Compound Name:	CLS-TA, triamcinolone acetonide injectable suspension
Protocol Number:	CLS1004-201
IND Number:	115683
NCT Number:	NCT03126786
Protocol Title	**TYBEE**: Randomized, Double Masked, Controlled Study Comparing the Safety and Efficacy of Suprachoroidal CLSTA with Intravitreal Aflibercept versus Aflibercept Alone in Subjects with Diabetic Macular Edema
Sponsor:	Clearside Biomedical, Inc. 900 North Point Parkway, Suite 200 Alpharetta, GA 30005
Issue Date: **Protocol Amendment 1 Date:**	14 April 2017 19 January 2018

Clinical Protocol CLS1004-201

Project:	1004
Compound Number/Name:	CLS-TA (triamcinolone acetonide injectable suspension) 40 mg/mL
Protocol Number:	CLS1004-201
IND Number:	115683
Phase:	2
Protocol Title:	**TYBEE:** Randomized, Double Masked, Controlled Study Comparing the Safety and Efficacy of Suprachoroidal CLS-TA with Intravitreal Aflibercept versus Aflibercept Alone in Subjects with Diabetic Macular Edema
Sponsor:	Clearside Biomedical, Inc. 900 North Point Parkway, Suite 200 Alpharetta, GA 30005
Primary Medical Monitor:	Peter Nicholas, MD Telephone: (919) 259-9521
Principal Investigator:	To be appointed before the end of the study
Amendment 1.0 Issue Date:	19 January 2018
Issue Date:	14 April 2017
Sponsor Signatory:	**Jennifer Kissner, PhD**

CONFIDENTIAL

SIGNATURE PAGE

This study protocol amendment has been reviewed and approved by the undersigned persons. It is confirmed that the information and guidance given in this protocol amendment complies with scientific principles, the guidelines of Good Clinical Practices, the Declaration of Helsinki in the latest relevant version and the applicable legal and regulatory requirements.

Sponsor Signatory: **Jennifer Kissner, Ph.D.** **Vice President, Clinical Development** **Clearside Biomedical, Inc.**	***ELECTRONIC SIGNATURE ON FILE***	***19 Jan 2018***

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for CLS- TA (triamcinolone acetonide injectable suspension) 40 mg/mL. I have read the CLS1004-201 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Clinical Lead, Sponsor	Kathleen Billman kathleen.billman@clearsidebio.com	678.894.0703
Medical Monitor	Peter Nicholas, MD	919.259.9521
Principal Investigator	*The Coordinating Principal Investigator will be appointed by the Sponsor before the end of the study. As part of his or her responsibilities, the Coordinating Principal Investigator will review the final Clinical Study Report and will sign the report to confirm that it accurately describes the conduct and results of the study.*	

2. SYNOPSIS

Name of Sponsor/Company: Clearside Biomedical, Inc.	
Name of Investigational Product: CLS-TA (triamcinolone acetonide injectable suspension) 40 mg/mL EYLEA® (aflibercept) Injection	
Name of Active Ingredient: Triamcinolone Acetonide Aflibercept	
Title of Study: Randomized, Double Masked, Controlled Study Comparing the Safety and Efficacy of Suprachoroidal CLS-TA with Intravitreal Aflibercept versus Aflibercept alone in Subjects with Diabetic Macular Edema	
Study centers: Approximately 30 sites	
Principal Investigator: Multicenter	
Studied period (years): Estimated date first subject enrolled: 2Q2017 Estimated date last subject completed: 3Q2018	**Phase of development:** 2

Objectives:

The primary objective of this Phase 2 study is to compare the effects of suprachoroidal (SC) CLS-TA administered with intravitreal (IVT) aflibercept versus IVT aflibercept alone as measured by best corrected visual acuity (BCVA) change from baseline at Week 24 in subjects with treatment-naïve diabetic macular edema (DME)

Secondary:

- To compare the effect of SC CLS-TA administered with IVT aflibercept versus IVT aflibercept alone in central subfield thickness (CST) as measured by change from baseline at Week 24.
- To compare the effect of SC CLS-TA administered with IVT aflibercept every 3 months versus IVT aflibercept alone as measured by the number of additional IVT aflibercept injections required over 24 weeks through visit 5 (Week 12) and from Visit 5 (Week 12) through Visit 8 (Week 24).
- To evaluate monthly mean changes from baseline in BCVA as measured by ETDRS letters read
- To evaluate monthly mean changes from baseline in CST as measured by SD-OCT
- To evaluate mean monthly changes in excess retinal thickness from baseline excess retinal thickness in CST

Safety:

- To evaluate the incidence of treatment-emergent adverse events and serious adverse events, grouped by organ system, relatedness to study treatment, and intensity
- To evaluate the effect of study therapy on intraocular pressure and on the incidence of adverse event

• To evaluate the effect of study therapy on the incidence of and progression of potential cataractous changes to the lens
Number of subjects (planned): Approximately 70 subjects
Diagnosis and main criteria for inclusion: Treatment-naïve subjects diagnosed with DME
Investigational product, dosage, and mode of administration: CLS-TA (triamcinolone acetonide injectable suspension) 40 mg/mL injected suprachoroidally; EYLEA (aflibercept) 2 mg/0.05 mL, injected intravitreally
Reference therapy, dosage and mode of administration: EYLEA (aflibercept) 2 mg/0.05 mL, intravitreal injection
Criteria for evaluation: **Efficacy Endpoint:** The efficacy endpoint is the mean change from baseline in BCVA using Early Treatment of Diabetic Retinopathy Study (ETDRS) letters read at Week 24 (Month 6). **Secondary Endpoints:** • Mean change from baseline in CST at Visit 8 (Week 24) • Mean monthly changes in BCVA using ETDRS letters read • Mean monthly changes in excess retinal thickness from baseline excess retinal thickness in CST • Mean number of additional intravitreal aflibercept injections administered through Visit 8 (Week 24), through visit 5 (week 12) and from Visit 5 (week 12) through visit 8 (week 24) • Number and percentage of subjects gaining ≥5, ≥10, and ≥15 ETDRS letters at Visit 8 (Week 24) **Safety Endpoints:** • Incidence of treatment-emergent adverse events and serious adverse events, grouped by organ system, relatedness to study treatment, and intensity • Mean change from baseline in IOP at each follow-up visit • Percentage of subjects exhibiting an IOP change from baseline of 6-10mm Hg, 11-15 mm Hg, 16-20 mm Hg, and > 20 mm Hg at each visit • Number/percentage of subjects requiring institution of IOP lowering medications • Number/percentage of subjects experiencing an IOP ≥ 30 mm Hg • Number /percentage of subjects experiencing a ≥ 10 mm increase from baseline in IOP at any visit • Mean change in lens grading at each visit
Statistical methods: The primary efficacy analysis comparing outcomes from the ACTIVE treatment group with CONTROL treatment using the mean change from baseline (Visit 2, Day 0) BCVA at Week 24 will

be performed using a Mixed Model for Repeated Measurements (MMRM). This model will include treatment (Active or Control), visit (Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12), Visit 6 (Week 16), Visit 7 (Week 20), and Visit 8 (Week 24) and the 2-way interactions of treatment and visit, and the BCVA baseline will be included as the covariate. The dependent variable is the mean change from baseline BCVA at each time point. Taking into account the correlation of the BCVA measurements at each visit, the covariance structure may be assumed to be unstructured. The two-sided 90% confidence interval for the difference in the mean change from baseline in the ACTIVE and CONTROL treatment groups will be presented. The p-values for testing the treatment difference will also be reported based on MMRM model.

The primary analysis will be performed on the ITT population, with a supportive analysis conducted on the PP analysis set.

Treatment groups in secondary endpoints will be compared using a similar MMRM as used for the primary efficacy endpoint analysis, if appropriate. A descriptive analysis will be performed for all secondary endpoints. Additional analyses, for example, Kaplan-Meier method for time to first additional IVT aflibercept injection) will be added if appropriate, and these analyses will be detailed in the SAP and finalized before the study database lock.

For safety endpoints, incidence of TEAEs and SAEs, grouped by organ system, relatedness to study drug, and intensity will be summarized. Also the incidence of changes in safety parameters including: IOP, slit-lamp biomicroscopy, indirect ophthalmoscopy, imaging parameters, and vital sign measurements will be summarized.

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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
AMD	Age-related macular degeneration
ANCOVA	Analysis of covariance
BCVA	Best corrected visual acuity
CRC	Central reading center
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/angiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IA	IVT aflibercept
ICH	International Council for Harmonisation
IOP	Intraocular pressure
IRB	Institutional Review Board
ITT	Intent-to-treat
IVT	Intravitreal
IWRS	Interactive web response system
LOCF	Last observation carried forward
MAR	Missing at random
ME	Macular edema
MMRM	Mixed model for repeated measurements

Abbreviation or Specialist Term	Explanation
PI	Principal Investigator The Investigator who leads the study conduct at an individual study center. Every study center has a Principal Investigator.
PP	Per-protocol
PRN	Pro re nata; As needed
RVO	Retinal vein occlusion
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Suprachoroidal
SCS	Suprachoroidal space
SD-OCT	Spectral-domain optical coherence tomography
TA	Triamcinolone acetonide
TEAE	Treatment-emergent adverse event
VEGF	Vascular endothelial growth factor
VA	Visual acuity
YAG	Yttrium-Aluminum-Garnet

5. INTRODUCTION

Clearside Biomedical, Inc., is developing a proprietary formulation of triamcinolone acetonide (CLS-TA) as a candidate for treating diabetic macular edema (DME) to be administered via suprachoroidal injection either with or without an intravitreal (IVT) anti-VEGF agent. This Phase 2, multicenter, randomized, masked, controlled, parallel-group study is designed to evaluate and compare the safety and efficacy of suprachoroidal (SC) injection of CLS-TA administered in combination with intravitreal aflibercept (EYLEA®; Regeneron; Tarrytown, NY) given on a quarterly basis in relationship to monthly intravitreal aflibercept in subjects with DME.

Treatment of eye diseases using a suprachoroidal injection approach is novel; a drug can be precisely administered to and through the SCS using a minimally invasive injection procedure, and thereby have high exposure to the retina and choroid with the potential for pharmacological action because of high local concentration at the site of disease. Suprachoroidal injection of CLS-TA has been shown in animal models to distribute TA dominantly to posterior segment ocular tissues while limiting exposure to anterior structures in the eye, thereby providing the potential for efficacy and safety benefits. The purpose of this Phase 2 study is to obtain information on the safety and efficacy of suprachoroidal CLS-TA used with intravitreal aflibercept initially on quarterly basis and compare these effects to when intravitreal aflibercept is used alone and given monthly as monotherapy, in subjects with DME; further, a fixed dosing regimen for the first 12 weeks (Month 3) is followed by a protocol predefined as needed dosing regimen for the second 12 week portion through Week 24 (Month 6) after assigned arm treatment is administered at the Week 12 visit.

5.1. Disease Background and Scientific Rationale

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 United States (US) health care dollars are spent on DM care and the total annual attributable cost for DM is well over a quarter of a trillion dollars (ADA, 2013). While the burden of DM continues to rise globally, recent encouraging data suggest that the prevalence of DM within the United States may be plateauing with approximately 50% of adults affected with frank DM (13%) or pre-DM (38%) (Menke, 2015). Approximately 1/3 of patients with DM in the United States have DR and an estimated 7% will progress to the diagnosis of DME (Ding, 2012; Narayan, 2003). One of the most frequent end-organ manifestations of DR is DME, which is the most common cause of visual loss among working-age populations (Bourne, 2014; Chen, 2010; Sivaprasad, 2012).

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 (Early Treatment Diabetic Retinopathy Study research group, 1985). More recently, both IVT anti-VEGF-A and steroid injections have proven effective in DME management (Boyer, 2014; Campochiaro, 2012; Korobelnik, 2014; Nguyen, 2012; Wells, 2015) and have progressively replaced focal laser as the primary treatment of center-involving DME with visual acuity (VA) loss (Boyer, 2014; Brown, 2015; Campochiaro, 2012; Elman, 2010; Korobelnik, 2014; Mitchell, 2011; Nguyen, 2012). 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 (Brown, 2015; Elman, 2011; Korobelnik, 2014; Mitchell, 2011). Currently, 4 agents are approved by the US Food and Drug Administration (FDA) for the treatment of DME: EYLEA® (aflibercept) Injection (Regeneron), LUCENTIS® (ranibizumab injection) (Genentech), OZURDEX® (dexamethasone intravitreal implant) (Allergan), and ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg (Alimera Sciences). In addition, 1 agent is regularly used off label, AVASTIN® (bevacizumab) (Genentech).

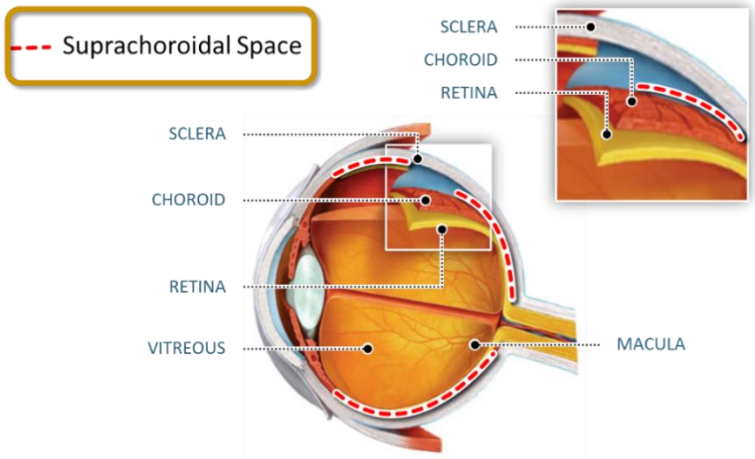
Anti-VEGF IVT injections have become the overwhelming choice for first-line treatment for DME associated with VA loss (2015 American Society of Retina Specialists Global Trends in Retina Survey). The only prospective trial directly comparing the 3 commercially available anti-VEGF agents was recently reported by the Diabetic Retinopathy Clinical Research Network (DRCR.net): Protocol-T, A comparative effectiveness study of intravitreal aflibercept, bevacizumab and ranibizumab for DME (Wells, 2015; Well, 2016). 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 IVT injections through 2 years, approximately 50% 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, IVT triamcinolone acetonide (TA) was as effective at improving VA as ranibizumab (Elman, 2010). No formulation of TA, by any route of administration, is currently approved by the FDA for the treatment of DME.

5.2. Description of Investigational Product

CLS-TA (triamcinolone acetonide injectable suspension) 40 mg/mL, is a preservative-free, terminally sterilized, aqueous suspension, formulated for administration into the eye. It will be administered as an injection of 4 mg in 100 µL into the SCS using Clearside's proprietary SCS™ microinjector. The 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) 40 mg/mL, is available in the Investigator's Brochure.

Aflibercept IVT injection is a prescription medicine approved in the United States and Europe as well as other global markets. Aflibercept is approved for the treatment of patients with Wet Age-related Macular Degeneration (AMD), ME following retinal vein occlusion (RVO), DME, and DR in patients with DME. Full prescribing information for aflibercept for the treatment of DME, the recommended dose for EYLEA intravitreal injection is 2 mg/0.05 mL administered by IVT injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg/0.05 mL via IVT injection once every 8 weeks (2 months).

5.3. Summary of Clinical Experience and Justification for Dose Selection

Triamcinolone acetonide has been used safely and effectively in human ocular therapeutics to treat conditions involving inflammation for over 50 years. The initial recommended dose of the TA formulation approved by the US FDA for ocular indications is 4 mg in 100 µL (TRIESENCE Prescribing Information, 2007). The dose of CLS-TA administered as an SC injection will be similar (40 mg/mL). TRIESENCE® (triamcinolone acetonide injectable suspension) 40 mg/mL, (Alcon) and CLS-TA contain the same active and inactive ingredients at approximately the same concentrations. Both formulations are preservative free, aqueous suspensions that have been terminally sterilized and designed for ophthalmic use.

Clearside has completed 2 clinical trials in patients with non-infectious uveitis and 1 clinical trial in patients with RVO.

The completed clinical study, CLS1001-101 (NCT01789320), was a Phase 1/2, open-label, safety and tolerability study in subjects with intermediate, posterior, or pan non-infectious uveitis (Goldstein, 2016). Each subject received a single SC injection of 4 mg in 100 µL TA (TRIESENCE). Nine of the 11 subjects in the safety analysis set (82%) completed the 26-week study. All subjects had at least 1 adverse event (AE), with a total of 37 AEs reported. One serious adverse event (unrelated pulmonary emboli; SAE) occurred. No deaths were reported. No significant increases in intraocular pressure (IOP) were reported. The most commonly reported AE, eye pain, was reported in 5 subjects. All subjects in the per-protocol analysis set (n=8) showed improvements in best corrected visual acuity (BCVA) in this study.

The completed clinical study, CLS1001-201 (NCT02255032), was a Phase 2, randomized, masked, dose-controlled, safety and efficacy study in subjects with ME associated with non-infectious uveitis. Twenty-two subjects were assigned to receive a single SC injection of CLS-TA, either 4 mg in 100 µL or 0.8 mg in 100 µL in a 4:1 randomization. Subjects in the 4.0 mg treatment group were observed to have a mean reduction in central subfield thickness (CST) of 164 microns (p=0.002) when measured from Baseline at 2 months. Mean improvement in BCVA was 9.2 ETDRS letters (p=0.0004) when measured from Baseline at 2 months. One SAE (unrelated atrial fibrillation) occurred. No subjects discontinued due to an AE, and there were no Investigator-reported increases in IOP at follow-up visits.

The completed clinical study, CLS1003-201 (CT02303184), was a Phase 2, randomized, masked safety and efficacy study in subjects with ME following RVO. Forty-six subjects were randomly assigned 1:1 to either a suprachoroidal (SC) injection of CLS-TA administered with an intravitreal injection of aflibercept (combination therapy; combo; ACTIVE), or an intravitreal

(IVT) injection of aflibercept alone (monotherapy; mono; 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.

Clearside is conducting a phase 1/2, open-label study in subjects with DME associated with diabetes mellitus to study the safety, tolerability, and preliminary efficacy of CLS-TA. 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. 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.

Safety profiles have been similar in all 3 completed studies with eye pain being the most commonly reported AE. Additional information regarding clinical experience with TA administered suprachoroidally is available in the Investigator's Brochure.

6. TRIAL OBJECTIVES AND PURPOSE

The purpose of this trial is to evaluate the safety and efficacy of suprachoroidal CLS-TA used with intravitreal aflibercept in subjects with DME associated with DM.

6.1. Primary Efficacy Objective

The primary objective of this Phase 2 study is to compare the effects of SC CLS-TA administered with IVT aflibercept versus IVT aflibercept alone as measured by BCVA change from baseline at Week 24 in subjects with treatment-naïve DME.

6.2. Secondary Efficacy Objectives

- To compare the effect of SC CLS-TA administered with IVT aflibercept versus IVT aflibercept alone in central subfield thickness (CST) as measured by change from baseline at Week 24.
- To compare the effect of SC CLS-TA administered with IVT aflibercept every 3 months versus IVT aflibercept alone as measured by the number of additional IVT aflibercept injections required over 24 weeks through visit 5 (Week 12) and from Visit 5 (Week 12) through Visit 8 (Week 24)
- To evaluate monthly mean changes from baseline in BCVA as measured by ETDRS letters read
- To evaluate monthly mean changes from baseline in CST as measured by SD-OCT
- To evaluate mean monthly changes in excess retinal thickness from baseline excess retinal thickness in CST

6.3. Safety Objectives

- To evaluate the incidence of treatment-emergent adverse events and serious adverse events, grouped by organ system, relatedness to study treatment, and intensity
- To evaluate the effect of study therapy on intraocular pressure and on the incidence of adverse events and initiation of therapy related to potential elevations of intraocular pressure
- To evaluate the effect of study therapy on the incidence of and progression of potential cataractous changes to the lens

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

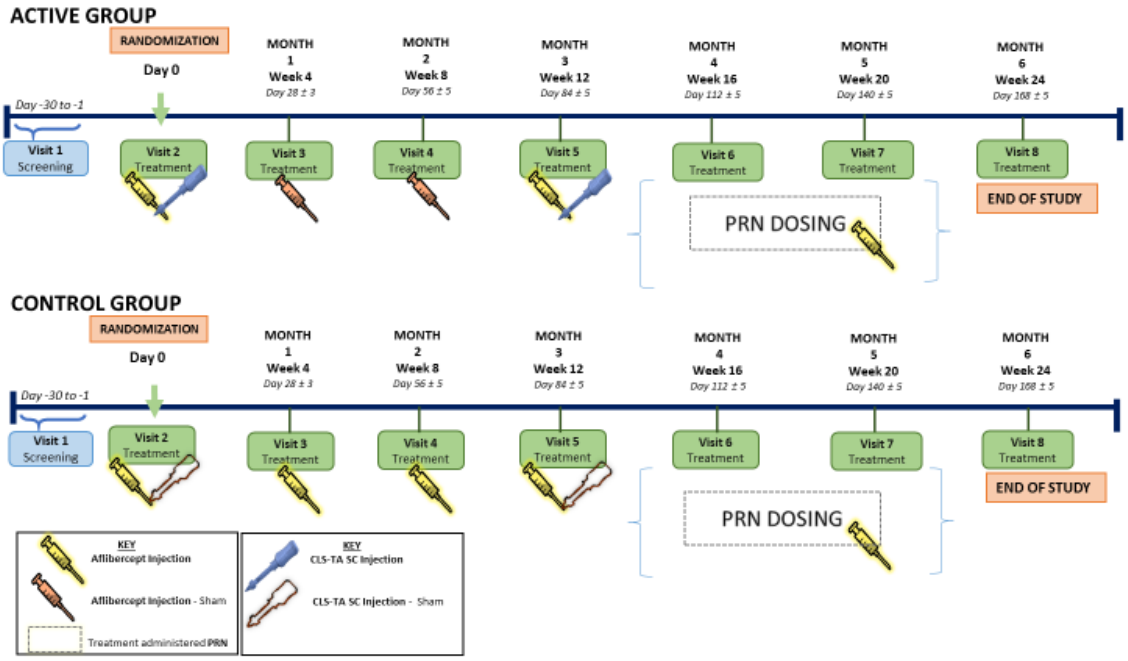
This is a Phase 2, multicenter, randomized, double-masked, controlled, parallel-group study of 6 months duration in treatment-naïve subjects with DME. This study is projected to enroll approximately 70 subjects, randomly assigned 1:1 to one of two treatment groups.

The study design includes up to 8 clinic visits over approximately 24 weeks. Subjects will attend visits for Screening (Visit 1, Days -30 to 0); Randomization and Baseline (Visit 2, Day 0 before dosing); Dosing and Evaluation (Visit 2 after dosing to Visit 5, Day 0 through Week 12); As-needed (PRN) Dosing and Follow-up (Visit 6 through Visit 7, Week 16 through Week 20), and End of Study (Visit 8, Week 24).

PRN Dosing and Follow-up Period:

At the conclusion of the dosing and evaluation period (Day 0 through Week 12), subjects will be followed for safety through Visit 8 (Week 24). Subjects will be treated, as needed (PRN), with aflibercept.

Figure 2: Study Design



7.2. Endpoints

7.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the mean change from baseline in BCVA ETDRS letters read at Week 24 (Month 6).

7.2.2. Secondary Efficacy Endpoints

- Mean monthly changes in BCVA using ETDRS letters read
- Mean change from baseline in CST at Visit 8 (Week 24)
- Mean monthly changes in excess retinal thickness from baseline excess retinal thickness in CST
- Mean number of additional intravitreal aflibercept injections administered through Visit 8 (Week 24), through visit 5 (Week 12) and from Visit 5 (Week 12) through Visit 8 (Week 24).
- Number and percentage of subjects gaining ≥5, ≥10, and ≥15 ETDRS letters at Visit 8 (Week 24)

7.2.3. Safety Endpoints

- Incidence of treatment-emergent adverse events (TEAE) and SAEs, grouped by organ system, relatedness to study treatment, and intensity
- Mean change from baseline in IOP at each follow-up visit
- Percentage of subjects exhibiting an IOP change from baseline of 6-10 mmHg, 11-15 mmHg, 16-20 mmHg, and > 20 mmHg at each visit.
- Number/percentage of subjects requiring institution of IOP lowering medications
- Number/percentage of subjects experiencing an IOP ≥ 30 mm Hg
- Number /percentage of subjects experiencing a ≥ 10 mm increase from baseline in IOP at any visit
- Mean change in lens grading at each visit

7.3. Number of Subjects

Approximately 70 subjects with DME who are naïve to treatment will be enrolled into 1 of 2 treatment groups.

7.4. Treatment Assignment

Subjects enrolled in this study will present with DME in the study eye. After Screening (Day -30 to Day -1) and Baseline assessments on Day 0, subjects will be randomly assigned 1:1 to 1 of 2 treatment groups.

TREATMENT ARM	Number of Subjects
ACTIVE: IVT aflibercept [2 mg (0.05 mL)] + SC CLS-TA [40 mg/mL]	~35
CONTROL: Intravitreal aflibercept [2 mg (0.05 mL)] + sham SC	~35

After randomization, subjects will receive treatment as follows:

ACTIVE: IVT aflibercept (2 mg/0.05 mL) + SC CLS-TA (40 mg/mL)

Subjects randomly assigned at Baseline to the ACTIVE group will receive an IVT injection of aflibercept followed by an SC injection of CLS-TA at Visit 2 (Day 0) and Visit 5 (Week 12). Subjects will receive sham IVT injections at Weeks 4 and 8 to maintain masking.

CONTROL: IVT aflibercept (2 mg/0.05 mL) injection + sham SC procedure

Subjects randomly assigned at Baseline to the CONTROL group will receive monthly IVT aflibercept injections beginning at Visit 2 (Day 0) and continuing through Visit 5 (Week 12). To maintain masking, subjects in the CONTROL group will also receive a sham SC procedure on Visit 2 (Day 0) and Visit 5 (Week 12).

All subjects will return for monthly (every 4 weeks) visits through Visit 8 (Week 24) to assess safety and efficacy. Beginning at Week 4 and applying also to Week 8, if any of the additional criteria (Section 9.4.1) are met in the study eye, IVT aflibercept should be administered. Beginning at Week 16 (Visit 6) continuing through Week 20 (Visit 7), if any of the additional criteria (Section 9.4.1) are met in the study eye, all subjects will be treated PRN with IVT aflibercept.

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 the 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 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of the termination or suspension and of the reasons.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Inclusion Criteria

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

1. Has a clinical diagnosis of type 1 or type 2 DM
2. Is at least 18 years of age, understands the language of the informed consent, and is willing and able to provide written informed consent before any study procedures

An eye is eligible for participation in the study if the following criteria are met:

3. Has DME with central involvement (> 300 μm in the central subfield on spectral-domain optical coherence tomography [SD-OCT], confirmed by the CRC) in the study eye
4. Has an ETDRS BCVA score of ≥ 20 letters read and ≤ 70 letters read in the study eye
5. Is naïve to local pharmacologic treatment for DME in the study eye

8.2. 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. Has evidence of or history of ME with etiology other than DME in a study eye
2. Has a history of panretinal photocoagulation or focal laser photocoagulation in the study eye within 90 days of screening
3. Has a IOP > 21 mmHg in the study eye at Visit 1 (Day -30 to -1); subjects are not excluded if IOP is <22 mmHg in the study eye with no more than 1 IOP-lowering medication as long as there is no history of glaucoma and the subject has a normal optic nerve and no evidence of visual field loss
4. Has a history of any previous ophthalmic surgeries in a study eye within 90 days of screening
5. Has High Risk Proliferative Diabetic Retinopathy in a 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. Has a history of any previous treatment in the study eye with an ocular corticosteroid implant (eg, ILUVIEN, OZURDEX, RETISERT)
7. Has a history of pars plana vitrectomy or a history of cataract extraction or Yttrium-Aluminum-Garnet (YAG) laser capsulotomy within the 3 months before treatment at Visit 2 (Day 0)
8. Has a history of an ocular procedure or condition in the study eye within the 3 months before randomization that, in the Investigator's opinion, could compromise globe or retinal integrity (eg, staphyloma, high myopia, predisposition to scleral thinning)

9. Has evidence of or a history of any ocular condition in the study eye that, in the opinion of the Investigator, would put the subject at risk due to study treatment or procedures (eg, active ocular infection, history of a SC hemorrhage, chalazion, significant blepharitis)
10. Has scarring from laser photocoagulation in the study eye that would compromise VA; or scarring or abnormality from other macular condition, in the investigator's medical judgement, would limit BCVA (such as an epiretinal membrane or macular hole)
11. Has had >3 macular laser photocoagulation treatments; or has had photocoagulation or cryotherapy in the study eye within the 6 months before Visit 2 (Day 0)
12. Has significant media opacity precluding evaluation of retina and vitreous in the study eye. This includes cataract that is felt to be a major contributor to reduced visual acuity and/or likely to undergo surgical repair within 3 months of randomization
13. Has a history of glaucoma or optic nerve head change consistent with glaucoma damage; or ocular hypertension in the study eye requiring more than one medication
14. Has ocular hypertension in the study eye requiring more than one medication to maintain IOP < 22 mm Hg at baseline
15. Has a history of glaucoma surgery (filtration surgery/trabeculectomy or tube shunt) in the study eye; has a history of laser trabeculoplasty in the study eye
16. Has a history of clinically significant IOP elevation in response to corticosteroid treatment ("steroid responder")

8.2.2. General Exclusion Criteria

Individuals are ineligible for participation in this study if he/she meets the following criteria:

17. Is a female who is pregnant, lactating or planning a pregnancy or is a female subject of childbearing potential who does not agree to submit to a pregnancy test at Screening; Females of childbearing potential must agree to use an acceptable method of contraception throughout participation in the study. Acceptable methods of contraception include double barrier methods (condom with spermicide or diaphragm with spermicide), hormonal methods (oral contraceptives; implantable, transdermal, or injectable contraceptives), or an intrauterine contraceptive device with a documented failure rate of less than 1% per year. Abstinence may be considered an acceptable method of contraception at the discretion of the Investigator, but the subject must agree to use 1 of the acceptable birth control methods if she becomes sexually active
18. Has any uncontrolled systemic disease that, in the opinion of the Investigator, would preclude participation in the study (eg, infection, uncontrolled elevated blood pressure, cardiovascular disease, poor glycemic control) or put the subject at risk due to study treatment or procedures.
19. Has had a myocardial infarction, other acute cardiac event requiring hospitalization, stroke, transient ischemic attack, or treatment for acute congestive heart failure within 1 month before enrollment
20. Has received systemic steroid, anti-VEGF, or pro-VEGF treatment within 4 months before Visit 2 (Day 0) or anticipated use during the study

21. Has a likely need for hospitalization or surgery within the study period, including planned elective surgery or hospitalization
22. Has a known hypersensitivity to any component of the formulation of TA, aflibercept, fluorescein, topical anesthetics, or the antiseptic used to prepare the eye for injection according to the Investigator's standard practice
23. Has uncontrolled blood pressure (defined as ≥180/110 mmHg systolic/diastolic, resting) at Visit 2 (Day 0)
    a. Uncontrolled BP at screening may be treated before Visit 2
24. Has a history of chronic renal failure requiring dialysis or kidney transplant
25. Has required the initiation of intensive (a pump or daily injections) insulin treatment for poor glycemic control within the 4 months prior to randomization or it is anticipated that such treatment may be needed during the next 4 months.
26. Is currently enrolled in an investigational drug or device study or has used an investigational drug within 30 days of entry into this study or participated in an ocular device study in the last 90 days.

8.3. Subject Withdrawal Criteria

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

Subjects who withdraw prematurely from the study will be asked to complete study assessments at the Early Termination Visit. If an SAE is unresolved at the time of the subject's final study visit, the Investigator should make every attempt to follow up until the SAE is resolved or stabilized, the subject is lost to follow-up, or there is some other resolution of the event.

8.4. Visit Procedure Descriptions

8.4.1. General Procedures

The study will consist of up to 8 study visits over approximately 24 weeks. All ocular assessments at Visit 1 (Screening) and Study Exit or Visit 8 (Week 24) will be performed on both eyes. Intraocular pressure will be assessed in both eyes at all visits. Data for all other ocular assessments at all other visits (Visits 2 to 7) will be collected for the study eye only.

Subjects will be screened for entry at Visit 1 (Days -30 to -1) and the study eye identified. Each eligible subject will return to the clinic within 30 days to be randomly assigned and treated at Visit 2 (Day 0). After baseline assessments and randomization on Day 0, subjects will receive an IVT injection of aflibercept (according to the Prescribing Information) in the study eye, followed by either a sham SC injection or a SC injection of CLS-TA in the study eye, depending on the group assigned at randomization. Subjects will be assessed after injection for safety.

Subjects in the CONTROL group will receive IVT injections of aflibercept at Visits 2 through 5. Subjects in the ACTIVE group will receive a sham IVT injection at Visits 3 and 4 (Weeks 4 and 8) to ensure masking is maintained.

After the completion of the dosing period (12 weeks), subjects will enter the PRN dosing period of the study to be observed and assessed for PRN treatment beginning at Visit 6 (Week 16) through Visit 7 (Week 20). Evaluation for PRN dosing will be similarly conducted at Visit 8 (Week 24) and the requirement whether criteria for intravitreal aflibercept are met will be recorded. Since the Week 24 visit is the exit visit, whether or not intravitreal anti-VEGF agent is administered is left to the discretion of the Investigator.

Subjects in the CONTROL group will receive sham SC injections at Week 12 to maintain masking. Additional safety follow-up visits will occur approximately every 4 weeks through Month 6 (Visit 3 through Visit 8; Weeks 4, 8, 12, 16, 20, and 24).

8.4.2. Re-Screening Procedures

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

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

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

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

1. Obtain written informed consent
2. Assign subject number
3. Collect demographic data and medical and ocular history
4. Review concomitant medications
5. Perform resting heart rate and blood pressure measurements
6. Collect blood and urine for central laboratory tests, including serum for pregnancy test in females of childbearing potential, before fluorescein angiogram (FA)
7. Perform a review of body systems
8. Perform ophthalmic assessments on both eyes:
    a. ETDRS BCVA
    b. Slit-lamp biomicroscopy, including dilated lens grading
    c. IOP
    d. Dilated indirect ophthalmoscopy
    e. SD-OCT*
9. Select study eye/confirm study eye
10. Perform photographic evaluations:*

a. FA

b. Fundus photos

11. Schedule subject to return for Visit 2, Baseline Evaluation

NOTE: *All images (SD-OCT, fundus photographs, and FA) should be uploaded to the central reading center (CRC).

8.4.4. Visit 2 (Day 0) and Visit 5 (Week 12)

Visit 2 must occur within 30 days of Visit 1 (Screening) and may only occur once the subject is determined to be eligible for treatment, which includes central laboratory results and confirmation of eligibility based on SD-OCT reading by the CRC being received and reviewed by the Investigator. No subject may be treated without CRC confirmation of eligibility.

The Visit 2 randomization procedures should not be conducted until the subject is deemed eligible based on meeting all of the inclusion and none of the exclusion criteria. Once randomly assigned, subjects will remain in the same treatment group for the duration of participation in the study.

8.4.4.1. Pre-dose Procedures: Visit 2 (Day 0) and Visit 5 (Week 12)

The following procedures must be performed before the injection (the same day as the injection):

1. Assess AEs
2. Review changes to concomitant medications
3. Perform resting heart rate and blood pressure
4. Collect urine for pregnancy test in females of childbearing potential
5. Perform ophthalmic assessments on the study eye only:
    a. ETDRS BCVA
    b. Slit-lamp biomicroscopy, including dilated lens grading
    c. IOP (both eyes)
    d. Dilated indirect ophthalmoscopy
    e. SD-OCT
6. Review eligibility criteria *(Visit 2 only)*
    a. If subject continues to be eligible for randomization based on results from screening and Visit 2 assessments in Section 8.2.3, subjects will be randomly assigned via the interactive web response system (IWRS) to receive either an IVT injection of aflibercept in conjunction with either sham or active SC injection of CLS-TA in the study eye.
7. Log onto the IWRS and randomly assign subject to treatment

8.4.4.2. Injection Procedures: Visit 2 (Day 0) and Visit 5 (Week 12)

The injection should be performed the same day as the pre-injection procedures. For details on the injection procedure, please see the Investigator Site File. The subject, non-injecting physician, Sponsor, study coordinator, visual acuity technician, and the CRC will be masked to treatment. The injecting physician and supporting study staff who are present during the injection procedure must be designated as unmasked for the study. Unmasked personnel should not perform efficacy assessments at any visit.

1. Confirm the study eye
2. Retrieve study drug kit number assigned by IWRS
3. Prepare eye for injection according to the Investigator's standard practice
4. The UNMASKED injecting Investigator should perform IVT injection of aflibercept, SC injection of CLS-TA, and all sham procedures to the study eye

8.4.4.2.1. IVT Injection of aflibercept:

1. Prepare study eye for IVT injection of aflibercept according to the Investigator's standard practice
2. Administer aflibercept IVT injection according to the Prescribing Information. *The sites of the IVT injection and the SC injection should be approximately 2 or more clock hours apart. A temporal quadrant is the recommended location for SC injections.*
3. Assess study eye by indirect ophthalmoscopy immediately after the injection,
4. Measure IOP after injection (study eye)

8.4.4.2.2. SC Injection of CLS-TA (ACTIVE) OR sham procedure (CONTROL):

1. When the study eye IOP is < 30 mm Hg, either spontaneously or by treatment, as determined by the Investigator, prepare study eye for SC injection according to the Investigator's standard practice
2. Administer SC injection of 100 µL of CLS-TA or sham procedure approximately 2 or more clock hours from the site of the IVT injection
3. Assess study eye by indirect ophthalmoscopy immediately after the injection

8.4.4.3. Post-Dose Procedures: Visit 2 (Day 0) and Visit 5 (Week 12)

The following assessments must occur after the IVT injection, SC injection, or sham procedures:

1. Assess AEs
2. Review changes to concomitant medications
3. Perform ophthalmic assessments on the study eye only:
    a. Slit-lamp biomicroscopy
    b. Evaluate IOP 10 to 30 minutes after injection

i. If IOP remains elevated, subject must remain on site until IOP is under control according to the Investigator's best medical judgment.

ii. If IOP is < 30 mmHg, the subject may leave the clinic

c. Indirect ophthalmoscopy

4. Schedule time for subject to return for next visit

8.4.5. Visit 3 (Week 4) and Visit 4 (Week 8)

The following procedures must be performed before the injection (the same day as the injection):

1. Assess AEs
2. Review changes to concomitant medications
3. Perform resting heart rate and blood pressure measurements
4. Perform ophthalmic assessments on the study eye only, unless otherwise specified:
    a. ETDRS BCVA
    b. Slit-lamp biomicroscopy, including dilated lens grading
    c. IOP (both eyes)
    d. Dilated indirect ophthalmoscopy
    e. SD-OCT

8.4.5.1. Injection Procedure: Visit 3 (Week 4) and Visit 4 (Week 8)

1. Confirm the study eye
2. Retrieve study drug kit number assigned by IWRS
3. Prepare eye for injection according to the Investigator's standard practice
4. The UNMASKED injecting Investigator should administer IVT injection of aflibercept OR sham IVT procedure to the study eye. (All subjects who meet PRN criteria will receive IVT aflibercept regardless of the arm to which they are assigned).
5. Assess study eye by indirect ophthalmoscopy immediately after the injection
6. Measure IOP after injection (study eye)
7. Schedule time for subject to return for next visit

8.4.6. Visit 6 (Week 16) and Visit 7 (Week 20)

The following procedures must be performed before the injection (the same day as the injection):

1. Assess AEs
2. Review changes to concomitant medications
3. Perform resting heart rate and blood pressure measurements
4. Perform ophthalmic assessments on the study eye only, unless otherwise specified:

a. ETDRS BCVA
b. Slit-lamp biomicroscopy, including dilated lens grading
c. IOP (both eyes)
d. Dilated indirect ophthalmoscopy
e. SD-OCT

8.4.6.1. Injection Procedure: Visit 6 (Week 16) and Visit 7 (Week 20)

1. If treatment is required, confirm the study eye
2. Retrieve aflibercept
3. Prepare eye for injection according to the Investigator's standard practice
4. The UNMASKED injecting Investigator should administer IVT injection of aflibercept. (All subjects who meet PRN criteria will receive IVT aflibercept regardless of the arm to which they are assigned).
5. Assess study eye by indirect ophthalmoscopy immediately after the injection
6. Measure IOP after injection (study eye)
7. Schedule time for subject to return for next visit

8.4.7. Visit 8 (Week 24) End of Study/Early Termination

Visit 8 is the final study visit. Subjects who terminate early should complete all Visit 8 assessments.

1. Assess AEs
2. Review changes to concomitant medications
3. Perform resting heart rate and blood pressure measurements
4. Collect blood and urine for central laboratory tests, including serum for pregnancy test in females of childbearing potential, before fluorescein angiogram (FA)
5. Perform a review of body systems
6. Perform ophthalmic assessments on both eyes:
    a. ETDRS BCVA
    b. Slit-lamp biomicroscopy, including dilated lens grading
    c. IOP
    d. Dilated indirect ophthalmoscopy
    e. SD-OCT
7. Perform photographic evaluations:
    a. FA
    b. Fundus photograph

8.4.8. Unscheduled Visits

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

9. TREATMENT OF SUBJECTS

9.1. Treatments to be Administered

Subjects will be assigned to 1 of 2 treatment groups in the study based upon randomization assignment.

Treatment in the ACTIVE group will consist of 2 unilateral SC injections of 40 mg/mL of CLS-TA administered 12 weeks apart (Visits 2 and 5), in conjunction with 2 unilateral injections of IVT aflibercept to the study eye. Subjects in the ACTIVE group will also receive sham IVT procedures to maintain masking at visits where the SC CLS-TA injection is not being administered (Visits 3 and 4).

Treatment in the CONTROL group of the study will consist of 4 unilateral IVT injections of aflibercept administered 4 weeks apart (Visits 2 through 5) in conjunction with 2 sham SC procedures administered 12 weeks apart (Visits 2 and 5) in the study eye.

Subjects will be assigned to either of the following groups:

1. ACTIVE: IVT aflibercept [2 mg (0.05 mL)] + SC CLS-TA [40 mg/mL]
2. CONTROL: IVT aflibercept [2 mg (0.05 mL)] + SC sham procedure

Approximately 70 subjects will be randomly assigned in a 1:1 ratio where approximately 35 subjects will be assigned to the ACTIVE group and approximately 35 subjects will be assigned to the CONTROL group.

Sham IVT and sham SC procedures will be performed using needleless hubs attached to the appropriate syringe to maintain masking. This is a non-invasive procedure.

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

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

9.2. Study Eye Determination

The study eye will be the eye receiving the IVT aflibercept, SC CLS-TA injection, or the sham procedures depending upon the group to which the subject is randomly assigned. The determination of the study eye will be based on Screening/Baseline information and will be determined before randomization.

The eye that is not designated as the study eye will be denoted as the fellow eye.

9.3. Fellow Eye Treatment

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 study. Medications used in the fellow eye will be recorded in the subject's medical chart and the case report form (CRF).

9.4. Additional Treatment

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

9.4.1. Additional Therapy Criteria

Beginning at Week 4 (Visit 3) and applying also to Week 8 (Visit 4), if any of the following criteria are met in a study eye, IVT aflibercept should be administered. These evaluations will be carried out by the masked investigator for all subjects in the study, regardless of initial treatment arm assignment.

- Macular edema (ME), defined as intraretinal or subretinal fluid (new or persistent), in conjunction with a CST ≥ 340 μm as measured by SD-OCT.
- A decrease in BCVA of 6 letters or greater between the current visit and the BCVA reading from the previous visit with an increase in CST of > 50 μm from the previous visit, associated with new fluid.
- A decrease in BCVA of 10 letters or greater from the best measurement (during the study) with an increase in CST of > 50 μm from the previous visit, associated with new fluid.

9.4.2. PRN Period Treatment Criteria

During the PRN dosing period (Visits 6 through 7 [Weeks 16 through 20]), treatments based on the criteria defined above in 9.4.1 may be administered using IVT aflibercept. The study arms will remain masked and additional dosing is limited to the criteria above. The frequency of treatment is at the Investigator's discretion during this period. All subjects will continue to be assessed for safety during the PRN dosing period.

9.5. Concomitant Treatments

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

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

- Increases to topical ophthalmic non-steroidal anti-inflammatory drugs in the study eye
- Any corticosteroid implant (e.g. OZURDEX, ILUVIEN, or RETISERT) in the study eye
- Topical, periocular, or IVT corticosteroids in the study eye
- High dose systemic corticosteroids (>10 mg/day of prednisone or equivalent) for more than 14 days
- Any IVT agents except those specified in the study protocol

- Systemic anti-angiogenic drugs (anti-VEGF) including, for example, bevacizumab
- Any investigational drug or device

In cases where there is anticipated need for any of the treatments listed here during the study, or if a subject presents to the Investigator having initiated treatment during the study with one of these treatments, it is the responsibility of the Investigator to notify the Sponsor immediately. If additional therapy is necessary to treat worsening of DME or DR in the study eye and normal standard of care requires additional intervention, the treatment(s) should be recorded in the subject's CRF and should follow the guidelines presented for rescue criteria. Subjects will not be discontinued from the study because of initiation of or change in a prohibited medication or treatment.

9.6. Treatment Compliance

Study drug will be administered only 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' randomized treatment assignments will be protected by using a masked allocation schedule created by a clinical allocation schedule system. Subjects, non-injecting physicians, site technicians measuring BCVA, and the CRC for images will be masked to treatment assignments. The randomization code will not be available to these individuals until after the study is completed and the database is locked.

In the event of a medical need, the injecting physician and supporting study staff who are present during the injection procedure are unmasked, thus immediate emergency unmasking is not necessary. Emergency unmasking of subjects by other Investigators or authorized clinical site personnel will occur via the IWRS.

Site technicians, CRC personnel, and designated readers and graders should not unmask the subject's randomized treatment assignment without the Sponsor's approval unless immediately required in response to an SAE. If the Sponsor is not notified before the unmasking event, the Investigator must immediately contact the Sponsor informing them of the specific details of the occurrence. The Sponsor personnel involved in the collection, interpretation, analysis, review, or any decision-making stemming from the study data will remain masked to subject status for the duration of the study unless otherwise warranted.

The subject will be masked to treatment throughout the study. The subject shall not discuss the study drug with any masked study personnel. All designated readers and graders, the subjects, the Sponsor's masked personnel, and masked monitors involved in reporting, obtaining, and reviewing the clinical evaluations for subjects will not be aware of the specific randomized treatment assignment for any subject.

Only study staff who are designated by the Investigator to prepare and administer study drug and conduct test article accountability may know the randomized treatment assignment. The unmasked Investigator and staff may not participate in efficacy assessments. The unmasked Investigator may participate in ophthalmic examinations before and after injection for safety.

Designee(s) will not discuss the test article with other site personnel or the Sponsor monitors and will instruct subjects not to discuss the study drug or appearance of the packaging with the Investigator, sub-Investigator(s) or any other study staff while the study is ongoing. This level of masking will be maintained throughout the conduct of the study.

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

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

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

CLS-TA (triamcinolone acetonide injectable suspension) 40 mg/mL, 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 SCHOTT 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 (active SC kit and sham SC kit) will be supplied to each site by the Sponsor and will be labeled for "Investigational Use only".

Commercially available aflibercept, needles, and syringes necessary for IVT administration and sham IVT administration will be provided by the Sponsor.

10.3. Study Drug Storage

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

Aflibercept should be stored according to the approved label.

10.4. Study Drug Preparation

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

Preparation of aflibercept will be performed according to the approved label.

10.5. Administration

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

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

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

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

Administration of aflibercept will be according to the approved label.

10.6. Study Drug Accountability

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

Study drug shipment records will be verified and accountability performed by comparing the shipment inventory sheet with the actual quantity of study drug kits received at the site. Accurate records of receipt and disposition of the study drug and injectors (eg, dates, quantity, subject number, kits used, kits unused) must be maintained by the Investigator or his/her designee.

10.7. Study Drug Handling and Disposal

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

11. ASSESSMENT OF EFFICACY

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

11.1. Best Corrected Visual Acuity

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

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

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

Retinal thickness and disease characterization will be assessed via SD-OCT. The SD-OCT instrument and technician must be certified before screening any subjects. The technician is encouraged to use the same certified equipment throughout the subject's study participation. All images should be taken by the same technician, whenever possible, on each subject per research site. Images will be sent to the CRC for analysis and interpretation in a masked fashion.

12. ASSESSMENT OF SAFETY

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

12.1. Safety Parameters

12.1.1. Vital Signs

Resting heart rate and resting blood pressure (systolic and diastolic, preferably on the same arm each time) will be measured at every visit after the subject has rested for about 5 minutes.

12.1.2. Review of Body Systems

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

12.1.3. Laboratory Assessments

Non-fasting clinical laboratory tests will be performed at Visits 1 and 8. These laboratory tests include serum chemistry, hematology, and urinalysis and are to rule out any underlying disease that may exclude the subject from participation.

12.1.3.1. Pregnancy Screen

Pregnancy tests will be performed on all females of childbearing potential. Serum or urine pregnancy tests are acceptable and will be performed at Visits 1, 2, 5 and 8.

12.1.3.2. Ophthalmic Screening

12.1.3.2.1. Intraocular Pressure

Intraocular pressure will be measured in both eyes by applanation tonometery and results will be recorded in mm Hg. Where available, Goldmann applanation tonometry should be used at all visits. Tonopens may be used for post-injection pressure checks and in cases where no Goldmann is available. The technician is encouraged to use the same tonometry method for all pre-injection and non-injection measurements throughout the subject's study participation. At any visit where both IVT aflibercept/sham and SC CLS-TA/sham injections are to be administered, IOP will be measured 3 times: before IVT aflibercept injection, after IVT aflibercept injection but before SC CLS-TA injection, and after SC CLS-TA injection. 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.

12.1.3.2.2. Slit lamp Biomicroscopy

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

Slit lamp examination of the iris is to rule out neovascularization of the iris (NVI).

12.1.3.2.3. Cataract Lens Grading

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

12.1.3.2.4. Indirect Ophthalmoscopy

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

12.1.3.2.5. Fluorescein Angiography

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

12.1.3.2.6. Fundus Photography

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

12.2. Adverse and Serious Adverse Events

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition after or during exposure to a pharmaceutical product, whether or not considered causally related to the product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered. This includes any laboratory value that is considered clinically significant by the Investigator or that requires additional testing or additional therapy.

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

12.2.1.2. Serious Adverse Event

An SAE is an AE occurring during any study phase (ie, baseline, treatment, washout, or follow-up), and at any dose of the investigational product, comparator, or placebo, that fulfils 1 or more of the following:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent 1 of the outcomes listed above.

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

12.2.2. Relationship to Study Drug

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

12.2.3. Recording Adverse Events

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

12.2.4. Intensity

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

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

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

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

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

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

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

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

12.2.5. Reporting Adverse Events

All SAEs (related and unrelated) will be recorded from the signing of the consent form until the end of study participation. Any SAEs considered related to the investigational product and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported to Clearside Biomedical, or its designee, within 1 business day of the first awareness of the event. The Investigator must complete, sign, and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy by fax to Clearside Biomedical, or its designee.

Additional follow-up information, if required or available, should be faxed to Clearside Biomedical, or its designee, within 1 business day of receipt. The information should be recorded

on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the CRF and/or study file.

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

12.2.6. Follow-up of AEs and SAEs

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

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

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

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

13. STATISTICS

A detailed statistical analysis plan (SAP) 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 70 subjects randomly assigned 1:1 to 1 of 2 treatment groups. Assignment of subjects to treatment groups will be performed via the IWRS.

13.2. Determination of Sample Size and Level of Significance

The sample size of the study is based on the primary variable of the study: the change from baseline mean BCVA at Week 24.

The sample size was determined such that the difference in visual acuity between the ACTIVE treatment group (SC CLS-TA administrated with IVT aflibercept) and CONTROL treatment group (IVT aflibercept) could be estimated within +/- five ETDRS letters. Week 24 data from the Eylea prescribing information were used to estimate the variance. The pooled standard deviation was 9.17 letters. With 28 subjects per arm, a two-sided 90% confidence interval with a distance from the mean difference to the limits (half of interval width) will be less than 5 letters.

To account for a drop-out rate of approximately 5%, at least 30 patients per group will be randomized. In the event that the withdrawal rate exceeds 5%, additional patients may be enrolled to ensure that at least 58 patients complete the Week 12 study period. The sample size calculation was performed using NCSS PASS (NCSS LLC, Kaysville, Utah).

13.3. Subject Disposition and Demographic and Baseline Characteristics

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

13.4. Analysis Populations

13.4.1. Safety Population

The Safety Population will include all randomly assigned subjects who are administered at least 1 dose of the study drug. All safety analyses will be based on the Safety Population.

13.4.2. Intent-to-Treat Population

The Intent-to-treat (ITT) Population will include all randomized subjects who have received at least 1 study treatment. Subjects will be analyzed as originally allocated after randomization. The ITT Population will be used for efficacy analyses.

13.4.3. Per Protocol Population

The Per-protocol (PP) Population will include all subjects in the ITT population who do not have significant protocol deviations and who complete the Week 12 visit. The rules for determining

exclusions from the PP Population will be finalized after a clinical review of the data and resolution of all queries but before unmasking of treatment assignments.

13.5. Analysis Methods

Efficacy and safety endpoints are provided in Section 7.2.

13.5.1. Primary Efficacy Analysis

The primary analysis is to compare the outcome from the ACTIVE treatment group with the CONTROL treatment, using the mean change from baseline (Visit 2, Day 0) BCVA at Week 24.

The primary efficacy analysis comparing ACTIVE with CONTROL on the mean change from baseline (Visit 2, Day 0) BCVA at Week 12 will be performed using a Mixed Model for Repeated Measurements (MMRM). This model will include treatment (ACTIVE or CONTROL), visit (Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12), Visit 6 (Week 16), Visit 7 (Week 20) and Visit 8 (Week 24), and the 2-way interactions of treatment and visit, and the BCVA baseline will be included as the covariate. The dependent variable is the mean change from baseline BCVA at each time point. Taking into account the correlation of the BCVA measurements at each visit, the covariance structure may be assumed to be unstructured. The two-sided 90% confidence interval for the difference in the mean change from baseline in the ACTIVE and CONTROL treatment group will be presented. The p-values for testing the treatment difference will also be reported based on MMRM.

The primary analysis will be performed on the ITT population, with a supportive analysis conducted on the PP analysis set.

13.5.1.1. Sensitivity Analyses of Primary Efficacy Endpoint

To evaluate the robustness of the analysis of the primary efficacy endpoint, sensitivity analyses will be performed using an analysis of covariance (ANCOVA) model in the ITT population. These sensitivity analyses will be detailed in the SAP and finalized before the study database lock.

13.5.2. Secondary Efficacy Analysis

13.5.2.1. Secondary Efficacy Endpoints

- Mean monthly changes in BCVA using ETDRS letters read
- Mean change from baseline in CST at Visit 8 (Week 24)
- Mean monthly changes in excess retinal thickness from baseline excess retinal thickness in CST
- Mean number of additional intravitreal aflibercept injections administered through Visit 8 (Week 24) through visit 5 (Week 12) and from Visit 5 (Week 12) through Visit 8 (Week 24).

A descriptive analysis will also be performed for all secondary endpoints. Additional analysis (eg: Kaplan-Meier method for time to first additional IVT aflibercept injection) will be added appropriately and these analyses will be detailed in the SAP and finalized before the study database lock.

13.5.3. Subgroup Analysis

No subgroup analyses are planned.

13.5.4. Safety Analysis

13.5.4.1. Extent of Exposure

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

13.5.4.2. Safety Endpoints

- Incidence of TEAEs and SAEs, grouped by organ system, relatedness to study drug, and intensity
- Incidence of changes in safety parameters including: IOP, slit-lamp biomicroscopy, indirect ophthalmoscopy, imaging parameters, and vital sign measurements

13.5.5. Schedule of Analyses

Additional safety and descriptive efficacy data will be collected through Week 24. Treatment codes will be broken at Month 6. Investigators, subjects, and study personnel who have contact with the Investigators or subjects will remain masked throughout the study.

Procedure for Accounting for Missing, Unused, or Spurious Data

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

For the primary efficacy endpoint analysis, missing data will be compensated for by the statistical analysis model. Specifically, an MMRM analysis will be used for the primary efficacy analysis. The MMRM analysis uses all available data to compensate for missing values and is generally recommended for handling missing data (Siddiqui, 2009) when the missing mechanism is Missing at Random (MAR).

For the ANCOVA model, the Last Observation Carried Forward (LOCF) method will be used if visits are missed in the ITT Population.

For the intent to treat population, all data points will be set to missing after a subject's receipt of a rescue medication only following the Week 12 evaluation and treatment when both groups will be dosed PRN.

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

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of Clearside Biomedical, Inc., will visit 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, Inc., or its representatives. This will be documented in a Clinical Study Agreement between Clearside Biomedical, Inc., and the Investigator.

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

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the CRFs, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the CRFs with the subject's medical records at the hospital or practice and other records relevant to the study. This will require direct access to all original records for each subject (eg, clinic charts)
- Record and report any protocol deviations not previously sent to Clearside Biomedical, Inc.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to Clearside Biomedical, Inc., 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, Inc., a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Clearside Biomedical, Inc., 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 (GCP) guidelines of the International Council for Harmonisation (ICH), and any applicable regulatory requirements. The Investigator should contact Clearside Biomedical, Inc., immediately if contacted by a regulatory agency about an inspection.

14.3. Institutional Review Board

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 subject 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 GCP and all applicable regulatory requirements, Clearside Biomedical, Inc., may conduct a quality assurance audit.

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

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

16. ETHICS

16.1. 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, Inc., or designee before he or she can enroll any subject into the study.

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

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

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

16.2. Ethical Conduct of the Study

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

16.3. Written Informed Consent

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

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

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

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

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

17.2. Retention of Records

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

18. PUBLICATION POLICY

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

19. LIST OF REFERENCES

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20. APPENDICES

APPENDIX A: Study Design and Schedule of Assessments, Visits 1-5

Visit #	Visit 1	Visit 2		Visit 3		Visit 4		Visit 5	
Visit Type	Screening	Randomization/Treatment Baseline Evaluation		Dosing and Evaluation					
Visit Window	Day -30 to -1	Day 0		Week 4 Day 28 ± 3		Week 8 Day 56 ± 5		Week 12 Day 84 ± 5	
Assessments		Pre-dose	Post-dose	Pre-dose	Post-dose	Pre-dose	Post-dose	Pre-dose	Post-dose
Informed Consent	•								
Assign Subject Number	•								
Assign Randomization Number		•							
Demographics, Medical & Ocular History	•								
Eligibility Criteria	•	•							
Assess Adverse Events	•	•	•	•	•	•	•	•	•
Concomitant Medication Review	•	•	•	•	•	•	•	•	•
Resting Heart Rate and Blood Pressure	•	•		•		•		•	
Urine Pregnancy Test		•						•	
Central Laboratory Tests[1]	•								
Review of Systems	•								
BCVA	•	•		•		•		•	
Slit-lamp Biomicroscopy[2]	•	•	•	•		•		•	•
IOP	•	•	•	•	•	•	•	•	•
Dilated Indirect Ophthalmoscopy	•	•		•		•		•	
Indirect Ophthalmoscopy			•		•		•		•
SD-OCT	•	•		•		•		•	
Select Study Eye/Confirm Study Eye	•	•		•		•		•	
Fluorescein Angiogram	•								
Fundus Photos	•								
IWRS/Randomize		•							
IVT Aflibercept or Sham Injection[3,]		•		•		•		•	
SC CLS-TA or Sham Injection[3,4]		•						•	

APPENDIX A: Study Design and Schedule of Assessments, Visits 6-8

Visit #	Visit 6		Visit 7		Visit 8
Visit Type	PRN Dosing and Follow Up				End of Study
Visit Window	Week 16 Day 112 ± 5		Week 20 Day 140 ± 5		Week 24 Day 168 ± 5
Assessments	Pre-dose	Post-dose	Pre-dose	Post-dose	
Demographics, Medical & Ocular History					
Eligibility Criteria					
Assess Adverse Events	•	•	•	•	•
Concomitant Medication Review	•	•	•	•	•
Resting Heart Rate and Blood Pressure	•		•		•
Urine Pregnancy Test					
Central Laboratory Tests[1]					•
Review of Systems					•
BCVA	•		•		•
Slit-lamp Biomicroscopy[2]	•		•		•
IOP	•	•	•	•	•
Dilated Indirect Ophthalmoscopy	•		•		•
Indirect Ophthalmoscopy		•		•	
SD-OCT	•		•		•
Select Study Eye/Confirm Study Eye	•		•		
Fluorescein Angiogram					•
Fundus Photos					•
IWRS/Randomize					
IVT Aflibercept or Sham Injection[3,]	PRN		PRN		
SC CLS-TA or Sham Injection[3,4]					

1. Central laboratory test samples should be collected before FA being performed; central laboratory tests include a serum pregnancy test for females of child-bearing potential.
2. Any finding of cataract should be graded.
3. All injection/sham procedures should be administered the same day as the pre-injection assessments.
4. Suprachoroidal or sham injection dependent on study treatment group assigned should be performed after the IVT aflibercept injection (once IOP is < 30 mmHg).

APPENDIX B: Summary of Changes

Amendment 1

Section Changed	Previous Protocol (Changed From)	**Modified Protocol (Changed To)**	**Reason for Change**	**Impact on Subjects (Risk/Benefit)**
2.0 6.1	The primary objective of this Phase 2 study is to compare the effects of SC CLS-TA administered with IVT aflibercept versus IVT aflibercept alone as measured by BCVA change from baseline at Week 12 in subjects with treatment-naïve DME	The primary objective of this Phase 2 study is to compare the effects of SC CLS-TA administered with IVT aflibercept versus IVT aflibercept alone as measured by BCVA change from baseline at Week 24 in subjects with treatment-naïve DME	Six months is a more appropriate evaluation time frame for this therapeutic approach in patients with diabetic macular edema; thus the 3-month primary endpoint has been changed to a 6-month primary endpoint	None
2.0 6.2	To compare the effect of SC CLS-TA administered with IVT aflibercept versus IVT aflibercept alone in central subfield thickness (CST) as measured by change from baseline at Week 12.	Deleted text	Six months is a more appropriate evaluation time frame for this therapeutic approach in patients with diabetic macular edema; thus the 3-month primary endpoint has been changed to a 6-month primary endpoint	None

APPENDIX B: Summary of Changes

Amendment 1

2.0 6.2	To compare the effect of SC CLS-TA administered with IVT aflibercept versus IVT aflibercept alone as measured by BCVA at Week 24	Deleted Text	Six months is a more appropriate evaluation time frame for this therapeutic approach in patients with diabetic macular edema; thus the 3-month primary endpoint has been changed to a 6-month primary endpoint	None
2.0 6.2	Additional text added to original protocol	To evaluate mean monthly changes in excess retinal thickness from baseline excess retinal thickness in CST	Additional endpoint to describe change in retinal thickness	None
2.0 6.2	To compare the effect of SC CLS-TA administered with IVT aflibercept every 3 months versus IVT aflibercept alone as measured by the number of IVT aflibercept injections required over 24 weeks	To compare the effect of SC CLS-TA administered with IVT aflibercept every 3 months versus IVT aflibercept alone as measured by the number of IVT aflibercept injections required over 24 weeks through visit 5 (week 12) and from Visit 5 (week 12) through Visit 8 (week 24)	Endpoint clarification for analysis to expand the endpoint to include analysis both at Week 12 and week 24	None

APPENDIX B: Summary of Changes

Amendment 1

2.0 7.1 7.3 13.1	This study is projected to enroll approximately 60 subjects, randomly assigned 1:1 to one of two treatment groups.	This study is projected to enroll approximately 70 subjects, randomly assigned 1:1 to one of two treatment groups.	Updated to reflect enrollment metrics to allow for a slightly larger population which will produce more robust evaluation of the therapy and to reflect the enrollment metrics	None
7.4 9.1 13.2	Approximately 60 subjects will be randomly assigned in a 1:1 ratio where approximately 30 subjects will be assigned to the ACTIVE group and approximately 30 subjects will be assigned to the CONTROL group.	Approximately 70 subjects will be randomly assigned in a 1:1 ratio where approximately 35 subjects will be assigned to the ACTIVE group and approximately 35 subjects will be assigned to the CONTROL group.	Updated to reflect enrollment metrics to allow for a slightly larger population which will produce more robust evaluation of the therapy and to reflect the enrollment metrics	None
7.2.1	The primary efficacy endpoint is the mean change from baseline in BCVA ETDRS letters read at Week 12 (Month 3).	The primary efficacy endpoint is the mean change from baseline in BCVA ETDRS letters read at Week 24 (Month 6).	Six months is a more appropriate evaluation time frame for this therapeutic approach in patients with diabetic macular edema; thus the 3-month primary endpoint has been changed to a 6-month primary endpoint	None

APPENDIX B: Summary of Changes

Amendment 1

2.0 7.2.2 13.5.2.1	Mean change from baseline in CST at Visit 5 (Week 12) and mean change from baseline in BCVA at Visit 8 (week 24)	Deleted text	To maintain consistency with change to 6-month primary endpoint	None
2.0 7.2.2 13.5.2.1	Additional text added	Mean monthly changes in BCVA using ETDRS letters read and mean monthly changes in excess retinal thickness from baseline excess retinal thickness in CST	Additional endpoint to evaluate endpoints monthly	None
2.0 7.2.2	Number and percentage of subjects gaining ≥5, ≥10, and ≥15 ETDRS letters at Visit 5 (Week 12)	Number and percentage of subjects gaining ≥5, ≥10, and ≥15 ETDRS letters at Visit 8 (Week 24)	Six months is a more appropriate evaluation time frame for this therapeutic approach in patients with diabetic macular edema; thus the 3-month primary endpoint has been changed to a 6-month primary endpoint	None

APPENDIX B: Summary of Changes

Amendment 1

2.0 7.2.2	Mean number of additional intravitreal aflibercept injections administered through visit 8 (week 24)	Mean number of additional intravitreal aflibercept injections administered through visit 8 (week 24), through visit 5 (week 12) and from Visit 5 (week 12) through visit 8 (week 24)	Endpoint clarification for analysis to expand the endpoint to include analysis both at week 12 and 24	None
12.1.3.2.4	Indirect ophthalmoscopy should be performed according to the Investigator's standard procedure.	Indirect ophthalmoscopy should be performed according to the Investigator's standard practice.	Clarified procedure vs. standard of practice	None
13.2	The sample size of the study is based on the primary variable of the study: the change from baseline mean BCVA at Week 12	The sample size of the study is based on the primary variable of the study: the change from baseline mean BCVA at Week 24	Six months is a more appropriate evaluation time frame for this therapeutic approach in patients with diabetic macular edema; thus the 3-month primary endpoint has been changed to a 6-month primary endpoint.	None
2.0 13.2	With 28 subjects per arm, a two-sided 95% confidence interval with a distance from the	With 28 subjects per arm, a two-sided 90% confidence interval with a distance from the	Wider confidence intervals allow for	None

APPENDIX B: Summary of Changes

Amendment 1

13.5.1	mean difference to the limits (half of interval width) will be less than 5 letters.	mean difference to the limits (half of interval width) will be less than 5 letters.	evaluation of trends in this Phase 2 study	
2.0 13.5.1	The primary analysis is to compare the outcome from the ACTIVE treatment group with the CONTROL treatment, using the mean change from baseline (Visit 2, Day 0) BCVA at Week 12.	The primary analysis is to compare the outcome from the ACTIVE treatment group with the CONTROL treatment, using the mean change from baseline (Visit 2, Day 0) BCVA at Week 24.	To maintain consistency with change to 6-month primary endpoint	None
2.0 13.5.1	This model will include treatment (ACTIVE or CONTROL), visit (Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12), and the 2-way interactions of treatment and visit, and the BCVA baseline will be included as the covariate	This model will include treatment (ACTIVE or CONTROL), visit (Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12), Visit 6 (Week 16), Visit 7 (Week 20) and Visit 8 (Week 24), and the 2-way interactions of treatment and visit, and the BCVA baseline will be included as the covariate	Six months is a more appropriate evaluation time frame for this therapeutic approach in patients with diabetic macular edema; thus the 3-month primary endpoint has been changed to a 6-month primary endpoint.	None

APPENDIX B: Summary of Changes

Amendment 1

13.5.5	Treatment codes will be broken at Month 3	Treatment codes will be broken at Month 6	To maintain consistency with change to 6-month primary endpoint	None
13.5.5	No adjustment for the analysis at Week 24 is required because the final analysis of efficacy is at Month 3 and data from all subsequent visits will be descriptive only.	Deleted text	To maintain consistency with change to 6-month primary endpoint	None

Clearside Biomedical, Inc. - Document Approval

CLS-CLIN-000195 v2.0: CLS1004-201 Study TYBEE Protocol Amendment 1

Clinical Approved This electronic signature indicates agreement by the individual that, with respect to their area of responsibility, the document is acceptable.	Jennifer Kissner Vice President, Clinical Development 22-Jan-2018 20:37:59 GMT+0000 Electronic signatures are certified as the legally binding equivalent of a traditional handwritten signature.

Regulatory Approved This electronic signature indicates agreement by the individual that, with respect to their area of responsibility, the document is acceptable.	Barbara Bauschka Senior Director, Regulatory Operations 22-Jan-2018 22:13:43 GMT+0000 Electronic signatures are certified as the legally binding equivalent of a traditional handwritten signature.

Approved: 22 Jan 2018 - CLS-CLIN-000195 v2.0