Compound Name:	CLS-TA, triamcinolone acetonide injectable suspension
Protocol Number:	CLS1003-302
IND Number:	115683
NCT Number:	NCT03203447
Protocol Title	**TOPAZ**: A Randomized, Masked, Controlled Trial To Study The Safety And Efficacy Of Suprachoroidal CLS-TA In Combination With An Intravitreal Anti-VEGF Agent In Subjects With Retinal Vein Occlusion
Sponsor:	Clearside Biomedical, Inc. 900 North Point Parkway, Suite 200 Alpharetta, GA 30005
Issue Date: **Protocol Amendment 1 Date:**	21 June 2017 25 January 2018

1. PROTOCOL AND AMENDMENTS

Table 1: Protocol CLS1003-302

Original Protocol / Amendment	Date	Protocol Revision
Amendment 1.1	25 Jan 2018	Protocol with Amendment 1.1
Original Protocol	21 Jun 2017	Original

SUMMARY OF CHANGES

Protocol Amendment 1.1

Protocol Title:	A RANDOMIZED, MASKED, CONTROLLED TRIAL TO STUDY THE SAFETY AND EFFICACY OF SUPRACHOROIDAL CLS-TA IN COMBINATION WITH AN INTRAVITREAL ANTI-VEGF AGENT IN SUBJECTS WITH RETINAL VEIN OCCLUSION		
Protocol Number: IND:	CLS1003-302 115683	Original Version Date:	21 Jun 2017
Amendment Number:	1.1	Version Date:	25 Jan 2018

Amendment 1

Section Changed	Previous Protocol (Changed From)	Modified Protocol (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Title Page and Footer		Updated protocol title and document version and date	Protocol versioning	None
Investigator's Agreement	I have received and read the Investigator's Brochure for CLS-TA.	I have received and read the Investigator's Brochure for CLS-TA and the Investigator's Brochure for bevacizumab.	Addition of bevacizumab Investigator's Brochure	None
2. Synopsis	Removed references to EYLEA as study drug	Added reference to AVASTIN and LUCENTIS as study drug	Comparator drug modification	None
		Added text to describe study treatment arms, including endpoints	Describe changes to study treatment arms	None
		Modified statistical analysis information	Comparator drug modification	
4. List of Abbreviations	IWRS – Interactive web response system	IRT – Interactive response technology	System update	None
5. Introduction		Provide background and describe rationale for use of Avastin and Lucentis in conjunction with CLS-TA	Comparator drug modification	None
Section 6.4 Exploratory Objectives		Added 'To evaluate changes from baseline based on disease type, BRVO and CRVO. Subjects with HRVO data will be included with the CRVO group based on randomization.'	Addition of exploratory objective	None
Section 7.2.3 Exploratory Efficacy Endpoints		Added 'Changes from Baseline on visual and anatomic outcomes based on disease diagnosis of BRVO and CRVO. HRVO	Addition of exploratory efficacy endpoint	None

Amendment 1

Section Changed	Previous Protocol (Changed From)	Modified Protocol (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
		subjects will be included with the CRVO for analyses.'		
Section 7.3 Number of Subjects	Approximately 460 subjects with RVO who are naïve to treatment will be enrolled into one of two treatment groups.	Approximately 460 subjects with RVO who are naïve to treatment will be enrolled into one of four treatment groups.	Update treatment groups	None
Section 7.4 Treatment Assignment	After Screening (Day -30 to Day -1) and Baseline assessments on Day 0, subjects will be randomly assigned 1:1 to one of two treatment groups stratified by disease type (BRVO, CRVO). Randomization will proceed as described until either strata reaches 55% of the total number patients to be enrolled at which time only patients from the other strata will be enrolled.	After Screening (Day -30 to Day -1) and Baseline assessments on Day 0, subjects will be randomly assigned 1:1:1:1 to one of four treatment groups stratified by disease type (BRVO, CRVO). Randomization will proceed as described until either strata within a group reaches at least 50% of the total number patients to be enrolled in that group at which time only patients from the other strata will be enrolled.	Treatment group changes	None
Table 3. Subject Randomization	Remove reference to IVT aflibercept	Change treatments arms to include IVT Avastin and Lucentis	Comparator drug modification and number of subjects per treatment group	None
Figure 2. Study Treatment Schedule	Removed previous table	Insert new table	Updates to table	None
Section 6.3. Exploratory Objectives		To determine the safety and performance of the SCS microinjector when delivering SC CLS-TA	Endpoint added to capture microinjector exploratory objective	None
Section 7.2.5 Endpoints Related to SCS microinjector		Performance of the SCS microinjector, evidenced by injection parameters (location, eye quadrant, needle length, injection	Section added for microinjector endpoints	None

Amendment 1

Section Changed	Previous Protocol (Changed From)	Modified Protocol (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
		completion, and product complaints) at each SC injection visit (Visits 2, 5, 8)		
		Incidence of TEAEs and SAEs related to the SCS microinjector		
Section 8.3. Subject Withdrawal Criteria		Added text for subject withdrawal criteria	Update withdrawal criteria	None
Section 8.4. Visit Procedure Descriptions		PRN therapy will be aflibercept for all subjects, regardless of randomization group.	Identify PRN treatment	None
		Removed slit lamp ophthalmoscopy assessment post injections	Update to reflect common clinic procedures	None
Section 9.1. Treatments to be Administered		Adjusted to include Avastin and Lucentis	Clarify treatment administration	None
Section 9.4. Rescue Treatment		Updated section 9.4.1 title from Rescue Therapy Criteria to Supplemental Therapy Criteria	Clarify definition of rescue versus supplemental therapy	None
		Updated rescue to supplemental throughout the protocol		
Section 10.4 Study Drug Preparation		Updated to include preparation for additional anti-VEGF agents	Comparator drug modification	None
Section 12.2. Adverse and Serious Adverse Events		Updates throughout to clarify adverse events and reporting	Clarification of reporting procedures	None

Amendment 1

Section Changed	Previous Protocol (Changed From)	Modified Protocol (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Section 12.2.4. Exposure In Utero		Addition of new section	Addition of new section	None
Section 13. Statistical Considerations		Updates throughout the statistical analysis section	Comparator drug modification	None
References		Addition of references	Comparator drug modification	None
Throughout protocol		Various formatting changes	Formatting updates	None
		Replaced 'aflibercept' with 'intravitreal anti-VEGF agent' or 'IVT anti-VEGF agent' inclusive of LUCENTIS and AVASTIN	Change in comparator agents	
Appendix A		Removed post injection slit lamp ophthalmoscopy assessment	Update to reflect common clinic procedures	None
		Removed serum pregnancy test at Visit 8	Urine pregnancy test will be done at Visit 8	None

Amendment 1.1

Section Changed	Previous Protocol (Changed From)	Modified Protocol (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Section 8 Headers		Section Header Numbers added for ease in navigating document	Formatting updates	None
Section 12.2.4 Intensity	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.	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.	Section reference corrected	None
Section 12 Headers		Section Header Numbers updated to remove duplicate	Formatting updates	None

Clinical Protocol CLS1003-302

Project:	1003
Compound Number/Name:	CLS-TA (triamcinolone acetonide injectable suspension) 40 mg/mL
Protocol Number:	**CLS1003-302**
IND Number:	115683
EudraCT Number:	**2017-002089-37**
Phase:	3
Protocol Title:	**TOPAZ:** A RANDOMIZED, MASKED, CONTROLLED TRIAL TO STUDY THE SAFETY AND EFFICACY OF SUPRACHOROIDAL CLS-TA IN COMBINATION WITH AN INTRAVITREAL ANTI-VEGF AGENT IN SUBJECTS WITH RETINAL VEIN OCCLUSION
Sponsor:	Clearside Biomedical, Inc. 900 North Point Parkway, Suite 200 Alpharetta, GA 30005
Primary Medical Monitor:	Peter Nicholas, MD Telephone: (919) 259-9521
Global Principal Investigator:	To be appointed before the end of the study
Protocol Amendment 1.1	**25 January 2018**
Protocol Amendment 1:	14 December 2017
Issue Date:	21 June 2017
Sponsor Signatory:	Jennifer Kissner, PhD

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***	***25 Jan 2018***

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for CLS-TA and the Investigator's Brochure for bevacizumab. I have read the Lucentis Prescribing Information and Summary of Product Characteristics. I have read the CLS1003-302 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Telephone number
Primary Medical Monitor (24-Hour emergency contact)	Peter Nicholas, MD	(919) 259-9521
Sponsor Clinical Lead	Kathleen Billman	(678) 894-0703
Principal Investigator	*The Global Coordinating Principal Investigator will be appointed by the Sponsor before the end of the study. As part of his or her responsibilities, the Global 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 Company:
Clearside Biomedical, Inc.

Name of Study Drug:
CLS-TA, (triamcinolone acetonide injectable suspension) 40 mg/mL
LUCENTIS® (ranibizumab injection) for intravitreal injection
AVASTIN® (bevacizumab) injection

Name of Active Ingredient
Triamcinolone Acetonide
Ranibizumab
Bevacizumab

Title of Study: TOPAZ: A randomized, masked, controlled trial to study the safety and efficacy of suprachoroidal CLS-TA in combination with an intravitreal anti-VEGF agent in subjects with retinal vein occlusion

Study center(s): Approximately 150 sites globally

Protocol Number: CLS1003-302

Study Duration: 12 Months Estimated date first subject enrolled: 1Q2018 Estimated date last subject completed: 3Q2020	**Study Phase:** 3

Objectives:

Primary:

- To demonstrate that suprachoroidally injected CLS-TA in combination with an intravitreally injected anti-VEGF agent is superior to an intravitreally injected anti-VEGF agent alone using a best corrected visual acuity (BCVA) outcome measure.

Secondary:

- To determine the effect of suprachoroidally injected CLS-TA in combination with an intravitreally injected anti-VEGF agent on mean change from Baseline in BCVA
- To determine the effect of suprachoroidally injected CLS-TA in combination with an intravitreally injected anti-VEGF agent on mean change from Baseline in central subfield thickness

Safety:

- To evaluate the safety and tolerability of suprachoroidally injected CLS-TA used in combination with an intravitreally injected anti-VEGF as measured by reported adverse events and safety parameters

Number of Subjects: Approximately 460 (approximately 230 subjects per arm) randomly assigned 1:1:1:1 to one of four treatment groups stratified by disease (BRVO, CRVO). Subjects with HRVO will be included in this study in the CRVO group. Randomization will proceed as described until

either stratum within a group reaches approximately 50% of the total number patients to be enrolled in that group at which time only patients from the other stratum will be enrolled.

Diagnosis and main criteria for inclusion:

Treatment naïve patients diagnosed with macular edema secondary to retinal vein occlusion

Investigational product, dosage and mode of administration:

CLS-TA, triamcinolone acetonide injectable suspension, 4 mg in 0.10 mL, suprachoroidal (SC) injection

Lucentis (ranibizumab) Injection, 0.5 mg in 0.05 mL, intravitreal (IVT) Injection

Avastin (bevacizumab) Injection, 1.25 mg in 0.05 mL, IVT Injection (supplied in single use container)

Reference therapy, dosage and mode of administration:

Lucentis (ranibizumab) Injection 0.5 mg in 0.05 mL, IVT injection

Avastin (bevacizumab) Injection 1.25 mg in 0.05 mL, IVT Injection (supplied in single use container)

Standard of care therapy (PRN period):

EYLEA® (aflibercept) Injection 2 mg in 0.05 mL, IVT injection

Treatment Groups:

ACTIVE ARM:

Lucentis (0.5 mg/0.05 mL), IVT injection + CLS-TA (4 mg/0.10 mL), SC injection

Avastin (1.25 mg/0.05 mL), IVT injection + CLS-TA (4 mg/0.10 mL), SC injection

CONTROL ARM:

Lucentis (0.5 mg/0.05 mL), IVT injection + sham SC procedure

Avastin (1.25 mg/0.05 mL), IVT injection + sham SC procedure

Criteria for Evaluation:

The approximately 460 subjects (approximately 230 subjects per arm) will be randomly assigned 1:1:1:1 to one of four treatment groups. Of the four groups, two groups each will receive the combination of a suprachoroidal injection of CLS-TA and an intravitreal injection of an anti-VEGF agent (bevacizumab or ranibizumab) as the active (combination) arm; and two groups each will receive an intravitreal injection of an anti-VEGF agent alone, either bevacizumab or ranibizumab, used as a control (monotherapy) arm.

In terms of analysis, the consideration will be that there are two arms, an active (combination) arm and a control (anti-VEGF only) arm: the two active (combination) groups with CLS-TA and an anti-VEGF agent will be pooled as the active (combination) arm; and the two anti-VEGF only groups will be pooled as the control (monotherapy) arm. The primary outcome will be based on comparing best corrected visual acuity data from the active (combination) arm to that from the control (monotherapy) arm. Specifically, the primary endpoint is the proportion of subjects demonstrating ≥ 15 Early

Treatment of Diabetic Retinopathy Study letter improvement from Baseline in BCVA at Week 8 (Month 2).

Statistical Methods:

The primary endpoint is the proportion of subjects demonstrating ≥ 15 letter improvement from Baseline in ETDRS BCVA at Week 8 (Month 2).

The primary analysis is a test of superiority of CLS-TA (TA) administered suprachoroidally in combination with an anti-VEGF agent (IA) administered intravitreally vs an intravitreally administered anti-VEGF agent used alone. Tests will be conducted using two-sided *alpha* = 0.05. The formal hypothesis is:

H_0: IA + TA = IA
H_1: IA + TA ≠ IA

The primary analysis will use the Cochran-Mantel-Haenszel test to evaluate differences in the proportion of subjects in the two arms who show 15 or more letters improvement in BCVA at the Month 2 visit after adjusting for effects for disease type. Subjects who either receive rescue treatment or withdraw from the study prior to the Month 2 visit will be considered as treatment failures for the primary endpoint analysis.

In this trial since the primary comparison will be at Month 2, and as this is a single test, there are no multiplicity issues for the primary comparison. The model will include an interaction for adjunctive treatment by anti-VEGF agent type. This will be used in sensitivity testing to see if there is a similar response to the adjunct CLS-TA therapy between the two types of VEGF inhibitors in the two active (combination) groups (CLS-TA with ranibizumab, or CLS-TA with bevacizumab) that comprise the active (combination) arm.

Additional safety and descriptive efficacy data will be collected through approximately 12 months. Treatment codes will be broken at Month 2, and the final efficacy analysis will be conducted at this time. A descriptive follow-up safety and efficacy analysis will be performed at 6 months to allow filing for marketing authorization. Investigators, subjects, and study personnel who have contact with the Investigators or subjects will remain masked throughout the study. No adjustment for the follow-up analysis at Month 6 is required because the final analysis of efficacy is at Month 2 and data from all subsequent visits will be descriptive only.

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

TABLE OF CONTENTS

LIST OF TABLES

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4. LIST OF ABBREVIATIONS

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

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
AMD	Age-related macular degeneration
BCVA	Best corrected visual acuity
BRB	Blood-retinal barrier
BRVO	Branch retinal vein occlusion
CNV	Choroidal neovascularization
CRC	Central reading center
CRF	Case report form
CRVO	Central retinal vein occlusion
CST	Central subfield thickness
EDC	Electronic data capture
EQ-5D	EuroQol 5 Dimensions Questionnaire
ETDRS	Early Treatment of Diabetic Retinopathy Study
FA	Fluorescein angiography/angiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HRVO	Hemiretinal vein occlusion
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IOP	Intraocular pressure
IRB	Institutional Review Board
ITT	Intent-to-treat
IVT	Intravitreal
IRT	Interactive response technology

ME	Macular edema
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Non-steroidal anti-inflammatory drug
OCT	Optical coherence tomography
PHI	Protected health information
PRN	Pro re nata; As needed
RVO	Retinal vein occlusion
SAE	Serious adverse event
SC	Suprachoroidal
SCS	Suprachoroidal space
SD-OCT	Spectral-domain optical coherence tomography
TA	Triamcinolone acetonide
TEAEs	Treatment-emergent adverse events
VEGF	Vascular endothelial growth factor
VA	Visual acuity
VFQ-25	Visual Function Questionnaire

5. INTRODUCTION

Clearside Biomedical, Inc., is developing CLS-TA, a proprietary ophthalmic formulation of triamcinolone acetonide (TA) to be used adjunctively (in "combination") with an anti-VEGF agent to treat subjects with retinal vein occlusion (RVO).

A phase 3 trial, SAPPHIRE, in treatment naïve RVO subjects is currently ongoing. SAPPHIRE is a multicenter, randomized, masked, controlled, parallel group study and is designed to show that suprachoroidally injected CLS-TA in combination with the intravitreally injected anti-VEGF agent, aflibercept (EYLEA®), is superior to intravitreally injected aflibercept, the anti-VEGF agent alone, using best corrected visual acuity (BCVA) as an outcome measure.

This protocol, for the second phase 3 trial ("TOPAZ"), also in pharmacologic treatment naïve RVO subjects, will evaluate a similar concept to the one being studied in SAPPHIRE. TOPAZ will evaluate the potential to combine suprachoroidally injected CLS-TA with an intravitreally injected anti-VEGF agent. Specifically, the trial will evaluate ranibizumab and bevacizumab, the other two most commonly used anti-VEGF agents, each in combination with CLS-TA and compare these data to the monotherapy agents, ranibizumab and bevacizumab, used alone. TOPAZ is a multicenter, randomized, masked, controlled, parallel group study and is designed to show that suprachoroidally injected CLS-TA in combination with an intravitreally injected anti-VEGF agent is superior to an intravitreally injected anti-VEGF agent (ranibizumab, bevacizumab) used alone, using BCVA as outcome measure.

Suprachoroidal (SC) administration is a novel approach being evaluated for the treatment of posterior segment eye diseases; drugs can be delivered to the suprachoroidal space (SCS) with access to the retina and choroid via a minimally invasive procedure, a suprachoroidal injection. Data from animal models show distribution of triamcinolone acetonide (TA) dominantly in posterior segment ocular tissues (sclera, choroid, retinal pigmented epithelial (RPE) cells, retina) while limiting exposure to anterior structures including the lens in the eye following suprachoroidal injection of TA, thereby providing the rationale for improved efficacy (high drug exposure to the choroid, RPE and retina) and the potential for an enhanced safety profile (sparing of the anterior chamber and lens) in the case of TA.

In terms of the three commonly used anti-VEGF agents (aflibercept, ranibizumab and bevacizumab) in treatments of posterior segment eye diseases, data are available from several level 1 type studies in subjects with neovascular age related macular degeneration (neovascular AMD) where ranibizumab and bevacizumab have been compared and bevacizumab has been shown to be non-inferior to ranibizumab in improvement in visual acuity at the 12 month primary endpoint; the first of these studies was the Comparison of Age-Related Macular Degeneration Treatments Trial (CATT) (CATT Research Group 2011). All three agents have been evaluated in the Protocol T trial in subjects with diabetic macular edema (Wells, 2016). In subjects with RVO, comparative data between these anti-VEGF agents are limited to the one clinical trial with level 1 evidence, where aflibercept and bevacizumab were evaluated in subjects with central RVO (CRVO) and hemi RVO (HRVO), the SCORE2 study. Based on a comparison of mean change in visual acuity from baseline, bevacizumab was non-inferior to

aflibercept at the 6-month primary endpoint following six monthly injections of these agents in this parallel arm trial (Scott, 2017). Further, in a level 2 study comparing ranibizumab and bevacizumab, both agents were shown to be effective for the treatment of BRVO and produced similar visual and anatomic outcomes at 6 months (Son, 2017).

Corticosteroids exert effects in part by tackling multiple cytokines upregulated by inflammatory and ischemic insults and by restoring damaged blood-retinal barrier, are different from the anti-VEGF agents in their molecular targeting (their primary mechanism does not involve reversibly binding VEGF even though they can downregulate VEGF), and have been shown to be effective for the treatment of subjects with RVO (Ip, 2009; Scott, 2009; Ozurdex Prescribing Information 2014). More specifically, the corticosteroid, TA, has been shown to improve the visual acuity of subjects with RVO in the SCORE BRVO and SCORE CRVO trials conducted by the National Eye Institute (NEI) (https://nei.nih.gov/score/score_background). Further, CLS-TA, the ophthalmic formulation of TA from the Sponsor, has been validated in its ability to provide a significantly better early (month 2; $p<0.05$) visual acuity outcome in combination with the intravitreal agent aflibercept, when compared to intravitreal aflibercept when used alone, in a controlled, masked, randomized phase 2 trial, TANZANITE. Detailed data from TANZANITE are provided in the Investigator Brochure and in Section 5.3 of this protocol.

While CLS-TA, the Sponsor's proprietary aqueous, preservative-free, terminally-sterilized, injectable, suspension formulation of TA (40 mg/mL) is being evaluated in combination with aflibercept in the phase 3, SAPPHIRE trial, it is likely that combining CLS-TA with ranibizumab or combining CLS-TA with bevacizumab will show similar outcomes in terms of visual acuity improvements to the outcomes seen from combining CLS-TA with aflibercept. These three anti-VEGF agents have similar mechanisms of action in that their primary role is to reversibly bind and sequester VEGF, and these three agents have provided similar outcomes in improvements in visual acuity at the primary endpoints in adequately powered, well-controlled clinical trials in subjects with RVO (EYLEA Prescribing Information, 2017; EYLEA Summary of Product Characteristics, 2017; LUCENTIS Prescribing Information, 2017; LUCENTIS Summary of Product Characteristics, 2016; Scott, 2017).

The purpose of this phase 3, TOPAZ study, is to demonstrate the efficacy of CLS-TA when used in combination with an anti-VEGF agent (ranibizumab, bevacizumab) when compared to these anti-VEGF agents (ranibizumab, bevacizumab) alone using a BCVA outcome measure, in subjects who are pharmacologic treatment naïve for their RVO.

5.1. Disease Background and Scientific Rationale

Retinal vein occlusion is the second most common cause of vision loss due to retinal vascular disease with a worldwide prevalence of 16.4 million affecting mostly those over the age of 40. Data pooled from 15 population studies in the United States (US), Europe, Asia, and Australia suggest that there are approximately 520 new cases of RVO per million population. These include 442 and 80 cases per million, respectively, of BRVO and CRVO (Rogers, 2010).

RVO is a prevalent ischemic retinopathy, second only to diabetic retinopathy (Mitchell, 1996; Koh, 2016). The blockage of a retinal vein leads to hypoperfusion and ischemia accompanied by inflammation of the vasculature and edema in the area drained by the affected vein (Ehlers, 2011). The severity and prognosis depend on the location of the blockage. CRVO occurs when there is thrombosis that occludes the main outflow vessel of the eye and BRVO results from occlusion of a proximal branch of the central vein. After CRVO, venous return from the entire retina is compromised and after BRVO it is compromised from ≤50% of the retina. Thus, on average, CRVO tends to be more severe than BRVO. The retinal circulation is a closed system with little or no opportunity for collateral flow. Consequently, all blood that enters the retina through the central retinal artery must exit through the central retinal vein; therefore, obstruction of the central retinal vein or one of its main branches compromises perfusion to all of the retina (CRVO) or ≤50% of the retina (BRVO) resulting in retinal ischemia and upregulation of hypoxia-stimulated genes.

The major cause of decreased vision in patients with RVO is macular edema. A small clinical trial demonstrated that the hypoxia-regulated gene product VEGF is a particularly important stimulator of macular edema in RVO (Campochiaro, 2008), and this has since been confirmed in multicenter phase 3 trials. Intravitreal injection of VEGF-neutralizing proteins is now first line therapy for patients with macular edema due to retinal vein occlusion (Campochiaro, 2010; Brown, 2010; Brown, 2011; Campochiaro, 2011; Holz, 2013; Brown, 2013). In most patients, early visual outcomes show improvements in vision, but there are some patients who have a suboptimal response to VEGF suppression, probably because other hypoxia-stimulated pro-permeability factors play a role (Campochiaro, 2015). Patients who have a good response to VEGF suppression often require intraocular injections for many years; after 4 years of treatment, 50% of BRVO and 46% of CRVO patients have not had resolution of edema and still require intravitreal injections of a VEGF-neutralizing protein to control edema (Campochiaro, 2014). Therefore, additional treatment approaches are needed.

Corticosteroids provide an alternative approach that has theoretical appeal because they cause transcriptional repression of a large number of genes whose products participate in inflammation, vascular leakage, and angiogenesis (Yang-Yen, 1990; Schule, 1990; Heck, 1994) Intravitreal injection of triamcinolone acetonide, no more frequently than every 4 months, provided improvements in visual acuity in subjects with CRVO and in subjects with BRVO, but also induced cataract in many patients and increased intraocular pressure (IOP) in a substantial number of patients (Aref, 2015). Intravitreal injection of a dexamethasone implant reduces edema and improves vision in patients with RVO, but is also complicated by cataract in almost all patients and increased IOP in some patients (Boyer, 2014). In a level 1 study comparing ranibizumab with dexamethasone implant evaluated according to the European label, no difference was observed in BCVA between ranibizumab and dexamethasone at months 1 and 2. From month 3 to month 6, there was significant difference in BCVA gains in favor of ranibizumab (Hoerauf, 2016). Therefore, with efficacy appearing to favor the anti-VEGF agents, and because of the additional ocular side effects seen from intravitreal corticosteroids compared to those seen with intravitreal anti-VEGF agents, intravitreal corticosteroids are generally used as

second line treatment in patients with RVO who despite a long course of injections of a VEGF-neutralizing protein have residual edema or who cannot substantially extend the period between injections without recurrent edema.

Suprachoroidal injection provides a new route of local administration of drug to the eye, and that may have advantages for administration of corticosteroids. Data from animal models show distribution of TA dominantly in posterior segment ocular tissues (sclera, choroid, retinal pigmented epithelial (RPE) cells, retina) while limiting exposure to anterior structures including the lens in the eye following suprachoroidal injection of TA, thereby providing the rationale for improved efficacy (high drug exposure to the choroid, RPE and retina) and the potential for an enhanced safety profile because of sparing of the anterior chamber and lens by reducing the stimuli for cataract or increases in intraocular pressure.

Therefore, Clearside is approaching the treatment of RVO by adopting a dual strategy to optimize treatment for the patient. The use of an anti-VEGF agent adjunctively with a corticosteroid, might be particularly useful since these two agents tackle different complications of RVO through different mechanistic pathways. The anti-VEGF agent, reduces excess fluid through reversible VEGF binding and clearance, and is required frequently, often monthly. The other agent, a corticosteroid, causes transcriptional repression of a large number of genes whose products participate in inflammation, vascular leakage, and angiogenesis (Yang-Yen, 1990; Schule, 1990; Heck, 1994), reduces VEGF levels in addition to that of other cytokines and restores damaged blood-retinal barrier, and is usually used less often, about once every three to four months. Using the two types of agents together provides the potential advantage of tackling different aspects of the disease in parallel and, therefore, offers the potential for both a more rapid and a better outcome in terms of best corrected visual acuity (BCVA) improvement. Further, if each agent is able to contribute and sustain reduction in macular edema in addition to sustaining improvement in visual acuity, there is the potential to reduce the frequency of administration of therapy. Data supporting this hypothesis of using an anti-VEGF agent in combination with CLS-TA are available from the phase 2, TANZANITE, trial that Clearside, the Sponsor, conducted in treatment naïve RVO subjects. Data from TANZANITE showed that giving an intravitreal injection of aflibercept along with a suprachoroidal injection of CLS-TA (combination arm) at baseline provided improved visual acuity and macular edema reduction outcomes at all 3 months of the study compared with a control intravitreal injection of aflibercept only (control arm), and with the requirement for significantly fewer additional aflibercept injections based on the as needed criteria used in the three month follow-up period in that trial. More specifically, an early improvement in BCVA from the combination of aflibercept and CLS-TA in subjects with RVO was statistically significantly ($p<0.05$) better than the mean increase in BCVA from baseline seen from the monotherapy anti-VEGF (aflibercept) only arm. Further, the proportion of subjects gaining 15 or more ETDRS letters of BCVA was approximately 61% at month 2 in the combination arm in this trial; this kind of result is seen usually after 3-6 monthly anti-VEGF injections in subjects with RVO (EYLEA Prescribing Information, 2017; LUCENTIS Prescribing Information, 2017; Scott, 2017). Details regarding this phase 2

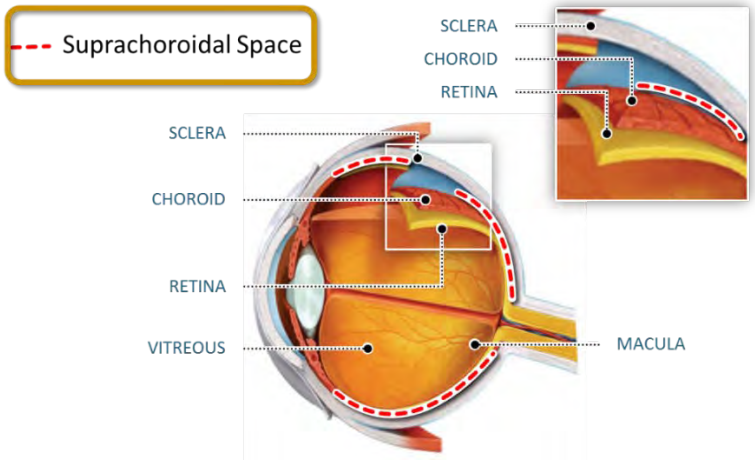
TANZANITE trial and the data can be found in Section 5.3 of this Protocol, and in the CLS-TA Investigator's Brochure.

While CLS-TA is being evaluated in combination with aflibercept in the phase 3, SAPPHIRE trial, it is likely that combining CLS-TA with ranibizumab or combining CLS-TA with bevacizumab will show similar outcomes in terms of visual acuity improvements to the visual acuity outcomes seen from combining CLS-TA with aflibercept. These three anti-VEGF agents have similar mechanisms of action in that their primary role is to reversibly bind and sequester VEGF, and these three agents have provided similar outcomes in improvements in visual acuity at the primary endpoints in adequately powered, well-controlled clinical trials in subjects with RVO.

5.2. Description of Investigational Product

CLS-TA, triamcinolone acetonide injectable suspension, is a preservative-free, terminally sterilized, aqueous suspension, formulated for administration into the eye. It will be administered as a suprachoroidal injection of 4 mg in 0.10 mL (40 mg/mL).

Figure 1: Anatomy of the eye highlighting the suprachoroidal space (SCS) between the sclera and choroid



Additional information regarding CLS-TA, triamcinolone acetonide injectable suspension, 40 mg/mL is available in its Investigator's Brochure.

Ranibizumab (Lucentis) is approved for the treatment of patients with Wet Age-related Macular Degeneration (AMD), macular edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR), and Myopic Choroidal Neovascularization (mCNV) in multiple regions, including the United States and Europe. Full prescribing information for ranibizumab can be found in the LUCENTIS Prescribing Information, 2017, and Summary of Product Characteristics, 2016. In this study, ranibizumab will be administered as an IVT injection of 0.5 mg in 0.05 mL.

Bevacizumab (Avastin) is a full-length recombinant humanized monoclonal antibody that blocks all isoforms of VEGF-A. It shares a similar molecular structure with ranibizumab, which was designed as a monocolonal antibody fragment from the same parent murine antibody. It is approved by the Food and Drug Administration (FDA) and other health authorities as a systemic therapy for the treatment of metastatic colorectal cancer, treatment of non-squamous non-small cell lung cancer, glioblastoma, and metastatic renal cell carcinoma (Avastin Prescribing Information, 2016, and Summary of Product Characteristics, 2017). However, bevacizumab is not approved for ophthalmic use in any jurisdiction, therefore additional information is available in its Investigator's Brochure. Bevacizumab will be supplied for this trial in single use containers and administered as an IVT injection of 1.25 mg in 0.05 mL.

5.3. Summary of Clinical Experience and Justification for Dose Selection

Triamcinolone acetonide (TA) has been used safely and effectively in human ocular therapeutics to treat conditions involving inflammation for over 50 years. The initial recommended dose of the TA formulation approved by the FDA for ocular indications is 4 mg in 0.10 mL (TRIESENCE® (triamcinolone acetonide injection, suspension)). The dose of CLS-TA administered as a single suprachoroidal injection is similar (4 mg in 0.10 mL). TRIESENCE and CLS-TA contain the same active and inactive ingredients at approximately the same concentrations (Triesence Prescribing Information, 2016). Both formulations are aqueous suspensions that are preservative-free, have been terminally sterilized and designed for ophthalmic use.

Clearside has completed 2 clinical trials in patients with non-infectious uveitis and one clinical trial in patients with 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. Each subject received a single SC injection of TA (4 mg in 100 µL; TRIESENCE). Nine of the 11 subjects in the safety analysis set (82%) completed the 26-week study. All subjects had at least one 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. Subjects in the per-protocol analysis set (n=8) showed improvements in mean improvements in best corrected visual acuity (BCVA) from baseline, and in mean reductions in macular edema from baseline in this study.

The completed clinical study, CLS1001-201 (NCT02255032), was a phase 2, randomized, masked safety and efficacy study in subjects with ME associated with non-infectious uveitis. Twenty-two subjects were randomly assigned to receive either a single SC injection of CLS-TA, 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; no subject was treated with IOP lowering medication.

The completed clinical study, CLS1003-201 (CT02303184), was a phase 2, randomized, masked safety and efficacy study in subjects with ME secondary to RVO. Forty-six subjects were randomly assigned 1:1 to either a SC injection of CLS-TA administered in combination with an IVT injection of aflibercept (ACTIVE), or an IVT injection of aflibercept alone (CONTROL). Subjects were evaluated over the three-month study period with monthly visits; additional intravitreal aflibercept treatments were determined using as needed (PRN) criteria that included the presence of central retinal fluid or losses in visual acuity. Since a key goal of the study was to determine if suprachoroidal CLS-TA affected the requirement for additional treatment when administered along with intravitreal aflibercept, a count of the requirement for additional intravitreal aflibercept injections over the 3-month trial served as the primary outcome measure. The study met the primary endpoint with sixty percent fewer additional IVT aflibercept injections ($p=0.013$) required in the ACTIVE group receiving the combination of SC CLS-TA and IVT aflibercept compared with subjects in the CONTROL arm who only received aflibercept at baseline. In terms of secondary endpoints, mean improvements from baseline in BCVA were 16, 20, and 19 ETDRS letters in the ACTIVE group and 11, 12, and 11 letters in the CONTROL group at Months 1, 2, and 3 respectively. Subjects were observed to have a mean reduction in CST of 446 µm in the ACTIVE (combination) group, and a 405 µm reduction in the CONTROL group when measured from Baseline at Month 1. Further, the approximately 450 µm reduction in CST in the ACTIVE (combination) group was maintained through the 3 months of the study while the CONTROL group showed only approximately 350 µm reductions in CST at both months 2 and 3. No subjects discontinued due to an AE and no SAEs were reported. A total of 4 subjects in the active group reported AEs pertaining to elevated IOP: 2 events each of ocular hypertension and IOP increase. All events were mild or moderate in intensity and considered to be related to study drug.

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

Current clinical practice worldwide involves the use of one of the three anti VEGF agents, aflibercept, ranibizumab, and bevacizumab, for the treatment of subjects with RVO, almost exclusively as the initial therapy. Several level 1 types of clinical trials have been conducted in the US, in Europe and in the other parts of the world, where each of these anti-VEGF agents have been evaluated for the treatment of subjects with various posterior segment ocular conditions, including subjects with RVO.

The three anti-VEGF agents used most commonly to treat subjects with RVO have similar mechanisms of action in that their primary role is to reversibly bind, sequester and enhance the clearance of VEGF. While there are finer mechanistic differences between aflibercept (binds VEGF-A, VEGF-B and placental growth factor) and the other two anti-VEGF agents (ranibizumab and bevacizumab only bind VEGF-A), these three agents have all provided similar outcomes in improvements in visual acuity at the primary endpoints in adequately powered,

well-controlled clinical trials in subjects with RVO (Eylea Prescribing Information, 2017; Eylea Summary of Product Characteristics, 2017, Lucentis Prescribing Information, 2017; Lucentis Summary of Product Characteristics, 2016 and Scott, 2017). Further, in subjects with neovascular AMD, bevacizumab has been shown to be non-inferior to ranibizumab in multiple independent level 1 studies; these include the CATT sponsored by the NEI in the US (CATT Research Group 2011), the Alternative Treatments to Inhibit VEGF in Age-related Choroidal Neovascularization (IVAN) Trial, sponsored by the National Institute for Health Research programme (United Kingdom) (Chakravarthy 2012) and the French Evaluation Group Avastin Versus Lucentis (GEFAL) Trial, sponsored by the Hospices Civils de Lyon (Kodijkian 2013). All three agents have also been evaluated in the Protocol T trial in subjects with diabetic macular edema (Wells, 2016) where subjects with good incoming vision (better than approximately 75 ETDRS letters read) showed similar visual acuity outcomes at evaluations at 12 and 24 months from baseline. In subjects with RVO, comparative data between these anti-VEGF agents are limited to the one clinical trial with level 1 evidence, where aflibercept and bevacizumab were evaluated in subjects with central RVO (CRVO) and hemi RVO (HRVO), the SCORE2 study. Based on a comparison of mean change in visual acuity from baseline, bevacizumab was non-inferior to aflibercept at the 6-month primary endpoint following six monthly injections of each agent in this parallel arm trial (Scott, 2017). Further, in a level 2 study comparing ranibizumab and bevacizumab, both agents were shown to be effective for the treatment of BRVO and produced similar visual and anatomic outcomes at 6 months (Son, 2017). These data show that in subjects with RVO, these two anti-VEGF agents provide similar visual acuity outcomes at month 6 when given monthly for 6 months. Further, the data from aflibercept or ranibizumab from five level 1 phase 3 clinical trials, with 3 in subjects with CRVO and 2 in subjects with BRVO (Eylea Prescribing Information, 2017; Lucentis Prescribing Information, 2017) show comparable gains of between 15 and 18 ETDRS letters in terms of change from baseline in BCVA. Therefore, the data from SCORE2 along with that from the five phase 3 trials from aflibercept and ranibizumab suggest that all three commonly used anti-VEGF agents, when given monthly for 6 months, lead to similar visual acuity outcomes in subjects with RVO.

Although intravitreal corticosteroid therapy is a readily available treatment option for macular edema secondary to RVO, initial first-line treatment is with intravitreal anti-VEGF therapy, and is used most commonly in almost every case for treatment naïve RVO subjects, except for rare exceptions. This is due to the perception that anti-VEGF treatments are more efficacious and safer than corticosteroid therapy. In the one adequately powered, well controlled randomized, masked comparative, COMRADE C trial, where ranibizumab and dexamethasone implant were compared in CRVO subjects, the perception that the anti-VEGF agent provides better outcomes than the corticosteroid was validated because, although at month 1 and month 2 the visual acuity data were comparable, ranibizumab was significantly better than dexamethasone implant from month 3 through month 6 when each agent was administered according to the European label (Hoerauf, 2016). It has become common that corticosteroid therapy is typically used as a rescue therapy for eyes that have an unsuccessful result with initial anti-VEGF therapy. Aflibercept is generally perceived to be best anti-VEGF therapy for posterior segment eye diseases in part

because of the superior visual outcomes seen in diabetic macular edema (DME) subjects with vision 20/50 or worse in the Protocol T trial (Wells, 2016).

This study aims to consider the safety and efficacy of SC CLS-TA combined with IVT ranibizumab, and SC CLS-TA combined with IVT bevacizumab for the treatment of eyes of subjects with RVO. While CLS-TA, is being evaluated in combination with aflibercept in the phase 3, SAPPHIRE trial, it is likely that combining CLS-TA with ranibizumab or combining CLS-TA with bevacizumab will show similar outcomes in terms of visual acuity improvements to combining CLS-TA with aflibercept. CLS-TA itself has been validated in its ability to provide a significantly better early (month 2; $p<0.05$) visual acuity outcome in combination with the IVT agent aflibercept, when compared to IVT aflibercept when used alone, in a controlled, masked, randomized phase 2 trial, TANZANITE. Since these three anti-VEGF agents have similar mechanisms of action in that their primary role is to reversibly bind and sequester VEGF, and these three agents have provided similar outcomes in improvements in visual acuity at the primary endpoints in adequately powered, well-controlled clinical trials, this phase 3, TOPAZ, trial is designed to evaluate whether suprachoroidally injected CLS-TA in combination with an intravitreally injected anti-VEGF agent (ranibizumab, bevacizumab) is superior to intravitreally injected anti-VEGF agent (ranibizumab, bevacizumab) used alone, using BCVA as outcome measure at month 2.

With the first phase 3, SAPPHIRE trial, which evaluates the use of CLS-TA combined with aflibercept for the treatment of RVO, and this phase 3, TOPAZ trial, which will evaluate CLS-TA combined with either bevacizumab or ranibizumab for the treatment of RVO, the outcome will provide understanding of the safety and efficacy of CLS-TA with all commonly utilized anti-VEGF agents for the treatment of RVO.

6. STUDY OBJECTIVES AND PURPOSE

The purpose of this study is to demonstrate the safety and efficacy of suprachoroidally injected CLS-TA ("suprachoroidal CLS-TA") used in combination with an intravitreally injected anti-VEGF agent ("intravitreal anti-VEGF agent") in subjects with RVO.

6.1. Primary Objective

To demonstrate that in pharmacologic treatment naïve subjects with RVO, suprachoroidal (SC) CLS-TA administered with an intravitreal (IVT) anti-VEGF agent is superior to IVT anti-VEGF agent alone using a best corrected visual acuity (BCVA) outcome.

6.2. Secondary Objectives

The secondary objectives of the study are:

- To determine the effect of SC CLS-TA administered in conjunction with an IVT anti-VEGF agent on mean change from Baseline in BCVA
- To determine the effect of SC CLS-TA administered in conjunction with an IVT anti-VEGF agent on mean change from Baseline in CST

6.3. Safety Objective

The safety objectives of the study are:

- To evaluate the safety and tolerability of SC CLS-TA administered with an IVT anti-VEGF agent as measured by reported adverse events and safety parameters

6.4. Exploratory Objectives

The exploratory objectives of the study are:

- To determine the effect of SC CLS-TA administered with an IVT anti-VEGF agent on change from Baseline in subject-reported outcomes.
- To determine the effect of SC CLS-TA administered with an IVT anti-VEGF agent on changes from Baseline in complications associated with RVO; these evaluations will include changes in neovascularization and perfusion status, and analyses based on whether or not these complications were present at baseline.
- To evaluate changes from baseline based on disease type, BRVO and CRVO. Subjects with HRVO data will be included with the CRVO group based on randomization.
- To determine the safety and performance of the SCS microinjector when used to inject SC CLS-TA

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a phase 3, multicenter, randomized, masked, controlled, parallel group study of approximately 12 months duration in pharmacologic treatment-naïve subjects with RVO. This study is projected to enroll approximately 460 subjects, randomly assigned 1:1:1:1 to one of four treatment groups stratified by disease (BRVO, CRVO). Subjects with HRVO will be included in this study. Randomization will proceed as described until either stratum within a group reaches approximately 50% of the total number patients to be enrolled in that group at which time only patients from the other stratum will be enrolled.

The study design includes 12 clinic visits over approximately 50 weeks. Subjects will participate in 5 periods: Screening (Visit 1, Days -30 to -1); Randomization and Baseline (Visit 2, Day 0 before dosing); Dosing and Evaluation (Visit 2 [after dosing] to Visit 8, Day 0 through Week 24); PRN Dosing and Follow-up (Visit 9 to 11; Weeks 30 through 42); and End of Study (Visit 12; Week 48).

7.2. Endpoints

7.2.1. Primary Efficacy Endpoint

The primary endpoint is the proportion of subjects demonstrating ≥ 15 letter improvement from Baseline in Early Treatment of Diabetic Retinopathy Study (ETDRS) BCVA at Visit 4 (Month 2).

7.2.2. Secondary Efficacy Endpoints

- Mean change from Baseline (Visit 2, Day 0) in BCVA at Visit 4 (Week 8) and Visit 8 (Week 24)
- Mean change from Baseline (Visit 2, Day 0) in CST at Visit 4 (Week 8) and Visit 8 (Week 24)

7.2.3. Exploratory Efficacy Endpoints

- Change from Baseline (Visit 2, Day 0) in subject-reported outcomes at Visit 8 (Week 24) as measured by the Visual Function Questionnaire (VFQ-25) and the EuroQol 5 Dimensions Questionnaire (EQ-5D)
- Change from Baseline in signs and complications of RVO (eg, neovascularization, perfusion) at Visit 8 (Week 24) and Visit 12 (Week 48)
- Changes from Baseline on visual and anatomic outcomes based on disease diagnosis of BRVO and CRVO. HRVO subjects will be included with the CRVO for analyses.

7.2.4. Safety Endpoints

- Incidence of treatment-emergent adverse events (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 signs

7.2.5. Endpoints Related to SCS microinjector

- Performance of the SCS microinjector, evidenced by injection parameters (location, eye quadrant, needle length, injection completion, and product complaints) at each SC injection visit (Visits 2, 5, 8)
- Incidence of TEAEs and SAEs related to the SCS microinjector

7.3. Number of Subjects

Approximately 460 subjects with RVO who are naïve to treatment will be enrolled into one of four treatment groups.

7.4. Treatment Assignment

Subjects enrolled in this study will be eligible upon a finding of RVO in the study eye. After Screening (Day -30 to Day -1) and Baseline assessments on Day 0, subjects will be randomly assigned 1:1:1:1 to one of four treatment groups stratified by disease type (BRVO, CRVO). Randomization will proceed as described until either stratum within a group reaches at least 50% of the total number patients to be enrolled in that group at which time only patients from the other strata will be enrolled.

Table 3: Subject Randomization

TREATMENT ARM	Number of Subjects
ACTIVE: IVT injection of Lucentis (0.5 mg/0.05 mL) + SC injection of CLS-TA (4 mg/0.10 mL)	~115
OR IVT injection of Avastin (1.25 mg/0.05 mL) + SC injection of CLS-TA (4 mg/ 0.10 mL)	~115
CONTROL: IVT injection of Lucentis (0.5 mg/0.05 mL) + sham SC procedure	~115
OR IVT injection of Avastin (1.25 mg/0.05 mL) + sham SC procedure	~115

Dosing and Evaluation Period: After randomization, subjects will receive treatment as follows:

ACTIVE (combination): IVT injection of anti-VEGF agent + suprachoroidal injection of CLS-TA (4 mg/100 μL) SC injections:

Subjects randomly assigned at Baseline to the ACTIVE group will receive an IVT injection of anti-VEGF agent followed by a SC injection of CLS-TA on Visit 2 (Day 0), Visit 5 (Week 12) and Visit 8 (Week 24). Subjects will receive an intravitreal injection of anti-VEGF agent only at Visit 3 (Week 4).

After the Baseline visit, subjects will return for 6 monthly (every 4 weeks) visits through Visit 8 (Week 24) to assess safety and efficacy. Evaluation for, and determination of the requirement for additional therapy based on established criteria will take place at Visit 4 (Week 8) and from Visit 6 (Week 16) through end of study. To maintain masking, subjects not receiving additional therapy on Week 8, and Weeks 16 and 20 will receive sham IVT injections.

CONTROL (anti-VEGF): IVT injection of anti-VEGF agent + sham SC procedure

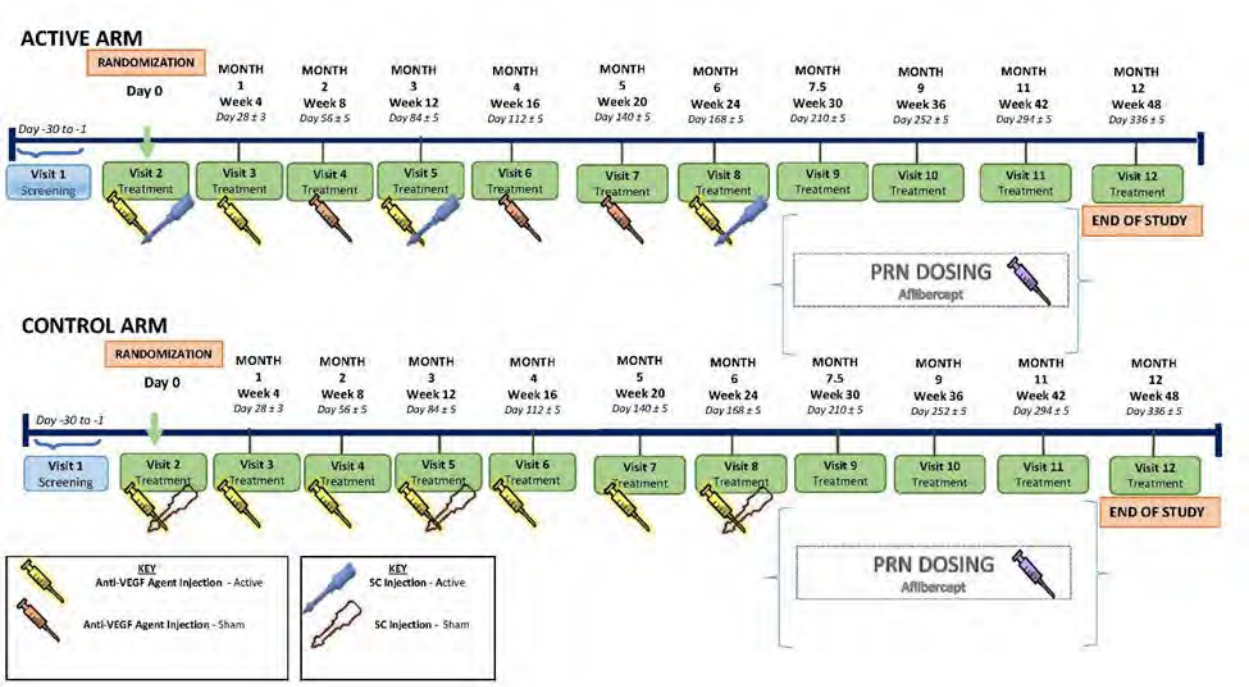
Subjects randomly assigned at Baseline to the CONTROL group will receive monthly IVT anti-VEGF agent injections beginning at Visit 2 (Day 0) and continuing through Visit 8 (Week 24). To maintain masking, subjects in the CONTROL group will also receive a sham SC procedure on Visit 2 (Day 0), Visit 5 (Week 12) and Visit 8 (Week 24).

Subjects will return for 6 monthly (every 4 weeks) visits through Visit 8 (Week 24) to assess safety and efficacy and to determine whether additional therapy is needed based on established criteria.

PRN Dosing and Follow-up Period:

At the conclusion of the dosing and evaluation period (Day 0 through Week 24), subjects will be followed for safety through Visit 12 (Week 48). Subjects will be treated, as needed (PRN), with an intravitreal injection of aflibercept.

Figure 2: Study Treatment Schedule



7.5. Criteria for Study Termination

The study or parts of the study may be discontinued by the Sponsor, or at the recommendation of an Investigator after consultation with Sponsor, at any time.

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

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

1. Has a clinical diagnosis of RVO in the study eye within ≤ 6 months screening;
2. Has a CST of ≥ 300 μm in the study eye as measured by spectral-domain optical coherence tomography (SD-OCT) with intraretinal or subretinal fluid and confirmed by the central reading center (CRC);
3. Has an ETDRS BCVA score of ≥ 20 letters read and ≤ 70 letters read in the study eye; at least 20 letters in the non-study eye;
4. Is naïve to local pharmacologic treatment for RVO in the study eye;
5. 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, and is willing to comply with the instructions and attend all scheduled study visits.

8.2. Exclusion Criteria

8.2.1. Ophthalmic Exclusion Criteria

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

1. Has ME with etiology other than RVO;
2. Has, in the study eye, used any topical ocular corticosteroid in the 10 days before treatment at Visit 2 (Day 0); has at any time received any intraocular or periocular corticosteroid injection, an OZURDEX® implant, a RETISERT® implant, or an ILUVIEN® implant;
3. Has evidence of or history of any ophthalmic condition in the study eye that may have an associated neovascularization or edema component including, but not limited to, age-related macular degeneration (AMD), diabetic retinopathy, diabetic macular edema (DME), retinal detachment, central serous chorioretinopathy, scleritis, optic neuropathy, or retinitis pigmentosa;
4. Has a history of rubeosis irides or other neovascularization in the study eye; any active vitreous hemorrhage in the study eye within the last 90 days;
5. Has a history of any vitreoretinal surgery (scleral buckle placement, pars plana vitrectomy, retrieval of dropped nucleus or intraocular lens, sheathotomy) ever in the study eye or any ocular surgery in the 3 months before randomization. Prior cataract extraction or Yttrium-Aluminum-Garnet (YAG) laser capsulotomy is allowed but must have been performed at least 3 months before Visit 2 (Day 0);

6. 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);
7. An 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);
8. Has scarring from laser photocoagulation or from other cause in the study eye that would compromise visual acuity; has an epiretinal membrane that is a major contributor to reduced visual acuity
9. 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);
10. 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;
11. History of glaucoma, optic nerve head change consistent with glaucoma damage; or ocular hypertension in the study eye requiring more than one medication;
12. 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;
13. Has a history of glaucoma surgery (filtration surgery/trabeculectomy or tube shunt) in the study eye; has a history of laser trabeculoplasty or MIGs surgery in the study eye;
14. 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 meet the following criteria:

15. Is a female subject 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 one of the acceptable birth control methods if she becomes sexually active;

16. 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; NOTE: Uncontrolled BP at screening may be treated before Visit 2;
17. Has a myocardial infarction or stroke within 90 days of treatment;
18. Has a likely need for hospitalization or surgery within the study period, including planned elective surgery or hospitalization;
19. Has a known hypersensitivity to any component of the formulation of TA, ranibizumab, bevacizumab, aflibercept, fluorescein, topical anesthetics, or the antiseptic used to prepare the eye for injection according to the Investigator's standard practice;
20. 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.
21. History of any inflammatory or other medical condition that the investigator might reasonably anticipate will require treatment with high-dose corticosteroids (more than 10mg/day oral prednisone or the equivalent) for more than 14 days.

8.2.3. Randomization Criteria

Subjects are eligible for randomization at Visit 2 if the following criteria are met:

1. The CRC confirms ME by SD-OCT (from Visit 1 SD-OCT data), with intraretinal, sub-RPE, or subretinal fluid;
2. The CRC confirms a retinal thickness of ≥ 300 μm in the central subfield from the Visit 1 SD-OCT data;
3. The subject gains no more than 10 letters of vision in BCVA between the Screening visit and Randomization (Visit 2) in the study eye;
4. The subject continues to meet all of the inclusion and none of the exclusion criteria.

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. Investigators may withdraw a subject from the study because a new health condition appears or an existing condition worsens that requires care or medication prohibited by the protocol and it is in the subject's best interest to exit the study, according to the Investigator's clinical judgement. In the event that a subject develops a medical condition that requires treatment with a medication prohibited by this protocol (i.e. if the treating physician determines, using best medical judgment, that such medications are medically necessary for the subject's welfare), then a protocol deviation will be recorded. In such cases, provided the investigator determines that it is

in the subject's best interest to continue in the study, the Sponsor's preference is to retain such subjects in the study. For a list of prohibited medications, please see Section 9.5.

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 12 study visits over approximately 50 weeks. Subjects are expected to attend all study visits. All ocular assessments at Visit 1 (Screening) and Visit 12 (Week 48) will be performed on both eyes. IOP will be collected in both eyes at all visits. Data from all other ocular assessments at all other visits 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 an anti-VEGF agent (following the Investigator's standard practice for IVT injections) in the study eye, followed by either a sham SC injection or an active SC dose of CLS-TA in the study eye, depending on the group assigned at randomization. Subjects will be assessed after injection for safety.

Additional safety follow-up visits will occur approximately every 4 weeks through Month 6 (Visits 3 through 8; Weeks 4, 8, 12, 16, 20 and 24). Subjects in the CONTROL group will receive IVT injections of an anti-VEGF agent at each of these visits. Subjects in the ACTIVE group will receive an IVT injection of an anti-VEGF agent at Visit 3 (Week 4); a sham IVT injection will be performed at Visit 4, 6 and 7 (Weeks 8, 16 and 20) to ensure masking is maintained. The subject will receive the same anti-VEGF agent per the protocol schedule, throughout the first 24 weeks of the study.

At Visit 5 (Week 12) and Visit 8 (Week 24) subjects will receive another IVT injection of anti-VEGF agent (following the Investigator's standard practice for IVT injections) in the study eye, followed by either a sham SC injection or an active SC dose of CLS-TA in the study eye), depending on the group assigned at Visit 2 (Day 0).

After the completion of the Dosing and Evaluation Period (6 months), subjects will enter the PRN Dosing and Follow-up Period of the study to be observed and receive PRN treatment every 6 weeks at Visit 9 (Week 30), Visit 10 (Week 36), and Visit 11 (Week 42). PRN therapy will be aflibercept for all subjects, regardless of randomization group.

The final visit of the study occurs at Visit 12 (Week 48).

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 (resting 5 mins) and blood pressure measurements
6. Collect blood and urine for central laboratory tests before fluorescein angiogram (FA), including serum pregnancy test on females of childbearing potential
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. Perform photographic evaluations:*
    a. FA
    b. Fundus photograph
10. Assess AEs
11. Determine study eye based upon eligibility criteria
12. Schedule subject to return for Visit 2, Randomization/Treatment

NOTE:

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

8.4.4. Visit 2 (Day 0), Visit 5 (Week 12) and Visit 8 (Week 24)

Visit 2 must occur within 30 days of Visit 1 (Screening) and may only occur once 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, Visit 5 and Visit 8 (Day 0, Week 12 and Week 24)
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 (resting 5 mins) and blood pressure
4. Administer VFQ-25 and EQ-5D *(Visit 2 and Visit 8 only)*
5. Collect urine for pregnancy test in females of child-bearing potential
6. Collect blood and urine for central lab tests before FA, (*Visit 8 only)*
7. Perform ophthalmic assessments on the study eye only, unless otherwise designated:
    a. ETDRS BCVA (both eyes)
    b. Slit-lamp biomicroscopy, including dilated lens grading
    c. IOP (both eyes)
    d. Dilated indirect ophthalmoscopy
    e. SD-OCT
8. Perform photographic evaluations *(Visit 8 only)*:
    a. Fluorescein angiogram (FA)
    b. Fundus photograph
9. Review eligibility criteria *(Visit 2 only)*

    If subject continues to be eligible for randomization based on results from screening and Visit 2 assessments, and subject meets all randomization criteria in 8.2.3, subjects

will be randomly assigned via the interactive response technology (IRT) to receive an IVT injection of an assigned anti-VEGF agent in conjunction with either sham or active SC injection of CLS-TA in the study eye.

10. Log onto the IRT and randomly assign subject to treatment

8.4.4.2. Injection Procedures: Visit 2 (Day 0), Visit 5 (Week 12) and Visit 8 (Week 24)

Injections 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 IRT
3. Prepare eye for injection according to the Investigator's standard practice
4. The UNMASKED injecting Investigator should perform IVT injection of assigned anti-VEGF agent, SC injection of CLS-TA, and all sham procedures to the study eye

8.4.4.2.1. IVT Injection of anti-VEGF agent:

1. Prepare study eye for IVT injection of assigned anti-VEGF agent
2. Administer anti-VEGF agent IVT injection following the Investigator's standard practice for IVT injections. *The location of the IVT injection and the SC injection should be approximately 2 or more clock hours apart on the globe. 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

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. NOTE: This is a separate, additional preparation prior to the second injection.
2. Administer SC injection of 0.10 mL of CLS-TA or sham procedure approximately 2 or more clock hours on the globe from the location of the IVT injection
3. Assess study eye by indirect ophthalmoscopy immediately after the injection,

8.4.5. Post-Dose Procedures: Visit 2 (Day 0), Visit 5 (Week 12) and Visit 8 (Week 24)

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. Evaluate IOP 10 to 30 minutes after injection
    b. If IOP remains elevated, subject must remain on site until IOP is under control according to the Investigator's best medical judgment.
    c. If IOP is < 30 mmHg, the subject may leave the clinic
4. Schedule time for subject to return for next visit

8.4.6. Visits 3, 4, 6, and 7 (Weeks 4, 8, 16, and 20)

8.4.6.1. Pre-dose Procedures: Visit 3 (Week 4), Visit 4 (Week 8), 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 (seated 5 mins) and blood pressure measurements
4. Perform ophthalmic assessments on the study eye only, unless otherwise designated:
    a. ETDRS BCVA
    b. Slit-lamp biomicroscopy, including dilated lens grading
    c. IOP (both eyes)
    d. Dilated indirect ophthalmoscopy
    e. SD-OCT

8.4.6.2. Injection Procedure: Visit 3 (Week 4), Visit 4 (Week 8), Visit 6 (Week 16), and Visit 7 (Week 20)

1. Confirm the study eye
2. Retrieve assigned anti-VEGF agent
3. Prepare eye for injection according to the Investigator's standard practice

4. The UNMASKED injecting Investigator should administer IVT injection of anti-VEGF agent OR sham IVT procedure to the study eye. (All subjects receive an IVT injection of anti-VEGF agent at Visit 3 (Week 4)).
5. Assess study eye by indirect ophthalmoscopy immediately after the injection,
6. Measure IOP after injection

8.4.6.3. Post-Dose Procedures: Visit 3 (Week 4), Visit 4 (Week 8), Visit 6 (Week 16), and Visit 7 (Week 20)

1. Assess AEs
2. Review changes to concomitant medications
3. Perform ophthalmic assessments on the study eye only:
    a. Evaluate IOP 10 to 30 minutes after injection
    b. If IOP remains elevated, subject must remain on site until IOP is under control according to the Investigator's best medical judgment.
    c. If IOP is < 30 mmHg, the subject may leave the clinic
4. Schedule time for subject to return for next visit

8.4.7. Visits 9, 10, and 11 (Weeks 30, 36, and 42)

Beginning at Visit 9 (Week 30) through Visit 11(Week 42), study treatments will be administered PRN. Investigators, subjects, and study personnel will remain masked during the PRN Dosing and Follow-up Period.

8.4.7.1. Pre-dose Procedures: Visit 9 (Week 30), Visit 10 (Week 36), and Visit 11 (Week 42)

The following assessments must be performed; however, dosing is PRN:

1. Assess AEs
2. Review changes to concomitant medications
3. Perform resting heart rate (seated 5 mins) and blood pressure measurements
4. Perform ophthalmic assessments on the study eye only, unless otherwise designated:
    a. ETDRS BCVA
    b. Slit-lamp biomicroscopy, including dilated lens grading
    c. IOP (both eyes)
    d. Dilated indirect ophthalmoscopy
    e. SD-OCT
    f. Confirm study eye

8.4.7.2. PRN Injection procedure: Visit 9 (Week 30), Visit 10 (Week 36), and Visit 11 (Week 42)

If subject qualifies for PRN therapy according to the Additional Therapy Criteria listed in Section 9.4.1, the following injection and post-dose procedures should be performed, consistent with the subject's treatment group:

1. Confirm the study eye
2. Retrieve study drug kit number assigned by IRT
3. Prepare eye for injection according to the Investigator's standard practice
4. The UNMASKED injecting Investigator should perform IVT injection of aflibercept

8.4.7.2.1. IVT Injection of aflibercept:

1. Prepare study eye for IVT injection of aflibercept
2. Administer aflibercept IVT injection according to the instructions in the approved label.
3. Assess study eye by indirect ophthalmoscopy immediately after the injection,
4. Measure IOP after injection

8.4.7.2.2. Post-Dose Procedures: Visit 9 (Week 30), Visit 10 (Week 36), and Visit 11 (Week 42)

The following assessments must occur after the IVT injection:

1. Assess AEs
2. Review changes to concomitant medications
3. Perform ophthalmic assessments on the study eye only:
    a. Evaluate IOP 10 to 30 minutes after injection
    b. If IOP remains elevated, subject must remain on site until IOP is under control according to the Investigator's best medical judgment.
    c. If IOP is < 30 mmHg, the subject may leave the clinic
4. Schedule time for subject to return for next visit

8.4.8. Visit 12 (Week 48) End of Study/Early Termination

Visit 12 is the final study visit. Subjects who terminate early should complete all Visit 12 assessments.

1. Assess AEs
2. Review changes to concomitant medications
3. Perform resting heart rate (seated 5 mins) and blood pressure measurements

4. Collect blood and urine for central laboratory tests, including serum pregnancy test on females of child-bearing potential
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. Administer VFQ-25 and EQ-5D
8. Perform photographic evaluations:
    a. FA
    b. Fundus photograph

8.4.9. 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 one of four treatment groups in the study based upon randomization assignment.

Treatment in each of the two groups in the ACTIVE (combination) arm will consist of three unilateral SC injections of 4 mg of CLS-TA in 0.10 mL administered 12 weeks apart (Visits 2, 5, and 8), along with 4 IVT injections of an anti-VEGF agent (bevacizumab or ranibizumab) in to the study eye over 24 weeks according to the study schedule. Subjects in the ACTIVE arm will also receive sham IVT procedures to maintain masking at visits where the SC CLS-TA injection is not being administered (Visit 4, 6, and 7). Beginning with Visit 9 (Week 30), subjects will be assessed for PRN treatment that will consist of IVT aflibercept based on PRN criteria (Section 9.4.2).

Treatment in each of the two groups in the CONTROL (monotherapy) arm of the study will consist of 7 unilateral IVT injections of an anti-VEGF agent (bevacizumab or ranibizumab) administered 4 weeks apart (Visits 2 through 8) along with three sham SC procedures administered 12 weeks apart (Visits 2, 5, and 8) in to the study eye according to the study schedule. Beginning with Visit 9 (Week 30), subjects will be assessed for PRN treatment that will consist of an IVT injection of aflibercept based on PRN criteria (Section 9.4.2). These subjects would have received either ranibizumab or bevacizumab (control) only up to week 24, but will now receive an IVT injection of aflibercept when needed in the latter 24 weeks of the study, similar to the treatment that the subjects receive in the other arm during this period of the trial. In this manner, there is consistency of evaluation in this latter portion of the study.

Subjects will be assigned to either of the following arms:

1. **ACTIVE**: IVT anti-VEGF agent [Lucentis (0.5 mg/0.05 mL) or Avastin (1.25 mg/0.05 mL)] + SC CLS-TA [4 mg /0.10 mL]
2. **CONTROL**: IVT anti-VEGF agent [Lucentis (0.5 mg/0.05 mL) or Avastin (1.25 mg/0.05 mL)] + SC sham procedure

Approximately 460 subjects will be randomly assigned to a group in a 1:1:1:1 ratio where approximately 230 subjects will be assigned to the ACTIVE (combination) treatment (115 to each group) and approximately 230 subjects will be assigned to the CONTROL treatment (115 to each 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 anti-VEGF agent, 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.

If both eyes meet study criteria, the eye with the better chance of achieving an improvement in BCVA, in the Investigator's opinion, should be used as the study eye. If both eyes qualify for the study and appear similar in their chance of improvement, the right eye should be designated as the study eye. The eye that is not designated as the study eye will be denoted as the fellow eye.

9.3. Fellow Eye Treatment

Only one study eye of each subject may be treated in the study.

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. Supplemental Therapy Criteria

Beginning at Week 8 (Visit 4) through and including Week 20 (Visit 8), if any of the following criteria are met in the study eye, the intravitreal anti-VEGF agent the subject is randomized to will be administered.

- Macular edema (ME), defined as intraretinal, subretinal or sub-RPE 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.

- If vision is worse than approximately 70 letters read and there is new or persistent intraretinal or sub-retinal fluid or sub-RPE fluid, that in the opinion of the investigator is affecting vision, even if CST <340 µm.

9.4.2. PRN Criteria

During the PRN Dosing and Follow-up Period (Visits 9 through 11 [Weeks 30 through 42]), study arm will remain masked and additional dosing is limited to the criteria above. PRN treatment will consist of an IVT injection of aflibercept for all subjects regardless of randomization. All subjects will continue to be assessed for safety during the PRN Dosing and Follow-up 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 is prohibited at any time during the study:

- Increases to topical ophthalmic non-steroidal anti-inflammatory drugs in the study eye
- Any corticosteroid implant (ie, 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
- Macular (grid/focal) laser
- 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 RVO 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 supplemental therapy criteria. Subjects will not be discontinued from the study because of initiation of or change in a prohibited medication.

9.6. Treatment Compliance

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

9.7. Randomization and Masking

Subjects' randomized treatment assignments will be protected 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 IRT.

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.

In cases where subjects meet supplemental therapy criteria, the masking of the subject, non-injecting physician, and site technician measuring BCVA should be maintained. The masked physician will perform pre-injection exam procedures in accordance with standard subject visits. If the masked physician determines the subject meets supplemental therapy criteria, the masked physician will provide written confirmation to the injecting physician informing them of the need to administer supplemental therapy. As the injecting physician is unmasked, and has knowledge of the treatment to be administered, the injecting physician should utilize written information from the masked physician in conjunction with their knowledge of subject treatment, to determine the appropriate therapy to be administered, if any.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

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

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

Avastin is a preservative-free, clear to slightly opalescent, colorless to pale brown, sterile solution. Each carton is for single eye use only.

Additional information regarding Avastin is available in the bevacizumab Investigator's Brochure.

Lucentis is a sterile, colorless to pale yellow solution. Each carton is for single eye use only.

Additional information regarding Lucentis is available in the LUCENTIS Prescribing Information, 2017 and Summary of Product Characteristics, 2016.

Eylea is a sterile, clear, colorless to pale yellow solution. Each carton is for single eye use only.

Additional information regarding Eylea is available in the EYLEA Prescribing Information, 2017 and Summary of Product Characteristics, 2017.

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 indicating the product is for investigational use only.

Commercially available Lucentis, Avastin and Eylea, 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-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.

The anti-VEGF agent should be stored according to the label for the agent in the trial.

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 the anti-VEGF agent will be performed according to the details for ranibizumab, bevacizumab, and aflibercept as described in the Investigative Site File. The same technique is followed for the initial treatments, additional treatments through week 24, and the PRN portion through the end of the trial.

10.5. Administration

CLS-TA will be administered as a single SC injection of 4 mg in 0.10 mL.

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. Investigators will be trained by Clearside Biomedical, Inc. staff or their designees. SC injection procedure training will consist of a video, instructional training and hands on training utilizing the microinjector.

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 all anti-VEGF agents will be per the Investigator's standard practice for IVT injections.

10.6. Study Drug Accountability

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

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

10.7. Study Drug Handling and Disposal

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

return to the Sponsor (or designee). All study drug and injector accounting procedures must be completed before the study is considered complete.

11. ASSESSMENTS OF EFFICACY

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

11.1. Best Corrected Visual Acuity (BCVA)

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.

11.3. Visual Function Questionnaire

The VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. The VFQ-25 takes approximately 10 minutes on average to administer in the interviewer format. A trained technician will administer this questionnaire to the subject.

11.4. EuroQol 5 Dimensions Questionnaire

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

12. ASSESSMENTS OF SAFETY

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

12.1. Safety Parameters

12.1.1. Intraocular Pressure

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

12.1.2. 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).

12.1.2.1. Cataract Lens Grading

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

12.1.3. Indirect Ophthalmoscopy

Indirect ophthalmoscopy should be performed according to the Investigator's standard clinical 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, absence of neovascularization.

12.1.4. 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.

12.1.5. Fundus Photography

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

12.1.6. Resting Heart Rate and Blood Pressure

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.

12.1.7. Pregnancy Test

Pregnancy tests will be performed on all females of childbearing potential. Urine pregnancy tests will be performed at Visits 2, 5 and 8. Serum tests will be performed at Visits 1 and 12.

12.1.8. Central Laboratory Tests

Non-fasting clinical laboratory tests will be performed at Visits 1, 8 and 12. These laboratory tests include serum chemistry, hematology, and urinalysis and are to rule out any underlying disease that may exclude the subject from participation.

12.1.9. Review of Body Systems

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

12.2. Adverse and Serious Adverse Events

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition after or during exposure to a pharmaceutical product, whether or not considered causally related to the product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered. This should be considered when a subject requires new or additional treatment for a pre-existing illness, or other medical condition. Lack of, or insufficient clinical response should not be recorded as an adverse event.

In addition, clinically significant changes in objective findings (e.g., laboratory, ECG, X-ray, Physical examination) should also be considered as to whether these are adverse events. The criteria for determining whether an objective finding should be reported as an adverse event are as follows:

1. Associated with accompanying symptoms; and/or
2. Requires medical/surgical intervention; and/or
3. Leads to a change in trial dosing, or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy; and/or
4. Leads to any of the outcomes included in the definition of serious adverse event; and/or
5. Is considered to be an adverse event as determined by the investigator, or Sponsor.

Any abnormal test result that is determined to be an error, does not require reporting as an adverse event, provided the result has been validated by a repeat test result.

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

12.2.1.2. Serious Adverse Event

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

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

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

*A life-threatening event is one that places the subject at immediate risk of death from the event as it occurred; not hypothetically that had the reaction occurred in a more severe form, it may have caused, or could cause death.

**Hospitalization is defined as any "formal in-patient admission" (even if less than 24 hours). For chronic, or long-term in-patients, in-patient admission also includes transfer within the hospital to an acute/intensive care in-patient unit.
In-patient admission does not include:

- Emergency Room visits
- Outpatient/same-day/ambulatory procedures and observation
- Hospice facilities and respite care
- Rehabilitation facilities, skilled nursing facilities, nursing homes
- Admission for treatment of a pre-existing condition, not associated with an adverse event, or worsening of the condition.
- Social admission (e.g. subject needs a place to sleep)
- Optional admission not associated with a precipitating clinical adverse event (e.g. elective cosmetic surgery)

***Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered serious when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include: allergic bronchospasm requiring intensive treatment in an emergency room, or at home, blood dyscrasias, or convulsions that do not result in inpatient admission.

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 (Not related or Related). Adverse events are assessed as either related to the injection procedure, or to the study drug (CLS-TA, bevacizumab, ranibizumab, aflibercept). The relationship to trial treatment will be assessed utilizing the following definitions:

Not Related: There is not a reasonable possibility (no valid reason) that the adverse event is related to the injection procedure, or to the trial study drug.

Related: There is a reasonable possibility (even if undetermined) that the adverse event is related to the injection procedure or to the trial study drug.

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, 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. An AE of severe intensity may not be considered serious.

12.2.5. Exposure In Utero

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.

12.2.6. 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 24 hours of the first awareness of the event. The Investigator must complete, sign, and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy by fax to Clearside Biomedical, or its designee.

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

The investigator or Clearside Biomedical (or third parties if applicable), if appropriate, is responsible for reporting suspected serious unexpected adverse reactions to the competent authorities in all the Member States and/or countries concerned, and to the Ethics Committee in compliance with current legislation.

12.2.7. Follow-up of AEs and SAEs

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

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

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

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

12.2.8. End of Trial

The end of the trial is defined as the last subject's last visit (Visit 12), as this will be the final date that data is collected from a trial participant.

13. STATISTICAL CONSIDERATIONS

A detailed statistical analysis plan will be prepared for this study. The plan will contain a discussion of the statistical methods, a description of the computational algorithms and data handling conventions, and specifications for the data summaries and listings. It will be finalized before database lock. This study will be analyzed by comparing the combination (active) arm, with an anti-VEGF agent and CLS-TA, to the anti-VEGF monotherapy (control) arm. The active arm will consist of two active groups: one group will receive anti-VEGF (ranibizumab) and corticosteroid (CLS-TA) and the other group will receive anti-VEGF (bevacizumab) and corticosteroid (CLS-TA) at randomization. The control arm will likewise consist of two groups: one group will receive anti-VEGF (ranibizumab only) and the other group will receive anti-VEGF (bevacizumab only) at randomization.

13.1. Randomization

There will be approximately 460 subjects randomly assigned 1:1:1:1 to one of the four treatment groups described above, each stratified by disease (BRVO, CRVO). HRVO subjects will be enrolled in this study and analyzed in the CRVO arm. Randomization will proceed as described until either stratum within a group reaches at least 50% of the total number patients to be enrolled in that group at which time only patients from the other stratum will be enrolled. Assignment of subjects to treatment groups will be performed via the IRT.

13.2. Determination of Sample Size and Level of Significance

With a total sample size of 460 subjects in a 1:1:1:1 randomization, this study will have 90% power to detect a difference of 15% between treatments if the actual proportion of subjects showing improvement of 15 letters is 0.50 for the control anti-VEGF agent arm at 2 months.

Power was based on a Pearson chi-squared difference in proportions of subjects showing improvement in BCVA at Month 2. The estimate for the IVT anti-VEGF agent proportion was set at 0.5, which is a worst-case scenario analysis because the variance of the proportion was maximal at 0.5. This, in turn, makes the power estimate robust with regard to the actual value of the IVT anti-VEGF agent proportion. The proportion for SC injection of CLS-TA adjunctive to anti-VEGF agent (combination) was estimated over a range of values. A minimal clinical effect of 15% greater improvement was selected. For 90% power, this will require 227 subjects/group.

13.3. Subject Disposition and Demographic and Baseline Characteristics

Subject disposition and demographic, and baseline characteristics will be summarized descriptively by treatment group, treatment arm, 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 one 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. Subjects will be analyzed as originally allocated after randomization. The ITT Population will be used for efficacy analyses. Missing data will be imputed using the last observation carried forward (LOCF) method. If a subject receives rescue therapy, LOCF will be used for the primary analysis using last available data from prior to administration of the rescue therapy.

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. 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. Missing data will not be imputed in the PP population. There will also not be any imputations of data for subjects who receive rescue therapy in the PP population.

13.5. Analysis Methods

Efficacy and safety endpoints are provided in Section 7.2.

13.5.1. Primary Efficacy Analysis

The primary endpoint is the proportion of subjects demonstrating ≥ 15 letter improvement from Baseline in ETDRS BCVA at Week 8 (Month 2).

The primary analysis is a test of superiority of suprachoroidally injected CLS-TA when used adjunctively (in “combination”) with intravitreally injected anti-VEGF agent. The primary analysis will use the Cochran-Mantel-Haenszel test to evaluate differences in the proportion of subjects in the two arms who show 15 or more letters improvement in BCVA at the 2-month visit after adjusting for effects for disease type. Subjects who either receive rescue therapy or withdraw from the study prior to the 2-month visit will be considered as treatment failures for the primary endpoint analysis.

Tests to evaluate the treatment superiority of suprachoroidally injected CLS-TA (TA) in combination with intravitreally injected anti-VEGF agent (IA) compared with IVT anti-VEGF agent alone will be conducted using a two-sided *alpha* = 0.05

The formal hypothesis is:

H_0: IA + TA = IA

H_1: IA + TA ≠ IA

The Breslow-Day test will be used to assess homogeneity of results across Investigators.

These methods were chosen because the subjects are stratified by RVO disease type, that is, CRVO and BRVO. For measures such as BCVA, differences across strata may be large enough to have impact on the overall results.

The Cochran-Mantel-Haenszel test adjusts for differences in results between disease types and the Breslow-Day test assesses homogeneity of results across Investigators.

13.5.1.1. 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 a placebo-based multiple imputation Pattern Mixture Model (PMM) and a tipping point analysis of the PMM in the ITT population. These sensitivity analyses will be detailed in the statistical analysis plan (SAP) and finalized prior to the study database lock.

13.5.2. Secondary Efficacy Analysis

13.5.2.1. Secondary Efficacy Endpoint

- Mean change from Baseline (Visit 2, Day 0) in BCVA at Visit 4 (Week 8) and Visit 8 (Week 24)
- Mean change from Baseline (Visit 2, Day 0) in CST at Visit 4 (Week 8) and Visit 8 (Week 24)

13.5.2.2. Exploratory Endpoints

- Change from Baseline (Visit 2, Day 0) in subject-reported outcomes at Visit 8 (Week 24) as measured by the VFQ-25 and the EQ-5D
- Change from Baseline in signs and complications of RVO (eg, neovascularization, perfusion) at Visit 8 (Week 24)
- Changes from Baseline based on disease type, CRVO or BRVO.

13.5.3. Subgroup Analysis

Subgroup analyses, if any, will be detailed in the statistical analysis plan. All these analyses will be considered as exploratory.

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 signs

13.5.5. Schedule of Analyses

Additional safety and descriptive efficacy data will be collected through approximately one year, the end of the study. Treatment codes will be broken at Month 2, and the final efficacy analysis will be conducted at this time. A descriptive follow-up safety and efficacy analysis will be performed at 6 months to allow filing the marketing authorization. Investigators, subjects, and study personnel who have contact with the Investigators or subjects will remain masked throughout the study. No adjustment for the analysis at Month 6 or at Month 12 are required because the final analysis of efficacy is at Month 2 and data from all subsequent visits will be descriptive only.

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

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

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

Likewise, the LOCF method will be used if a subject requires rescue therapy. The last recorded data before the rescue will be carried forward to all subsequent visits for the ITT Population. No imputation for rescue medications will be used in the PP Population. All data points will be set to missing after a subject's receipt of a rescue medication in the PP Population only.

Details of the methodology for handling missing or partial dates will be addressed in the Statistical Analysis Plan.

14. DIRECT ACCESS TO SOURCE DOCUMENTS

14.1. Study Monitoring

Before an investigator can enter a subject into the study, a representative of Clearside Biomedical, Inc. will visit the study site to:

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

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

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

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

14.2. Audits and Inspections

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

The Investigator should contact Clearside Biomedical immediately if contacted by a regulatory agency about an inspection.

14.3. Institutional Review Board/Independent Ethics Committee

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

15. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

16. ETHICS

16.1. 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 or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Clearside Biomedical, Inc. will provide this information to the Principal Investigator.

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

16.2. Ethical Conduct of the Study

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

16.3. Written Informed Consent

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

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

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

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

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

17.2. Retention of Records

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

18. PUBLICATION POLICY

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

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20. APPENDICES

APPENDIX A: Study Design and Schedule of Assessments, Visits 1-6

Visit #	Visit 1	Visit 2		Visit 3		Visit 4		Visit 5		Visit 6	
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		Week 16 Day 112 ± 5	
Assessments		Pre-dose	Post-dose	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	•	•		•		•		•		•	
VFQ-25 & EQ-5D		•									
Fluorescein Angiogram	•										
Fundus Photos	•										
IRT/Randomize		•									
IVT Anti-VEGF agent or Sham Injection		•		•		•		•		•	
SC CLS-TA or Sham Injection[3,4]		•						•			

APPENDIX A: Study Design and Schedule of Assessments, Visits 7-12

Visit #	Visit 7		Visit 8		Visit 9		Visit 10		Visit 11		Visit 12
Visit Type	Dosing and Evaluation				PRN Dosing and Follow Up						End of Study
Visit Window	Week 20 Day 140 ± 5		Week 24 Day 168 ± 5		Week 30 Day 210 ± 5		Week 36 Day 252 ± 5		Week 42 Day 294 ±5		Week 48 Day 336 ± 5
Assessments	Pre-dose	Post-dose	Pre-dose	Post-dose	Pre-dose	Post-dose	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	•		•		•		•		•		
VFQ-25 & EQ-5D			•								•
Fluorescein Angiogram			•								•
Fundus Photos			•								•
IRT/Randomize											
IVT Anti-VEGF agent or Sham Injection[3,]	•		•		PRN		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 (except Visit 8).
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 anti-VEGF agent injection (once IOP is < 30 mmHg).

APPENDIX B: Summary of Changes for Amendments

Amendment 1

Section Changed	Previous Protocol (Changed From)	Modified Protocol (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Title Page and Footer		Updated protocol title and document version and date	Protocol versioning	None
Investigator's Agreement	I have received and read the Investigator's Brochure for CLS-TA.	I have received and read the Investigator's Brochure for CLS-TA and the Investigator's Brochure for bevacizumab.	Addition of bevacizumab Investigator's Brochure	None
2. Synopsis	Removed references to EYLEA as study drug	Added reference to AVASTIN and LUCENTIS as study drug	Comparator drug modification	None
		Added text to describe study treatment arms, including endpoints	Describe changes to study treatment arms	None
		Modified statistical analysis information	Comparator drug modification	
4. List of Abbreviations	IWRS – Interactive web response system	IRT – Interactive response technology	System update	None
5. Introduction		Provide background and describe rationale for use of Avastin and Lucentis in conjunction with CLS-TA	Comparator drug modification	None
Section 6.4 Exploratory Objectives		Added 'To evaluate changes from baseline based on disease type, BRVO and CRVO. Subjects with HRVO data will be included with the CRVO group based on randomization.'	Addition of exploratory objective	None

APPENDIX B: Summary of Changes for Amendments

Amendment 1

Section Changed	Previous Protocol (Changed From)	Modified Protocol (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Section 7.2.3 Exploratory Efficacy Endpoints		Added 'Changes from Baseline on visual and anatomic outcomes based on disease diagnosis of BRVO and CRVO. HRVO subjects will be included with the CRVO for analyses.'	Addition of exploratory efficacy endpoint	None
Section 7.3 Number of Subjects	Approximately 460 subjects with RVO who are naïve to treatment will be enrolled into one of two treatment groups.	Approximately 460 subjects with RVO who are naïve to treatment will be enrolled into one of four treatment groups.	Update treatment groups	None
Section 7.4 Treatment Assignment	After Screening (Day -30 to Day -1) and Baseline assessments on Day 0, subjects will be randomly assigned 1:1 to one of two treatment groups stratified by disease type (BRVO, CRVO). Randomization will proceed as described until either strata reaches 55% of the total number patients to be enrolled at which time only patients from the other strata will be enrolled.	After Screening (Day -30 to Day -1) and Baseline assessments on Day 0, subjects will be randomly assigned 1:1:1:1 to one of four treatment groups stratified by disease type (BRVO, CRVO). Randomization will proceed as described until either strata within a group reaches at least 50% of the total number patients to be enrolled in that group at which time only patients from the other strata will be enrolled.	Treatment group changes	None
Table 3. Subject Randomization	Remove reference to IVT aflibercept	Change treatments arms to include IVT Avastin and Lucentis	Comparator drug modification and number of subjects per treatment group	None

APPENDIX B: Summary of Changes for Amendments

Amendment 1

Section Changed	Previous Protocol (Changed From)	Modified Protocol (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Figure 2. Study Treatment Schedule	Removed previous table	Insert new table	Updates to table	None
Section 6.4. Exploratory Objectives		To determine the safety and performance of the SCS microinjector when delivering SC CLS-TA	Endpoint added to capture microinjector exploratory objective	None
Section 7.2.5 Endpoints Related to SCS microinjector		Performance of the SCS microinjector, evidenced by injection parameters (location, eye quadrant, needle length, injection completion, and product complaints) at each SC injection visit (Visits 2, 5, 8)	Section added for microinjector endpoints	None
		Incidence of TEAEs and SAEs related to the SCS microinjector		
Section 8.3. Subject Withdrawal Criteria		Added text for subject withdrawal criteria	Update withdrawal criteria	None
Section 8.4. Visit Procedure Descriptions		PRN therapy will be aflibercept for all subjects, regardless of randomization group.	Identify PRN treatment	None
		Removed slit lamp ophthalmoscopy assessment post injections	Update to reflect common clinic procedures	None

APPENDIX B: Summary of Changes for Amendments

Amendment 1

Section Changed	Previous Protocol (Changed From)	Modified Protocol (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Section 9.1. Treatments to be Administered		Adjusted to include Avastin and Lucentis	Clarify treatment administration	None
Section 9.4. Rescue Treatment		Updated section 9.4.1 title from Rescue Therapy Criteria to Supplemental Therapy Criteria Updated rescue to supplemental throughout the protocol	Clarify definition of rescue versus supplemental therapy	None
Section 10.4 Study Drug Preparation		Updated to include preparation for additional anti-VEGF agents	Comparator drug modification	None
Section 12.2. Adverse and Serious Adverse Events		Updates throughout to clarify adverse events and reporting	Clarification of reporting procedures	None
Section 12.2.5. Exposure In Utero		Addition of new section	Addition of new section	None
Section 13. Statistical Considerations		Updates throughout the statistical analysis section	Comparator drug modification	None
References		Addition of references	Comparator drug modification	None

APPENDIX B: Summary of Changes for Amendments

Amendment 1

Section Changed	Previous Protocol (Changed From)	Modified Protocol (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Throughout protocol		Various formatting changes	Formatting updates	None
		Replaced 'aflibercept' with 'intravitreal anti-VEGF agent' or 'IVT anti-VEGF agent' inclusive of LUCENTIS and AVASTIN	Change in comparator agents	
Appendix A		Removed post injection slit lamp ophthalmoscopy assessment	Update to reflect common clinic procedures	None
		Removed serum pregnancy test at Visit 8	Urine pregnancy test will be done at Visit 8	None

APPENDIX B: Summary of Changes for Amendments

Amendment 1.1

Section Changed	Previous Protocol (Changed From)	Modified Protocol (Changed To)	Reason for Change	Impact on Subjects (Risk/Benefit)
Section 8 Headers		Section Header Numbers added for ease in navigating document	Formatting updates	None
Section 12.2.4 Intensity	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.	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.	Section reference corrected	None
Section 12 Headers		Section Header Numbers updated to remove duplicate	Formatting updates	None