Compound Name:	CLS-AX, axitinib injectable suspension
Protocol Number:	CLS1002-101
IND Number:	132228
NCT Number:	NCT04626128
Protocol Title	OASIS: Open-label, dose-escalation, phase 1/2a study of the safety and tolerability of suprachoroidally administered CLS-AX following intravitreal anti-VEGF therapy in subjects with neovascular age-related macular degeneration
Sponsor:	Clearside Biomedical, Inc. 900 North Point Parkway, Suite 200 Alpharetta, GA 30005
Issue Date: **Protocol Amendment 1 Date:** **Protocol Amendment 2 Date:** **Protocol Amendment 3 Date:** **Protocol Amendment 4 Date:**	15 October 2020 26 March 2021 13 December 2021 08 March 2022 15 April 2022

A. SUMMARY OF CHANGES

Protocol Amendment 4

Protocol Title:	**OASIS**: OPEN-LABEL, DOSE-ESCALATION, PHASE 1/2A STUDY OF THE SAFETY AND TOLERABILITY OF SUPRACHOROIDALLY ADMINISTERED CLS-AX FOLLOWING INTRAVITREAL ANTI-VEGF THERAPY IN SUBJECTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION		
Protocol Number: IND:	CLS1002-101 132228	Original Version Date:	15 October 2020
Amendment Number:	4	Version Number and Date:	Version 5, 15 April 2022

Note: for clarity, deleted text will be denoted with a ~~strikethrough~~ and additional/altered text will appear in **bold**.
Minor editorial changes to improve readability will not be documented.

Amendment 4			
Sections Changed and Reasons	**Initial Protocol (Change From)**	**Modified Protocol (Changed To)**	**Impact on Subjects (Risk/Benefit)**
Title Page		**Protocol Amendment 4 Date: 15 April 2022**	None.
Reason for Change	To document the approval date of protocol amendment 4.		
Revision History		Version Number: **5.0** Date: **15 April 2022** Revision summary: **Protocol Amendment 4**	None.
Reason for Change	To document the protocol revision history to include Protocol Amendment 4.		
Section 8.4.4.1 Visit 2 (Day 1) Pre CLS-AX Suprachoroidal Injection Procedures, Step 7	New procedure added.	Addition of the following procedure: **g. Fundus autofluorescence imaging*, **.**	None.
Reason for Change	Following the Cohort 3 safety data review by the SMC, it was recommended by the Investigators that fundus autofluorescence imaging of the study eye be added at Visit 2 (Baseline) and Visit 5 (Week 12) in order to aid in detection of potential retinal pathologies.		
Section 8.4.4.1 Visit 2 (Day 1) Pre CLS-AX Suprachoroidal Injection Procedures, Step 7	**NOTE:** * All images (SD-OCT, fundus photographs and fluorescein angiography) should be uploaded to the Central Reading Center.	**NOTE:** * All images (SD-OCT, fundus photographs, **fundus autofluorescence imaging** and fluorescein angiography) should be uploaded to the Central Reading Center.	None.

Amendment 4			
Sections Changed and Reasons	**Initial Protocol (Change From)**	**Modified Protocol (Changed To)**	**Impact on Subjects (Risk/Benefit)**
Reason for Change	FAF images will be uploaded to the Central Reading Center. Images will be graded for informational purposes only if the need arises.		
Section 8.4.4.1 Visit 2 (Day 1) Pre CLS-AX Suprachoroidal Injection Procedures	** OCT-A is considered an optional procedure for those Investigator sites possessing the necessary equipment.	** OCT-A **and fundus autofluorescence imaging are**~~is~~ considered ~~an~~ optional procedures for those Investigator sites possessing the necessary equipment.	None.
Reason for Change	Fundus autofluorescence imaging will be considered an optional procedure for those sites that have the equipment.		
Section 8.4.6 Visit 5 (Week 12) End of Study/Early Termination Step 10	10. 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*, f. OCT-A**.	10. Perform ophthalmic assessments on both eyes**, unless otherwise designated**: a. ETDRS BCVA, b. Slit-lamp biomicroscopy, including dilated lens grading, c. IOP, d. Dilated indirect ophthalmoscopy, e. SD-OCT*, f. OCT-A**, **g. Fundus autofluorescence imaging (study eye only)*, **.**	None.
Reason for Change	Following the Cohort 3 safety data review by the SMC, it was recommended by the Investigators that fundus autofluorescence imaging of the study eye be added at Visit 2 (Baseline) and Visit 5 (Week 12) in order to aid in detection of potential retinal pathologies.		

Amendment 4			
Sections Changed and Reasons	**Initial Protocol (Change From)**	**Modified Protocol (Changed To)**	**Impact on Subjects (Risk/Benefit)**
Section 8.4.6 Visit 5 (Week 12) End of Study/Early Termination Step 10	**NOTE:** * All images (SD-OCT, fundus photographs and fluorescein angiography) should be uploaded to the Central Reading Center.	**NOTE:** * All images (SD-OCT, fundus photographs, **fundus autofluorescence imaging** and fluorescein angiography) should be uploaded to the Central Reading Center.	None.
Reason for Change	FAF images will be uploaded to the Central Reading Center. Images will be graded for informational purposes only, if the need arises.		
Section 8.4.6 Visit 5 (Week 12) End of Study/Early Termination Step 10	** OCT-A is considered an optional procedure for those Investigator sites possessing the necessary equipment.	** OCT-A **and fundus autofluorescence imaging are**~~is~~ considered ~~an~~ optional procedure**s** for those Investigator sites possessing the necessary equipment.	None.
Reason for Change	Fundus autofluorescence imaging will be considered an optional procedure for those sites that have the equipment.		
Section 12.1.14 Fundus Autofluorescence Imaging	New section.	**12.1.14 Fundus Autofluorescence Imaging** **Fundus autofluorescence imaging will be obtained at those Investigator sites possessing the necessary equipment. Specific assessments will not be pre-specified but may include evaluating abnormal regions of hyper- and/or hypo-autofluorescence for diagnosing of potential retinal and RPE abnormalities. Fundus autofluorescence images should be taken prior to the fluorescein angiography. All images should be taken by the same photographer, whenever possible, on all subjects per research site.**	None.

Amendment 4			
Sections Changed and Reasons	**Initial Protocol (Change From)**	**Modified Protocol (Changed To)**	**Impact on Subjects (Risk/Benefit)**
		Digital equipment will be registered, and photographers certified for the imaging procedures. De-identified images will be uploaded to the Central Reading Center. Fundus autofluorescence images will be obtained at Visit 2 (Baseline, Day 1) prior to the administration of CLS-AX, and at Visit 5 (Week 12).	
Reason for Change	Following the Cohort 3 safety data review by the SMC, it was recommended by the Investigators that fundus autofluorescence imaging of the study eye be added at Visit 2 (Baseline) and Visit 5 (Week 12) in order to aid in detection of potential retinal pathologies. Fundus autofluorescence imaging will be an optional procedure for sites possessing the necessary equipment.		
Appendix A Time and Events Schedule	New assessment added.	**Fundus Autofluorescence Imaging [h,i]**	None.
Reason for Change	Following the Cohort 3 safety data review by the SMC, it was recommended by the Investigators that fundus autofluorescence imaging of the study eye be added at Visit 2 (Baseline) and Visit 5 (Week 12) in order to aid in detection of potential retinal pathologies. Fundus autofluorescence imaging will be an optional procedure for sites possessing the necessary equipment (footnote h) and will only be collected for the study eye (footnote i).		
Appendix A Time and Events Schedule	New footnote.	**[i] Completed for Study Eye only at Visit 2 (Baseline, Day 1) and Visit 5 (Week 12).**	None.
Reason for Change	Fundus autofluorescence imaging will be assessed at Visit 2 (Baseline, Day 1) and Visit 5 (Week 12) in the study eye only.		

Project:	1002
Compound Number/Name:	CLS-AX (axitinib injectable suspension)
Protocol Number:	CLS1002-101
IND Number:	132228
Phase:	1/2a
Protocol Title:	OASIS: OPEN-LABEL, DOSE-ESCALATION, PHASE 1/2A STUDY OF THE SAFETY AND TOLERABILITY OF SUPRACHOROIDALLY ADMINISTERED CLS-AX FOLLOWING INTRAVITREAL ANTI-VEGF THERAPY IN SUBJECTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION
Sponsor:	Clearside Biomedical, Inc. 900 North Point Parkway, Suite 200 Alpharetta, GA 30005
Primary Medical Monitor:	Benjamin I. Rubin, M.D.
Principal Investigator:	To be appointed before the end of the study

Protocol Amendment 4 Date:	15 April 2022
Protocol Amendment 3 Date:	08 March 2022
Protocol Amendment 2 Date:	13 December 2021
Administrative Change Date:	19 November 2021
Protocol Amendment 1 Date:	26 March 2021
Issue Date:	15 October 2020

SIGNATURE PAGE

This study protocol 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: **Thomas Ciulla, M.D.** **Chief Medical Officer** **Clearside Biomedical, Inc.**	***ELECTRONIC SIGNATURE ON FILE***
Sponsor Signatory: **Barbara Bauschka** **Vice President, Regulatory Operations** **Clearside Biomedical, Inc.**	***ELECTRONIC SIGNATURE ON FILE***
Sponsor Signatory: **Colette Hall, M.D.** **Vice President, Medical and Safety** **Clearside Biomedical, Inc.**	***ELECTRONIC SIGNATURE ON FILE***

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for CLS-AX (axitinib injectable suspension). I have read the CLS1002-101 Protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone number
Clinical Study Leader	Georgina Debrah	Clearside Biomedical, Inc. 900 North Point Parkway, Suite 200 Alpharetta, GA 30005 USA (678) 254-2345
Responsible Physician	Thomas Ciulla, M.D.	Clearside Biomedical, Inc. 900 North Point Parkway, Suite 200 Alpharetta, GA 30005 USA (678) 392-2318
Drug Safety Physician	Colette Hall, M.D.	Clearside Biomedical, Inc. 900 North Point Parkway, Suite 200 Alpharetta, GA 30005 USA (678) 820-4178
Primary Medical Monitor (24-Hour Emergency Contact)	Benjamin I. Rubin, M.D.	MedTrials, Inc. 7801 Renoir Court Potomac, MD USA (301) 509-4451

CLINICAL LABORATORIES AND MEDICAL INSTITUTIONS

Table 2: Names and Addresses of Institutions

Reading Center	Name and Address
Central Laboratory	ACM Global Laboratories 160 Elmgrove Park Rochester, NY 14624 USA
Electrocardiogram Reading Center	Clario 1818 Market Street Suite 2600 Philadelphia, PA 19103-3600 USA
Pharmacokinetic Evaluation	Covance Laboratories 8211 SciCor Drive Indianapolis, IN 46214 USA
Central Reading Center for Fundus Photographs, Fluorescein Angiograms and Spectral Domain Optical Coherence Tomography	Merit CRO, Inc. 6527 Normandy Lane #100 Madison, WI 53719 USA

REVISION HISTORY

Table 3: Revision History

Version Number	Date	Revision summary
Draft	19 May 2020	Initial release version for IND.
1.0	15 October 2020	Initial release of protocol.
2.0	26 March 2021	Protocol Amendment 1.
2.1	19 November 2021	Administrative Change 1.
3.0	13 December 2021	Protocol Amendment 2.
4.0	08 March 2022	Protocol Amendment 3.
5.0	15 April 2022	Protocol Amendment 4.

2. SYNOPSIS

Name of Sponsor/Company:
Clearside Biomedical, Inc.

Name of Investigational Product:
CLS-AX (axitinib injectable suspension)

Name of Active Ingredient:
Axitinib

Title of Study:
OASIS: Open-label, dose-escalation, phase 1/2a study of the safety and tolerability of suprachoroidally administered CLS-AX following intravitreal anti-VEGF therapy in subjects with neovascular age-related macular degeneration

Study centers: Multi-Center

Principal Investigators: Multi-Center

Studied period: 16 Week Duration	**Phase of development:**
Estimated date first subject enrolled: December 2020 Estimated date last subject completed: September 2022	Phase 1/2a

Background and Rationale:

Currently, anti-vascular endothelial growth factor (VEGF)-A drugs are the standard of care for the treatment of neovascular age-related macular degeneration (nAMD) (Flaxel, 2020); however, an unmet need remains for significantly improving and maintaining visual acuity in most patients (Rofagha, 2013, CATT, 2016, Singer, 2012).

Axitinib demonstrates intrinsic high potency and achieves pan-VEGF inhibition through tyrosine kinase receptor blockade (INLYTA, 2018, Hu-Lowe, 2008); axitinib is a second-generation tyrosine kinase inhibitor (TKI) that potently inhibits vascular endothelial growth factor receptors VEGFR-1, VEGFR-2, and VEGFR-3 at picomolar concentrations, and inhibits platelet-derived growth factor receptors (PDGFR) and c-KIT receptors to a significantly lesser degree, by stabilizing the receptor kinase domain in an inactive conformation. In preclinical work by independent investigators, axitinib effectively inhibited corneal, retinal and choroidal angiogenesis in multiple preclinical models (Riquelme, 2018, Yuan, 2015, Giddabasappa, 2016, Nakano, 2016, Kang, 2013). Topical axitinib more effectively inhibited experimental corneal neovascularization than other topical tyrosine kinase receptor inhibitors in a preclinical model (Yuan, 2015). Furthermore, experimental oral axitinib not only inhibited choroidal neovascularization, but also caused regression of established neovascularization (Kang, 2013). Importantly, in-vitro assessment has revealed better biocompatibility with ocular cells than other tyrosine kinase inhibitors (Thiele, 2013).

Suprachoroidal (SC) injection is a novel drug-dispensing approach that is a minimally invasive office-based procedure, performed using Clearside's proprietary injection device, the SCS Microinjector®. A SC injection is the term used to describe this intraocular injection procedure performed in the pars plana approximately 4 – 4.5 mm posterior to the limbus, resulting in a sub-scleral dispensing of drug product into the suprachoroidal space (SCS) which is the transition region between the sclera and the choroid. Immediately after the SC injection procedure, injectate moves posteriorly from the site of the injection, with the fluid being absorbed dominantly into the inner sclera, choroid, retinal pigment epithelial (RPE) cells, and retina. Clearside Biomedical Inc. ("Clearside") is developing a proprietary formulation of axitinib, CLS-AX (axitinib injectable suspension) to treat nAMD by injection into the

SCS. Utilizing this approach enables nearly direct access to the tissue layers affected in nAMD, i.e., the retina and choroid. Suprachoroidal delivery of CLS-AX results in ocular distribution of axitinib at high concentrations in the choroid, RPE cells, and retina for at least 3 months while maintaining low to no exposure in the aqueous humor, lens and systemic circulation (based on data from animal models). Given the ability to directly access the target site, favorable ocular pharmacokinetics, and potent pan-VEGF receptor activity, CLS-AX provides the potential for maintenance of efficacy outcomes in patients with nAMD previously treated with anti-VEGF agents.

Objectives:

Primary:

To assess safety and tolerability of a single dose of CLS-AX in subjects with neovascular age-related macular degeneration who show stable visual acuity following ≥3 injections with an intravitreal anti-VEGF therapy in the preceding 5 months.

Secondary:

1. To evaluate and compare the effect of 4 cohort regimens involving a single dose of CLS-AX over 3 months on visual function and ocular anatomy and the need for additional treatment with intravitreal aflibercept.
2. To evaluate the pharmacokinetics of the 4 cohort regimens of a single dose of CLS-AX over 3 months.

Exploratory:

To evaluate the safety and performance of the SCS Microinjector.

Study Design:

This is a Phase 1/2a open-label, dose-escalation study to assess the safety and tolerability of single doses of CLS-AX administered suprachoroidally following at least 3 prior treatments (the last of which will be administered at the Screening visit) with an intravitreal (IVT) anti-VEGF agent in nAMD subjects. The study design includes 4 dose cohorts of approximately 5 enrolled subjects in each cohort, with an overall enrolled total not to exceed 25 subjects in the 4 cohorts. Subject eligibility will be established at Visit 1, Screening (Day -28 ± 3 days). Eligible subjects will receive an IVT injection of aflibercept, 2 mg (0.05 mL), at Visit 1, Screening (Day -28 ± 3 days), followed by a suprachoroidal injection of CLS-AX at Visit 2, Baseline (Day 1) upon enrollment. Subjects return for safety and tolerability assessments, visual function and ocular anatomy assessments, and the need for additional treatment at Visits 3, 4, and 5 (Weeks 4, 8 and 12), (Follow-up Period). Further, additional treatments will be administered at Visits 3 and 4 (Weeks 4 and 8) based on PRN criteria and will consist of aflibercept (2 mg (0.05 mL) administered by IVT injection) unless other therapy is medically necessary. [redacted] The 4 dose cohorts will include the following:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

All cohorts will be assessed for safety and tolerability and effects on visual function and ocular anatomy as outlined in the time and events schedule.

Dose escalation will proceed following review of the safety data by the Safety Monitoring Committee (SMC) and after the SMC makes a recommendation regarding the next higher dose cohort initiation.

Number of subjects (planned): Not to exceed 25 subjects.

Diagnosis and main criteria for inclusion:

Inclusion criteria:

Subjects are eligible for participation in this study if s/he meets all of the following criteria at the Screening (Visit 1) and Baseline (Visit 2) visits:

1. Diagnosis of neovascular age-related macular degeneration in the study eye.
2. Active subfoveal choroidal neovascularization (CNV) secondary to AMD of any lesion type in the study eye with photos and/or fluorescein angiography (FA) and/or spectral-domain optical coherence tomography (SD-OCT) showing:
   a. Total lesion area (including CNV, hemorrhage, fibrosis, atrophy) [redacted]
   b. CNV component area of [redacted]
   c. CNV must not be associated with [redacted]
3. At Screening, [redacted] for neovascular AMD in the study eye with a meaningful response, for example, an improvement in vision and/or exudation, based on the Investigator's opinion.
4. Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual activity (BCVA) score of [redacted] in the study eye with:
   a. [redacted] between Screening (Visit 1) and Baseline (Visit 2).
5. Understands the language of the informed consent; willing and able to provide written informed consent prior to any study procedures; willing to comply with the instructions and attend all scheduled study visits.
6. At least 50 years of age.
7. Subjects of childbearing potential must agree to use acceptable methods 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 he or she becomes sexually active. Females of childbearing potential must consent to performance of a pregnancy test.

Exclusion criteria:

Ophthalmic Exclusion Criteria

Subjects are ineligible for participation in this study if s/he meets any of the following criteria at the Screening (Visit 1) or Baseline (Visit 2) visits:

1. Any active ocular disease or infection in the study eye other than nAMD, such as:
   [redacted]
2. CNV in the study eye due to other causes other than AMD, such as:
   [redacted]
3. CNV in the study eye with any of the following on photos and/or FA and/or SD-OCT:
   [redacted]
4. Other than IVT injected aflibercept, ranibizumab, bevacizumab, or brolucizumab, prior treatment for CNV in the study eye, including:
   [redacted]
5. Has [redacted] in the study eye precluding evaluation of the retina and vitreous.
6. Intraocular pressure [redacted]
7. Any concurrent condition in the study eye that, in the opinion of the Investigator, could reduce the potential for visual improvement or require medical or surgical intervention, such as:
   [redacted]

8. Any prior ocular surgery in the study eye, such as:

[redacted]

9. Has [redacted] in the study eye defined as a [redacted] or an [redacted] Has a prior history of [redacted]
10. In the study eye, any [redacted] at Baseline (Visit 2); any intraocular or periocular corticosteroid injection.
11. Concomitant therapy with any drug that may be toxic to the lens, retina or optic nerve, such as (examples for clarification purposes; list is not exhaustive):

[redacted]

General Exclusion Criteria

Subjects are not eligible for participation in this study if s/he meets any of the following criteria at the Screening (Visit 1) or Baseline (Visit 2) visits:

12. Female subjects who are pregnant, lactating or planning a pregnancy.
13. Uncontrolled systemic disease as follows:

[redacted]

14. Any other condition or therapy, which in the opinion of the Investigator, might pose a risk to the patient or make participation in the study not in the subject's best interest.
15. Has taken [redacted] in the 2 weeks prior to Baseline (Visit 2).

16. Has had surgery 2 weeks prior to Screening (Visit 1) or anticipates the need for hospitalization or surgery within the study period including 30 days after exiting the study.
17. Hypersensitivity to any component of CLS-AX, aflibercept, fluorescein, or to topical anesthetics.
18. Currently enrolled in an investigational drug or device study or has used an investigational drug or device within 30 days of the Screening visit.

Investigational product, dosage, and mode of administration:

A single administration of CLS-AX (axitinib injectable suspension) at Visit 2, Baseline (Day 1) dosed at 0.03 mg, 0.10 mg, 0.50 mg and 1.0 mg in 100 µL into the suprachoroidal space, administered with the SCS Microinjector.

Reference therapy, dosage, and mode of administration: None

Criteria for evaluation:

Primary: Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events, grouped by organ system, relatedness to study treatment, and severity.

Secondary:

[redacted]

Statistical Methods:

This is an open-label Phase 1/2a study and therefore, no formal statistical testing of the endpoints will be conducted. The observed and change from baseline values will be summarized descriptively for each cohort. Categorical variables will be summarized by counts and percentages and continuous variables by descriptive statistics (n, mean, standard deviation, standard error, median, minimum and maximum). Baseline is defined as the last assessment prior to administration of CLS-AX.

Sample size is not statistically driven as this is a Phase 1/2a study. [redacted]

Study Suspension and Dose-Escalation:

All subjects will receive IVT injected aflibercept, 2 mg (0.05 mL), at Screening (Visit 1) followed by a single dose of CLS-AX administered suprachoroidally at Baseline (Visit 2). Safety assessments from the visits at Week 4 (Visit 3), 8 (Visit 4) and 12 (Visit 5) following CLS-AX SC injection will be reviewed.

Suspension of the Study: The study enrollment will be immediately suspended, and no additional subjects will be enrolled, and no CLS-AX will be administered pending review of all appropriate study data by the Safety Monitoring Committee if:

- A treatment related serious adverse event is reported.

- ≥2 subjects experience a Grade 3 or higher non-serious treatment related adverse event, based on the CTCAE severity grading scale.
- ≥3 subjects within the same dose cohort experience a Grade 2 or higher non-serious treatment related adverse event in the same MedDRA system organ class.
- An AE or pattern of AEs, that, in the opinion of the sponsor, makes further dose escalation unadvisable.

If the clinical study is suspended, the Sponsor will inform the Investigators and the regulatory authorities of the suspension and the reason(s) for the suspension. The Investigator should promptly notify the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of the suspension and of the reasons.

Enrollment of subjects into the study will not be restarted until the Sponsor has decided upon the course of action to be taken and the IRB /IEC has been notified.

During the period of suspension, provided the Investigator determines that it is in the subjects' best interest to continue in the study, the Sponsor's preference is to retain enrolled subjects in the study until the final study visit (Visit 5, Week 12).

Dose Escalation:

Dose escalation following Cohorts 1 and 2:

After the last subject enrolled into a cohort has completed the final visit (Visit 5, Week 12) (or discontinued prematurely from the study), all safety data will be evaluated by the SMC. Following review of the data, the committee will make a recommendation regarding initiation of the next higher dose cohort.

Dose escalation during Cohort 3:

After the fourth subject enrolled into the cohort has completed at least Visit 3 (Week 4) (or discontinued prematurely from the study), all available safety data will be evaluated by the SMC. Following review of the data, the committee will make a recommendation regarding initiation of the next higher dose cohort.

[redacted]

Continued monitoring of safety parameters will be performed throughout the conduct of the cohort. At any time, if any safety signals or trends arise, these issues may be escalated to the SMC for review. The SMC may make recommendations for dose adjustments. [redacted]

Study drug administration at the next higher dose cohort may not proceed until the Investigator receives written confirmation from Clearside Biomedical, indicating the results from the previous dosed cohort were evaluated and it is permissible to proceed to the next higher dose cohort.

Additional therapy criteria:

All eligible subjects will receive an intravitreal aflibercept injection of 2 mg (0.05 mL), at Screening (Visit 1; Day -28 ± 3 days) followed by a single dose of CLS-AX administered suprachoroidally at

Baseline (Visit 2; Day 1). Subjects will be assessed for additional therapy at Visits 3, 4, and 5 (Weeks 4, 8, and 12). [redacted]

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 4: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
AMD	Age-related macular degeneration
BCVA	Best corrected visual acuity
BSS	Balanced saline solution
CABG	Coronary artery bypass surgery
C_{max}	Maximum serum concentration
CNV	Choroidal neovascularization
CRF	Case report form
CST	Central subfield retinal thickness
CTCAE	Common Terminology Criteria for Adverse Events
CVA	Cerebrovascular accident
DLT	Dose limiting toxicity
ECG	Electrocardiogram
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiogram
GCP	Good Clinical Practice
GI	Gastrointestinal
IB_4	isolectin B_4
IC50	50% inhibitory concentration
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IOP	Intraocular pressure
IRB	Institutional Review Board
IVT	Intravitreal(ly)
nAMD	Neovascular age-related macular degeneration
NCI	National Cancer Institute
NVI	Neovascularization of the iris
NYHA	New York Health Association
MedDRA	Medical Dictionary for Regulatory Applications

Table 4: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
OCT-A	Optical coherence tomography angiography
PCV	Polypoidal choroidal vasculopathy
PD	Pharmacodynamics
PDGFR	Platelet-derived growth factor receptor
PK	Pharmacokinetics
PRN	Pro re nata; “when necessary”
PSVT	Paroxysmal supraventricular tachycardia
PTCA	Percutaneous transluminal coronary angioplasty
RAP	Retinal angiomatous proliferation
RPE	Retinal pigment epithelial
SAE	Serious adverse event
SC	Suprachoroidal
SCS	Suprachoroidal space
SD-OCT	Spectral Domain Optical Coherence Tomography
SMC	Safety Monitoring Committee
SOC	Systemic organ class
SVT	Supraventricular tachycardia
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
YAG	Yttrium-Aluminum-Garnet

5. INTRODUCTION

In developed countries, neovascular age-related macular degeneration (nAMD) is the leading cause of irreversible central blindness (Congdon, 2004, The Eye Disease Prevalence Research Group, 2004, Wong, 2014). Age-related macular degeneration (AMD) pathogenesis is complex and still not fully understood. However, many of the mechanisms involved are already partially known and, specifically for the 10-15% of AMD classified as the neovascular type, include the vascular endothelial growth factor (VEGF) signaling pathway. In nAMD, abnormal blood vessel growth results in choroidal neovascularization (CNV) in the choriocapillaris, a layer of capillaries situated immediately below Bruch's membrane, under the retina and macula. Choroidal neovascularization leads to the leakage of blood, lipids, and serum into the retinal layers and causes the macula to bulge or lift up from its normal position, distorting or destroying central vision (Ambati, 2003). In nAMD, VEGF-A, which acts at VEGF receptors 1 and 2 (VEGFR-1, VEGFR-2), has been shown to promote abnormal blood vessel growth and is therefore an appropriate target for treatment.

Currently, anti-VEGF-A drugs are the standard of care for the treatment of nAMD (Flaxel, 2020); however, an unmet need remains for significantly improving and maintaining visual acuity in most patients (Rofagha, 2013, CATT, 2016, Singer, 2012). Specifically, there may be a ceiling of efficacy with current anti-VEGF-A agents, as increased anti-VEGF-A dosage or more intense regimens yield no additional best corrected visual acuity (BCVA) benefit (Heier, 2012, Busbee, 2013, Schmidt-Erfurth, 2014). Recent data on VEGF regulation may be relevant, as anti-VEGF-A therapy has been shown to upregulate other members of the VEGF family in both macular degeneration (Cabral, 2018) and colon cancer patients (Lieu, 2013); this secondary upregulation of other members of the VEGF family may account for "resistance" to VEGF-A therapy (Lieu, 2013). Furthermore, the current treatment paradigm of frequent intravitreal (IVT) injections is burdensome. For example, recent large "real-world" retrospective studies of nAMD demonstrated that patients are undertreated receiving only 6 to 7 injections on average, yielding only a mean 1 to 3 letters gained in BCVA one year after initiation of treatment (Ciulla, 2020, Rao, 2018).

Axitinib demonstrates intrinsic high potency and achieves pan-VEGF inhibition through tyrosine kinase receptor blockade (INLYTA, 2018, Hu-Lowe, 2008); it is a second-generation tyrosine kinase inhibitor (TKI) that inhibits vascular endothelial growth factor receptors VEGFR-1, VEGFR-2, and VEGFR-3 at picomolar concentrations, and inhibits platelet-derived growth factor receptors (PDGFR) and c-Kit receptors to a significantly lesser degree, by stabilizing the receptor kinase domain in an inactive conformation. Axitinib is currently approved in an oral tablet formulation (INLYTA®) for the treatment of advanced renal cell carcinoma after failure of 1 prior systemic therapy. In preclinical work by independent investigators, axitinib has shown promising results in animal models of ocular angiogenesis. Specifically, it effectively inhibited corneal, retinal and choroidal angiogenesis in multiple preclinical models (Riquelme, 2018, Yuan, 2015, Giddabasappa, 2016, Nakano, 2016, Kang, 2013). Topical axitinib more effectively inhibited corneal neovascularization than other topical tyrosine kinase receptor inhibitors in a preclinical model (Yuan, 2015). Furthermore, oral axitinib not only inhibited choroidal neovascularization, but also caused regression of established neovascularization in a preclinical model (Kang, 2013), a highly desired therapeutic effect for the treatment of human nAMD. In a cell culture study, axitinib consistently exhibited superior cell viability among five different

ocular cell lines, even under conditions of oxidative stress, compared to other tyrosine kinase inhibitors previously assessed in nAMD clinical trials (Thiele, 2013).

Clearside Biomedical Inc. ("Clearside", "Sponsor") is developing a proprietary formulation of axitinib, CLS-AX (axitinib injectable suspension) to treat nAMD by injection into the suprachoroidal space (SCS). Suprachoroidal (SC) injection is a novel drug-dispensing approach that employs the SCS Microinjector®, a proprietary piston syringe and a needle approximately 1 mm in length. A SC injection is the term used to describe this intraocular injection procedure performed in the pars plana approximately 4 - 4.5 mm posterior to the limbus, resulting in sub scleral dispensing of drug product into the SCS which is the transition region between the sclera and the choroid.

Immediately after the SC injection procedure, injectate moves posteriorly from the site of the injection, with the fluid being absorbed dominantly into the inner sclera, choroid, retinal pigment epithelial (RPE) cells, and retina (based on animal models). Suprachoroidal injection of CLS-AX, with a resulting ocular distribution of CLS-AX in high amounts into the choroid, RPE cells, and retina (based on data from animal models) provides the potential for robust and sustained efficacy outcomes in patients with nAMD. While there is high exposure to CLS-AX in the retina, RPE cells, and choroid, there is also lower exposure to CLS-AX in the anterior segment and the lens, providing the potential for a reduced incidence of ocular adverse events. Systemic levels of axitinib following SC injection are low to below the limits of quantification. Further, these systemic levels of axitinib are vastly below levels observed following oral administration of axitinib. Suprachoroidal injection with Clearside's SCS Microinjector has been evaluated in humans in the Sponsor's clinical development program for an ocular corticosteroid (XIPERE™, triamcinolone acetonide injectable suspension, previously known as CLS-TA) for suprachoroidal use, approved in 2021 by the US FDA for the treatment of macular edema associated with uveitis (XIPERE Prescribing Information, 2021). Suprachoroidal injections may be associated with increased ocular pressure at the time of injection, therefore subjects should be appropriately assessed following completion of the suprachoroidal injection. Additionally, risks of ocular toxicity and/or inflammation have been mitigated through the single dose escalation design of this clinical trial, with an initial dose based on preclinical toxicology studies in two species. Procedural risks, such as hemorrhage, infection, ocular hypertension, and retinal tear or detachment, have been assessed to be low and acceptable in previous clinical studies with CLS-TA, which have utilized the identical injector design in over 1000 injection procedures.

Nonclinical pharmacodynamic (PD) studies demonstrate reduced fluorescein leakage and reduced growth of new blood vessels after SC injection of CLS-AX, while pharmacokinetic (PK) studies demonstrate durability via SC injection, supporting the potential to reduce treatment burden associated with frequent IVT injections.

- In a laser-induced porcine model of CNV, 8 pigs were administered SC injections of 4 mg of CLS-AX in the right eye and balanced salt solution (BSS) in the left eye. At 1 and 2 weeks after the laser-induced injury, the eyes treated with CLS-AX had a significantly smaller mean area of fluorescence compared to the BSS-treated eyes ($P<0.009$). Quantification of neovascularization was performed on retinal flat mount tissue by measuring the isolectin B_4 (IB_4) signal. This analysis revealed that eyes treated with CLS-AX had significantly lower IB_4 signal than BSS treated eyes ($P=0.0297$).

- Similar results were obtained in a rat laser induced CNV model following SC injections of CLS-AX once weekly for 2 weeks. Decreases in the incidence of clinically important lesions (scores of 3 or 4) were noted in animals given 0.4 mg/eye CLS-AX, where 8/20 eyes (40%) showed a general improvement (scores of 0 to 2) and attained statistical significance by Day 21, compared to 2/20 eyes (10%) receiving control (saline). These results indicate that SC injection of CLS-AX significantly reduced fluorescein leakage and growth of new blood vessels at the site of the retinal laser lesion as compared to saline treatment.

With respect to PK, a 10-week study was performed in pigmented Dutch Belted rabbits to determine ocular tissue distribution after a single SC administration of CLS-AX. The injection was well tolerated. Retinal levels were maintained above the *in vitro* 50% inhibitory concentration (IC50) with a SC injection of CLS-AX at 0.03 mg/eye and at 0.1 mg/eye for the entire duration of the study.

Systemic absorption of axitinib following SC administration of CLS-AX was assessed in two non-GLP compliant 2-week single dose tolerability studies (with toxicokinetics (TK)) in rabbits and monkeys, one GLP compliant 4-week single dose toxicity studies in rabbits (with TK and a 26 week recovery period), and one GLP compliant 4-week single dose toxicity study in monkeys (with TK); all by SC injection. Plasma from blood collected from rabbits and monkeys during the conduct of 4-week toxicity studies was analyzed using an LC-MS/MS method. The lower limit of quantification (LLOQ) was 2 ng/mL in both species.

- In the 2-week single dose rabbit toxicity study, CLS-AX was administered as a single unilateral SC injection (100 µL/right eye) to male New Zealand White rabbits (3/group) at 0 (vehicle), 0.4, 1.5, or 4.0 mg axitinib/right eye once on Day 1. Blood samples were collected on day 1 pre-dose and 0.5, 1, 2, 4, 12, and 24 hours post-dose. Axitinib was below the LLOQ in all plasma samples except two samples (one animal given 1.5 mg/right eye [2.11 ng/mL] and one animal given 4.0 mg/right eye [2.28 ng/mL]) from the 1-hour time point.
- In the 4-week single dose rabbit toxicity study with a 26-week recovery phase, CLS-AX was given as a single bilateral SC injection (100 µL/eye) to male and female pigmented Dutch Belted rabbits (5 animals/sex/group) at 0 (vehicle), 0.105, 1.05, or 4.2 mg axitinib/eye once on day 1. Blood samples were collected on day 1 pre-dose and 0.25, 0.5, 1, 6, 12, and 24 hours post-dose, and on days 28, 29 or 30, 60, 91, 120, and 150. Axitinib was detected in one plasma sample (one animal given 4.2 mg/ eye [3.05 ng/mL]) from the 0.25-hour time point on Day 1. All other samples were below the LLOQ.
- In the 2-week single dose monkey toxicity study, CLS-AX was administered as a single unilateral SC injection (100 µL/right eye) to male cynomolgus monkeys (2/group) at 0 (vehicle), 4.0, 6.0, or 8.0 mg axitinib/right eye once on Day 1. Blood samples were collected on day 1 pre-dose, and 0.5, 1, 2, 4, 8, and 24 hours post-dose. Axitinib was not detected in any plasma samples at any intervals during this study.
- In the 4-week single dose monkey toxicity study, CLS-AX was administered as a single unilateral SC injection (100 µL/right eye) to male and female cynomolgus

monkeys (3 animals/sex/group) at 0 (vehicle), 0.11, 1.1, or 4.2 mg axitinib/ right eye once on day 1. Blood samples were collected on Day 1 at pre-dose and 0.25, 0.5, 1, 6, 12, and 24 hours post-dose. Axitinib was not detected in any plasma samples at any intervals during this study.

These data suggest that suprachoroidal CLS-AX injection results in distribution and duration of CLS-AX that could be beneficial for the potential treatment of neovascular AMD. Based on these results it is also anticipated that there will be minimal systemic exposure in humans; the blood collection time points chosen in this protocol are expected to maximize the possibility of capturing C_{max} and should allow for the characterization of the elimination profile of CLS-AX.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

To assess safety and tolerability of a single dose of CLS-AX in subjects with neovascular age-related macular degeneration who show stable visual acuity following ≥3 injections with an intravitreal anti-VEGF therapy in the preceding 5 months.

6.2. Secondary Objectives

To evaluate and compare the effect of 4 cohort regimens of a single dose of CLS-AX over 3 months on visual function and ocular anatomy and the need for additional treatment with intravitreal aflibercept.

To evaluate the pharmacokinetics of the 4 cohort regimens of a single dose of CLS-AX over 3 months.

6.3. Exploratory Objectives

To evaluate the safety and performance of the SCS Microinjector.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

[redacted]

Subjects will be screened and if eligible, will receive IVT administered aflibercept, 2 mg (0.05 mL), in the study eye at the Screening visit (Visit 1; Day -28 ± 3 days). Subjects who do not satisfy all the inclusion and exclusion criteria at Screening (Visit 1) or Baseline (Visit 2) will be exited from the study and will be considered screen failures. [redacted]

Subjects will then participate in three monthly follow-up visits (Visits 3, 4, 5; Weeks 4, 8, 12, respectively) for safety and tolerability assessments, visual function, and ocular anatomy assessments, and to determine whether additional aflibercept therapy is needed based upon predefined criteria described in the protocol.

Criteria for the early termination or suspension of the study are described in Section 7.6. Dose escalation criteria are described in Section 7.6.3.

See Appendix A for the Time and Events Schedule.

7.2. Endpoints

7.2.1. Primary Endpoint

The primary endpoint for evaluating the tolerability of the four dose cohorts will be based on the incidence of treatment-emergent adverse events (TEAEs), and serious adverse events (SAEs). Treatment-emergent adverse events are defined as an event that emerges during treatment with CLS-AX having been absent pre-treatment or worsens relative to the pre-treatment state.

7.2.2. Secondary Endpoints

Secondary endpoints for evaluating the tolerability and the effect of the four dose cohorts will include:

- [redacted]
- [redacted]
- [redacted]

[redacted]

7.2.3. Pharmacokinetic Endpoints

Axitinib systemic blood concentrations prior to study treatment administration at Baseline (Visit 2), [redacted]

Subjects satisfying the additional therapy criteria at Visit 3 (Week 4), will have blood samples taken prior to the administration of IVT injected aflibercept.

7.3. Number of Subjects

Approximately five subjects with nAMD who show stable visual acuity following at least [redacted] before Baseline (Visit 2) will be enrolled at the Baseline (Visit 2) visit if all inclusion and none of the exclusion criteria continue to be met into each of 4 dose cohorts, in a dose-escalation fashion, for a total of approximately 20 CLS-AX dosed subjects, not to exceed 25 subjects.

7.4. Treatment Assignment

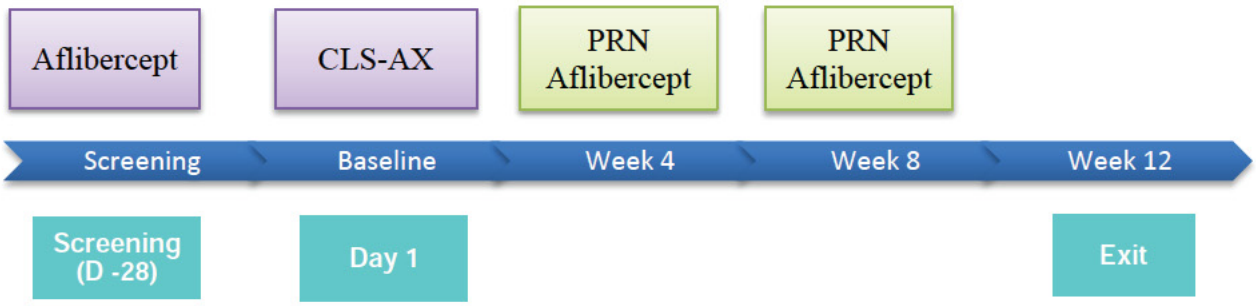
Eligible subjects will be diagnosed with nAMD in the study eye. After Screening (Visit 1; Day -28 ± 3 days) assessments, eligible subjects will be administered IVT aflibercept 2 mg (0.05 mL). Following Baseline (Visit 2; Day 1) assessments, eligible subjects will be administered a single dose of CLS-AX suprachoroidally (Table 5).

Table 5: Dose Cohorts

Dose Cohorts	Approximate Number of Subjects
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted] Figure 1 presents the study treatment schedule.

Figure 1: Study Treatment Schedule



Following the review of the safety data, the Safety Monitoring Committee (SMC) will make a recommendation regarding initiation of the next higher dose cohort.

7.5. Dose Adjustment Criteria

All eligible subjects will receive an [redacted] Subjects will receive a single dose of CLS-AX during the study.

Modification and/or stoppage of the study drug dose is prohibited.

7.5.1. Safety Criteria for Adjustment or Stopping Doses

Not applicable.

7.5.2. Pharmacokinetic Criteria for Adjustment or Stopping Doses

Not applicable.

7.6. Criteria for Study Termination and Suspension

7.6.1. Early Discontinuation of the Study

The study or parts of the study may be discontinued by the Sponsor, at any time.

If the clinical study is prematurely terminated, the Sponsor will inform the Investigators and the regulatory authorities of the termination and the reason(s) for the termination. The Investigator should promptly notify the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of the termination and of the reasons.

7.6.2. Suspension of the Study

The study enrollment will be immediately suspended, and no additional subjects will be enrolled, and no CLS-AX will be administered pending review of all appropriate study data by the Safety Monitoring Committee if:

1. A treatment related SAE is reported.
2. ≥2 subjects experience a Grade 3 or higher non-serious treatment related adverse event, based on the Common Terminology Criteria for Adverse Events (CTCAE) severity grading scale (Table 10).

3. ≥3 subjects within the same dose cohort experience a Grade 2 or higher non-serious treatment related adverse event in the same MedDRA system organ class.
4. An AE or pattern of AEs that in the opinion of the Sponsor makes continuation of the trial unadvisable.

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

Enrollment of subjects into the study will not be restarted until the Sponsor has decided the course of action to be taken and the IRB/IEC has been notified.

During the period of suspension, provided the Investigator determines that it is in the subjects' best interest to continue in the study, subjects currently in the study (post Baseline visits) will continue with the protocol specified visit schedule. The Sponsor's preference is to retain enrolled (post Baseline Visit) subjects in the study until the final study visit (Visit 5, Week 12).

7.6.3. Dose-Escalation Criteria

Dose escalation following Cohorts 1 and 2:

After the last subject enrolled into a cohort has completed the final visit (Visit 5, Week 12) (or discontinued prematurely from the study), all safety data will be evaluated by the SMC. Following review of the data, the committee will make a recommendation regarding initiation of the next higher dose cohort.

Dose escalation during Cohort 3:

After the fourth subject enrolled into the cohort has completed at least Visit 3 (Week 4) (or discontinued prematurely from the study), all available safety data will be evaluated by the SMC. Following review of the data, the committee will make a recommendation regarding initiation of the next higher dose cohort.

Dose escalation will proceed following review of the totality of the safety data by the SMC and after the SMC makes a recommendation regarding the next dose cohort. [redacted]

Continued monitoring of safety parameters will be performed throughout the conduct of the cohort. At any time, if any safety signals or trends arise, these issues may be escalated to the SMC for review. The SMC may make recommendations for dose adjustments. [redacted]

To implement dose escalation decisions, the available toxicity information (e.g., AEs, electrocardiograms (ECGs), diagnostic testing abnormalities, and all laboratory abnormalities regardless of dose-limiting toxicities (DLTs) assessments) will be evaluated by the SMC.

Recommendations for initiating the next higher cohort will be the responsibility of the SMC based on the totality of all available safety data. Study drug administration at the next higher dose cohort may not proceed until the Investigator receives written confirmation from Clearside Biomedical, indicating the available results from the previous dosed cohort were evaluated and it is permissible to proceed to the next higher dose cohort.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

Subjects are eligible for participation in this study if s/he meets all of the following criteria at the Screening (Visit 1) and Baseline (Visit 2) visits:

1. Diagnosis of neovascular age-related macular degeneration in the study eye.
2. Active subfoveal choroidal neovascularization (CNV) secondary to AMD of any lesion type in the study eye with photos and/or fluorescein angiography (FA) and/or spectral-domain optical coherence tomography (SD-OCT) showing:
   a. Total lesion area (including CNV, hemorrhage, fibrosis, atrophy) [redacted]
   b. CNV component area of [redacted]
   c. CNV must not be associated with [redacted]
3. At Screening, [redacted], for example, an improvement in vision and/or exudation, based on the Investigator's opinion.
4. Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA score of [redacted]
5. Understands the language of the informed consent; willing and able to provide written informed consent prior to any study procedures; willing to comply with the instructions and attend all scheduled study visits.
6. At least 50 years of age.
7. Subjects of childbearing potential must agree to use acceptable methods 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 he or she becomes sexually active. Females of childbearing potential must consent to performance of a pregnancy test.

8.2. Subject Exclusion criteria:

8.2.1. Ophthalmic Exclusion Criteria

Subjects are ineligible for participation in this study if s/he meets any of the following criteria at the Screening (Visit 1) or Baseline (Visit 2) visits:

1. Any active ocular disease or infection in the study eye other than nAMD, such as:
   [redacted]
2. CNV in the study eye due to other causes other than AMD, such as:
   [redacted]
3. CNV in the study eye with any of the following on photos and/or FA and/or SD-OCT:
   [redacted]
4. Other than IVT injected aflibercept, ranibizumab, bevacizumab, or brolucizumab, prior treatment for CNV in the study eye, including:
   [redacted]
5. Has significant [redacted] precluding evaluation of the retina and vitreous.
6. Intraocular pressur [redacted]

7. Any concurrent condition in the study eye that, in the opinion of the Investigator, could reduce the potential for visual improvement or require medical or surgical intervention, such as:

[redacted]

8. Any prior ocular surgery in the study eye, such as:

[redacted]

9. Has [redacted] Has a prior history of [redacted].
10. In the study eye, [redacted] any intraocular or periocular corticosteroid injection.
11. Concomitant therapy with any drug that may be toxic to the lens, retina or optic nerve, such as (examples for clarification purposes; list is not exhaustive):

[redacted]

8.2.2. General Exclusion Criteria

Subjects are not eligible for participation in this study if s/he meets any of the following criteria at the Screening (Visit 1) or Baseline (Visit 2) visits:

12. Female subjects who are pregnant, lactating or planning a pregnancy.
13. Uncontrolled systemic disease as follows:

[redacted]

[redacted]

14. Any other condition or therapy, which in the opinion of the Investigator, might pose a risk to the patient or make participation in the study not in the subject's best interest.
15. Has take [redacted] the 2 weeks prior to Baseline (Visit 2).
16. Has ha [redacted] including 30 days after exiting the study.
17. Hypersensitivity to any component of CLS-AX, aflibercept, fluorescein, or to topical anesthetics.
18. Currently enrolled in an investigational drug or device study or has used an investigational drug or device within 30 days of the Screening visit.

NOTE:

At Screening (Visit 1) the Investigator should use his/her best judgement to determine subject eligibility based on all in-office assessments completed and current data available prior to proceeding with the IVT aflibercept injection. Further assessments of eligibility to remain in the study and proceed to Baseline (Visit 2) will be based on the available in-office assessments as well as the Screening (Visit 1) results obtained from the Central Reading Centers and Central laboratory.

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 (Visit 5). For subjects who withdraw consent, no further study-

related activities will be conducted. If a 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 Description

8.4.1. General Procedures

The study will consist of 5 study visits over approximately 16 weeks. Subjects are expected to attend all study visits. All ocular assessments at Visit 1 (Screening) and Visit 5 (Week 12) will be performed on both eyes. Intraocular pressure 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, Screening (Days -28 ± 3 days) and the study eye will be identified. Eligible subjects will receive an IVT aflibercept 2 mg (0.05 mL) injection in the study eye. Each subject will return to the clinic 28 ± 3 days later to confirm eligibility at Baseline (Visit 2; Day 1). After Baseline (Visit 2; Day 1) assessments and eligibility has been confirmed, subjects will receive [redacted] Subjects will be assessed after injection for safety.

Additional safety follow-up visits will occur approximately every 4 weeks through Week 12 (Visit 3, 4 and 5; Weeks 4, 8 and 12 respectively). [redacted]

The final visit of the study occurs at Visit 5 (Week 12).

8.4.2. Rescreening Procedures

Subjects may be rescreened if the reason for their initial screening failure has changed. A subject who is designated as a screen failure at Visit 1 (Day -28 ± 3 days) may be rescreened up to 2 additional times, for a total of 3 screenings, upon Sponsor approval.

Subjects may only be rescreened 8 days or more after their last screening/rescreening visit date. Rescreened subjects are required to sign a new informed consent form and must have all the Screening (Visit 1) assessments repeated.

8.4.3. Visit 1 – Screening (Day -28 ± 3 days)

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. Eligible subjects will receive an IVT aflibercept 2 mg (0.05 mL) injection in the study eye. 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 prior and concomitant medications:
   a. Review prior IVT anti-VEGF therapies for preceding 3 years
   b. Review prior and concomitant medications within 30 days (3 years for significant ophthalmic medications) prior to Screening.
5. Obtain [redacted]
6. Obtain [redacted]
7. Perform [redacted]
8. Collect [redacted]
9. Collect urine and perform pregnancy test in females of child-bearing potential.
10. [redacted]
11. Perform ophthalmic assessments on both eyes:
    [redacted]
12. Perform photographic evaluations on both eyes:*
    [redacted]
13. Assess adverse events.
14. Determine study eye based upon eligibility criteria (Section 8.1, Section 8.2, Section 9.2). The Investigator should use his/her best judgement to determine eligibility based on all assessments completed and current data available at the Screening visit prior to proceeding with the IVT aflibercept injection. Further assessments of eligibility to proceed to Visit 2 (Baseline) will be based on the available in office assessments and the Screening Visit results obtained from the Central Reading Centers and Central laboratory.

NOTE:

[redacted]

[redacted]

8.4.3.1. Aflibercept IVT Injection Procedure

Aflibercept injections should be performed the same day as the Screening procedures. For details on the aflibercept intravitreal (IVT) injection procedure, consult the Prescribing Information.

1. Confirm the eligible study eye (see Section 9.2).
2. Prepare the eye for injection according to the Prescribing Information for aflibercept.
3. The Investigator should administer IVT aflibercept 2 mg (0.05 mL) injection according to the Prescribing Information.
4. Assess the study eye by indirect ophthalmoscopy immediately after the injection.
5. Measure study eye IOP 10 to 30 minutes after injection.
6. If IOP remains elevated, the subject must remain on site until IOP is under control according to the Investigator's best medical judgment.
7. If IOP is <30 mmHg, then the subject may leave the clinic.
8. Assess adverse events, concomitant and prior medications.
9. Schedule subject to return for Visit 2. Visit 2 may not be combined with Visit 1.

8.4.4. Visit 2 - Baseline (Day 1)

Baseline (Visit 2) must occur 28 ±3 days from Visit 1 (Screening) and may only occur once the subject is determined to be eligible to receive treatment with CLS-AX, which includes meeting all inclusion and none of the exclusion criteria, and confirmation of eligibility based on Central Reading Center and central laboratory results from Visit 1 (Screening) being received and reviewed by the Investigator. [redacted]

Visit 2 may not be combined with Visit 1.

8.4.4.1. Visit 2 (Day 1) Pre CLS-AX Suprachoroidal Injection Procedures

The following procedures must be performed before the CLS-AX SC injection (the same day as the injection):

1. Assess adverse events.
2. Review changes to medications.

3. Obtain [redacted]
4. Assess for changes to medical and ocular history.
5. Collect [redacted]
6. Collect [redacted]
7. Perform ophthalmic assessments on the study eye only, unless otherwise designated:

   [redacted]
8. Perform photographic evaluations on the study eye only:

   [redacted].
9. Confirm eligibility based on Inclusion and Exclusion criteria.

If subject continues to be eligible for enrollment based on meeting all the inclusion and none of the exclusion criteria from Screening (Visit 1) assessments and Baseline (Visit 2) assessments, the subject will receive a SC injection of CLS-AX in the study eye.

NOTE:

[redacted]

8.4.4.2. CLS-AX Suprachoroidal Injection Procedures

Injections should be performed the same day as the pre-injection procedures by a physician who has been trained to perform SC injections of CLS-AX. For details on the injection procedure, see the Drug Administration Manual.

1. Confirm the study eye (see Section 9.2).
2. Retrieve study drug kit number assigned.
3. Prepare the eye for suprachoroidal injection with adequate anesthesia and a broad-spectrum microbicide.
4. Administer suprachoroidal injection of 100 µL of CLS-AX (0.03 mg (Cohort 1) or 0.10 mg (Cohort 2) or 0.50 mg (Cohort 3) or 1.0 mg (Cohort 4).

8.4.4.3. CLS-AX Suprachoroidal Injection Post Dose Procedures

The following assessments must occur after the suprachoroidal injection:

1. Assess adverse events.
2. Review changes to concomitant medications.
3. Obtain [redacted]
4. Perform [redacted]
5. Collect [redacted]
6. Perform ophthalmic assessments on the study eye only:
   [redacted]
7. Complete the SCS Microinjector Use Questionnaire.

NOTE:

[redacted]

8.4.5. Visits 3 and 4 (Weeks 4 and 8)

At Visit 3 (Week 4) and Visit 4 (Week 8) IVT injections of aflibercept will be administered in the study eye only as needed for additional therapy based on pre-defined criteria described in Section 9.4.1 after the following procedures have been performed. The following procedures must be performed:

1. Confirm the study eye (Section 9.2).
2. Assess AEs.
3. Review changes to concomitant medications.
4. Obtain [redacted]
5. Assess for changes to medical and ocular history.
6. Perform [redacted]
7. Collect [redacted]
8. Collec [redacted]
9. Perform ophthalmic assessments on the study eye only, unless otherwise designated:

[redacted]

10. Perform photographic evaluations on the study eye only:

[redacted]

11. Subjects will be evaluated for the need of additional therapy with aflibercept. If the predefined criteria (Section 9.4.1) are met, then IVT aflibercept will be administered.

NOTE:

[redacted]

8.4.5.1. Additional IVT Aflibercept Procedure

If the subject's study eye qualifies for the additional therapy according to the Additional Therapy Criteria listed in Section 9.4.1, then the following injection and post-dose procedures should be performed:

1. Prepare the study eye for injection according to the Prescribing Information for aflibercept.
2. The Investigator should administer the IVT injection of aflibercept 2 mg (0.05 mL) according to the Prescribing Information.

8.4.5.2. Post IVT Injection of Aflibercept

The following assessment must occur after the IVT injection of aflibercept if the subject's study eye met Additional Therapy Criteria listed in Section 9.4.1 and has received an IVT injection of aflibercept as a result.

1. Assess adverse events.
2. Review changes to concomitant medications.
3. Perform ophthalmic assessments on the study eye only:

[redacted]

4. Schedule time for subject to return for the next visit.

8.4.6. Visit 5 (Week 12) End of Study/Early Termination

Visit 5 (Week 12) is the final study visit. Subjects who prematurely discontinue from the study should complete all Visit 5 assessments.

1. Confirm study eye.
2. Assess adverse events.
3. Review changes to concomitant medications.
4. Obtain [redacted]
5. Assess for changes to medical and ocular history.
6. Perform [redacted]
7. Collect [redacted].
8. Collect [redacted]
9. Perform a [redacted]
10. Perform ophthalmic assessments on both eyes, unless otherwise designated:
    [redacted]
11. Perform photographic evaluations on both eyes:
    [redacted]
12. Determine if the subject's study eye qualifies for the additional therapy according to the Additional Therapy Criteria listed in Section 9.4.1. Subjects satisfying the additional therapy criteria at Visit 5 (Week 12) will complete all Visit 5 assessment per protocol, exit the study and revert to standard of care as determined by the Investigator. Subjects will then be released to the physician's care.

NOTE:

[redacted]

8.4.7. 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, unless the visit results in study discontinuation at which point an attempt should be made to collect all Visit 5 assessments and the visit documented as such.

9. TREATMENT OF SUBJECTS

9.1. Treatment Regimen, Dosing, and Duration

Treatment in each cohort will consist of a single unilateral IVT injection of aflibercept in the study eye at Visit 1 (Screening; Day -28 ± 3 days) and a single unilateral suprachoroidal injection of CLS-AX in 100 µL administered in the study eye on Visit 2 (Day 1). Subjects will be assessed for additional treatment at Visits 3, 4, and 5 (Weeks 4, 8, and 12). Additional treatments will be administered at Visits 3 and 4 (Weeks 4 and 8) based on PRN criteria (Section 9.4.1) and will consist of aflibercept (2 mg) administered by IVT injection unless other therapy is medically necessary. Subjects satisfying the additional therapy criteria at Visit 5 (Week 12) will revert to standard of care, as determined by the Investigator, after completing all Visit 5 assessments and exiting from the study.

Subjects will be enrolled into the following 4 cohorts in a dose-escalation fashion:

[redacted]

Enrollment into the next higher dose cohort will be based on the recommendation of the SMC following review of the safety data (Section 7.6.3). Approximately five subjects will be enrolled into each cohort, for a total of approximately 20 subjects, not to exceed 25 subjects.

All suprachoroidal 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 instruction on use of the SCS Microinjector can be found in the Study Drug Administration Manual.

9.2. Study Eye Determination

The study eye will be the eye receiving the IVT injection of aflibercept at Visit 1 (Screening) followed by a CLS-AX SC injection at Visit 2 (Day 1). The determination of the study eye will be based on Visit 1 (Screening) information.

[redacted]

9.3. Fellow Eye Treatment

Subjects may have bilateral nAMD, but only one study eye may be enrolled in this study.

[redacted]

[redacted]

9.4. Additional Treatment

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

9.4.1. Additional Therapy Criteria

At Visit 3 (Week 4), Visit 4 (Week 8) and Visit 5 (Week 12) subjects will be evaluated for the need for additional therapy for nAMD in the study eye based on the following criteria. [redacted]

Additional treatment will be aflibercept, 2 mg (0.05 mL) administered by IVT injection unless other therapy is medically necessary; even if additional therapy is given, the subjects will remain in the study and followed until Visit 5 (Study Exit).

9.5. Concomitant Medications

Concomitant medications administered for the treatment of existing or new comorbidities, not otherwise prohibited by the protocol, will be recorded in the subject's source document(s) and the CRF.

9.5.1. Prohibited Medications

Subjects must not receive any treatments in the study eye for nAMD or any systemic treatments for nAMD not approved in the protocol. 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:

In cases where there is anticipated need for any of the treatments listed here during the study (post Screening Visit), 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 nAMD in the study eye and normal standard of care requires additional intervention, the treatment(s) should be recorded in the subject's source document(s) and CRF and should follow the guidelines presented for additional 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 medication will only be administered by trained study Investigators at the site. No study medication will be dispensed to subjects; therefore, subject treatment compliance is not applicable.

9.7. Randomization and Masking

This is a Phase 1/2a dose-escalation study. Subjects will not be randomly assigned to a treatment or dose cohort.

Enrollment of subjects into the next higher dose cohort will not proceed until the SMC recommends initiation following review of all available safety data (Section 7.6.3).

This is an open-label study; no masking is necessary.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

CLS-AX (axitinib injectable suspension), 1 mg/mL or 10 mg/mL, is a sterile aqueous suspension intended for intraocular ophthalmic administration. [redacted]

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

10.2. Study Drug Packaging and Labeling

The study drug kits for suprachoroidal injection of CLS-AX will be supplied to each site by the Sponsor and will be labeled for "Investigational Use only." Details regarding the preparation, storage and administration of study drug will be available in the Sponsor provided Drug Administration Manual.

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

10.3. Study Drug Storage

CLS-AX will be stored at [redacted] Details regarding the preparation, storage and administration of study drug will be available in the Sponsor provided Drug Administration Manual.

Aflibercept should be stored according to the approved label.

10.4. Study Drug Preparation

Details regarding the preparation, storage and administration of study drug will be available in the Sponsor provided Drug Administration Manual.

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

10.5. Administration

CLS-AX will be [redacted]

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

Detailed instructions on the CLS-AX injection procedure can be found in the Sponsor provided Drug Administration Manual.

The date and time of the injection will be recorded in the subject's source document(s) and the CRF. All needles used, the needle length used for injection, the injection quadrant, and distance from the limbus will be recorded.

Administration of aflibercept will be according to the approved label.

10.6. SCS Microinjector Use Questionnaire

[redacted]

10.7. 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 study drug and microinjectors received at the site. Accurate records of receipt and disposition of the study drug and microinjectors (e.g., dates, quantity, subject number, kits used, kits unused) must be maintained by the Investigator or his/her designee.

10.8. 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 with the Sponsor's approval. Any used microinjectors and vials of study drug involved in a product complaint must be maintained and returned (if requested) to the Sponsor (or designee). All study drug and microinjector accounting procedures must be completed before the study is considered complete.

11. PHARMACOKINETIC ASSESSMENTS

11.1. Blood Sample Collection

Qualified study personnel will collect blood samples via venipuncture for measurements of axitinib plasma concentrations from those subjects who have provided their consent. [redacted] Blood samples will be processed and shipped to a central lab as outlined in the laboratory manual.

Approximately [redacted] each time point.

Based on the presented results from preclinical studies (Section 5) the time points chosen in this protocol for collecting blood samples [redacted]

11.2. Urine Sample Collection

No urine samples will be collected for pharmacokinetic assessment.

12. ASSESSMENT OF SAFETY

For additional information on an assessment, see the Investigator's Site File. Measurements obtained from the assessments of safety will be recorded in the subject's source document(s) and the CRF.

12.1. Safety Variables

Safety assessments will includ [redacted] In office urine pregnancy assessment will be performed. All safety assessments will be assessed at visits as specified in the Time and Events Schedule in Appendix A.

12.1.1. Best Corrected Visual Acuity

Best corrected visual acuity will be evaluated by ETDRS using standardized lighting and standardized lanes. The results shall be reported as the number of letters read correctly. 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 visual acuity (VA) equipment/lanes. BCVA will be assessed at all visits.

12.1.2. 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. [redacted]

12.1.3. Optical Coherence Tomography Angiography

Choroidal neovascular membranes will be classified and follow-up structural changes after the suprachoroidal injection will be assessed via OCT-A at those Investigator sites possessing the necessary equipment. The OCT-A 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. [redacted]

12.1.4. 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. IOP will be measured 2 times at all visits in which a study treatment is administered including the IVT aflibercept injection at Screening (Visit 1), the CLS-AX injection at Baseline (Visit 2), and any additional IVT aflibercept injection administered PRN at Visits 3 and 4 (Weeks 4 and 8): before treatment and 10 to 30 minutes after treatment. 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. IOP will be assessed at all visits.

12.1.5. 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, pupil 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). Slit lamp biomicroscopy will be assessed at all visits.

12.1.5.1. 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. Cataract classification will be based on the Lens Opacities Classification System III (LOCS III) grading scale (Chylack, 1993). Grading should be done by the same Investigator, whenever possible, on each subject per research site.

12.1.5.2. Anterior Chamber Cells

Anterior chamber cells will be assessed clinically using a field size of 1 mm slit beam and using a standardized grading scale ranging from 0 to 4+, as defined in Table 6 (SUN, 2005).

Table 6: Anterior Chamber Cells Grading Scale

Score	Cells in Field
0	<1
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50

12.1.5.3. Anterior Chamber Flare

Anterior chamber flare will be assessed clinically via slit lamp using a standardized scale ranging from 0 to 4+, as defined in Table 7 (SUN, 2005).

Table 7: Anterior Chamber Flare Grading Scale

Score	Description
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

12.1.6. Indirect Ophthalmoscopy

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

12.1.6.1. Vitreous Haze

Vitreous haze will be assessed clinically via indirect ophthalmoscopy using a standardized photographic scale ranging from 0 to +4, as defined in Table 8 (Nussenblatt, 1985 as modified in Lowder, 2011).

Table 8: Scale for Determining Degree of Vitreous Haze

Score	Description
0	No inflammation
+0.5	Trace inflammation (slight blurring of the optic disc margins and/or loss of the nerve fiber layer reflex)
+1	Mild blurring of the retinal vessels and optic nerve
+1.5	Optic nerve head and posterior retina view obscuration greater than +1, but less than +2
+2	Moderate blurring of the optic nerve head
+3	Marked blurring of the optic nerve head
+4	Optic nerve head not visible

12.1.7. Fluorescein Angiography

[redacted]

[redacted]

12.1.8. Fundus Photography

[redacted]

12.1.9. Vital Signs

[redacted]

12.1.10. Weight and Height

[redacted]

12.1.11. Review of Body Systems (Physical Examination)

[redacted]

12.1.12. 12-Lead Electrocardiogram Assessment

[redacted]

12.1.13. Laboratory Assessments

[redacted]

Analytes to be evaluated are listed in Table 9.

Table 9: Clinical Laboratory Analytes to be Tested

Laboratory Assessment	Analytes
Serum chemistry	Alanine amino transferase; serum albumin; alkaline phosphatase; aspartate amino transferase; bilirubin, direct and total; total serum calcium; total carbon dioxide; serum chloride; total creatine kinase; serum creatinine; gamma glutamyl transaminase; glucose; lactate dehydrogenase; serum potassium; total serum protein; serum sodium; total cholesterol; triglycerides; urea
Hematology	CBC including hemoglobin (Hgb), Hemoglobin A1c, platelet count (PLT), red blood cell (RBC), white blood cell (WBC) and hematocrit (Hct); WBC differentials of: basophils, eosinophils, lymphocytes, monocytes and total neutrophils
Urinalysis (Macro)	Bilirubin; blood; glucose; ketone; protein; specific gravity; pH

12.1.13.1. Pregnancy Screen

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

12.1.14. Fundus Autofluorescence Imaging

[redacted]

12.2. Adverse and Serious Adverse Events

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event (AE)

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition in a subject participating in a clinical study, whether or not considered to have a causal relationship with the study drug, SCS Microinjector (e.g., endophthalmitis, choroidal hemorrhage, etc.) or study procedure (e.g., AEs related to the volume of the injection such as transient increase in intraocular pressure). In clinical studies, an AE can include an

undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

All AEs that occur after any subject has signed informed consent, or during the study participation, whether or not they are related to the study drug, SCS Microinjector system or study procedure, must be recorded on the appropriate form provided. Each AE is to be evaluated for duration, intensity, and causal relationship with the study medication or other factors.

At every visit, patients should be asked about AEs in an open-ended manner as well as asked about the status of any previously reported AEs.

When possible, a specific disease or syndrome rather than an individual associated sign or symptom should be identified by the Investigator and recorded on the form. If an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the form.

NOTE: A significant or unexpected worsening or exacerbation of the condition/indication under investigation should be reported as an AE. However, anticipated day-to-day fluctuations or expected progression of the disease under investigation (based upon the Investigator's clinical judgment) are not to be considered AEs.

12.2.1.2. Clinical Laboratory Abnormalities and other Abnormal Assessments as Adverse Events and Serious Adverse Events

Abnormal laboratory findings (e.g., clinical chemistry, hematology, and urinalysis) or other abnormal assessments (e.g., ocular assessments, ECGs, and vital signs) that are judged by the Investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE or SAE. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following exposure to study drug are to be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the Investigator as more severe than expected for the patient's condition, or that are present at the start of the study and do not worsen, should not be reported as AEs or SAEs.

The Investigator will exercise medical and scientific judgment in deciding whether an abnormal laboratory or assessment is clinically significant and if it requires reporting.

12.2.1.3. Serious Adverse Event (SAE)

An SAE is defined as an AE that meets any of the following criteria:

- Results in death.
- It is immediately life-threatening NOTE: The term "life threatening" refers to an event in which the patient is at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.
- It requires in-patient hospitalization or prolongation of existing hospitalization. NOTE: Hospitalization for an elective or procedure planned prior to the signing of

the informed consent to treat a preexisting condition is not considered an SAE unless it results in one of the other outcomes listed in this section.

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

All SAEs that occur after any subject has signed informed consent, whether or not they are related to the study, must be recorded on the forms provided.

12.2.2. Evaluating Adverse Events

12.2.2.1. Intensity/Severity Grade

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: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

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

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:

Table 10: CTCAE Intensity Grades

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

12.2.2.2. Assessment of Causality

The Investigator is responsible for making an assessment of the causal relationship between the AE and the study drug, drug delivery system, and/or study procedure based on the available information.

The causal relationship of the AE is assessed using a binary system, and AEs are classified as either Related or Unrelated to the study drug, drug delivery system, and/or study procedure.

In assessing this relationship, the Investigator should consider the potential etiologies for the observed AE. An AE may be related to:

- The study drug(s).
- Other concomitant medications.
- Underlying disease pathology.
- A pre-treatment condition.
- A procedure performed in the course of the study.
- Other alternative reason.

Among the potential etiologies, the Investigator should make a determination based on the most likely causal relationship. The causality assessment provided for an AE or SAE should be accompanied by all available supporting evidence, including but not limited to supporting laboratory tests, histopathology, history of the presenting event, medical history, temporal association, and results of relevant diagnostic procedures.

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 on the CRF. Information about AEs will be collected from the time of signing of the consent form until 30 days after the end of study participation. Detailed information regarding all SAEs should be collected from the signing of the informed consent until the end of the study. SAEs that are considered related to the use of study drug, the drug delivery system, and/or study procedure by the Investigator may be reported by the Investigator if they occur after the end of the study. The Investigator must continue to follow the patient until the SAE has resolved, the condition has become chronic in nature, the condition stabilizes (in the case of persistent impairment), the patient experiences a fatal outcome or is lost to follow up.

The AE term should be reported in standard medical terminology as concisely as possible. In general, the AE recorded should not be a procedure, outcome, or clinical/laboratory measurement, but should reflect the event leading to the procedure, outcome or the cause of the clinical/laboratory abnormality, if known. Whenever possible, AEs should be evaluated and recorded as a diagnosis, rather than as individual signs or symptoms. However, if a definitive diagnosis is not possible, the individual signs and symptoms should be recorded. 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 patient to discontinue the study.

12.2.4. Reporting Adverse Events

All AEs (related and unrelated) will be recorded from the signing of consent form until 30 days after the end of study participation. All SAEs occurring during subject participation, and all SAEs considered related to the study drug, drug delivery system, and/or study procedure and discovered by the Investigator at any time after the study should be reported. All such SAEs must be reported to Clearside Biomedical, or its designee, within one 24 hours of the knowledge of the occurrence 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 email (CLS001Safety@medtrials.com) to Clearside Biomedical, or its designee.

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

Clearside Biomedical and/or its designee is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify and submit required safety information to their IRB or IEC. This information includes, but is not limited to, any safety alert letter received from the Sponsor and any SAEs occurring at their investigative site.

Investigators will also be notified of all unexpected, serious, drug-related events, drug delivery system related events and study procedure related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB or IEC of these additional SAEs. A copy of these reports must be retained at the investigative site and file in the Trial Master File.

12.2.5. Follow-up of AEs and SAEs

All AEs and SAEs reported during study conduct must be followed until resolution, or until the Investigator assesses them as stable or chronic, the subject withdraws consent, or the subject is lost to follow-up. Subjects will be followed for any treatment-related, drug delivery system related, and/or study procedure related SAEs reported at the end of participation until the condition stabilizes, the event is otherwise explained, the subject is lost to follow-up, the subject withdraws consent, or the subject experiences a fatal outcome.

> **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 unless deemed necessary by the Investigator or the Sponsor.

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, the use of the drug delivery system, and/or study procedure, 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.

12.2.6. Exposure *in utero* During Clinical Trials

The Sponsor must be notified of any patient who becomes pregnant while participating in the clinical trial. Although pregnancy is not considered an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator or designee to report any pregnancy in a subject that occurs during the study. Should a patient in the study become pregnant, the site must complete the Exposure *in utero* reporting form. Notification should be made within 24 hours of awareness of the event.

It is the responsibility of the Investigator, or designee, to report any pregnancy and the anticipated date of birth that occurs while receiving, or within 30 days of discontinuing the study drug, via the Exposure in utero reporting form. If the pregnancy is to be terminated, the anticipated date of termination should be provided.

If it is the partner, rather than the subject, who is found to be pregnant, after obtaining the partner's consent, the Exposure *in utero* reporting form should be completed with the anticipated date of birth/termination and details regarding the partner should be entered in the narrative section of the form.

The patient/partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date of birth/termination, the Investigator should notify the Sponsor. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets criteria for immediate classification as an SAE (i.e., post-partum complications, spontaneous abortion, miscarriage, still birth, neonatal death, or congenital anomaly (even of an aborted fetus), the Investigator should follow the procedures for reporting an SAE. Note, elective termination of a pregnancy would not meet criteria as an SAE and in these cases a follow up pregnancy report should be provided by the Investigator.

12.2.7. Complaint Handling

Clearside collects product complaints on study drugs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by Clearside will be reported via product complaint forms.

The complainant (the Investigator, site staff, etc.) or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- Recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose.
- Emailing the completed product complaint form within 24 hours of awareness to Clearside at the following address: complaints.QA@clearsidebio.com.
- Returning a Study drug/drug delivery system for investigation when directed by Clearside.

13. STATISTICS

A detailed statistical analysis plan will be prepared for this study. The plan will contain a discussion of the statistical methods, a description of the computational algorithms, data handling conventions, and specifications for the data summaries and listings. It will be finalized before the last subject enrolled into the first cohort has completed the study.

13.1. Randomization

Not applicable.

13.2. Determination of Sample Size and Level of Significance

Sample size for this study was not statistically motivated as this is a Phase 1/2a trial. It is planned to screen approximately 60 subjects in order to enroll a total of approximately 20 subjects, not to exceed 25 subjects (approximately 5 per dose cohort).

This is an open-label Phase 1/2a study; therefore, no formal statistical testing of the endpoints will be conducted. [redacted]

13.3. Subject Disposition and Demographic and Baseline Characteristics

Subject disposition and demographic and baseline characteristics will be summarized descriptively by dose cohort and overall.

13.4. Analysis Populations

13.4.1. Safety Population

The Safety Population will include all enrolled subjects who are administered CLS-AX, and from whom at least one post-Baseline safety measurement is obtained.

In the safety analysis, all subject data will be used; no data will be excluded due to protocol deviations.

All safety analyses will be based on the Safety Population.

13.4.2. Pharmacokinetic Population

The Pharmacokinetic Population will include all subjects that provide blood samples for CLS-AX concentration analysis. All pharmacokinetic analyses will be based on the Pharmacokinetic Population.

13.5. Analysis Methods

Analyses of all safety data will be performed on the Safety Population. All safety outcomes will be summarized by dose cohort. Ophthalmic safety, including ocular adverse events, will be presented for the study eye and separately for the fellow-eye.

Safety endpoints are provided in Section 7.2. Additional endpoints will be described in the statistical analysis plan.

13.5.1. Schedule of Analyses

The study duration per cohort will consist of up to 4 weeks of screening followed by a 12-week post-treatment period.

Cohorts 1 and 2:

Analyses of study data for evaluating each dose cohort will be performed after all subjects enrolled into the dose cohort have completed the Week 12 visit (or have been discontinued from the study prior to this visit) and the data has been locked.

Cohort 3:

Analyses of all available safety data will be performed after the fourth subject enrolled into the dose cohort has completed at least Visit 3 (Week 4) (or discontinued prematurely from the study prior to this visit). These analyses will include all available study data and will be performed on data that has not been fully audited.

Analysis of study data will be performed after all subjects enrolled into the dose cohort have completed the Week 12 visit (or have been discontinued from the study prior to this visit) and the data has been locked.

At study completion:

Analyses of study data for comparing across dose cohorts will be performed after all subjects enrolled into the last cohort have completed the Week 12 visit (or have been discontinued from the study prior to this visit) and the data has been locked.

13.5.2. Safety Analysis

The summary of adverse events (and SAEs) will be limited to TEAEs. Treatment-emergent adverse events are defined as an event that emerges during treatment with CLS-AX having been absent pre-treatment or worsens relative to the pre-treatment state.

For summarizing adverse events, each reported adverse event term will be coded to a preferred term and its corresponding system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Summary tables will be presented by dose cohort.

Summary tables of TEAEs will be produced for the following categories divided into Study Eye TEAEs, Fellow Eye TEAEs, ocular TEAEs, non-ocular TEAEs and overall TEAEs, grouped by SOC and preferred term:

- All TEAEs.
- All treatment-related TEAEs.
- All TEAEs leading to study discontinuation.
- All SAEs.

- All treatment-related SAEs.
- All TEAEs leading to death.
- All TEAEs related to the SC procedure, based on the Investigator's assessment.

For each summary, adverse events will be summarized by presenting the number and percentage of subjects reporting each event at least once, and the total number of events reported.

13.5.3. Secondary Safety Analyses

Secondary safety analyses will be performed on all subjects in the Safety Population. Ocular safety will be assessed by evaluating IOP, BCVA and outcomes obtained from the slit-lamp biomicroscopy, indirect ophthalmoscopy, SD-OCT, fundus photography and angiography examinations. Summaries will be provided for each dose cohort for the Study eye.

Systemic safety will be assessed by evaluating vital signs, clinical laboratory tests, 12-lead electrocardiograms and concomitant medications. Summaries will be provided for each dose cohort.

13.5.4. Subgroup Analysis

No subgroup analyses are planned.

13.5.5. Interim Analysis

The schedule of analyses of safety data from each cohort are described in Section 13.5.1. No formal statistical testing will be conducted. All inferential statistics will be for descriptive purposes only; therefore, no adjustments will be made to the type 1 error rate to account for multiple analyses of the data.

13.5.6. Pharmacodynamic Analysis

Not applicable.

13.5.7. Pharmacokinetic Analysis

Standard population PK parameters will be calculated from plasma CLS-AX concentrations. To characterize the population PK of CLS-AX, PK parameters will be related to dose cohort. Analysis will be conducted according to the nonlinear mixed-effects approach and will provide estimates of population characteristics that define the population distribution of the PK parameters.

13.5.8. Procedure for Accounting for Missing Data

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

No imputation for missing data will be used in the Safety Populations.

Algorithms for handling partial or incomplete dates for adverse events, concomitant medications, and diagnoses will be defined in the statistical analysis plan.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of Clearside Biomedical, Inc or its designee will assess the investigational study site to:

- Determine the adequacy of the facilities and personnel.
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Clearside Biomedical, Inc. or its designee. This will be documented in a Clinical Study Agreement between Clearside Biomedical, Inc. and the Investigator.
- Ensure adequate training of Principal Investigator/sub-Investigators for use of the microinjector.

During the study, a monitor from Clearside Biomedical, Inc. or representative will have regular contacts (oral, written, onsite, virtual) with the investigational site, for the following:

- Provide information and support to the Investigator (s).
- Confirm that facilities and personnel remain acceptable.
- Confirm that the investigational team is adhering to applicable standards for conducting trials (e.g., ICH, GCP) the protocol, that data are being accurately recorded in the case report forms, and that study drug accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject's medical records at the hospital or practice, and other source documents relevant to the study. This will require direct access to all original records for each patient (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to Clearside Biomedical, 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 site to perform audits or inspections, including source data verification. The purpose of a Clearside Biomedical, Inc audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded,

analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The Investigator should contact Clearside Biomedical, Inc immediately if contacted by a regulatory agency about an inspection.

14.3. Institutional Review Board (IRB)

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

During study conduct, Clearside or it's agent(s) or designee(s) will conduct periodic monitoring visits to ensure the protocol and Good Clinical Practice (GCPs) are being followed. The progress of the study will also be monitored by written, e-mail, and telephone communications between personnel at the study site and the Sponsor and its agent(s) or designee(s). The Investigator will allow Sponsor monitors, or designee(s), direct access 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 to perform verification and to confirm that the data recorded on CRFs is accurate.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Clearside, or companies working with or on behalf of Clearside, and/or to inspection by appropriate regulatory authorities.

It is important that the Investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, and other relevant documents, e.g., recruitment advertisements, if applicable, 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 patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. 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.

All correspondence with the IRB/IEC should be retained in the Investigator File.

16.2. Ethical Conduct of the Study

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

The Investigator will inform Clearside and/or its agent(s) immediately of any urgent safety measures taken by the Investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the Investigator becomes aware of.

16.3. Written Informed Consent

The Principal Investigator(s) at each center will be responsible for ensuring that the patient is given full and adequate oral and written information about the nature, purpose, 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 informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements. The informed consent document used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Clearside and/or its agent(s) before use. 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. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Clearside and should not be made available in any form to third parties, except for authorized representatives of Clearside or appropriate regulatory authorities, without written permission from Clearside.

The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required.

17.2. Inspection of Records

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

17.3. Retention of Records

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

18. FINANCING AND INSURANCE

18.1. Finance

This study is supported by Clearside Biomedical, Inc.

18.2. Insurance

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

19. PUBLICATION POLICY

All information concerning CLS1002-101 and the operations of Clearside Biomedical, Inc., such as patent, applications, formulas, manufacturing processes, basic scientific data or formulation information not previously published, are considered CONFIDENTIAL and shall remain the sole property of Clearside Biomedical Inc. The Investigator agrees to use this information only in accomplishing this study and will not use it for other purposes without the written consent of Clearside Biomedical Inc. 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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