rise in IOP 30 min post injection
- Mean change in lens grading based on standardized cataract grading system assessment

13.4.2.3. Additional Endpoints

- User evaluation and information pertaining to the use of the microinjector during the injection procedure
- Triamcinolone acetonide blood concentrations prior to the each dose (Visits 2 and 5), 4 weeks following the first dose (Visit 3) and at 24 weeks (Visit 8)
- Percentage change in anterior chamber cells and flare and vitreous haze
- Mean change from baseline in ETDRS BCVA
- Mean change from baseline in CST

- Percentage of subjects with <300 micron CST
- Percentage of subjects with a decrease in systemic concomitant uveitis medications
- Percentage of subjects in whom any additional therapy was initiated to manage uveitis

13.4.2.4. Subgroup analysis

No subgroup analyses are planned.

13.4.3. Pharmacokinetic Analysis

Standard population PK parameters will be calculated from plasma CLS-TA concentrations. Samples from approximately 35 subjects enrolled in the study will be available for analysis. Analyses will be conducted according to the nonlinear mixed-effects approach and will provide estimates of population characteristics (intrinsic and extrinsic factors) that describe the population distribution of the PK parameters.

13.4.4. Procedure for Accounting for Missing, Unused or Spurious Data

Any missing, unused, or spurious data will be noted in the final clinical study report.

No imputation is planned for safety data. Methodology for handling missing or partial dates will be addressed in the Statistical Analysis Plan.

14. DIRECT ACCESS TO SOURCE DOCUMENTS

14.1. Study Monitoring

Before an investigator can enter a subject into the study, a representative of Clearside Biomedical, Inc will visit the study site (unless waiver criteria are met) to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence and the responsibilities of Clearside Biomedical, Inc or its representatives. This will be documented in a Clinical Study Agreement between Clearside Biomedical, Inc and the Investigator.

During the study, a monitor from Clearside Biomedical, Inc or its representative will have regular contacts with the study site to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the CRFs, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts).
- Record and report any protocol deviations not previously sent to Clearside Biomedical, Inc or designee.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to Clearside Biomedical, Inc or designee and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

14.2. Audits and Inspections

Authorized representatives of Clearside Biomedical, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the study site to perform audits or inspections, including source data verification. The purpose of a Clearside Biomedical audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The Investigator should contact Clearside Biomedical immediately if contacted by a regulatory agency about an inspection.

14.3. Institutional Review Boards/Independent Ethics Committees

The Principal Investigator must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval and all materials approved by the IRB/IEC for this study, including the subject consent form and recruitment materials, must be maintained by the Investigator and made available for inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

The progress of the study will be monitored by onsite, written, e-mail, and telephone communications between personnel at the study site and the Sponsor. The Investigator will allow Sponsor monitors, or designee(s), to inspect all CRFs; subject records (source documents); signed Informed Consent Forms; records of study drug receipt, storage, and disposition; and regulatory files related to the study.

At the time of database lock, the clinical database will be audited to ensure accuracy of the data, as well as to provide an estimated error rate for the final, locked database. The audit will involve a comparison of CRF values with values from data listings generated from the clinical database. Values identified as critical safety and efficacy variables will be confirmed for 100% of the subjects. In addition, a random sample of subjects will be selected for which all data values, excluding comment fields, will be checked. The number of subjects whose data will be randomly reviewed will be determined to provide sufficient accuracy for the estimated error rate of the clinical database.

16. ETHICS

16.1. Ethical Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to Clearside Biomedical, Inc, or designee, before he or she can enroll any subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Clearside Biomedical, Inc will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Council for Harmonisation Guideline for Good Clinical Practice, and applicable regulatory requirements.

16.3. Written Informed Consent

The Principal Investigator(s) at each site will ensure that the subject is given full and adequate oral and written information about the nature, purpose, and possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the subject.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

Clearside Biomedical Inc, and designees, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

17.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved, 2 years after the discontinuance of the test article for investigation or according to local regulation. If it becomes necessary for Clearside Biomedical, Inc or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

18. PUBLICATION POLICY

The institutions and Investigators participating in this study shall have no right to publish or present the results of this study without the prior written consent of Clearside Biomedical, Inc.

19. REFERENCES

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20. APPENDICES

APPENDIX A. TIME AND EVENTS SCHEDULE

Visit #	**Visit 1**	**Visit 2**		**Visit 3**	**Visit 4**	**Visit 5**		**Visit 6**	**Visit 7**	**Visit 8**
Visit Type	**Screening**	**Treatment #1**		**Follow-Up**		**Treatment #2**		**Follow-Up**		**End of Study**
Visit Window	**Day -30 to 0**	**Day 0**		**Week 4** Day 28 ± 5	**Week 8** Day 56 ± 5	**Week 12** Day 84 ± 5		**Week 16** Day 112 ± 5	**Week 20** Day 140 ± 5	**Week 24** Day 168 ± 5
Assessments		**Pre-dose[5]**	**Post-dose**			**Pre-dose**	**Post-dose**			
Informed Consent	√									
Assign Subject Number	√									
Demographics, Medical & Ocular History	√									
Eligibility Criteria	√	√								
Assess AEs	√	√	√	√	√	√	√	√	√	√
Con Med Review	√	√	√	√	√	√	√	√	√	√
Resting HR & BP	√	√				√				√
Lab Tests[1]	√									√
Review of Body Systems	√									√
BCVA[4]	√	√		√	√	√		√	√	√
Slit lamp Biomicroscopy[2, 4]	√	√	√	√	√	√	√	√	√	√
IOP[6]	√	√	√	√	√	√	√	√	√	√

Visit #	**Visit 1**	**Visit 2**		**Visit 3**	**Visit 4**	**Visit 5**		**Visit 6**	**Visit 7**	**Visit 8**
Visit Type	**Screening**	**Treatment #1**		**Follow-Up**		**Treatment #2**		**Follow-Up**		**End of Study**
Visit Window	**Day -30 to 0**	**Day 0**		**Week 4** Day 28 ± 5	**Week 8** Day 56 ± 5	**Week 12** Day 84 ± 5		**Week 16** Day 112 ± 5	**Week 20** Day 140 ± 5	**Week 24** Day 168 ± 5
Assessments		**Pre-dose[5]**	**Post-dose**			**Pre-dose**	**Post-dose**			
Dilated Indirect Ophthalmoscopy[4]	√	√	√	√	√	√	√	√	√	√
SD-OCT[4]	√	√		√	√	√		√	√	√
PK Blood Draw		√		√		√				√
Select Study Eye/Confirm Study Eye	√					√				
Fluorescein Angiogram[4]	√									√
Fundus Photos[4]	√									√
Study Drug Treatment[3]		INJECT[3]				INJECT[3]				

1. Central lab test samples should be collected prior to fluorescein angiogram being performed; local labs include a urine or serum pregnancy test for females of child bearing potential
2. Any finding of cataract should be graded
3. Injection should be administered the same day as the pre-injection assessments at Visit 1/2 and at Visit 5
4. Completed for both eyes at Visit 1 and Visit 8; study eye only for all other visits
5. If Visit 1 and Visit 2 occur on the same day, the Screening procedures can replace the Pre-dose procedures of Visit 2
6. IOP collected for both eyes, except post-injection when data are collected for study eye only

APPENDIX B: SUMMARY OF CHANGES

Amendment 1

Section Changed	Initial Protocol 1.0 (Changed From)	Protocol version 2.0 (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Throughout protocol	Miscellaneous typographical and formatting errors as well as clarifications for readability		To correct typographical and formatting errors and improve readability	None
Cover page	1220 Old Alpharetta Rd., Suite 300 Alpharetta, GA 30005	900 North Point Parkway, Suite 200 Alpharetta, GA 30005	Clearside Biomedical, Inc. Address change	None
List of Abbreviations		PK – Pharmacokinetics	To include the term: pharmacokinetics (PK)	None
7.2.3. Additional Endpoints and 13.4.2.3. Additional Endpoints	Percentage change in anterior chamber cells and vitreous haze	Percentage change in anterior chamber cells and flare, and vitreous haze	To include percentage change in flare as an additional endpoint	None
Section 8.2.1. Ophthalmic Exclusion Criteria #5		History of any vitreoretinal surgery (examples include but are not limited to scleral buckle, retrieval of a dropped nucleus or intraocular lens) in the study eye; prior photocoagulation and IVT injections are acceptable; prior cataract extraction, Yttrium-Aluminum-Garnet laser capsulotomy, and pars plana vitrectomy is allowed, but must have been performed at least 3 months prior to Visit 2	To exclude subjects who have had vitreoretinal surgery except the allowed surgeries that are listed.	None

Amendment 1

Section Changed	Initial Protocol 1.0 (Changed From)	Protocol version 2.0 (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Section 8.2.1. Ophthalmic Exclusion Criteria #6	Has had cyclodestructive procedures or filtration surgeries in the study eye in the 3 months prior to Visit 2	Has had cyclodestructive procedures, filtration surgeries, or laser trabeculoplasty in the study eye in the 3 months prior to Visit 2	To exclude subjects who have had laser trabeculoplasty	None

Amendment 1

Section Changed	Initial Protocol 1.0 (Changed From)	Protocol version 2.0 (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Section 8.2.2. General Exclusion Criteria #17, 18, & 19		17. Has taken systemic corticosteroids at doses greater than 20 mg per day for oral prednisone (or equivalent for other corticosteroids) in the 2 weeks prior to Visit 2; subjects on 20 mg or less per day can be enrolled; decreases and termination of dose are allowable during the study 18. Is currently using prescribed nonsteroidal anti-inflammatory drugs (excluding over the counter use) unless the dose has been stable for at least 2 weeks prior to Visit 2, decreases and termination of dose are allowable during the study 19. Is currently using prescribed immunomodulatory therapies, unless the dose has been stable for at least 2 weeks prior to Visit 2; decreases and termination of dose are allowable during the study	To clarify that decreases or termination in doses of systemic corticosteroid, immunomodulatory and NSAID therapy are allowed during the study	None

Amendment 1

Section Changed	Initial Protocol 1.0 (Changed From)	Protocol version 2.0 (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Section 8.4. Visit Procedure Descriptions & Appendix A	All ocular assessments at Visit 1 and Visit 8 will be performed on both eyes. Data for ocular assessments at all other visits (Visits 2-7) will be collected on the study eye only. 5. Perform ophthalmic assessments on the study eye only: a. ETDRS BCVA b. Slit-lamp biomicroscopy a. IOP (Goldmann applanation tonometry) c. Dilated ophthalmoscopy d. SD-OCT and upload images to the CRC	All ocular assessments at Visit 1 and Visit 8 will be performed on both eyes. IOP will be collected in both eyes at all visits. All other ocular assessments at all other visits (Visits 2-7) will be collected on the study eye only. 5. Perform ophthalmic assessments on the study eye only, unless otherwise designated: a. ETDRS BCVA b. Slit-lamp biomicroscopy a. IOP (Goldmann applanation tonometry, both eyes) c. Dilated ophthalmoscopy d. SD-OCT and upload images to the CRC	To collect IOP data on the fellow eye at all visits for comparison to the study eye IOP	Additional risk common to IOP collection procedure
Section 8.4. Visit Procedure Descriptions	Slit-lamp biomicroscopy	Slit-lamp biomicroscopy, including dilated lens grading	To be consistent with the Time and Events Schedule (Appendix A)	None

Amendment 1

Section Changed	Initial Protocol 1.0 (Changed From)	Protocol version 2.0 (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
9.4.1. Rescue Criteria	A ≥ 1.5-step increase from baseline (Day 0) in the level of inflammation (eg, anterior chamber cells or vitreous haze) or an increase from 3+ to 4+	A ≥ 1.5-step increase from baseline (Day 0) in the level of inflammation (eg, anterior chamber cells or flare, or vitreous haze) or an increase from 3+ to 4+	To include anterior chamber flare as an example of a sign of inflammation	None
		A decrease of 10 or more ETDRS BCVA letters read from the best ETDRS BCVA data observed during the study, along with an increase in other signs or complications associated with the patient's uveitis	To ensure that any subjects who experience a substantial decrease in BCVA, along with worsening of uveitis, receive appropriate treatment	This additional criterion will ensure that study eyes are never undertreated
13. Statistical Considerations		Pharmacokinetic analyses to determine systemic levels of triamcinolone acetonide following suprachoroidal injection will be described in a separate detailed plan.	To include an analysis of the pharmacokinetic data collected	None

Amendment 1

Section Changed	Initial Protocol 1.0 (Changed From)	Protocol version 2.0 (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Section 2. Synopsis and Section 6.2. Secondary Objectives	The secondary objectives of the study are: • To assess changes to signs and complications of uveitis • To collect use information on the suprachoroidal injection procedure	The secondary objectives of the study are: • To assess changes to signs and complications of uveitis • To collect use information on the suprachoroidal injection procedure • To determine systemic exposure to triamcinolone acetonide after suprachoroidal injection	To include an objective for determining the systemic exposure to triamcinolone acetonide after suprachoroidal injection	None
Section 7.1 Overall Study Design, Section 7.2.3. Additional Endpoints, and Section 13.4.2.3. Additional Endpoints		• Triamcinolone acetonide blood concentrations prior to the first dose (Visit 2), 4 weeks following the first dose (Visit 3), 12 weeks following the first dose (and prior to the second dose, Visit 5) and at 12 weeks after the second dose (24 weeks, Visit 8)	To describe the timing of blood draws for collection of pharmacokinetic data from all subjects	None
Section 8.4. Visit Procedure Descriptions and Appendix A		Collect a blood sample for PK analysis; for Visit 2 and 5; blood must be collected PRIOR to dosing	To collect blood samples for pharmacokinetic data from all subjects	There is an additional risk common to blood draw procedures

Amendment 1

Section Changed	Initial Protocol 1.0 (Changed From)	Protocol version 2.0 (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
11.3. Pharmacokinetics Assessments		Blood samples for measurement of CLS-TA plasma concentrations will be collected by venipuncture by qualified study personnel. A single blood sample will be obtained from each subject at the following time points: Day 0 (Visit 2) pre-dose, Week 4 (Visit 3) any time during visit, Week 12 (Visit 5) pre-dose and Week 24 (Visit 8) any time during visit. Blood samples will be processed and shipped to a central lab as outlined in the manual of procedures for the study.	To describe the collection of blood samples for pharmacokinetic analysis	None
13.3.2. Pharmacokinetics Population		Pharmacokinetic population will include all subjects who are administered at least one dose of CLS-TA. Analysis will be conducted on all samples collected during the study.	To describe the population to be included in pharmacokinetic analysis	None

Amendment 1

Section Changed	Initial Protocol 1.0 (Changed From)	Protocol version 2.0 (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Section 13.4.3. Pharmacokinetics Analysis		Standard population PK parameters will be calculated from plasma CLS-TA concentrations. Samples from approximately 35 subjects enrolled in the study will be available for analysis. Analyses will be conducted according to the nonlinear mixed-effects approach and will provide estimates of population characteristics (intrinsic and extrinsic factors) that describe the population distribution of the PK parameters.	To describe the analysis of pharmacokinetic data	None
Section 12.1.9. Resting Heart Rate and Blood Pressure	Resting heart rate and resting blood pressure (systolic and diastolic, preferably on the same group each time) will be measured at every visit after the subject has rested for about 5 minutes.	Resting heart rate and resting blood pressure (systolic and diastolic, preferably on the same group each time) will be measured at Visits 1, 2, 5 and 8 after the subject has rested for about 5 minutes.	To clarify that resting heart rate and resting blood pressure should be measured at specified visits	None