Compound Name:	CLS-TA, triamcinolone acetonide injectable suspension
Protocol Number:	CLS1001-303
IND Number:	115683
NCT Number:	NCT02952001
Protocol Title	**MAGNOLIA**: Multi-center, Non-Interventional Extension Study of the Safety and Efficacy of CLS-TA for the Treatment of 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:**	13 October 2016 14 December 2016

CLEARSIDE BIOMEDICAL

Clinical Protocol CLS1001-303

Project:	1001
Compound Number/Name:	CLS-TA, triamcinolone acetonide injectable suspension
Protocol Number:	CLS1001-303
IND Number:	115,683
Phase:	non-interventional
Protocol Title:	**MAGNOLIA:** Multi-Center, Non-Interventional Extension Study of the Safety and Efficacy of CLS-TA for the Treatment of Macular Edema associated with Non-Infectious Uveitis
Sponsor:	Clearside Biomedical, Inc. 1220 Old Alpharetta Rd., Suite 300 Alpharetta, GA 30005, USA
Issue Date:	14 December 2016

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

14 DEC 2016
Date

CONFIDENTIAL

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

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for CLS-TA. I have read the CLS1001-303 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date of Signature

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Telephone Number
Clinical Leader, Sponsor	Ellie Smith Ellie.Smith@clearsidebio.com	+1 678 448 4717
Medical Monitor	David Hoelscher, MD David.Hoelscher@chiltern.com	Direct: +1 324 990 0299 Mobile: +1 512 694 8829 Fax: +1 423 968 3567
	Rupali Mokashi, MD Rupali.Mokashi@chiltern.com	Direct: +11 91 22 4098 2767 Mobile: +11 91 96 1934 8439 Fax: +11 91 22 4098 2727

2. SYNOPSIS

Name of Sponsor/Company: Clearside Biomedical, Inc.	
Name of Investigational Product: Triamcinolone Acetonide (CLS-TA) Injectable Suspension	
Name of Active Ingredient: Triamcinolone Acetonide	
Title of Study: MAGNOLIA: Multi-Center, Non-Interventional Extension Study of the Safety and Efficacy of CLS-TA for the Treatment of Macular Edema associated with Non-Infectious Uveitis	
Study center(s): Multi-Center	
Principal Investigator: Multi-Center	
Studied period: 6 Month Duration Estimated date first patient enrolled: October 2016 Estimated date last patient completed: September 2017	**Phase of development:** Non-interventional study
Objectives: **Primary:** Demonstrate the maintenance of efficacy of CLS-TA, up to 6 months following exit from Parent study, as shown by the need for additional therapy or the increase in maintenance therapy, for the symptoms of uveitis. **Secondary:** Determine the maintenance of safety of CLS-TA up to 6 months following exit from Parent study, as demonstrated by incidence of adverse events related to Parent study investigational product	
Number of patients (planned): approximately 30	
Diagnosis and main criteria for inclusion: Participation in CLS1001-301, non-infectious uveitis Phase 3 (Parent) study without additional therapy for uveitis	
Investigational product, dosage and mode of administration: No investigational product administered in this study	
Reference therapy, dosage and mode of administration: None	
Criteria for evaluation: **Efficacy:** Mean time to additional uveitis therapy or change in maintenance therapy for uveitis **Safety:** Incidence of Adverse Events and serious adverse events grouped by organ system, relatedness to Parent study investigational product, and severity	
Statistical methods: All data collected in the study database will be presented in the listings. Listings will include change from baseline. Baseline is the Crossover Visit. Time to Rescue Therapy will be analyzed using Kaplan-Meier analysis including 95% confidence intervals, log rank p-value for difference between treatments, and quartiles.	

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

TABLE OF CONTENTS

LIST OF TABLES

4. LIST OF ABBREVIATIONS

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

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse Event
BCVA	Best Corrected Visual Acuity
CRF	Case Report Form
CST	Central Subfield Thickness
ETDRS	Early Treatment of Diabetic Retinopathy Study
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee
IOP	Intraocular Pressure
IRB	Institutional Review Board
IND	Investigational New Drug
ITT	Intent-to-Treat
IVT	Intravitreal
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Non-Steroidal Anti-Inflammatory Drug
OCT	Optical Coherence Tomography
PP	Per Protocol
SAE	Serious Adverse Event
SCS	Suprachoroidal Space
SD-OCT	Spectral-Domain Optical Coherence Tomography
TA	Triamcinolone Acetonide
VEGF	Vascular Endothelial Growth Factor

5. INTRODUCTION

5.1 Disease Background

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

5.2 Scientific Rationale

All subjects entering this trial will have received either CLS-TA or sham procedure from the Parent study, CLS1001-301, as masked investigational product. The objective of the Parent study is to evaluate the safety and efficacy of suprachoroidally administered CLS-TA for the treatment of macular edema associated with non-infectious uveitis. Two doses or CLS-TA or a sham procedure will be performed in the Parent study on each subject enrolled at Day 0 and Month 3 visits and the primary endpoint will be evaluated 6 months following the enrollment.

In addition to providing a robust efficacy and improved safety profile over currently used corticosteroid delivery methods, suprachoroidal administration of precisely delivered local corticosteroid therapy may provide a longer cessation of uveitis symptoms and reduced steroid sensitivity. This potential benefit will be evaluated in this extension study of non-infectious uveitis patients who participated in the Parent study and who have not received additional therapy for uveitis.

5.3 Description of Investigational Product

All subjects entering this trial will have received either CLS-TA or sham procedure from the Parent study, CLS1001-301, as masked investigational product. There will be no investigational product in this study.

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

5.4 Summary of Clinical Experience

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.

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 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. No significant increases in IOP were reported. The most commonly reported AE, eye pain, was reported in 4 subjects.

The completed clinical study, CLS1001-201, is a Phase 2, randomized, masked safety and efficacy study in subjects with macular edema associated with non-infectious uveitis. Twenty-two subjects were randomized to either a single suprachoroidal injection of CLS-TA, 4 mg in 100 µL or 0.8 mg in 100 µL. Subjects in the 4.0mg treatment arm were observed to have a mean reduction in central subfield of thickness (CST) of 164 microns (p=0.002) when measured from baseline at 2 months. No subjects discontinued due to Adverse Event and there were no investigator-reported increases in IOP at follow-up visits.

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

6. TRIAL OBJECTIVES AND PURPOSE

The purpose of this study is to characterize the continued clinical benefit(s) regarding safety and efficacy of suprachoroidally administered CLS-TA, triamcinolone acetonide injectable suspension, for the treatment of macular edema associated with non-infectious uveitis. This study will be a non-interventional extension of the Parent study, CLS1001-301.

6.1. Primary Objective

Demonstrate the maintenance of efficacy of CLS-TA, up to 6 months following exit from Parent study, as shown by the need for additional therapy or the increase in maintenance therapy, for the symptoms of uveitis.

6.2. Secondary Objectives

Determine the maintenance of safety of CLS-TA up to 6 months following exit from Parent study, as demonstrated by incidence of adverse events related to Parent study investigational product

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a non-interventional extension study of up to 6 months for subjects completing the Parent study. The Parent study is a Phase 3, multicenter study to assess the safety and efficacy of 4 mg of CLS-TA administered via suprachoroidal injection compared to a sham procedure in the treatment of subjects with macular edema associated with non-infectious uveitis.

The study design of the Extension study includes 4 clinic visits over a maximum of 24 weeks. Subject eligibility will be established at Visit 1 during the crossover day from the Parent study to the extension study (Day 0). Follow-up visits will be conducted every 6 weeks up to 24 weeks (Visit 4). At Visit 4, subjects will have a final evaluation conducted 24 weeks following study entry (48 weeks from Parent study randomization). Parent study masking will remain in effect until the Parent study is unmasked.

7.2. Number of Subjects

The study population will include approximately 30 adult subjects that successfully complete the Parent study without requiring additional therapy to treat symptoms for uveitis as defined by the protocol. The expected duration of participation in the study is up to 24 weeks from study entry. The complete inclusion and exclusion criteria are presented below in Section 8.

7.3. Treatment Assignment

This is a non-interventional extension study. There will be no investigational product administered in this study.

7.4. Criteria for Study Termination

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.

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.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

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

1. Enrolled in the Parent study, CLS1001-301, through Visit 8/Month 6

2. 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

8.2. Subject Exclusion Criteria

1. Received additional therapy for the treatment of uveitis or prohibited medication as defined in Section 6.2 of the Parent protocol, CLS1001-301
2. Require additional therapy for the treatment of uveitis or prohibited medication as defined in Section 6.2 of the Parent protocol, CLS1001-301 at the time of the Crossover visit

8.3. Subject Withdrawal Criteria

Subjects may withdraw from the study at any time and for any reason without obligation. Subjects may be removed from the study at the Investigator's discretion or if they require Rescue due to disease progression that warrants further treatment.

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 4 assessments (Section 20.1. - Appendix A). 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 9.2.2.).

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

No study drug will be administered in the MAGNOLIA study.

9.1.1. Study Eye Determination

The study eye will remain the same as in the Parent study, CLS1001-301.

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

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

9.2. Concomitant Medications

9.2.1. Medications for treatment of uveitis

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. The list of medications provided below is not intended to be comprehensive, but rather to help guide the Investigator's medical judgment. If any of these medications are used during the study, the subject will be considered to have received additional therapy for uveitis and should be exited from the study (Section 19.1.).

- Increases in dose of 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)
- Increases to dose of systemic immunosuppressant drugs
- Acetazolamide (Diamox®)
- Any investigational drug or device

In cases where a subject presents with a medication not included on the above 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.

9.2.2. 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

If at any time during the study 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 loss of 10 or more ETDRS BCVA letters due to uveitis from either of the previous two visits
- CSF > 320 µm OR an increase in CST of ≥100 microns or 20%, whichever is lower, from either of the previous two visits
- In the investigator's medical judgement, the uveitic complications in the study eye have worsened and the condition needs to be addressed

9.3. Treatment Compliance

Once a subject has been treated with additional therapy, the subject should be exited from the study per the Schedule of Assessments (Section 20.1 - Appendix A).

9.4. Randomization and Blinding

While there will be no randomization in this non-interventional extension study, the masking from the Parent study will be protected in this trial until the Parent study has completed and is appropriately unmasked.

10. STUDY DRUG MATERIALS AND MANAGEMENT

Not Applicable

11. ASSESSMENT OF EFFICACY

11.1. Best Corrected Visual Acuity (BCVA)

Best Corrected Visual Acuity (BCVA) will be measured using ETDRS electronic visual acuity (eVA) and will be collected at every visit. 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 chart. If Roman letters are not familiar to the subject, Tumbling E charts may be used.

11.2. Central Subfield Thickness as Measured by SD-OCT

Retinal thickness and disease characterization will be assessed at every visit via spectral domain optical coherence tomography (SD-OCT) (Heidelberg SPECTRALIS® or Zeiss CirrusTM). The SD-OCT instrument and technician must be certified prior to enrolling 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.

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

12.1.1. Intraocular Pressure

Intraocular pressure (IOP) will be measured by applanation tonometery (Tonopen or Goldmann) at every visit 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.

12.1.2. Slit-Lamp Biomicroscopy

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

12.1.2.1. 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.

12.1.2.2. 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

12.1.2.3. 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)

12.1.3. Dilated Ophthalmoscopy

A dilated fundus examination at every visit 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.

12.1.3.1. 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

12.2. Adverse and Serious Adverse Events

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event (AE)

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:

- o 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
- o 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")

12.2.1.2. Serious Adverse Event (SAE)

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

- 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

12.3. Relationship to Study Drug

Causality 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

12.4. Recording Adverse Events

Adverse events spontaneously reported by the patient/subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. The AE term should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the study.

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

12.5. Reporting Serious Adverse Events

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.

12.5.1. Transmission of SAE Reports

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.

SAE 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.

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.

12.5.2. 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.

13. STATISTICS

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.

13.1. Randomization

There will be approximately 30 subjects enrolled from the Parent study, CLS1001-301, where there were two masked arms (4.0 mg CLS-TA and sham). No additional randomization is planned for this study.

13.2. Determination of Sample Size and Level of Significance

The sample size of approximately 30 subjects at approximately 40 centers was based on clinical considerations appropriate for a non-interventional extension study.

13.3. Subject Disposition, Demographic and Baseline Characteristics

Subject disposition, demographic, and baseline characteristics (sourced from the Parent study) will be summarized descriptively by treatment group and overall.

13.4. Analysis Population

13.4.1. Safety Population

Safety population will include all enrolled subjects who successfully complete the crossover visit (Day 0). The Safety Population will be used for safety analyses.

13.4.2. Intent-to-Treat Population

Intent-to-treat (ITT) population includes all enrolled subjects. ITT population will be used for efficacy analyses.

13.5. Analysis Methods

13.5.1. Primary Efficacy Endpoint

Time to rescue therapy (dosing with a drug when efficacy of the Parent study investigational products is no longer adequate)

13.5.2. Primary Efficacy Analysis

All data collected in the study database will be presented in the listings. Listings will include change from baseline. Baseline is the Crossover Visit.

Time to Rescue Therapy will be analyzed using Kaplan-Meier analysis including 95% confidence intervals, log rank p-value for difference between treatments, and quartiles.

13.5.3. Safety Endpoint

- 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 Parent study baseline measurement at each follow-up visit
- Percentage of subjects whose IOP increases to a reading > 30 mmHg at each follow-up visit
- Percentage of subjects who require 1 or more additional IOP lowering medications at any follow-up visit

13.5.4. Safety Analysis

13.5.4.1. 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.

13.5.4.2. Cataract Lens Grading

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

13.5.4.3. Slit-Lamp Biomicroscopy

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

13.5.4.4. Dilated Indirect Ophthalmoscopy

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

13.5.4.5. 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) in the parent study or, if pre-existing, worsening after Day 0 in this extension study.

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

13.5.4.6. Prior and Concomitant Medications

Concomitant medications specific to ocular indications will be carried over from the parent study and entered as ongoing or new medications at the Crossover Visit (Day 0), then any additional medications or deletions will be recorded in the study and will be summarized.

13.5.5. Interim Analysis

There is no interim analysis planned for this study.

13.5.6. Extent of Exposure

There will be no exposure to CLS-TA or SHAM device in this study.

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

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

No imputation is planned for the safety data set.

13.5.8. Multiplicity

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

13.5.9. Procedure for Reporting Deviations from the Statistical Analysis Plan

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

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Site qualification visits for this study will be waived due to the fact that a member of the Clearside Biomedical team or representative have monitored the site for the parent study during the last 6 months and the adequacy of the Investigator, site personnel and facilities have been documented in the site monitoring visit reports (with exception in the event that significant staff or facility changes have occurred since the last visit).

During the study, a monitor from Clearside Biomedical or representative will have regular contacts with the investigational site, for the following:

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

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

14.2. Audits and Inspections

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

14.3. Institutional Review Board (IRB)

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Clearside Biomedical may conduct a quality assurance audit. Please see Section 14.2 for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

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

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

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

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

16.2. Ethical Conduct of the Study

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

16.3. Written Informed Consent

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

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

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

17. DATA HANDLING AND RECORD KEEPING

17.1. Inspection of Records

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

17.2. Retention of Records

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

18. 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 Clearside Biomedical.

19. LIST OF REFERENCES

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20. APPENDICES

20.1. Appendix A: Schedule of Assessments

Assessment	Crossover[1]	Extension Study Visit				Early Termination
Parent Study	Week 24	Week 30	Week 36	Week 42	Week 48	
Extension Study	Day 0	Week 6	Week 12	Week 18	Week 24	
Informed Consent	X					
Inclusion/ Exclusion	X					
Assess AEs	X	X	X	X	X	X
Con Med Review	X	X	X	X	X	X
BCVA[2]	X	X	X	X	X	X
Slit lamp Biomicroscopy[2,3]	X	X	X	X	X	X
IOP[2]	X	X	X	X	X	X
Dilated Indirect Ophthalmoscopy[2]	X	X	X	X	X	X
SD-OCT[2]	X	X	X	X	X	X

1 Same as parent study Week 24 visit. Ensure these procedures are completed. Do not repeat if done in parent study.

2 All ophthalmic assessments should be completed for the study eye only

3 Any finding of cataract should be graded

20.2. Appendix B: SUMMARY OF CHANGES FOR AMENDMENTS

Section Changed	Initial Protocol (Changed From)	Modified Protocol (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Throughout protocol	Miscellaneous incorrect reference section numbers	Reference section numbers corrected	To correct reference section numbers	None
Section 20.1. Appendix A Schedule of Assessments	Footnote #2. All ophthalmic assessments should be completed for both eyes	Footnote #2. All ophthalmic assessments should be completed for the study eye only	To clarify that assessments are only required for study eye	None