Compound Name:	CLS-TA, triamcinolone acetonide injectable suspension
Protocol Number:	CLS1001-301
IND Number:	115683
NCT Number:	NCT02595398
Protocol Title	PEACHTREE: A Phase 3, Randomized, Masked, Controlled Clinical Trial to Study the Safety and Efficacy of Triamcinolone Acetonide Injectable Suspension (CLS-TA) for the Treatment of Subjects with Macular Edema associated with Non-Infectious Uveitis
Sponsor:	Clearside Biomedical, Inc. 900 North Point Parkway, Suite 200 Alpharetta, GA 30005
Issue Date: **Protocol Amendment 1 Date:** **Protocol Amendment 2 Date:** **Protocol Amendment 3 Date:**	25 August 2015 24 November 2015 22 July 2016 12 April 2017

Clinical Protocol CLS1001-301

Project:	1001
Compound Number/Name:	CLS-TA, triamcinolone acetonide injectable suspension
Protocol Number:	CLS1001-301
IND Number:	115683
Phase:	3
Protocol Title:	**PEACHTREE:** A **P**hase 3, Randomiz**E**d, M**A**sked, **C**ontrolled Clinical Trial to Study the Safety and Efficacy of Triamcinolone Acetonide Injectable Suspension (CLS-TA) for t**H**e **TR**eatment of Subjects with Macular **E**dema associated with Non-Infectious Uv**E**itis
Sponsor:	Clearside Biomedical, Inc. 900 North Point Parkway, Suite 200 Alpharetta, GA 30005
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Amendment #1 Issue Date:	24NOV2015

Jennifer Kissner, Ph.D. — 12 April 2017
Vice President, Clinical Development — Date
Clearside Biomedical, Inc.

CONFIDENTIAL

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Clinical Protocol CLS1001-301
Investigator Signature Page

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by the Sponsor, Clearside Biomedical, Inc. (Clearside).
- Not to implement any deviations from or changes to the protocol without agreement from the Sponsor and prior review and written approval from the Institutional Review Board / Ethics Committee (IRB/IEC), except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am thoroughly familiar with the appropriate use of the investigational drug(s), as described in this protocol and any other information provided by the Sponsor including, but not limited to the following: the current investigator's brochure or equivalent document provided by Clearside and approved product label, if applicable.
- That I am aware of, and will comply with, "good clinical practices" (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the investigational drug(s) and of their study-related duties and functions as described in the protocol.
- To periodic on-site monitoring of the case report forms (CRFs) and source documents by Clearside or designee and to on-site inspection of CRFs and source documents by appropriate regulatory authorities, including but not limited to the US Food and Drug Administration (FDA), local governing regulatory bodies, and IRB/IEC inspectors.
- That I have been informed that certain regulatory authorities require the Sponsor to obtain and supply details about the investigator's ownership interest in the Sponsor or study drug, and more generally about his/her financial ties with the Sponsor. Clearside will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply Clearside with any information regarding ownership interest and financial ties (including those of my spouse and dependent children);
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study; and
- Agree that Clearside may disclose this information about such ownership interests and financial ties to regulatory authorities.

Investigator Name (Print)	**Investigator Signature**	**Date**

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
BCVA	Best Corrected Visual Acuity
CRF	Case Report Form
CST	Central Subfield Thickness
EDC	Electronic Data Capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
EQ-5D	European Quality of Life 5-Dimensions
FA	Fluorescein Angiography
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Institutional Ethics Committee
IOP	Intraocular Pressure
IRB	Institutional Review Board
IND	Investigational New Drug
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IVT	Intravitreal
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Non-Steroidal Anti-Inflammatory Drug
OCT	Optical Coherence Tomography
PK	Pharmacokinetics
PP	Per Protocol
SAE	Serious Adverse Event
SCS	Suprachoroidal Space
SD-OCT	Spectral-Domain Optical Coherence Tomography
TA	Triamcinolone Acetonide
TEAEs	Treatment Emergent Adverse Events
VEGF	Vascular Endothelial Growth Factor
VFQ	Visual Function Questionnaire

1. INTRODUCTION

1.1. Disease Background

Clearside is developing drugs to treat unmet or underserved blinding eye diseases. Part of this drug development strategy involves a novel approach using suprachoroidal administration to deliver drugs in high bioavailability via this local treatment paradigm to precisely access specific areas of the eye. Clearside's developmental efforts have focused on uveitis where there is need for a locally administered medically beneficial therapy, which has the potential to provide a more encompassing and differentiating efficacious and safe treatment for patients. Based upon results from preclinical data in animal models of uveitis and from early clinical data in uveitis patients, the suprachoroidal approach for the treatment of uveitis is being developed to fulfill this unmet need.

Uveitis is a general term used to describe a set of ocular inflammatory diseases. The whole eye can be affected in uveitis or the inflammation may dominate in specific locations of the eye. Uveitis is therefore classified by anatomic location within the eye as being anterior-, intermediate-, posterior- or pan-uveitis (Nussenblatt 1985) according to the primary site of inflammation. Each of these categories, however, encompasses a number of conditions that can be characterized further along other dimensions. Uveitis can be described by temporal features based on the onset (sudden or insidious), the duration (limited or persistent) and the course (acute, recurrent or chronic); and according to its etiology, in terms of being infectious or noninfectious, with the latter subgroup comprising entities that are either autoimmune, traumatic, idiopathic, or masquerade conditions (neoplastic or drug-induced disorders mimicking uveitis).

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 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 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 macular edema (Lardenoye, 2006).

Macular edema, the major cause of visual loss in uveitis, is defined as abnormal thickening of the macula associated with the accumulation of fluid in the outer plexiform and the inner nuclear layers of the retina, and occasionally the intracellular spaces as a result of the breakdown of the blood-retinal barrier (Dick, 1994; Cho, 2009).

1.2. Scientific Rationale

Uveitis is commonly treated with corticosteroids and other immunomodulatory agents; such treatments are either systemic or local. Systemic treatments are most commonly intravenous or oral whereas local treatments are either topical drops, intra-ocular or peri-ocular injections or implants. If the uveitis dominantly affects the anterior segment, topical steroid drops may be

effective therapy. In almost all other cases, steroids for initial treatment are given orally while non-steroidal immunosuppressive treatments are administered intravenously. Depending on the specific kind of uveitis both steroid and other immunosuppressive therapy may be used at the same time. Higher oral steroid doses, 60-80 mg/day, used for initial treatment are then tapered to a maintenance dose of <10 mg/day for management of ongoing uveitis. Based both on the specific differential diagnosis and on investigator preference, treatments in clinical practice tend to vary, although guidelines for the use of both steroids and other immunosuppressive agents are available (Jabs, 2000).

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 that could result in glaucoma, progression of glaucoma, and to both the formation and the progression of cataracts (Karim, 2013).

Topical corticosteroids given as eye drops for anterior uveitis, have not shown that they are capable of reducing complications of uveitis such as macular edema in a consistent manner. Since macular edema is the leading cause of sight threatening blindness in uveitis, methods other than topical drops are usually used when macular edema, or other local complications persist in uveitis. Intravitreal injections of corticosteroids, or implantation of sustained corticosteroid delivery devices in or proximal to the vitreous can be used to administer therapeutic agents so that they are available to the posterior segment, provide local therapy, and reduce macular edema and other local uveitic complications (Ghate, 2007). While the intravitreal route of administration enables availability of the drug to the posterior segment, the procedure leads to significant exposure of the administered corticosteroid to anterior segment ocular structures. Similar issues plague periocular corticosteroid administration. Cataract formation, elevated intraocular pressure that can lead to glaucoma and worsening of pre-existing glaucoma are common adverse effects of periocular and intraocular administration of corticosteroid treatments.

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 clinical data and it has the potential for reducing the amount of drug dosed because of the high bioavailability of drug in the retina and choroid. 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.

1.3. Description of Investigational Product

CLS-TA, triamcinolone acetonide injectable suspension (CLS-TA), 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.

CLS-TA must be stored under ambient temperature conditions at ca. 20° - 25° C (68° - 77° F); do not freeze. CLS-TA should be protected from light by storing in the carton provided.

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

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

1.4. Summary of Clinical Experience and Justification for Route of Administration and Dose Selection

TA has been safely and effectively used in human ocular therapeutics to treat ocular conditions involving inflammation for over 50 years. The initial recommended dose of the TA formulation (Triesence®) approved by the FDA for ocular indications is 4 mg in 100 µL.

Clearside is developing CLS-TA, a proprietary TA formulation, for the treatment of non-infectious uveitis by administration to the SCS. 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.

The dose of CLS-TA, administered as a single suprachoroidal injection, will be 4 mg in 100 µL. Clearside has one completed and one ongoing clinical study of up to 4 mg TA administered suprachoroidally to subjects with non-infectious uveitis.

The completed clinical study, CLS1001-101, was a Phase 1/2, open-label, safety and tolerability study in subjects with intermediate-, posterior-, or pan- non-infectious uveitis. Each subject received a single suprachoroidal injection of 4 mg in 100 µL TA (Triesence). Nine (9) of the 11 subject 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 event (unrelated pulmonary emboli; SAE) occurred. No deaths were reported.

Approximately half of the reported AEs were ocular events. No significant increases in IOP were reported. Nine ocular AEs, in four subjects, were considered possibly related to TA. The most commonly reported AE, eye pain, was reported in 5 subjects. There were no serious adverse events (SAEs) reported as related to the study drug. No systemic AEs were reported as related to study drug.

The ongoing clinical study, CLS1001-201, is a Phase 2, randomized, masked safety and efficacy study in subjects with macular edema associated with non-infectious uveitis. Each subject will receive a single suprachoroidal injection of CLS-TA, 4 mg in 100 µL or 0.8 mg in 100 µL. As of 31JUL2015, 11 subjects have been enrolled into this study and 5 have completed the study. As of this date, fourteen AEs have been reported; 8 of the AEs in 4 subjects are ocular in nature and none have been reported as serious.

Additional information regarding clinical experience with TA administered to the SCS, is available in the Investigator's Brochure.

1.5. GCP Compliance

This clinical trial will be conducted in accordance with the principles of the Declaration of Helsinki, and in compliance with the International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP) guidelines and other applicable regulatory requirements. The Investigator and all clinical study staff will conduct the clinical study in compliance with the protocol. The Investigator will ensure that all personnel involved in the conduct of the study are

qualified to perform their assigned responsibilities through relevant education, training and experience.

1.6. Population to be Studied

The study population includes approximately 150 adult subjects to be enrolled at approximately 60 study sites. To participate in the study, subjects must be 18 years or older with macular edema associated with non-infectious uveitis of any etiology, and from among those with anterior-, intermediate-, posterior- or pan-uveitis. The expected duration of participation in the study is up to 27 weeks. The complete inclusion and exclusion criteria are presented below in Section 4.

2. TRIAL OBJECTIVES AND PURPOSE

The purpose of this study is to evaluate the safety and efficacy of suprachoroidally administered CLS-TA, triamcinolone acetonide injectable suspension, for the treatment of macular edema associated with non-infectious uveitis.

2.1. Primary Objective

The primary objective of the study is to demonstrate the efficacy of CLS-TA as shown by the change from baseline in BCVA in subjects with macular edema associated with non-infectious uveitis

2.2. Secondary Objective

- To determine mean change from baseline in central subfield thickness

2.3. Additional Objectives

- To determine systemic exposure to triamcinolone acetonide following suprachoroidal injection of CLS-TA
- To determine the change from baseline with respect to subject-reported outcomes

3. TRIAL DESIGN

3.1. Endpoints

3.1.1. Primary Endpoint

The primary endpoint is the proportion of subjects with a change from baseline of ≥ 15 letters in ETDRS BCVA at Visit 8 (24 weeks), subsequent to suprachoroidal injections of CLS-TA or sham injection procedures, in subjects with macular edema associated with non-infectious uveitis.

3.1.2. Secondary Endpoint

- Mean change from baseline in CST as measured by SD-OCT at 24 weeks (Visit 8)

3.1.3. Additional Endpoints

- Triamcinolone acetonide blood concentrations prior to each dose (Visit 2 and 5), 4 weeks following the first dose (Visit 3) and at 24 weeks (Visit 8)
- Change from baseline in subject reported outcomes as measured by the Visual Function Questionnaire, VFQ-25 and the EQ-5D questionnaire at Visit 8 (24 weeks)

3.1.4. Safety Endpoints

- Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), grouped by organ system, relatedness to study treatment and severity
- Percentage of subjects whose IOP increases are > 10 mmHg from their own baseline measurement at each follow-up visit (except Visit 2 & 5 [post-dose])
- Percentage of subjects whose IOP increases to a reading > 30 mmHg at each follow-up visit (except Visit 2 & 5 [post-dose])
- Percentage of subjects who require 1 or more additional IOP lowering medications at any follow-up visit (except Visit 2 & 5 [post-dose])

3.2. Description of Study and Duration of Participation

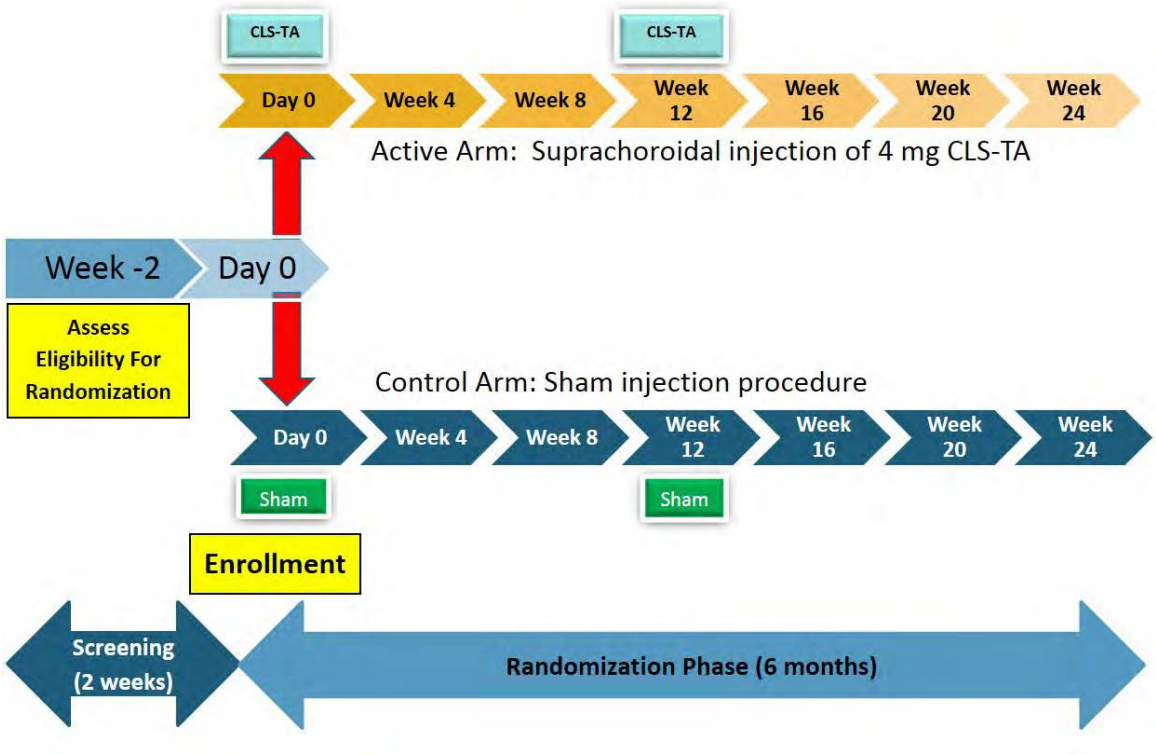
3.2.1. Description of Trial Design

This is a Phase 3, randomized, masked, sham-controlled, multicenter study to assess the safety and efficacy of 4 mg of CLS-TA administered via suprachoroidal injection compared to a sham injection procedure in the treatment of subjects with macular edema associated with non-infectious uveitis.

The study design includes 8 clinic visits over a maximum of 27 weeks. Subject eligibility will be established at Visit 1 during the screening process (Day -14 to -1). Eligible subjects will return to the clinic for Visit 2, Randomization (Day 0). Qualified subjects will be randomized to receive two unilateral suprachoroidal injections of CLS-TA administered to the study eye or two unilateral sham injection procedures administered to the study eye, approximately 12 weeks apart (Visit 2 and Visit 5). Follow-up visits will be conducted monthly up to 24 weeks (Visit 8).

Subjects will have a final evaluation conducted 24 weeks (Visit 8) following initial randomization. Approximately 25% of the subjects will be included in a pharmacokinetic evaluation for the study. Figure 1 below depicts the study overview:

Figure 1: Study Overview



3.2.2. Trial Treatments

Subjects will be randomized at Visit 2 to Active or Control arms in a 3:2 ratio.

Subjects randomized to the Active arm will receive unilateral suprachoroidal injections of 4 mg (100 µL of 40 mg/mL) CLS-TA at Day 0 (Visit 2) and Week 12 (Visit 5).

Subjects randomized to the Control arm will receive unilateral sham injection procedures in which no drug or vehicle will be administered, at Day 0 (Visit 2) and Week 12 (Visit 5). The sham injection procedure will mimic the active injection in order to maintain the subject's masking.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

4.1. Inclusion Criteria

Subjects 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 and from among those with anterior-, intermediate-, posterior- or pan-uveitis
2. Macular edema associated with non-infectious uveitis defined by:
    - A retinal thickness of ≥ 300 microns in the central subfield, with fluid as measured by SD-OCT (using the Heidelberg SPECTRALIS® or Zeiss Cirrus™) and confirmed by the Central Reading Center
3. ETDRS BCVA score of ≥ 5 letters read (20/800 Snellen equivalent) and ≤ 70 letters read (20/40 Snellen equivalent) in the study eye
4. 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
5. At least 18 years of age

4.2. Exclusion Criteria

4.2.1. Ophthalmic Exclusion Criteria

Subjects are 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. Has macular edema with etiology other than uveitis
3. Any active ocular disease or infection in the study eye other than uveitis
4. 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
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 or filtration surgeries 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 intravitreal injection of anti-VEGF 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

4.2.2. General Exclusion Criteria

Subjects 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 (e.g., 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
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 if no increase in dosing is anticipated for the duration of the study; 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, and no increase in dosing is anticipated for the study duration; 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, and no increase in dosing is anticipated for the study duration; decreases and termination of dose are allowable during the study

20. Has taken any fingolimod or any other drug in the 6 weeks prior to Visit 2, where the drug is known to induce macular edema

4.3. Subject Discontinuation/Withdrawal from Clinical Study

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 discontinue for any reason will not be replaced and their subject numbers will not be reassigned or re-used.

If a subject withdraws from the study or if the Investigator removes a subject from the study, the Investigator should make every attempt to complete all Visit 8 assessments (Section 5.1.10.). If an SAE is unresolved at the time of the subject's final study visit, 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. If at any time during the study a subject is considered at immediate risk for a vision-threatening event due to study participation, the subject should be treated as soon as necessary, with the investigator determining appropriate care or additional therapy (Section 6.2.2.). Subjects should not be discontinued from the study due to additional therapy or due to an AE unless the Investigator determines it to be in the subject's best interest.

4.3.1. Discontinuation of the Clinical Study

The study or parts of the study may be discontinued by the Sponsor or at the recommendation of an Investigator after consultation with Sponsor, at any time. This may be based on a significant number of AEs of a similar nature that warrant such action or at the request of the Sponsor.

If the clinical study is prematurely terminated or suspended, the Sponsor will inform the Investigators and the regulatory authorities of the termination/suspension and the reason(s) for the termination/suspension. The Investigator should promptly notify the IEC/IRB of the termination or suspension and of the reasons.

4.3.2. Discontinuation of a Clinical Study Site

The Sponsor reserves the right to close the investigational site, or terminate the study in its entirety at any time, for reasonable cause. Reasons for the closure of any investigational site or termination of a study may include:

- Failure of the Investigator to accrue subjects into the study at an acceptable rate
- Failure of the Investigator to comply with applicable regulations and GCPs
- Submission of knowingly false information from the research facility to the sponsor, FDA, or other regulatory authorities
- Insufficient adherence to protocol requirements and procedures

If the study is prematurely discontinued, all study data must be returned to the Sponsor. Additionally, the site must conduct final disposition of all unused study drugs in accordance with Sponsor procedures. Study termination and follow-up will be performed in compliance with the conditions set forth in regulatory guidelines.

5. PROCEDURES

5.1. Visit Description

5.1.1. General Procedures

The study will consist of up to 8 study visits over a maximum of 27 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 performed on the study eye only. Subjects will be screened for entry (Visit 1) and then return to the clinic within 14 days to be randomized/treated (Visit 2). At randomization, subjects will receive either a single, unilateral, suprachoroidal injection of 4 mg/100 µL CLS-TA or a single, unilateral sham injection procedure in the study eye. Subjects will be assessed post injection for safety. Additional safety follow-up visits will occur monthly for 24 weeks. Subjects will receive a second injection of either 4 mg/100 µL CLS-TA or a sham injection procedure at Visit 5 (Week 12) based on their original randomization at Visit 2. The final study visit will occur at Visit 8 (Week 24).

5.1.2. Re-screening Procedures

A subject who is first designated as a screen failure prior to being randomized may be rescreened up to 2 additional times, for a total of three screenings, upon Sponsor approval. Subjects who are re-screened are required to sign a new consent form.

5.1.3. Visit 1 – Screening (Day -14 to -1)

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:

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 FA, including serum pregnancy test on females of childbearing potential
7. Perform ophthalmic assessments on both eyes:
    a. ETDRS BCVA
    b. Slit-lamp biomicroscopy, including dilated lens grading
    c. IOP
    d. Dilated indirect ophthalmoscopy
    e. Fundus photography

f. SD-OCT

g. FA

8. Perform a review of systems
9. Verify subject eligibility based on Inclusion/Exclusion requirements
10. Determine study eye based upon eye specific eligibility criteria
11. Schedule subject to return for Visit 2, Randomization/Treatment

NOTE: All images (SD-OCT, fundus photographs and FA) should be uploaded to the Central Reading Center. It will take approximately 2 business days for the Central Reading Center to confirm eligibility and the Central Laboratory report to arrive. Allow sufficient time between Visit 1 and Visit 2 in order to confirm eligibility through the Central Reading Center and Central Laboratory reports.

5.1.4. Visit 2 – Randomization/Treatment (Day 0)

Visit 2 must occur within 14 days of Visit 1 (Screening) and may only occur once a subject qualifies for randomization, which includes central lab results being received and reviewed and confirmation of qualification by the Central Reading Center.

Once eligibility is confirmed, subjects will be randomized via the IRT to receive a single, unilateral, suprachoroidal injection of CLS-TA (4 mg/100 µL) or a single, unilateral sham injection procedure. Once randomized, subjects will receive an additional single, unilateral suprachoroidal injection of CLS-TA (4 mg/100 µL) or a single, unilateral sham injection procedure approximately 12 weeks later (Visit 5). Subjects will remain in the same treatment arm for the duration of participation in the study.

The following procedures will be performed:

5.1.4.1. Pre-Injection Procedures

The following must be performed prior to the injection (the same day as the injection):

1. Assess for AEs
2. Review changes to concomitant medications
3. Review central lab results for any clinically significant abnormalities that would exclude the subject from entry
4. Review the results received from the Central Reading Center to confirm that subject qualifies based on CST
5. Review eligibility based on Inclusion/Exclusion criteria
6. Measure resting heart rate and blood pressure
7. Perform ophthalmic assessments on the study eye only, unless otherwise designated:
    a. ETDRS BCVA
    b. Slit-lamp biomicroscopy, including dilated lens grading

c. IOP (both eyes)

d. Dilated ophthalmoscopy

e. SD-OCT and upload images to the Central Reading Center

8. Administer VFQ-25 and EQ-5D
9. Collect a blood sample from those subjects participating in the PK procedure; blood must be collected PRIOR to dosing
10. Log onto the IRT system and randomize subject

5.1.4.2. Injection Procedure and Immediate Post-Injection Assessments

Injection should be performed the same day as the pre-injection procedures. For details on the injection procedure, please see the Manual of Procedures. The injecting physician and supporting study staff who are present during the injection are unmasked on a per subject basis. Unmasked personnel should not perform assessments for that subject at Visits 3,4,6,7 and 8. Unmasked personnel may also perform pre- and post-injection assessments, except BCVA, at Treatment visits (Visits 2 and 5) if masked staff are not available.

1. Confirm study eye
2. Retrieve study drug kit number assigned by IRT
3. Prepare eye for injection per the investigator's standard practice
4. The UNMASKED injecting investigator should administer suprachoroidal injection of CLS-TA or perform the sham injection procedure to the study eye; see Manual of Procedures for detailed instructions
5. Immediately following the injection, assess study eye by indirect ophthalmoscopy

5.1.4.3. 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 10 - 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. Schedule subject to return for next visit

5.1.5. Visit 3 – Week 4 Post Randomization Follow-Up (Day 28 ±5)

Visit 3 will occur approximately 4 weeks post randomization. The visit should be 28 ±5 days from Visit 2. The following Visit 3 procedures will be performed by masked study staff:

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 (both eyes)
    d. Dilated indirect ophthalmoscopy
    e. SD-OCT and upload images to the Central Reading Center
4. Collect a blood sample from those subjects participating in the PK procedure
5. Schedule subject to return for next visit

5.1.6. Visit 4 – Week 8 Post Randomization Follow-up Visit (Day 56 ±5)

Visit 4 will occur approximately 8 weeks post randomization. The visit should be 56 ± 5 days from Visit 2. The following Visit 4 procedures will be performed by masked 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 (both eyes)
    d. Dilated indirect ophthalmoscopy
    e. SD-OCT and upload images to the Central Reading Center
4. Schedule subject to return for next visit

5.1.7. Visit 5 – Week 12 – TREATMENT VISIT 2 (Day 84 ±5)

Visit 5 will occur approximately 12 weeks post randomization. At Visit 5, subjects will receive their second, single, unilateral study drug treatment. The randomization arm initially assigned to a subject will remain the same throughout the study. The treatment must be administered by an UNMASKED injecting physician only.

5.1.7.1. Pre-Injection Procedures

The following must be performed prior to the injection (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 (both eyes)
    d. Dilated indirect ophthalmoscopy
    e. SD-OCT and upload images to the Central Reading Center
6. Collect a blood sample from those subjects participating in the PK procedure; blood draw must be collected PRIOR to dosing

5.1.7.2. Injection Procedure and Immediate Post-Injection Assessments

For details on the injection procedure, please see the Manual of Procedures. The Visit 5 injection procedure should be identical to the Visit 2 injection procedure.

1. Confirm study eye
2. Retrieve study drug kit number assigned by IRT
3. Prepare eye for injection per the investigator's standard practice
4. The UNMASKED injecting investigator should administer a suprachoroidal injection of CLS-TA or perform the sham injection procedure in the study eye; see Manual of Procedures for detailed instructions
5. Immediately following the injection, assess study eye by indirect ophthalmoscopy

5.1.7.3. 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 10 - 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. Schedule subject to return for next visit

5.1.8. Visit 6 – Week 16 Post Randomization Follow-up Visit (Day 112 ±5)

Visit 6 will occur approximately 16 weeks post randomization. The visit should be 112 ± 5 days from Visit 2. The following Visit 6 procedures will be performed by masked 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 (both eyes)
    d. Dilated indirect ophthalmoscopy
    e. SD-OCT and upload images to the Central Reading Center
4. Schedule subject to return for next visit

5.1.9. Visit 7 – Week 20 Post Randomization Follow-up Visit (Day 140 ±5)

Visit 7 will occur approximately 20 weeks post randomization. The visit should be 140 ± 5 days from Visit 2. The following Visit 7 procedures will be performed by masked 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 (both eyes)
    d. Dilated indirect ophthalmoscopy
    e. SD-OCT and upload images to the Central Reading Center
4. Schedule subject to return for next visit

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

Visit 8 will occur approximately 24 weeks post randomization. The visit should be 168 ± 5 days from Visit 2 or at the time of early termination. The following Visit 8 procedures will be performed by masked 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 from those subjects participating in the PK procedure
6. Perform a review of systems
7. Administer VFQ-25 & EQ-5D
8. Perform ophthalmic assessments on both eyes:
    a. ETDRS BCVA
    b. Slit-lamp biomicroscopy, including dilated lens grading
    c. IOP
    d. Dilated indirect ophthalmoscopy
    e. Fundus photography and upload images to the Central Reading Center
    f. SD-OCT and upload images to the Central Reading Center
    g. FA and upload images to the Central Reading Center

5.1.11. Unscheduled Visit

To ensure subject safety during the trial, any subject who requires additional follow-up during the study for any reason should see the Investigator, even if such a visit does not fall within a scheduled study visit. The masked investigator/staff should complete assessments for an unscheduled visit whenever possible.

Any visit that occurs between the regularly scheduled visits must be documented in the Unscheduled Visit pages of the Electronic Case Report Form (eCRF). If the patient is discontinuing at the Unscheduled Visit, the procedures for Visit 8 (Week 24) should be completed as described in Section 4.3 and captured on the Visit 8 eCRFs, not on the eCRFs for an Unscheduled Visit.

6. TREATMENT OF SUBJECTS

6.1. Treatments to be Administered

Treatment will consist of two unilateral suprachoroidal injections of 4 mg of CLS-TA in 100 µL, or two sham injection procedures, administered 12 weeks apart, according to the randomization assignment.

Subjects will be randomized to either of the following groups:

1. Active: 4 mg CLS-TA, triamcinolone acetonide injectable suspension, 40 mg/mL in 100 µL
2. Control: sham injection procedure

Approximately 150 subjects will be randomized in a 3:2 ratio where approximately 90 subjects will be randomized to the Active arm and approximately 60 subjects will be randomized to the Control arm. The CLS-TA injections, or sham injection procedures, occur at Visit 2 (Day 0) and at Visit 5 (Day 84 ± 5).

The study drug kits will be supplied to the site. Each subject will be randomized to a study arm and be assigned a study drug kit at both Visit 2 (Day 0) and again at Visit 5 (Week 12). Each kit will be identical (either two active kits or two sham kits). Each kit will contain the following components:

Active Kit:

- Vial of CLS-TA (40 mg/mL)
- Clearside microinjector
- Vial access device (for drug transfer)
- 900 µm needle
- 1100 µm needle

Sham Kit:

- Vial of CLS-TA (40 mg/mL)
- Clearside microinjector
- Vial access device (for drug transfer)
- Sham hub

All study drug 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 study drug injection procedure can be found in the Manual of Procedures.

6.1.1. Study Eye Determination

The study eye will be the eye receiving the CLS-TA injection or the sham injection procedure depending upon the group to which the subject is randomized. The determination of the study eye will be based on Visit 1 (screening) information only.

If both eyes meet study criteria, then the eye, in the Investigator's opinion, with the better chance of achieving an improvement in BCVA should be used as the study eye. If both eyes qualify for the study, and appear similar in their chance of improvement, 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.

6.1.2. Treatment of the Fellow Eye (Non-Study Eye)

Subjects may have bilateral disease, but only one study eye may be enrolled.

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. Local medications are permitted for the fellow eye during the course of this trial. Medications used in the fellow eye will be recorded in the subject's medical chart and the case report form (CRF).

6.2. Concomitant Medications

6.2.1. Prohibited 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:

- Increases to topical ophthalmic NSAIDs in the study eye
- Any corticosteroid implant (ie, Ozurdex®, Iluvien® or Retisert®) in the study eye
- Topical, periocular or intravitreal corticosteroids in the study eye
- Increases in dose of systemic prednisone or other equivalent steroid (eg, dexamethasone), including, but not limited to, the following routes: oral, intravenous, intramuscular, in sufficient doses and/or for sufficient time such that the Investigator has concerns about additional ocular exposure to steroids in terms of safety and/or efficacy
- Anti-angiogenic drugs (anti-VEGF) in the study eye or systemically (including pegaptanib sodium, bevacizumab, ranibizumab, aflibercept)
- Increases to dose of systemic immunosuppressant drugs
- Fingolimod or any other drug known to induce ME
- Acetazolamide (Diamox®)
- 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.

6.2.2. 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.

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 should 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 microns 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 vitreous haze) or an increase from 3+ to 4+
- In the investigator's medical judgement, the uveitic complications in the study eye have not improved and the condition needs to be addressed

6.3. Treatment Compliance

Study drug will only be administered by trained study investigators (principal investigator or sub-investigator) in the office at Visit 2 and at Visit 5. The injecting physician will be unmasked per patient. No study drug will be dispensed to subjects; therefore, subject treatment compliance is not applicable.

The date and time of the injection will be recorded in the subject's medical chart and the CRF. All needles used and the needle length used for injection will also be recorded. All study drug kits (and all the components of each of the kits, such as the vial, the microinjector, etc.) will remain under the control of the study site staff at all times. Following injection, used microinjectors should be disposed of properly but used vials of study drug should be capped and maintained in the original box until accountability has been completed by the unmasked monitor.

6.4. Drug Accountability

Accountability of study drug kits will be conducted by an unmasked member of the site and verified by an unmasked monitor. Accountability will be ascertained by performing reconciliation between the number of study drug cartons (kits and their components) sent to the

site, and the number used and unused at the time of reconciliation. Unmasked site staff will be queried about any discrepancies.

Study drug shipment records will be verified and accountability performed by comparing the shipment inventory sheet to the actual quantity of drug and microinjectors received at the site. In addition, receipt of study drug cartons will be confirmed via the IRT. Accurate records of receipt and disposition of the study drug and microinjectors (eg, dates, quantity, subject number, kits used, kits unused, etc.) must be maintained by the unmasked investigator or his/her designee. Study drug will be stored ambient at 20 – 25° C (68 – 77° F) and this area should have limited, controlled access with temperature monitoring.

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

6.5. Masking / Unmasking

Subject randomization assignment will be protected using a masked allocation schedule created by a clinical allocation schedule system. Emergency unmasking of subjects by authorized clinical site personnel will occur via IRT according to procedures outlined in the Manual of Operations provided to the sites by the Sponsor. The Investigator should not unmask the subject's randomization assignment without the Sponsor's approval unless immediately required in response to a serious adverse event. If the Sponsor was not notified prior to the unmasking event, the Investigator must immediately contact the Sponsor informing them as to the specific details of the occurrence. The Sponsor personnel involved in the collection, interpretation, analysis, review, or any decisions stemming from the study data will remain masked as to subject status for the duration of the study unless otherwise warranted.

To maintain masking and minimize bias by the Investigator, sub-Investigator, all designated readers and graders, the subject, the Sponsor and monitors involved in reporting, obtaining and/or reviewing the clinical evaluations for a particular subject will not be aware of the specific randomization assignment for that subject. Only study staff who are designated by the Investigator to prepare and administer study drug and conduct test article accountability may know the randomization assignment. Both the masked or unmasked Investigator and staff may participate in evaluations conducted during the screening visit. The unmasked Investigator may participate in pre- and post-injection ophthalmic exams, except BCVA, at treatment visits (Visit 2 and 5). Otherwise unmasked personnel will not be involved in a subject's evaluations or assessments. Designee(s) will not discuss the test article with other site personnel or the Sponsor monitors and will instruct patients to not discuss the study drug or appearance of the packaging with the Investigator, sub-Investigator(s) or any other study staff while the study is ongoing. This level of masking will be maintained throughout the conduct of the study.

The external packaging for the test article and sham control will be identical.

The PK vendor analyzing samples will be unmasked to subject randomization codes and demographics in order to evaluate exposure levels. During the conduct of the study, Sponsor

staff working directly on the study will not have access to individually identifiable PK analysis data.

If masking is compromised, any masked personnel who become unmasked will not conduct any further masked clinical evaluations with the subject whose treatment has been unmasked. The investigational site will notify the IRB and Sponsor/designee; follow-up training will be required.

7. ASSESSMENTS OF EFFICACY

7.1. Best Corrected Visual Acuity (BCVA)

Best Corrected Visual Acuity (BCVA) will be measured using ETDRS electronic visual acuity (eVA). BCVA will be recorded as total letter score in each eye 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.

If eVA cannot be performed for any reason, BCVA will be measured using a standard ETDRS wall chart. If Roman letters are not familiar to the subject, Tumbling E charts may be used.

7.2. Central Subfield Thickness as Measured by SD-OCT

Retinal thickness and disease characterization will be assessed via spectral domain optical coherence tomography (SD-OCT) (Heidelberg SPECTRALIS® or Zeiss Cirrus™). The SD-OCT instrument and technician must be certified prior to screening any subjects. The technician is encouraged to use the same certified photography equipment throughout the subject's study participation. All photos should be taken by the same photographer, whenever possible, on each subject per research site. Images will be sent to a central reading facility for analysis and interpretation in a masked fashion.

7.3. Visual Function Questionnaire (VFQ-25)

The VFQ-25 [25] consists of a base set of twenty-five vision-targeted questions representing eleven vision-related constructs, plus an additional single-item general health rating question. The VFQ-25 takes approximately 10 minutes on average to administer in the interviewer format. A trained technician will administer this questionnaire to the subject.

7.4. EQ-5D

EQ-5D is a standardized measure of health status developed to provide a simple, generic measure of health for clinical and economic appraisal. EQ-5D is designed for self-completion by respondents. It is cognitively undemanding, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire. Subjects unable to read may have the EQ-5D read to them.

7.5. Pharmacokinetics Assessments

Approximately 25% of subjects will be enrolled in the pharmacokinetic portion of the study from select sites. Blood samples for measurement of CLS-TA plasma concentrations will be collected from those subjects who consent at participating sites, by venipuncture by qualified study personnel. A single blood sample will be obtained from each subject at the following time points: Day 0 (pre-dose), Week 4 visit (any time during visit), Week 12 visit (pre-dose) and Week 24 visit (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.

8. ASSESSMENTS OF SAFETY

8.1. Intraocular Pressure

Intraocular pressure (IOP) will be measured by applanation tonometery and results will be recorded in mmHg. Where available, Goldmann applanation tonometry should be used at all visits. Tonopens may be used for post-injection pressure checks and in cases where no Goldmann is available. A single measurement will be made at approximately the same time of day. The technician is encouraged to use the same tonometry method for all pre-injection and non-injection measurements 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.

8.2. 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.

8.2.1 Cataract Lens Grading

If an abnormal finding of cataract is noted for the lens during the slit-lamp exam, the cataract should be assessed for nuclear opalescence, cortical opacity and posterior subcapsular opacity. Graders must verify training on the grading procedure provided in the Manual of Procedures.

8.2.2 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 1 (SUN 2005).

Table 1: 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

8.2.3 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 2 (SUN 2005).

Table 2: 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)

8.3. Dilated Ophthalmoscopy

A dilated fundus examination will include an assessment of each of the following as normal or abnormal: vitreous, retina, macula, choroid and optic nerve. All abnormal findings will be described.

8.3.1 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 3 (Nussenblatt 1985 as modified in Lowder 2011).

Table 3: 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

8.4. Fluorescein Angiography

Fluorescein angiography (FA) images will be performed to examine the circulation of the retina. Study personnel who perform FA will be trained and certified by the central reading center prior to screening any subjects. Images will be sent to a central reading facility.

8.5. Fundus Photography

Fundus photographs will be collected to assess the disease and anatomical characteristics of the retina. Study personnel who perform FA will be trained and certified by the central reading center prior to screening any subjects. Images will be sent to a central reading facility.

8.6. Review of 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.

8.7. Clinical laboratory tests

Non-fasting blood and urine samples will be collected during the study. Samples will be sent to a central lab for analysis. Analytes to be evaluated are listed in Table 4.

Table 4: Clinical Laboratory Analytes to be Tested

Chemistry (serum)	Alanine amino transferase; serum albumin; alkaline phosphatase; aspartate amino transferase; bilirubin, direct and total; total serum calcium; total carbon dioxide; serum chloride; total creatine kinase; serum creatinine; gamma glutamyl transaminase; glucose; lactate dehydrogenase; serum potassium; total serum protein; serum sodium; total cholesterol; triglycerides; urea
Hematology	CBC including: hemoglobin (Hgb), platelet count (PLT), red blood cell (RBC), white blood cell (WBC) and hematocrit (Hct); WBC differentials of: basophils; eosinophils, lymphocytes, monocytes and total neutrophils
Urinalysis (Macro)	Bilirubin; blood; glucose; ketone; protein; specific gravity; pH
Pregnancy (serum)[a] [a]Women of childbearing potential at screening and study exit only	β-human chorionic gonadotropin (βHCG)

8.8. Vital signs

Resting heart rate and resting blood pressure (systolic and diastolic, preferably on the same arm each time) will be measured at Visits 1, 2, 5 and 8.

8.9. Evaluation of Adverse Events

Adverse events will be monitored continuously during the study beginning at the time of the subject's signing of the informed consent. Subjects will be instructed to report all AEs during the study. Subjects will be assessed for the occurrence of AEs at each visit. Thus, AEs may be reported by the subject, discovered by the study staff questioning or detected through study assessments. All AEs (serious and non-serious) must be recorded on the source documents and AE CRFs, regardless of the assumed causal relationship with the test article. The following information about each AE will be collected: severity, onset and resolution dates, frequency, seriousness, relationship to study treatment, action taken and outcome.

8.9.1. Definitions

An **adverse event (AE)** is any untoward medical occurrence associated with the use of a drug in humans and does not have to have a causal relationship with study treatment.

An AE can therefore be any unfavorable and unintended sign (that could include a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Whenever possible, the Investigator should group signs or symptoms that constitute a single diagnosis under a single AE term (eg, "cough, rhinitis and sneezing" might be grouped together as "upper respiratory tract infection").

An AE may include:

- Any sign, medical diagnosis or symptom
- Any new undesirable medical occurrence or unfavorable or unintended change of a pre-existing condition that occurs during or after test article administration.

  NOTE:

  - The disease under study (ie, non-infectious uveitis) or sign or symptom associated with the disease are not considered adverse events unless more severe than expected for the subject's condition
  - Symptoms associated with disease, which are consistent with the subject's usual clinical course are not considered adverse events, unless the subject experiences worsening of symptoms more severe than expected or unless the symptom(s) meet the criteria for an SAE
- Clinically significant (as determined by the Investigator) laboratory abnormalities, ophthalmic assessments or vital signs (eg, requiring discontinuation of test article, specific treatment or a change in subject management). If possible, abnormal laboratory results or changes in vital signs that meet the definition of an AE should be reported as a clinical diagnosis rather than the abnormal laboratory value (eg, "hypertension" rather than "blood pressure increased")

All baseline conditions and AEs identified during the clinical study from the time the subject signs the informed consent, through the subject's last day of study participation, will be documented on the appropriate CRF. Special considerations include:

- Baseline conditions are not considered adverse events unless the condition worsens following study drug administration
- Elective procedures or routinely scheduled treatments are not considered AEs; however, an untoward medical event occurring during the pre-scheduled elective procedure should be recorded as an AE
- Changes in pre-existing medical conditions, including changes in severity, frequency or character, during the protocol-defined reporting period should be recorded as AEs

- Overdose of either study drug or concurrent medication without any signs or symptoms is not considered adverse events
- Death itself is not considered an AE; it is instead the outcome of an AE
- Pregnancy is not considered an AE. Reports of pregnancy will be reported to the Sponsor in accordance with Section 8.9.4

A **treatment-emergent AE (TEAE)** is any AE temporally associated with the use of the study drug, whether or not considered causally related to the study drug that occurs after the subject receives the first dose of study drug.

A **serious adverse event (SAE)** includes any event, if in the view of either the Investigator or the Sponsor, results in any of the following outcomes.

- Death
- Life-threatening (ie, if in the view of the Investigator or Sponsor, the event's occurrence places the subject at immediate risk of death); it does not include an AE that, had it occurred in a more severe form, might have caused death
- In-patient hospitalization or prolongation of existing hospitalization
    - "In-patient" hospitalization means the subject has been formally admitted to a hospital for medical reasons. This may or may not be overnight. It does not include presentation at a casualty or emergency room.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly in the offspring of a subject who received study drug
- Important medical events that may not result in death, be life-threatening or require hospitalization may be considered an SAE 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 in this definition
    - Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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 a serious AE.

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity 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

C**ausality** is the relationship of an AE to study drug and will be assessed by the investigator as follows in Table 5:

Table 5: Causality Definitions

Causality	Definition
Related	There is a reasonable causal association with administration of the study drug; the event is confirmed by stopping and/or restarting the drug or is not explained by any other reasonable hypothesis
Not related	There is no causal or temporal relationship to the study drug; related to other etiologies such as concomitant medications or conditions

8.9.2. Adverse Event Reporting Procedures

The Investigator will assess subjects for the occurrence of AEs at all scheduled and unscheduled visits. The occurrence of AEs should be sought by non-direct questioning of the subject at each visit. At each study visit, study personnel should ask the following question: “Have you had any problems since your last visit?" Adverse events may also be detected when they are volunteered by the subject during and between visits or through study assessments. All AEs (serious or non-serious) reported by the subject will be reviewed by a qualified physician participating as an investigator in the study and must be recorded on the source documentation and AE CRF provided.

8.9.3. Prompt Reporting of SAEs to the Sponsor

An adverse event that is serious must be reported on an SAE form to the Sponsor immediately, but no later than 24 hours after the investigator becomes aware of the event.

Prompt reporting of a SAE requires:

- Completion and transmission of SAE information to the Sponsor within 24 hours of the investigator's knowledge of the event. The SAE information should be completed as thoroughly as possible before transmittal to the Sponsor. **It is very important that the investigator provide his/her assessment of causality to study treatment at the time of initial reporting of the SAE.**
- Prompt reporting of additional information for previously reported SAEs should follow the same reporting timeframe as initial reports.

If an ongoing SAE changes in intensity or the relationship to study drug, a follow-up SAE report should be sent to the Sponsor within 24 hours after the clinical site becomes aware of the change in status.

8.9.4. Pregnancy Reporting

Pregnancy alone is not an AE. However, any report of pregnancy during a female subject's participation in the study must be promptly reported to the Sponsor as soon as the Investigator is notified, using a Pregnancy Report Form.

The Sponsor should be notified of any updates on the status of the pregnancy as soon as the information becomes available and the site will complete the Pregnancy Follow-up Form.

8.9.5. Transmission of SAE Reports and Pregnancy Forms

SAE reporting information and pregnancy reporting information should be transmitted to the Sponsor via email or fax as provided below.

Chiltern, Inc.
GlobalSAEInbox@chiltern.com
Toll free fax US: 888-726-8416
Toll free fax India: 91-2266-459-811

Please refer to the study reference binder for complete contact information. Contact the Medical Monitor with any questions regarding a potential SAE.

8.9.6. Regulatory Reporting Requirements for SAEs

The Sponsor will determine which SAEs qualify for expedited reporting. Reports of those SAEs that qualify for expedited reporting will be unmasked for the individual subject and submitted to regulatory agencies in accordance with applicable local regulation. Expedited reports will also be distributed to Investigators without revealing the treatment assignment and will be submitted to IRB/IEC in accordance with institutional guidelines and local regulation.

8.9.7. 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.

9. STATISTICAL CONSIDERATIONS

A detailed statistical analysis plan will be prepared for this study. The plan will contain a discussion of the statistical methods, a description of the computational algorithms and data handling conventions, and specifications for the data summaries and listings. It will be finalized before database lock.

9.1. Randomization

There will be approximately 150 subjects randomized at a 3:2 ratio to the two treatment arms. Assignment of subjects to treatment arms will be performed via IRT.

9.2. Determination of Sample Size and Level of Significance

The sample size of approximately 150 subjects at approximately 50 centers was based on clinical considerations appropriate for a randomized Phase 3 study.

With a total sample size of 150 subjects in a 3:2 randomization this study will have 90% power to detect a difference between treatments if the actual proportion of subjects showing improvement of 15 letters or more is 0.60 for the treated group and 0.34 in the sham group.

Power analyses were conducted based on an assumption of the proportion of subjects gaining 15 or more letters in the CLS-TA treated arm to be 0.6 while those in the untreated (sham) arm gaining 15 or more letters to be 0.13. Calculations for power based on lower confidence limit used the observed result for the treated group and subtracted the lower confidence interval for the difference (0.2636) from that difference to estimate the sham result (0.3364).

Power analysis assumes that the parameter estimates are based on population values not sample results. An observed sample result is expected to overestimate population differences 50% of the time. By using a lower confidence interval estimate can be used to mitigate the risk that the sample estimate was larger than the population value. In this case, a lower 90% one sided confidence interval the difference in proportions was used to calculate an offset from the observed result that would be the lowest likely population estimate. The offset was added to the estimate for the control group to create conservative estimates. The conservative power calculations were performed based on the conservative estimates.

9.3. Subject Disposition, Demographic and Baseline Characteristics

Subject disposition, demographic, and baseline characteristics will be summarized descriptively by treatment group and overall.

9.4. Analysis Populations

9.4.1 Safety Population

Safety population will include all randomized subjects who are administered at least one dose of the study drug. All safety analyses will be based on safety population.

9.4.2 Intent-to-Treat Population

Intent-to-treat (ITT) population includes all randomized subjects who have received at least one study treatment. Subjects will be analyzed as originally allocated after randomization. ITT population will be used for efficacy analyses.

9.4.3 Per Protocol Population

Per-protocol (PP) population will include all subjects in the ITT population who do not have significant protocol deviations and who complete the 24 week visit. The rules for determining exclusions from the PP population will be finalized after a clinical review of the data and queries have been resolved but before unmasking treatment assignments.

9.4.4 Pharmacokinetic Population

Pharmacokinetic population will include all subjects in the pharmacokinetic portion of the study that provided blood samples for triamcinolone acetonide concentration analysis.

9.5. Analysis Methods

Efficacy and safety endpoints are provided in Section 3.1.

9.5.1. Primary Efficacy Analysis

The primary endpoint is the proportion of subjects with a change from baseline of ≥ 15 letters in ETDRS BCVA at Visit 8 (24 weeks), subsequent to suprachoroidal injections of CLS-TA or sham injection procedures, in subjects with macular edema associated with non-infectious uveitis.

A Cochran-Mantel-Haenszel test will be used to test differences in the proportion of subjects in the two groups who show 15 or more letters improvement in BCVA at the week 24 visit after adjusting for center effects.

The formal hypothesis is:

H_0: All $OR_{site}=1$ H_1: $OR_{site} \neq 1$

Where OR_{site} is the odds ratio adjusting for site

Missing data imputed by LOCF in the ITT population will be used for the primary efficacy analysis. Observed data in the PP population will be used for sensitivity analysis. See Section 9.5.8 for a description of the imputations for missing data.

9.5.2. Secondary Efficacy Analysis

9.5.2.1. Secondary Efficacy Endpoint

- Mean change from baseline in CST as measured by SD-OCT at 24 weeks (Visit 8)

9.5.2.2. Additional Endpoints

- Triamcinolone acetonide blood concentrations prior to each dose (Visit 2 and 5), 4 weeks following the first dose (Visit 3) and at 24 weeks (Visit 8)
- Change from baseline in subject reported outcomes as measured by the Visual Function Questionnaire (VFQ-25) and EQ-5D questionnaire at 24 weeks

9.5.3. Subgroup Analysis

No subgroup analyses are planned.

9.5.4. Pharmacokinetic Analysis

Standard population PK parameters will be calculated from plasma CLS-TA concentrations. To characterize the population PK of CLS-TA, PK parameters will be related to treatment arm. Samples from approximately 20 subjects in the Active arm will be available for analysis. Analysis will be conducted according to the nonlinear mixed-effects approach and will provide estimates of population characteristics (intrinsic and extrinsic factors) that define the population distribution of the PK parameters.

9.5.5. Safety Analysis

9.5.5.1. Safety Endpoints

- Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), grouped by organ system, relatedness to study medication, and severity
- Percentage of subjects whose IOP increases are > 10 mmHg from their own baseline measurement at each follow-up visit (except Visit 2 & 5 [post-dose])
- Percentage of subjects whose IOP increases to a reading > 30 mmHg at each follow-up visit (except Visit 2 & 5 [post-dose])
- Percentage of subjects who require 1 or more additional IOP lowering medications at any follow-up visit (except Visit 2 & 5 [post-dose])

9.5.5.2. Intraocular Pressure

The observed and change from baseline in IOP will be summarized descriptively at each visit. Descriptive statistics include n, mean, median, minimum and maximum values.

9.5.5.3. Cataract Lens Grading

The distribution of responses (n, %) will be tabulated for each category of response.

9.5.5.4. Slit-Lamp Biomicroscopy

The distribution of responses (n, %) will be tabulated for each category of response.

9.5.5.5. Dilated Indirect Ophthalmoscopy

The distribution of responses (n, %) will be tabulated for each category of response.

9.5.5.6. Fluorescein Angiography

FA will primarily be used to support SD-OCT analysis. In the event that grading occurs, the distribution of responses (n, %) will be tabulated for each category of response.

9.5.5.7. Fundus Photographs

Fundus photography will primarily be used to support SD-OCT analysis. In the event that grading occurs, the distribution of responses (n, %) will be tabulated for each category of response.

9.5.5.8. Clinical Laboratory Assessments and Urine Pregnancy Tests

The observations for each analyte will be summarized descriptively or tabulated categorically. Descriptive statistics include n, mean, median, minimum and maximum values.

9.5.5.9. Review of Systems

The proportion of subjects with abnormal body systems will be listed.

9.5.5.10. Vital Signs

The observations and change from baseline in vital signs will be summarized descriptively at each visit. Descriptive statistics include n, mean, median, minimum and maximum values.

9.5.5.11. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. TEAEs will be defined as any event occurring post treatment (injection) or, if pre-existing, worsening after Day 1.

The incidence of TEAEs will be summarized by MedDRA system organ class and preferred term. If the subject reports the same AE more than once, then that subject will only be counted once for the summary of that AE, using the most severe intensity and closest relationship to study treatment.

TEAEs will be summarized as follows:

- All TEAEs
- All TEAEs by intensity
- ALL TEAEs related to study drug
- Treatment-emergent SAEs
- TEAEs that lead to premature discontinuation of study drug
- If few AE are reported, AEs will only be provided in a listing

9.5.5.12. Prior and Concomitant Medications

Prior and concomitant medications taken from 30 days (3 years for significant ophthalmic medications) prior to Visit 1 (Screening) through the duration of the subjects' participation in the study will be summarized.

9.5.6. Interim Analysis

There is no interim analysis planned for this study.

9.5.7. Extent of Exposure

The extent of exposure (i.e., whether a subject received the injection and whether it was a complete or partial injection) will be listed.

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

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

Last Observation Carried Forward (LOCF) will be used if visits are missed in the ITT population. No imputation for missed visits will be used in the PP population. This provides an indication of the sensitivity of the data to missing observations.

Likewise, LOCF will be used if a subject requires rescue medication. All data points will be set to missing following a subject's receipt of a rescue medication; the last recorded data prior to the rescue will be carried forward to all subsequent visits for ITT. No imputation for rescue mediations will be used in the PP population.

No imputation is planned for the safety data set.

9.5.9. Multiplicity

Since there is only one primary endpoint, no multiplicity adjustments are required for the primary analysis.

9.5.10. Procedure for Reporting Deviations from the Statistical Analysis Plan

The statistical analysis plan will be completed prior to breaking treatment code.

Any deviations from the statistical analysis plan will be described and a justification given in the final clinical study report.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access of source data and documents (such as tests performed as a requirement for participation in the study and other medical records required to confirm information contained in the CRF such as medical history). In addition, the Investigator will permit members of the sponsor company to witness and record (video and/or audio) subject injections if the subject agrees in writing by providing informed consent and appropriate HIPAA authorization.

10.1. Investigator Training

The injecting physicians will be trained by the Sponsor on study drug injection and training will be documented. Only trained Investigators may administer study drug. Investigators and key support staff will be trained by the Sponsor regarding all aspects of this protocol. In addition, sites will be trained to perform imaging (SD-OCT, FA and fundus photos) per the protocol so that the data may be uploaded to a Central Reading Center. Only trained and certified visual acuity technicians may measure BCVA on study subjects using certified exam lanes.

It is the responsibility of the Investigator to train ancillary study staff if needed.

10.2. Monitoring

This study will be monitored in accordance with GCP and regulatory guidelines. By signing this protocol, the investigator agrees to periodic, on-site monitoring of all appropriate study documentation.

The progress of the study will be monitored by periodic on-site visits and frequent communications between the Sponsor (or designee) and the Investigator (either by phone, fax, email, or post).

During these contacts, the monitor will: check and assess the progress of the study; review study data collected; conduct source document verification; identify any issues and address their resolution.

The objectives of monitoring procedures are to verify that data are authentic, accurate, and complete; that the safety and rights of subjects are being protected; and that the study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements.

10.3. Audits

At its discretion, the Sponsor may conduct a quality assurance audit of this study. If such an audit occurs, the Investigator agrees to allow the auditor direct access to all relevant documents and to schedule his/her time and the time of his/her staff to permit meetings with the auditor to discuss findings and any relevant issues.

In addition, regulatory agencies may conduct a regulatory inspection of this study. If such an inspection occurs, the investigator agrees to allow the inspector direct access to all relevant documents and to schedule his/her time and the time of his/her staff to permit meetings with the auditor to discuss findings and any relevant issues.

11. 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 center 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 medication receipt, storage, and disposition, and regulatory files related to the study.

At the time of database lock, the clinical database will be audited in order 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 in order to provide sufficient accuracy for the estimated error rate of the clinical database.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

This protocol, the informed consent document, relevant supporting information, and all types of subject recruitment or advertisement information must be approved by the appropriate IRB/IEC before the study is initiated. Any amendments to the protocol must also be approved, where necessary, by the IRB/IEC prior to implementing changes in the study. Documentation of these approvals must be provided to the sponsor prior to the initiation of the amendment. The IRB/IEC used must comply with current GCP and guidelines.

The investigator's responsibilities regarding the IRB/IEC are as follows:

- Obtain IRB/IEC approval of the protocol, informed consent, and any advertisements to recruit subjects prior to their use
- Obtain IRB/IEC approval for any protocol amendments and informed consent revisions before implementing the changes
- Provide the IRB/IEC with any required information before and during the study.
- Submit progress reports to the IRB/IEC, as required, during the conduct of the study; request re-review and approval of the study, as needed; provide copies of all IRB/IEC re-approvals and relevant communication to the sponsor
- Notify the IRB/IEC within 10 days of all serious and unexpected AEs related to the study medications that are reported to you by the sponsor. The investigator is responsible for updating the IRB/IEC on the progress of the study and of any changes made to the protocol as deemed appropriate, but (in any case) at least once a year. The investigator must also keep the IRB/IEC informed of any AEs, according to the IRB/IEC policy.

12.2. Unanticipated Problems and Notification to Sponsor and IRB/IEC

The Investigator will be responsible for notifying the Sponsor within 24 hours of awareness and the IRB/IEC within 10 days of all unanticipated problems involving risk to subjects or others.

The regulations state that for studies conducted under 21 CFR part 312, investigators must report all "unanticipated problems" to the IRB [§§ 312.66, 312.53(c)(1)(vii), and 56.108(b)(1)].

As noted in FDA's Guidance on Adverse Event Reporting to IRBs – Improving Human Subject Protection (Jan 2009), the following AEs should be considered as unanticipated problems that must be reported to the IRB.

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome)
- A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (eg, tendon rupture, progressive multifocal leukoencephalopathy)

- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control).
- An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator's brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an unanticipated problem involving risk to human subjects.
- A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence
- Any other AE or safety finding (e.g., based on animal or epidemiologic data) that would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects

12.3. Informed Consent Requirements

The Investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation, in layman's terms, regarding the nature of the study, along with the aims, methods, objectives, and any potential risks. The informed consent document must be appropriately signed and dated by the subject or the subject's legally authorized representative and the person obtaining the consent (if required by the IRB/IEC) prior to conducting/obtaining any study-related assessments, including the discontinuation of any medications prohibited for the study.

If the informed consent document is amended during the study, the investigator must follow all applicable regulatory requirements pertaining to approval of the amended informed consent by the IRB/IEC and use of the amended form (including for ongoing subjects).

The informed consent document shall also contain the subject's authorization for the use and disclosure of his/her protected health information (PHI) in connection with the study. The authorization shall include at a minimum a clear description of the following: the duration of the authorization, the subject's right of access to the PHI (or any suspension thereof during the course of the study), type of information to be used/disclosed in the study, the names or classes of parties that may use or disclose the PHI, the purpose of the use/disclosure of PHI, the extent of the subject's right to revoke the authorization, the extent to which participation in the study is conditioned on signing the authorization, and the potential for re-disclosure of PHI.

Each informed consent will contain contact information with a phone number the subject should contact if they have medical concerns 24 hours a day.

The original and any amended signed and dated informed consents must be retained at the study site. A copy must be given to the subject or subject's legally authorized representative(s).

13. DATA HANDLING AND RECORD KEEPING

Study data will be processed and managed for clinical data management according to ICH Guidelines and US Food and Drug Administration regulations for the handling and analysis of data for clinical trials. Clinical study data will be captured in CRFs by study personnel at the clinical sites. CRFs will be monitored on a routine basis, with comparisons made to the various source documents maintained at the study sites.

13.1. Data Quality Control and Reporting

13.1.1. Source Documents

Source documents consist of, but are not limited to, in-patient hospital charts, clinic notes, out-patient records, original test results, laboratory data, worksheets, drug accountability records, consent forms, etc. Source documents must be available for review and inspection during on-site monitoring of the study by the Sponsor, their designees, IRB, and/or regulatory authorities.

It is required that the author of an entry in the source documents be identifiable. Direct access to source documentation must be allowed for the purpose of verifying that the data recorded on the eCRF are consistent with the original source data.

13.1.2. Case Report Forms

Source documentation for data collected in this study will be maintained at the investigative site. In cases where no source will be used, it will be noted in the investigator files. Subject CRF data will be collected by EDC. The EDC system will be Part 11 compliant and will have documented audit trail for all changes made to the CRF. Data in the EDC system will be periodically monitored for accuracy.

The investigator or designee must record all required subject data using the previously specified data collection method defined by Clearside. The investigator must sign and date a declaration on the CRF attesting to his/her responsibility for the quality of all data recorded and that the data represents a complete and accurate record of each subject's participation in the study.

ECRF data will be provided to the investigator at the end of the study and will need to be retained by the investigator.

13.1.3. Subject Tracking

A site drug accountability log, subject drug accountability logs, a subject identification log (to be retained by the Investigator only), and a subject screening/enrollment log may be used to track subject participation in the study. In addition, subject randomization assignments will be tracked in an electronic IWRS system.

13.1.4. Study Files

Each investigational center will maintain a special study file. This file is subject to monitoring and inspection as described under Section 10.2 and Section 10.3 of this protocol. This file may contain, but is not limited to, the following:

- Protocol and protocol amendments

- Safety reports that were submitted to regulatory authorities
- Investigator's Brochure
- IRB/IEC approvals
- IRB/IEC approved informed consent and authorization form
- IRB/IEC (or privacy board) waiver of authorization (if applicable)
- Investigational center notice of privacy practices (if applicable)
- IRB/IEC correspondence
- IRB/IEC membership list
- Study Communications/Correspondence (letters, memos, meeting notes, faxes, and printed emails)
- Signed Form FDA 1572 with corresponding curriculum vitae of Principal Investigator and listed Sub-Investigator(s)
- Site signature log
- Delegation of authority log
- Drug accountability records (receipt, dispensing, return or destruction)
- Laboratory normal ranges and certification
- Laboratory director's curriculum vitae
- SAE Reports (as applicable)
- Subject identification log
- Informed consent log
- Investigator(s) financial disclosure statement

13.2. Archiving of Data

The clinical database will be archived at Clearside and at the contract research organization responsible for data management for an agreed upon timeframe, if applicable.

13.3. Records Retention

The participating clinical center will retain all records related to the study in accordance with local and ICH GCP guidelines.

14. FINANCING AND INSURANCE

14.1. Finance

This study is supported by Clearside Biomedical, Inc.

14.2. Insurance

Documentation of product liability insurance is on file at Clearside Biomedical, Inc. and is available upon request.

15. PUBLICATION POLICY

The institution and investigators participating in this trial shall have no right to publish or present the results of this study without the prior written consent of the Sponsor.

16. REFERENCES

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17. 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**	**Randomization /Treatment #1**		**Follow-Up**		**Treatment #2**		**Follow-Up**		**End Of Study**
Visit Window	**Day -14 to -1**	**Day 0**		**Month 1** Week 4 Day 28 ± 5	**Month 2** Week 8 Day 56 ± 5	**Month 3** Week 12 Day 84 ± 5		**Month 4** Week 16 Day 112 ± 5	**Month 5** Week 20 Day 140 ± 5	**Month 6** Week 24 Day 168 ± 5
Assessments		**Pre-dose**	**Post-dose**			**Pre-dose**	**Post-dose**			
Informed Consent	√									
Assign Subject Number	√									
Demographics, Medical & Ocular Hx	√									
Eligibility Criteria	√	√								
Assess AEs	√	√	√	√	√	√	√	√	√	√
Con Med Review	√	√	√	√	√	√	√	√	√	√
Resting HR & BP	√	√				√				√
Central Lab Tests[1]	√									√
Review of Systems	√									√
BCVA[4]	√	√		√	√	√		√	√	√
Slit lamp Biomicroscopy[2, 4]	√	√	√	√	√	√	√	√	√	√
IOP[5]	√	√	√	√	√	√	√	√	√	√
Dilated Indirect Ophthalmoscopy[4]	√	√	√	√	√	√	√	√	√	√
SD-OCT[4]	√	√		√	√	√		√	√	√

Visit #	Visit 1	Visit 2		Visit 3	Visit 4	Visit 5		Visit 6	Visit 7	Visit 8
Visit Type	**Screening**	**Randomization /Treatment #1**		**Follow-Up**		**Treatment #2**		**Follow-Up**		**End Of Study**
Visit Window	**Day -14 to -1**	**Day 0**		**Month 1** Week 4 Day 28 ± 5	**Month 2** Week 8 Day 56 ± 5	**Month 3** Week 12 Day 84 ± 5		**Month 4** Week 16 Day 112 ± 5	**Month 5** Week 20 Day 140 ± 5	**Month 6** Week 24 Day 168 ± 5
Assessments		**Pre-dose**	**Post-dose**			**Pre-dose**	**Post-dose**			
VFQ-25 & EQ-5D		√								√
PK Blood Draw (optional)		√		√		√				√
Select Study Eye/Confirm Study Eye	√					√				
Fluorescein Angiogram[4]	√									√
Fundus Photos[4]	√									√
IWRS/Randomize		√				√				
Study Drug Treatment[3]		INJECT[3]				INJECT[3]				

1. Central lab test samples should be collected prior to FA being performed; central labs include a 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 2 and at Visit 5
4. Completed for both eyes at Visit 1 and Visit 8; study eye only for all other visits
5. IOP collected for both eyes, except post-injection when data is collected for study eye only

APPENDIX B. SUMMARY OF CHANGES FOR AMENDMENTS

Amendment 1

Section Changed	Initial Protocol (Changed From)	Modified Protocol (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
List of Abbreviations		EQ-5D: European Quality of Life 5-Dimensions	To Add an abbreviation and its associated definition	None
Section 4.2.1. Ophthalmic Exclusion Criteria	#5. History of any vitreoretinal surgery (scleral buckle, pars plana vitrectomy, retrieval of a dropped nucleus or intraocular lens, etc.; prior photocoagulation and IVT injections are acceptable)	#5. History of any vitreoretinal surgery (examples include but are not limited to scleral buckle, pars plana vitrectomy, retrieval of a dropped nucleus or intraocular lens; prior photocoagulation and IVT injections are acceptable)	To clarify that the surgeries provided are a partial list of potential excluded surgeries	None
Section 4.2.2. General Exclusion Criteria	#20. Has taken any interferon/fingolimod or any other drug in the 6 weeks prior to Visit 2, where the drug is known to induce macular edema	#20. Has taken any fingolimod or any other drug in the 6 weeks prior to Visit 2, where the drug is known to induce macular edema	Interferon has been removed from this criteria as it is not known to induce macular edema	None
Section 5.1.7. Visit 5 – Week 12 – TREATMENT VISIT 2	The randomization code and kit number initially assigned to a subject will remain the same throughout the study.	The randomization arm initially assigned to a subject will remain the same throughout the study.	To clarify that a new kit number will be assigned at Visit 5	None
Section 5.1.7.2. Injection Procedure and Immediate Post-Injection Assessments	Retrieve study drug kit number assigned by IRT AT VISIT 2	Retrieve study drug kit number assigned by IRT	To clarify that a new kit number will be assigned at Visit 5	None

Amendment 1

Section Changed	Initial Protocol (Changed From)	Modified Protocol (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Section 6.2.1. Prohibited Medications	Interferon / fingolimod or any other drug known to induce ME	Fingolimod or any other drug known to induce ME	Interferon has been removed from this list as it is not known to induce macular edema	
Section 6.2.2. Additional Treatment		In the investigator's medical judgement, the uveitic complications in the study eye have not improved and the condition needs to be addressed	To clarify that additional therapy may be implemented, at the Investigator's discretion, for those subjects whose uveitis symptoms are not improving	Investigator's discretion may be used to treat subjects who are not improving.
Section 6.5. Masking/Unmasking		Both the masked or unmasked Investigator and staff may participate in evaluations conducted during the screening visit.	To clarify which staff/investigators may conduct evaluations during the screening visit	None
	If masking is compromised, any personnel unmasked will not conduct any further masked clinical evaluations with the unmasked subject.	If masking is compromised, any masked personnel who become unmasked will not conduct any further masked clinical evaluations with the subject whose treatment has been unmasked.	To clarify who is eligible to conduct clinical evaluations following an unmasking event	None
Section 8.2.2. Cataract Lens Grading	Graders must verify training on the grading procedure.	Graders must verify training on the grading procedure provided in the Manual of Procedures.	To clarify where the cataract grading procedure is located	None

Amendment 1

Section Changed	Initial Protocol (Changed From)	Modified Protocol (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Section 8.7. Clinical Laboratory Tests; Table 4	Urinalysis: Bilirubin; blood; glucose; ketone; protein; specific gravity; urobilinogen and pH	Urinalysis: Bilirubin; blood; glucose; ketone; protein; specific gravity; pH	To remove urobilinogen from the analytes to be tested; bilirubin is a satisfactory measure of potential clinical problems	None
Throughout protocol	Miscellaneous typographical and formatting errors		To correct typographical and formatting errors	None

Amendment 2

Section Changed	Previous Protocol (Changed From)	Modified Protocol (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Throughout protocol	Miscellaneous typographical and formatting errors		To correct typographical and formatting errors	None

Amendment 2

Section Changed	Previous Protocol (Changed From)	Modified Protocol (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Section 4.2.1 Ophthalmic Exclusion Criteria, Criterion # 5	History of any vitreoretinal surgery (examples include but are not limited to scleral buckle, pars plana vitrectomy, retrieval of a dropped nucleus or intraocular lens; prior photocoagulation and IVT injections are acceptable) in the study eye; prior cataract extraction or Yttrium-Aluminum-Garnet laser capsulotomy is allowed, but must have been performed at least 3 months prior to Visit 2	History of any vitreoretinal surgery (examples include but are not limited to scleral buckle, retrieval of a dropped nucleus or intraocular lens; (prior photocoagulation and IVT injections are acceptable) in the study eye; 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 include pars plana vitrectomy as an allowed vitreoretinal surgery if conducted at least 3 months prior to subject randomization. 3 months is sufficient to allow healing; altered clearance from the vitreous is not a concern with this method of delivery.	None

Amendment 3

Section Changed	Previous Protocol (Changed From)	Modified Protocol (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Title 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
Section 1.6. Population to be Studied	The study population includes approximately 150 adult subjects to be enrolled at approximately 50 study sites.	The study population includes approximately 150 adult subjects to be enrolled at approximately 60 study sites.	To update the number of clinical sites participating on the study	None

Amendment 3

Section Changed	Previous Protocol (Changed From)	Modified Protocol (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Section 4.2.1 Ophthalmic Exclusion Criteria, Criterion # 17, 18, & 19	unless the dose has been stable for at least 2 weeks prior to Visit 2, and no change in dosing is anticipated for the study duration	unless the dose has been stable for at least 2 weeks prior to Visit 2, and no increase in dosing is anticipated for the study duration; decreases and termination of dose are allowable during the study	To clarify that decreases in doses of systemic corticosteroid, immunomodulatory and NSAID therapy are allowed during the study	None
Section 5. Procedures & Appendix A	All ocular assessments at Visit 1 and Visit 8 will be performed on both eyes. Ocular assessments at all other visits (Visits 2-7) will be performed on the study eye only. Perform ophthalmic assessments on the study eye only: 1. ETDRS BCVA 2. Slit-lamp biomicroscopy 3. IOP 4. Dilated ophthalmoscopy 5. SD-OCT and upload images to the Central Reading Center	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 performed on the study eye only. Perform ophthalmic assessments on the study eye only, unless otherwise designated: 6. ETDRS BCVA 7. Slit-lamp biomicroscopy 8. IOP (both eyes) 9. Dilated ophthalmoscopy 10. SD-OCT and upload images to the Central Reading Center	To collect IOP data on the fellow eye at all visits for comparison to the study eye IOP	None

Amendment 3

Section Changed	Previous Protocol (Changed From)	Modified Protocol (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Section 5. Procedures	Slit-lamp biomicroscopy	Slit-lamp biomicroscopy, including dilated lens grading	To clarify that dilated lens grading is to be conducted when a finding of cataract is noted during the slit lamp exam, consistent with the Time and Events Schedule (Appendix A)	None
Section 6.2.1. Prohibited Medications	Use of the following medications are prohibited at any time during the study: • Changes to topical ophthalmic NSAIDs in the study eye	Use of the following medications are prohibited at any time during the study: • Increases to topical ophthalmic NSAIDs in the study eye	To prohibit only increases in topical ophthalmic NSAIDs	None
	• Anti-angiogenic drugs (anti-VEGF) in the study eye or systemically (including pegaptanib sodium, bevacizumab, ranibizumab)	• Anti-angiogenic drugs (anti-VEGF) in the study eye or systemically (including pegaptanib sodium, bevacizumab, ranibizumab, aflibercept)	To clarify that aflibercept is an additional example of an anti-VEGF medication	None

Amendment 3

Section Changed	Previous Protocol (Changed From)	Modified Protocol (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Section 8.1. IOP Measurement	Intraocular pressure (IOP) will be measured by applanation tonometery (Goldmann or Tonopen) and results will be recorded in mmHg. 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.	Intraocular pressure (IOP) will be measured by applanation tonometery and results will be recorded in mmHg. Where available, Goldmann applanation tonometry should be used at all visits. Tonopens may be used for post-injection pressure checks and in cases where no Goldmann is available. A single measurement will be made at approximately the same time of day. The technician is encouraged to use the same tonometry method for all pre-injection and non-injection measurements 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.	To collect higher quality IOP measurements by requiring that the more accurate applanation equipment is used at all visits	None