Compound Name:	CLS-TA, triamcinolone acetonide injectable suspension
Protocol Number:	CLS1004-101
IND Number:	115683
NCT Number:	NCT02949024
Protocol Title	Open-label study of the safety and efficacy of suprachoroidal CLS-TA alone or in combination with intravitreal aflibercept for the treatment of diabetic macular edema
Sponsor:	Clearside Biomedical, Inc. 900 North Point Parkway, Suite 200 Alpharetta, GA 30005
Issue Date: **Protocol Amendment 1 Date:**	10 October 2016 23 June 2017

Clinical Protocol CLS1004-101

Project:	1004
Compound Number/Name:	CLS-TA, triamcinolone acetonide injectable suspension
Protocol Number:	**CLS1004-101**
Phase:	1/2
IND Number:	115683
Protocol Title:	**OPEN-LABEL STUDY OF THE SAFETY AND EFFICACY OF SUPRACHOROIDAL CLS-TA ALONE OR IN COMBINATION WITH INTRAVITREAL AFLIBERCEPT FOR THE TREATMENT OF DIABETIC MACULAR EDEMA**
Sponsor:	Clearside Biomedical, Inc. 1220 Old Alpharetta Rd., Suite #300 Alpharetta, GA 30005
Study Principal Investigator:	Charles C. Wykoff, MD, PhD **Telephone: (713) 524-3434**
Protocol Amendment 1 Date:	23 June 2017
Original Protocol Issue Date:	10 October 2016

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

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 CLS1004-101 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Telephone Number
Clinical Study Leader	Kathleen Billman	678.894.0703
Site Coordinating Leader	Cassie Cone	713.394.7537
Responsible Physician 24-Hour emergency contact	Charles Wykoff, MD, PhD	713.524.3434

2. SYNOPSIS

Name of Sponsor/Company:
Clearside Biomedical, Inc.

Name of Investigational Product:
CLS-TA, triamcinolone acetonide injectable suspension
Aflibercept

Name of Active Ingredient:
Triamcinolone Acetonide
Aflibercept

Title of Study:
CLS1004-101: Open-Label Study of the Safety and Efficacy of Suprachoroidal CLS-TA Alone or in Combination with Intravitreal Aflibercept for the Treatment of Diabetic Macular Edema

Study center(s): Multi-Center; approximately 3 US clinical sites

Principal Investigator: Charles Wykoff

Studied period: 6 Month Duration	**Phase of development:**
Estimated date first patient enrolled: 3Q2016 Estimated date last patient completed: 2Q2017	Phase 1/2

Objectives:

Primary: To demonstrate the safety and tolerability of suprachoroidal CLS-TA alone or in combination with intravitreal aflibercept in subjects with diabetic macular edema associated with diabetes mellitus

Secondary:

- To demonstrate the preliminary efficacy of suprachoroidal CLS-TA in eyes previously treated for diabetic macular edema
- To demonstrate the preliminary efficacy of suprachoroidal CLS-TA in combination with intravitreal aflibercept in treatment naïve diabetic macular edema eyes

Number of patients (planned): approximately 20

Diagnosis and main criteria for inclusion:
Treatment naïve or non-naïve patients diagnosed with diabetic macular edema

Investigational product, dosage and mode of administration:
CLS-TA, triamcinolone acetonide injectable suspension, 4 mg in 100 µL, suprachoroidal injection; EYLEA® (aflibercept) Injection, 2 mg in 50 µL, intravitreal injection

Reference therapy, dosage and mode of administration: None

Criteria for evaluation:

Safety:

- Incidence of treatment-emergent adverse events

- Observed and change from baseline intraocular pressure

Efficacy:

- Mean change from baseline in central subfield thickness
- Mean change from baseline in ETDRS best-corrected visual acuity
- Mean number of suprachoroidal injections of CLS-TA administered over 6 months

Exploratory:

- Scleral thickness
- Suprachoroidal space visualization

Statistical methods:

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

Re-Treatment Criteria:

Re-treatment will be assessed monthly starting at Month 2. Any subject who meets the following criteria should be treated for his/her DME:

- CSF > 320 µm AND not improved by at least 20% from either of the previous two visits [10% for CSF > 500 µm], (OR)
- Loss of 10 or more letters due to DME from either of the previous two visits

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

TABLE OF CONTENTS

LIST OF TABLES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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
CLS-TA	Clearside triamcinolone acetonide
CRF	Case report form
CST	Central subfield thickness
DM	Diabetes mellitus
DME	Diabetic macular edema
DR	Diabetic retinopathy
ETDRS	Early Treatment of Diabetic Retinopathy Study
FA	Fluorescein angiography
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IOP	Intraocular pressure
IRB	Institutional Review Board
IVT	Intravitreal
OAE	Other significant adverse event
OCT-A	Optical coherence tomography - angiography
PI	Principal Investigator The investigator who leads the study conduct at an individual study center. Every study center has a principal investigator.
SAE	Serious adverse event
SC / SCS	Suprachoroidal / Suprachoroidal space
SD-OCT	Spectral domain optical coherence tomography
TX	Treatment
VEGF	Vascular endothelial growth factor

5. INTRODUCTION

5.1. Disease Background

Diabetes mellitus (DM) and diabetic retinopathy (DR) are major contributors to human morbidity and mortality and have a staggering impact on societal productivity. More than 1 in 5 US health care dollars are spent on DM care and our total annual attributable cost for DM is well over a quarter of a trillion dollars[1]. While globally the burden of DM continues to rise, recent encouraging data suggest that the prevalence of DM within the USA may be plateauing with approximately 50% of our adults affected with frank DM (13%) or pre-DM (38%)[2]. One of the most frequent end-organ manifestations of DR is diabetic macular edema (DME), the most common cause of visual loss among working-age populations.[3-5]

The first validated treatment for DME, laser photocoagulation of the macula, was established by the Early Treatment of Diabetic Retinopathy Study (ETDRS) in the 1980s.[6] More recently, both intravitreal anti-vascular endothelial growth factor-A (VEGF) and steroid injections have proven effective in DME management[7-11] and have progressively replaced focal laser as the primary treatment of center-involving DME with visual acuity loss.[7, 12-17] Multiple large, randomized, controlled trials directly comparing focal laser with either anti-VEGF or steroid pharmacotherapies have confirmed superior visual and anatomic outcomes with VEGF blockade.[7, 13, 17, 18] Currently 4 agents are approved by the Food and Drug Administration for the treatment of DME: aflibercept (Eylea®, Regeneron), ranibizumab (Lucentis®, Genentech), dexamethasone (Ozurdex®, Allegan), fluocinolone acetonide (Iluvien®, Alimera), and one agent is regularly used off label, bevacizumab (Avastin®, Genentech).

5.2. Scientific Rationale

Anti-VEGF intravitreal injections have become the overwhelming choice for first line treatment of DME causing visual acuity loss[19]. The only prospective trial directly comparing the 3 commercially-available anti-VEGF agents was recently reported by the Diabetic Retinopathy Clinical Research Network (DRCR.net): Protocol-T, A comparative effectiveness study of intravitreal aflibercept, bevacizumab and ranibizumab for DME.[20, 21] Protocol-T involved 660 patients with center-involved DME and found that regardless of medication used and despite nearly 20 clinical visits and approximately 15 intravitreal injections through 2 years, a majority of eyes demonstrated persistent DME and met criteria for macular laser as the anti-VEGF therapy was incompletely effective at treating the DME. Therefore, a significant clinical unmet need remains to optimally treat patients with DME.

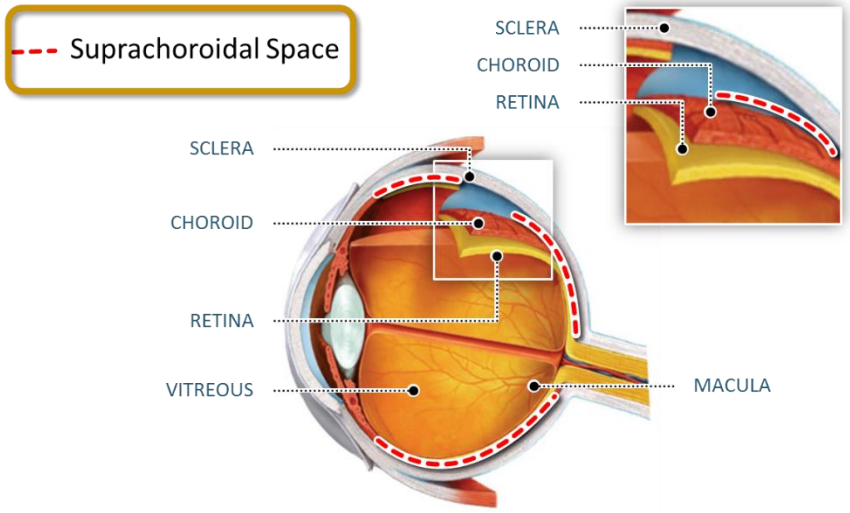
Intravitreal steroids have also proven effective for the management of DME. For example, the DRCR.net Protocol-I reported that among pseudophakic eyes, intravitreal triamcinolone acetonide was as effective at improving visual acuity as ranibizumab[16]. No formulation of triamcinolone acetonide is currently FDA approved for the treatment of DME.

5.3. Description of Investigational Product

CLS-TA, triamcinolone acetonide injectable suspension, is a preservative-free, terminally sterilized, aqueous suspension, formulated for administration into the eye. It will be administered as a single suprachoroidal injection of 4 mg in 100 microliters (μL) using Clearside's proprietary

SCS™ microinjector. The suprachoroidal space (SCS) is the region of the eye between the sclera and the choroid (Figure 1).

Figure 1: Anatomy of the Eye



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

Aflibercept (EYLEA®) is a Food and Drug Administration (FDA) approved prescription medicine. Full prescribing information for aflibercept in the treatment of diabetic macular edema involves injection of 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks for the first 5 injections followed by once every 8 weeks.
http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125387s043lbl.pdf.

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

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

Clearside is developing CLS-TA, a proprietary TA formulation for the treatment of non-infectious uveitis by suprachoroidal administration and has completed 2 clinical trials in patients with non-infectious uveitis and one clinical trial in patients with retinal vein occlusion.

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 unrelated serious adverse event (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, was 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 4.0 mg 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; further, a mean improvement in best corrected visual acuity (BCVA) with a gain of 9.2 letters when measured from baseline at 2 months was also seen. No subjects discontinued due to an adverse event and there were no investigator-reported increases in IOP at follow-up visits.

The completed clinical study, CLS1003-201, was a Phase 2, randomized, masked safety and efficacy study in subjects with macular edema following RVO. Forty-six subjects were randomized 1:1 to either suprachoroidal injection of CLS-TA administered in conjunction with an intravitreal injection of aflibercept (ACTIVE), or an intravitreal injection of aflibercept alone (CONTROL). Subjects were evaluated over the three month study period with monthly visits; additional intravitreal aflibercept treatments were determined using as needed (PRN) criteria that included the presence of central retinal fluid or losses in visual acuity. Since a key goal of the study was to determine if suprachoroidal CLS-TA affected the requirement for additional treatment when administered along with intravitreal aflibercept, a count of the requirement for additional intravitreal aflibercept injections over the 3-month trial served as the primary outcome measure. The study met the primary endpoint with sixty percent fewer additional IVT aflibercept injections (p=0.013) required in the ACTIVE group receiving the combination of SC CLS-TA and IVT aflibercept compared with subjects in the CONTROL arm. In terms of secondary endpoints, mean improvements from baseline in BCVA were 16, 20, and 19 ETDRS letters in the ACTIVE group and 11, 12, and 11 letters in the CONTROL group at Months 1, 2, and 3 respectively. Subjects were observed to have a mean reduction in CST of 446 µm in the ACTIVE (combination) group, and a 405 µm reduction in the CONTROL group when measured from Baseline at Month 1. Further, the approximately 450 µm reduction in CST in the ACTIVE (combination) group was maintained through the 3 months of the study while the CONTROL group showed only approximately 350 µm reductions in CST at both months 2 and 3. No subjects discontinued due to an AE and no SAEs were reported. A total of 4 subjects in the active group reported AEs pertaining to elevated IOP: 2 events each of ocular hypertension and IOP increase. All events were mild or moderate in intensity and considered to be related to study drug.

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

The current trial aims to evaluate the safety, tolerability and preliminary efficacy of CLS-TA with or without intravitreal aflibercept for the treatment of eyes with DME.

6. TRIAL OBJECTIVES AND PURPOSE

The purpose of this trial is to evaluate the safety and preliminary efficacy of suprachoroidal CLS-TA with or without intravitreal aflibercept in subjects with DME associated with diabetes mellitus.

6.1. Primary Objective

The primary objective of this trial is to demonstrate the safety and tolerability of suprachoroidal CLS-TA alone or in combination with intravitreal aflibercept in subjects with diabetic macular edema associated with diabetes mellitus

6.2. Secondary Objectives

- To demonstrate the preliminary efficacy of suprachoroidal CLS-TA in eyes previously treated for diabetic macular edema
- To demonstrate the preliminary efficacy of suprachoroidal CLS-TA in combination with intravitreal aflibercept in treatment naïve diabetic macular edema eyes

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a Phase 1/2, multicenter, open-label study in subjects with DME associated with diabetes mellitus.

Subjects will be screened and if eligible, will be assigned to a study arm at the Baseline Visit (Visit 1, Day 0).

Following the Baseline Visit, subjects will participate in six monthly follow-up visits (Visit 2-7; Weeks 4-24) for safety and efficacy assessments and to determine whether additional therapy is needed based upon predefined criteria elaborated in this protocol.

See Appendix A for the Schedule of Events.

7.2. Endpoints

7.2.1. Safety Endpoints

- Incidence of treatment-emergent adverse events (TEAE) and serious adverse events (SAEs), grouped by organ system, relatedness to study treatment and severity
- Mean change from baseline in intraocular pressure at each follow-up visit

7.2.2. Efficacy Endpoints

- Mean change from baseline in central subfield thickness at each follow-up visit
- Mean change from baseline in ETDRS best-corrected visual acuity at each follow-up visit
- Mean number of suprachoroidal injections of CLS-TA administered over 6 months

7.2.3. Exploratory Endpoint

- Scleral thickness
- Suprachoroidal space visualization

7.3. Number of Subjects

Approximately 20 subjects with DME will be enrolled into one of two treatment arms.

7.4. Treatment Assignment

Eligible subjects will be evaluated for previous treatment for DME in the study eye. Those subjects who have never received treatment in the study eye for DME or whose DME treatment in the study was more than 1 year prior to the screening date, at the PI's discretion, will be enrolled into the TX Naïve study arm. Those subjects who have received treatment for DME in the study eye within the last 12 months, will be enrolled into the Previous TX study arm as described below:

TREATMENT ARM	Number of Subjects
TX Naïve: IVT aflibercept [2 mg (50 µL)] + SC CLS-TA [4 mg (100 µL)]	~10
Previous TX: SC CLS-TA [4 mg (100 µL)]	~10

TX Naïve arm: an IVT injection of aflibercept [2 mg (50 µL)] followed by a suprachoroidal injection of CLS-TA, triamcinolone acetonide injectable suspension [4 mg (100 µL)]

Previous TX ARM: a suprachoroidal injection of CLS-TA, triamcinolone acetonide injectable solution [4 mg (100 µL)]

Subjects stratified into either of these 2 arms will be re-treated only with a suprachoroidal injection of CLS-TA starting at Month 2 (Visit 3; Week 8) if any retreatment criterion is met.

7.5. 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 IRB of the termination or suspension and of the reasons.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

The targeted study population is men or women 18 years and older with DME associated with diabetes mellitus

8.1. Subject Inclusion Criteria

A subject must meet the following criteria to be eligible for inclusion in this study:

1. Men or women ≥ 18 years of age with type 1 or type 2 diabetes mellitus
2. DME with central involvement (> 320 μm in the central subfield on SD-OCT) in the study eye
3. ETDRS BCVA letter score of 83 to 14, inclusive (Snellen equivalent of 20/25 to 20/500) 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

8.2. Subject Exclusion Criteria

An individual is ineligible for participation in this study if any of the following criteria are met:

8.2.1. Ophthalmic Exclusion Criteria

1. Evidence of DME due to any cause other than diabetes mellitus in the study eye
2. Panretinal photocoagulation or focal laser photocoagulation in the study eye within 90 days of screening
3. Intraocular pressure ≥ 22 mmHg or uncontrolled glaucoma (open angle or angle closure) in the study eye
4. History of any previous ophthalmic surgeries in the study eye within 90 days of screening
5. High Risk Proliferative Diabetic Retinopathy in the study eye, for whom enrollment into the study, in the principal investigator's opinion would put the eye at undue risk for vision loss
6. Any previous treatment in the study eye with ILUVIEN implant
7. Previous treatment for DME in the study eye (TX Naïve arm only); treatment in the study eye for DME greater than 1 year prior to screening can be considered as treatment naïve, at the principal investigator's discretion

8. Subjects previously treated for DME cannot have been treated in the study eye with an intravitreal injection of anti-VEGF or periocular corticosteroids within 90 days prior to screening (Previous TX arm only)
9. Subjects previously treated for DME cannot have been treated in the study eye with intraocular corticosteroids within 6 months prior to screening (Previous TX arm only)

8.2.2. General Exclusion Criteria

10. Known hypersensitivity to any component of the CLS-TA, fluorescein, or topical anesthetic
11. Uncontrolled blood pressure (defined as > 180/110 mm Hg systolic/diastolic, while seated)
12. If female, the subject must be non-pregnant, non-lactating and not planning a pregnancy. Females of childbearing potential must agree to use an acceptable method of contraception throughout participation in this 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.
13. Currently enrolled in an investigational drug or device study or has used an investigational drug or device within the last 30 days

8.3. Subject Withdrawal Criteria

A subject has the right to withdraw from the study at any time, for any reason and without repercussion. The investigator has the right to withdraw a subject from the study in the event of an intercurrent illness, need for treatment in the study eye that is beyond what is designated in the protocol, adverse event (AE), treatment failure, protocol violation, cure, and for administrative, or other reasons. Subjects who withdraw prematurely from the study will be asked to complete study assessments at the early termination visit. If an SAE is unresolved at the time of the subject's final study visit, the investigator should make every attempt to follow up until the SAE is resolved or stabilized, the subject is lost to follow-up, or there is some other resolution of the event.

8.4. Procedures

The study will consist of up to 7 study visits over approximately 6 months. Subjects are expected to attend all study visits. All ocular assessments will be performed on both eyes for all study visits. Subjects will be screened for entry and randomized/treated at Visit 1. At Visit 1 subjects will receive either a single, unilateral suprachoroidal injection of CLS-TA or an intravitreal injection of aflibercept followed by a suprachoroidal injection of CLS-TA. Subjects will be assessed post injection for safety. Additional safety follow-up visits will occur monthly over the 6-month study period. Subjects will be eligible to receive retreatment of CLS-TA from month 2-5, if specified criteria are met. The final study visit will occur at month 6 (Visit 7).

8.4.1. Screening/Baseline - Visit 1 (Day 0)

After the subject has provided informed consent, the following procedures will be collected:

1. Assign subject number
2. Collect demographics, medical and ocular history
3. Review current and prior concomitant medications
4. Measure resting heart rate and blood pressure
5. Collect blood for central lab tests prior to FA, including urine pregnancy test on females of childbearing potential
6. Perform ophthalmic assessments on both eyes:
    a. ETDRS BCVA
    b. IOP
    c. SD-OCT
    d. OCT-A (at participating sites)
    e. Fundus photography
    f. Fluorescein angiography
    g. Slit-lamp biomicroscopy
    h. Dilated indirect ophthalmoscopy
7. Verify subject eligibility based on Inclusion/Exclusion requirements
8. Determine study eye based upon eye specific eligibility criteria
9. Determine study arm based upon eligibility criteria

10. Administer study treatment per assigned study arm

8.4.1.1. IVT injection of aflibercept (TX Naive arm only)

1. Prepare study eye for IVT injection of aflibercept
2. Administer aflibercept IVT injection per package insert; it is recommended that the intravitreal injection and the SC injection are approximately 2 clock hours apart. The superior temporal quadrant is the recommended location for SC injections.
3. Measure IOP with contact tonometry after injection
    - SC injection should be administered following the IVT injection of aflibercept when the study eye IOP is < 30 mmHg, either spontaneously or by treatment, as determined by the investigator.
4. Immediately following the injection, assess study eye by indirect ophthalmoscopy

8.4.1.2. SC Injection of CLS-TA (Both study arms)

1. Select drug kit and document study kit number
2. Administer injection of 100 μL of CLS-TA into the SCS of the study eye using the Clearside microinjector, preferably in the superior temporal quadrant
3. For full description injection procedures, see Appendix B
4. Immediately following the injection, assess study eye by indirect ophthalmoscopy

8.4.1.3. Post-Dose Procedures

1. Assess post dose AE's
2. Review changes to concomitant medications
3. Evaluate IOP 10-30 minutes post injection
    - If IOP remains elevated, subject must remain on site until IOP is under control per investigator judgement
    - If IOP is < 30 mmHg, the subject may leave the clinic

8.4.2. Visit 2 – Month 1 (Day 30 ±3)

1. Review changes to concomitant medications
2. Assess adverse events
3. Perform ophthalmic assessments on both eyes:
    a. ETDRS BCVA
    b. IOP
    c. SD-OCT
    d. Slit-lamp biomicroscopy
    e. Dilated indirect ophthalmoscopy

8.4.3. Follow-up Procedures: Visit 3 [Month 2 (Day 60 ±3)]; Visit 4 [Month 3 (Day 90 ±3)]; Visit 5 [Month 4 (Day 120 ±3)]; Visit 6 [Month 5 (Day 150 ±3)]

1. Review changes to concomitant medications
2. Assess adverse events
3. Perform ophthalmic assessments on both eyes:
    a. ETDRS BCVA
    b. IOP
    c. SD-OCT
    d. Slit-lamp biomicroscopy
    e. Dilated indirect ophthalmoscopy
4. Evaluate re-treatment criteria, if yes:

8.4.3.1. SC Injection of CLS-TA (Both study arms)

1. Anterior segment SD-OCT (at sites with capability)
2. Select drug kit and document study kit number
3. Administer injection of 100 µL of CLS-TA into the SCS of the study eye using the Clearside microinjector, preferably in the superior temporal quadrant
4. For a full description of the SC injection procedure, see Appendix B

5. Immediately following injection, assess the study eye by indirect ophthalmoscopy

8.4.3.2. Post-Dose Procedures

1. Assess post dose AE's
2. Review changes to concomitant medications
3. Anterior segment SD-OCT (at sites with capability)
4. Evaluate IOP 10-30 minutes post injection
    - If IOP remains elevated, subject must remain on site until IOP is under control per investigator judgement
    - If IOP is < 30 mmHg, the subject may leave the clinic

8.4.4. Visit 7 – [Month 6 (Day 180 ±3)] End of Study Visit or Early Termination Visit

1. Review changes to concomitant medications
2. Assess adverse events
3. Collect blood for central lab tests prior to FA
4. Perform ophthalmic assessments on both eyes:
    a. ETDRS BCVA
    b. IOP
    c. SD-OCT
    d. Anterior segment SD-OCT (at sites with capability)
    e. OCT-A (at participating sites)
    f. Fundus photography
    g. Fluorescein angiography
    h. Slit-lamp biomicroscopy
    i. Dilated Indirect ophthalmoscopy

8.4.5. Unscheduled Visits

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 investigator/staff should complete assessments deemed necessary by evaluating investigators and should record the assessments as an Unscheduled Visit.

If a subject is early terming the procedures for Visit 7 (Month 6) should be completed.

8.4.6. Anterior Segment SD-OCT

Anterior segment SD-OCT imaging will be performed pre-and post-dose at visits where subject's meet re-treatment and at the exit visit. If a subject has exited the study, they will be called and asked to return for one visit to complete anterior segment SD-OCT imaging. Sites will have 3 months, after the subject has exited, to bring in subjects for anterior segment SD-OCT evaluation, for those subjects who have previously completed the study.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Treatments

Subjects will be assigned to one of two treatment arms in the study based upon prior treatment for DME in the study eye.

Treatment in the TX Naive arm will consist of one unilateral injection of IVT aflibercept in combination with one unilateral injection of SC CLS-TA in the same eye.

Treatment in the Previous TX arm of the study will consist of one unilateral injection of SC CLS-TA.

Subjects will be assigned to either of the following groups:

1. **TX Naive**: IVT aflibercept [2 mg (50 µL)] + SC CLS-TA [4 mg (100 µL)]
2. **Previous TX**: SC CLS-TA [4 mg (100 µL)]

Approximately 20 subjects will be assigned in a 1:1 ratio where approximately 10 subjects will be enrolled into the TX Naive arm and approximately 10 subjects will be enrolled into the Previous TX arm.

9.2. Study Eye Determination

The study eye will be the eye receiving the CLS-TA injection or the IVT injection of aflibercept followed by a CLS-TA injection depending upon the group to which the subject is enrolled. The determination of the study eye will be based on Visit 1 (screening/baseline) information.

If both eyes meet study criteria, the eye, in the Investigator's opinion, with the better chance of achieving an improvement in anatomic findings on SD-OCT 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.

9.3. Fellow Eye Treatment

The fellow eye may receive any standard of care therapies necessary for treatment.

9.4. Re-Treatment Criteria

Re-treatment will be assessed monthly starting at Month 2 through Month 5. Subjects in either arm who meet at least one of the following criteria will be allowed retreatment with SC CLS-TA:

1. CSF > 320 µm AND not improved by at least 20% from either of the previous two visits [10% of CSF > 500 µm], (OR)

2. Loss of 10 or more letters due to DME from either of the previous two visits

9.5. Concomitant Medications

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

- Any corticosteroid implant (i.e., Ozurdex®, Iluvien® or Retisert™) in the study eye
- Topical, periocular or intravitreal corticosteroids in the study eye
- Any intravitreal agents except those specified in the study protocol
- Systemic anti-angiogenic drugs (anti-VEGF) including e.g. pegaptanib sodium, bevacizumab, ranibizumab
- Any investigational drug or device

In cases where there is anticipated need for the above listed medications during the study or if a subject presents to the Investigator having initiated treatment during the study with one of these medications or classes of medications, it is the responsibility of the Investigator to notify the Sponsor immediately. If additional therapy is necessary to treat worsening of DME 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 re-treatment criteria. Subjects will not be discontinued from the study due to initiation/change in a prohibited medication.

9.6. Treatment Compliance

Study drug will only be administered by trained study investigators (principal investigator or sub-investigator) in the office. No study drug will be dispensed to subjects; therefore, subject treatment compliance is not applicable.

9.7. Randomization and Masking

Subjects will be assigned to a study arm based upon their DME treatment history. No randomization will occur in this study. This study is an open-label study; no masking is necessary.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

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

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

10.2. Study Drug Packaging and Labeling

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

Each Investigational Use kit will contain the following components:

CLS-TA Kit:

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

Sites will provide aflibercept, needles and syringes necessary for administration to subjects in the TX Naïve arm.

10.3. Study Drug Storage

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

10.4. Study Drug Preparation

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

10.5. Administration

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

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

Detailed instructions on the CLS-TA injection procedure can be found in Appendix B.

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.

10.6. Study Drug Accountability

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

Study drug shipment records will be verified and accountability performed by comparing the shipment inventory sheet to the actual quantity of drug and microinjectors received at the site. 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 investigator or his/her designee. Study drug will be stored ambient at 20 - 25ºC (68 - 77ºF) and this area should have limited, controlled access with temperature monitoring.

10.7. Study Drug Handling and Disposal

At the end of the study and after study drug kit accountability has been verified, all study drug (used and unused vials) and unused microinjector components will be returned to the Clearside (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 return to the Clearside (or designee). All study drug and microinjector accounting procedures must be completed before the study is considered complete.

11. ASSESSMENT OF EFFICACY

11.1. Best Corrected Visual Acuity

BCVA will be evaluated by ETDRS chart using standardized lighting and standardized lanes. The results shall be reported as number of letters read. Visual acuity testing should precede any examination requiring contact with the eye.

11.2. Central Subfield Thickness

Retinal thickness and disease characterization will be assessed via spectral domain optical coherence tomography (SD-OCT) and OCT angiography (OCT-A). OCT-A will only be collected at those sites with available equipment for collecting these images. The technician is encouraged to use the same equipment throughout the subject's study participation. All images should be taken by the same photographer, whenever possible, on each subject per research site.

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

12.1.1. Intraocular Pressure

Intraocular pressure (IOP) will be measured by applanation tonometery (Goldmann) and results will be recorded in mmHg. Tonometers must be calibrated for accuracy.

12.1.2. Biomicroscopy

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

12.1.3. Indirect Ophthalmoscopy

Dilated ophthalmoscopy should be performed according to the investigator's standard dilation procedure. This procedure should be the same for all subjects observed at the investigator's site. The fundus will be examined thoroughly and the following variables (including but not limited to): vitreous, retina, choroid, and optic nerve/disc. Dilated indirect ophthalmoscopy will be assessed at every visit.

12.1.4. Fluorescein Angiography

FA will be performed on the study eye only at all visits at which it is performed. Disease characterization will be assessed and will include the area of fluorescein leakage. The technician is encouraged to use the same equipment throughout the subject's study participation. All images should be taken by the same photographer, whenever possible, on each subject per research site.

12.1.5. Fundus Photography

Wide color fundus photos will be obtained. It is recommended that when both fundus photos and FA are conducted in the same visit, the Fundus Photos should be taken first. The technician is encouraged to use the same equipment throughout the subject's study participation. All photos should be taken by the same photographer, whenever possible, on all subjects per research site.

12.1.6. Heart Rate and Blood Pressure

Vital signs will be measured on subjects after they have been seated for about 5 minutes. Resting heart rate and resting blood pressure (systolic and diastolic, preferably on the same arm each time) will be measured at the Screening/Baseline Visit.

12.1.6.1. Laboratory Tests

Urine pregnancy tests will be performed on all women of childbearing potential at each treatment visit.

HbA1C will be collected on all subjects at Screening and Exit Visits.

12.2. Adverse and Serious Adverse Events

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event (AE)

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

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

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:

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

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

12.3. Relationship to Study Drug

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

12.4. 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. Clinically significant changes in laboratory values, blood pressure, and pulse need not be reported as AEs. However, abnormal values that constitute an SAE or lead to discontinuation of administration of study drug must be reported and recorded as an AE. Information about AEs and Serious Adverse Events (SAEs) will be collected from the signing of consent form until the end of the study. 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.

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 11.2.1.2. An AE of severe intensity may not be considered serious.

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

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

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

12.5. Reporting Adverse Events

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

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

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

13. STATISTICS

13.1. Population to be Studied

The study population will include approximately 20 adult subjects (18 years or older) with diabetic macular edema who meet all of the Inclusion criteria, and Exclusion criteria and receive some amount of study drug. Approximately 3 US sites will recruit subjects for this study.

This study is designed as an open-label study with two treatment groups. As all subjects will be assigned to a treatment group based upon DME treatment history, no randomization will occur.

13.2. Study Populations

All safety analyses will be presented for the safety population, which will include all subjects who received at least one dose of study drug. This is a safety and tolerability study however efficacy analyses will be presented for the safety population as well. Such an analysis will ensure that benefit to risk is properly evaluated.

13.3. Analysis

All data collected in the study database will be presented in the listings. Listings will include change from baseline. Baseline is the Visit 1 pre-dose.

Summary statistics from Investigator findings will be tabulated and summarized descriptively. For categorical outcomes (e.g., normal or abnormal). For continuous outcomes (e.g., change in IOP), descriptive summary statistics will include the sample size, mean, median, standard deviation, standard error, minimum and maximum values.

No other statistical analysis will be prepared for this study.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of Clearside Biomedical will evaluate the investigational study site to:

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

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

The progress of the study will be monitored by onsite, written, e-mail, and telephone communications between personnel at the study center and the Clearside Biomedical. The Investigator will allow Clearside Biomedical 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.

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Clearside Biomedical may conduct a quality assurance audit.

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 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 of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB 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 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), or his/her designee, 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 RECORDKEEPING

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. 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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2. Menke A, Casagrande S, Geiss L, et al. Prevalence of and Trends in Diabetes Among Adults in the United States, 1988-2012. JAMA : the journal of the American Medical Association. 2015;314(10):1021-1029.

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4. Chen E, Looman M, Laouri M, et al. Burden of illness of diabetic macular edema: literature review. Current medical research and opinion. 2010;26(7):1587-1597.

5. Bourne RR, Jonas JB, Flaxman SR, et al. Prevalence and causes of vision loss in high-income countries and in Eastern and Central Europe: 1990-2010. Br J Ophthalmol. 2014;98(5):629-638.

6. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. Arch Ophthalmol. 1985;103(12):1796-1806.

7. Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic macular edema. Ophthalmology. 2014;121(11):2247-2254.

8. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology. 2012;119(4):789-801.

9. Campochiaro PA, Brown DM, Pearson A, et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. Ophthalmology. 2012;119(10):2125-2132.

10. Boyer DS, Yoon YH, Belfort R, Jr., et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmology. 2014;121(10):1904-1914.

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13. Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal Aflibercept for Diabetic Macular Edema: 100-Week Results From the VISTA and VIVID Studies. Ophthalmology. 2015;122(10):2044-2052.

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15. Campochiaro PA, Brown DM, Pearson A, et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. Ophthalmology. 2012;119(10):2125-2132.

16. Diabetic Retinopathy Clinical Research N, Elman MJ, Aiello LP, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmology. 2010;117(6):1064-1077 e1035.

17. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology. 2011;118(4):615-625.

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20. APPENDICES

APPENDIX A – Schedule of Events

	Screen & Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Informed Consent	X						
Demographics	X						
Medical/Ophthalmic History	X						
Vitals	X						
Pregnancy Test[1]	X		X	X	X	X	
Inclusion/ Exclusion	X						
HbA1C	X						X
Concomitant Medications	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
BCVA (ETDRS)	X	X	X	X	X	X	X
Intraocular Pressure[2]	X	X	X	X	X	X	X
SD-OCT (OU)	X	X	X	X	X	X	X
OCT-Angiography (OU)[3]	X			X			X
Anterior segment SD-OCT[3]				X	X	X	X
Fundus Photography	X						X
Fluorescein Angiography	X						X
Indirect Ophthalmoscopy/ Slit Lamp	X	X	X	X	X	X	X
Intravitreal Aflibercept	X						
Study Drug Treatment	X		X	X	X	X	

1. Urine pregnancy test will be done for females of child bearing potential on treatment visits
2. IOP will be measured by applanation tonometry (Goldmann)
3. Sites with capability to acquire OCT-A

APPENDIX B – Suprachoroidal Injection Instructions

APPENDIX B TO BE INSERTED HERE PRIOR TO RELEASE

APPENDIX B TO BE INSERTED HERE PRIOR TO RELEASE

APPENDIX C: 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)
Title Page		IND number added	For protocol identification	None
Table 1: Emergency Contact Information	Site Coordinating Leader Name: Chelsey Moore Telephone Number: 713.394.7575 Responsible Physician: Charles Wykoff, MD	Site Coordinating Leader Name: Cassie Cone Telephone Number: 713.394.7537 Responsible Physician: Charles Wykoff, MD, PhD	To update Site Coordinating Leader and telephone number To correct the responsible physician's title	None
2. Synopsis		**Exploratory:** • Scleral thickness • Suprachoroidal space visualization	To add scleral thickness, and suprachoroidal space visualization as exploratory endpoints	None
7.2.3. Exploratory Endpoint		• Scleral space thickness • Suprachoroidal space visualization	To add scleral thickness, and suprachoroidal space visualization as exploratory endpoints	None

Amendment 1

Section Changed	Initial Protocol (Changed From)	Modified Protocol (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
8.4.3.1. SC Injection of CLS-TA (Both study arms)	1. Select drug kit and document study kit number 2. Administer injection of 100 µL of CLS-TA into the SCS of the study eye using the Clearside microinjector, preferably in the superior temporal quadrant 3. For a full description of the SC injection procedure, see Appendix B 4. Immediately following injection, assess the study eye by indirect ophthalmoscopy	1. Anterior segment SD-OCT (at sites with capability) 2. Select drug kit and document study kit number 3. Administer injection of 100 µL of CLS-TA into the SCS of the study eye using the Clearside microinjector, preferably in the superior temporal quadrant 4. For a full description of the SC injection procedure, see Appendix B 5. Immediately following injection, assess the study eye by indirect ophthalmoscopy	To add collection of anterior segment SD-OCT	None
8.4.3.2. Post-Dose Procedures	1. Assess post dose AE's 2. Review changes to concomitant medications 3. Evaluate IOP 10-30 minutes post injection • If IOP remains elevated, subject must remain on site until IOP is under control per investigator judgement • If IOP is < 30 mmHg, the subject may leave the clinic	1. Assess post dose AE's 2. Review changes to concomitant medications 3. Anterior segment SD-OCT (at sites with capability) 4. Evaluate IOP 10-30 minutes post injection • If IOP remains elevated, subject must remain on site until IOP is under control per investigator judgement • If IOP is < 30 mmHg, the subject may leave the clinic	To add collection of anterior segment SD-OCT	None

Amendment 1

Section Changed	Initial Protocol (Changed From)	Modified Protocol (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
8.4.4. Visit 7 – [Month 6 (Day 180 ±3)] End of Study Visit or Early Termination Visit	4. Perform ophthalmic assessments on both eyes: a. ETDRS BCVA b. IOP c. SD-OCT d. OCT-A (at participating sites) e. Fundus photography f. Fluorescein angiography g. Slit-lamp biomicroscopy h. Dilated Indirect ophthalmoscopy	4. Perform ophthalmic assessments on both eyes: a. ETDRS BCVA b. IOP c. SD-OCT d. Anterior segment SD-OCT (at sites with capability) e. OCT-A (at participating sites) f. Fundus photography g. Fluorescein angiography h. Slit-lamp biomicroscopy i. Dilated Indirect ophthalmoscopy	To add collection of anterior segment SD-OCT	None
8.4.6. Anterior Segment SD-OCT		Anterior segment SD-OCT imaging will be performed pre-and post dose at visits where subjects meet re-treatment and at the exit visit. If a subject has exited the study, they will be called and asked to return for one visit to complete anterior segment SD-OCT imaging. Sites will have 3 months, after the subject has exited, to bring in subjects who have previously completed the study.	To determine scleral and suprachoroidal space thickness	None

Amendment 1

Section Changed	Initial Protocol (Changed From)	Modified Protocol (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Appendix A – Schedule of Events		Added anterior segment SD-OCT to V4, V5, V6 and V7 (at sites with capability)	To add collection of anterior segment SD-OCT	None
Throughout protocol	Miscellaneous typographical and formatting errors		To correct typographical and formatting errors	None
Throughout protocol	Various	Miscellaneous administrative clarifications	To clarify various text throughout the protocol	None

Clearside Biomedical, Inc. - Document Approval

CLS-CLIN-000064 v1.0: CLS1004-101 Study Protocol with Amendment 1 - HULK (v2.0)

Regulatory Approved	Barbara Bauschka Senior Director, Regulatory Operations 27-Jun-2017 17:37:21 GMT+0000

Medical Approved	Rick Beckman Chief Medical Officer 27-Jun-2017 18:24:10 GMT+0000

Clinical Science Approved	Glenn Noronha Chief Scientific Officer 27-Jun-2017 20:18:08 GMT+0000

Clinical Approved	Jennifer Kissner Vice President, Clinical Development 06-Jul-2017 14:51:11 GMT+0000

Approved: 06 Jul 2017 - CLS-CLIN-000064 v1.0