Compound Name:	CLS-AX, axitinib injectable suspension
Protocol Number:	CLS1002-102
IND Number:	132228
NCT Number:	NCT05131646
Protocol Title	Extension study to evaluate the long-term outcomes of subjects following CLS-AX administration for age-related macular degeneration in the CLS-AX CLS1002-101 study
Sponsor:	Clearside Biomedical, Inc. 900 North Point Parkway, Suite 200 Alpharetta, GA 30005
Issue Date: **Protocol Amendment 1 Date:**	20 July 2021 26 January 2022

A. SUMMARY OF CHANGES

Protocol Amendment 1

Protocol Title:	**OASIS EXTENSION**: EXTENSION STUDY TO EVALUATE THE LONG-TERM OUTCOMES OF SUBJECTS FOLLOWING CLS-AX ADMINISTRATION FOR AGE-RELATED MACULAR DEGENERATION IN THE CLS-AX CLS1002-101 STUDY		
Protocol Number: IND:	CLS1002-102 132228	Original Version Date:	20 July 2021
Amendment Number:	1	Version Number and Date:	Version 2, 26 January 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 1			
Sections Changed and Reasons	**Initial Protocol (Change From)**	**Modified Protocol (Changed To)**	**Impact on Subjects (Risk/Benefit)**
Title Page		**Protocol Amendment 1 Date:**	None.
Reason for Change	To document the approval dates of protocol amendment 1.		
Synopsis Studied period	Estimated date last patient completed: Aug 2022	**Estimated date last patient completed: December~~Aug~~ 2022**	None.
Reason for Change	Due to the addition of Cohort 4 in OASIS, the estimated date of study completion has changed.		
Synopsis Study Design	This is an open-label, non-interventional extension study of up to 12 weeks in duration in subjects completing Cohorts 2 and 3 of the Parent study, CLS1002-101.	This is an open-label, non-interventional extension study of up to 12 weeks in duration in subjects completing Cohorts 2**, 3** and ~~4~~**3** of the Parent study, CLS1002-101.	None.
Reason for Change	A fourth cohort of approximately 5 subjects has been added to the study.		
Synopsis Study Design	The 2 dose cohorts from the Parent study will include subjects who received the following doses: • Cohort 2 (mid-range dose arm): 0.10 mg suprachoroidal injection of CLS-AX. • Cohort 3 (high-range dose arm): 0.30 mg suprachoroidal injection of CLS-AX.	The ~~3~~**2** dose cohorts from the Parent study will include subjects who received the following doses: • Cohort 2 (**low**-mid-~~range~~ dose arm): 0.10 mg suprachoroidal injection of CLS-AX. • Cohort 3 (high-**mid**~~range~~ dose arm): 0.~~3~~**5**0 mg suprachoroidal injection of CLS-AX. • **Cohort 4 (high dose arm): 1.0 mg suprachoroidal injection of CLS-AX.**	Potentially increased risk to subjects mitigated by lack of dose limiting toxicities in cohorts 1 and 2 (0.03 and 0.1 mg/eye respectively), SMC review for dose limiting toxicities prior to initiation of each cohort, and a human equivalent

Amendment 1			
Sections Changed and Reasons	**Initial Protocol (Change From)**	**Modified Protocol (Changed To)**	**Impact on Subjects (Risk/Benefit)**
			NOAEL of 2.2 mg/eye in monkeys.
Reason for Change	The dosage of Cohort 3 has been increased from 0.3 mg to 0.5 mg. A fourth cohort has been added to the study. Cohort 4 includes a single dose of CLS-AX 1.0 mg. These doses are supported by the lack of dose limiting toxicity in cohorts 1 and 2 (0.03 and 0.1 mg/eye respectively), as well as a human equivalent NOAEL of 2.2 mg/eye in monkeys (with a 2X scaling factor based on 2 mL and 4 mL vitreous volume in monkeys and humans, respectively).		
Synopsis Number of patients (planned)	Approximately 10 subjects	A maximum of 19 subjects.	None.
Reason for Change	A fourth cohort of approximately 5 subjects has been added to the study.		
Synopsis Inclusion criteria First bullet	Enrolled in and completed the Parent study, CLS1002-101, as part of Cohort 2 or Cohort 3.	Enrolled in and completed the Parent study, CLS1002-101, as part of Cohort 2, ~~or~~ Cohort 3, **or Cohort 4**.	None.
Reason for Change	A fourth cohort has been added to the study.		
Synopsis Statistical methods	Sample size is not statistically driven as this is an extension study of Cohorts 2 and 3 of the Parent study, CLS1002-101. In the Parent study, it is planned to enroll a total of approximately 15 subjects (approximately 5 subjects (Visit 2 (Baseline, Day 1)) in each of the 3 dose cohorts).	Sample size is not statistically driven as this is an extension study of Cohorts 2, **3** and ~~43~~ of the Parent study, CLS1002-101. In the Parent study, it is planned to enroll a total of approximately **20 to 25**~~15~~ subjects (approximately 5 subjects (Visit 2 (Baseline, Day 1)) in each of the ~~43~~ dose cohorts).	None.
Reason for Change	A fourth cohort of approximately 5 subjects has been added to the study.		
Table of Contents	List of Figures	~~List of Figures~~	None.

Amendment 1			
Sections Changed and Reasons	**Initial Protocol (Change From)**	**Modified Protocol (Changed To)**	**Impact on Subjects (Risk/Benefit)**
	No table of figure entries found.	~~No table of figure entries found.~~	
Reason for Change	Extraneous section header.		
Section 5 Introduction	Results from Cohort 1 of the open label, dose-escalation Parent study, CLS1002-101, support the rationale for conducting an extension of follow-up of subjects receiving CLS-AX in cohorts 2 and 3.	Results from Cohort 1 of the open label, dose-escalation Parent study, CLS1002-101, support the rationale for conducting an extension of follow-up of subjects receiving CLS-AX in cohorts 2**, 3** and ~~43~~.	None.
Reason for Change	A fourth cohort of approximately 5 subjects has been added to the study.		
Section 5 Introduction	Given the anticipated similar or longer durability of effect, a longer duration of follow-up is justified for cohorts 2 and 3, to more fully assess long-term safety, tolerability and effects on visual function and ocular anatomy.	Given the anticipated similar or longer durability of effect, a longer duration of follow-up is justified for cohorts 2**, 3** and ~~43~~, to more fully assess long-term safety, tolerability and effects on visual function and ocular anatomy.	None.
Reason for Change	A fourth cohort of approximately 5 subjects has been added to the study.		
Section 7.1 Overall Study Design	This is an open-label, non-interventional extension study of up to 12 weeks in duration in subjects participating in and completing Cohorts 2 and 3 of the Parent study, CLS1002-101.	This is an open-label, non-interventional extension study of up to 12 weeks in duration in subjects participating in and completing Cohorts 2**, 3** and ~~43~~ of the Parent study, CLS1002-101.	None.
Reason for Change	A fourth cohort of approximately 5 subjects has been added to the study.		
Section 7.1 Overall Study Design	The Parent study design includes 3 dose cohorts of approximately 5 enrolled subjects in each cohort.	The Parent study design includes ~~43~~ dose cohorts of approximately 5 enrolled subjects in each cohort.	None.
Reason for Change	A fourth cohort of approximately 5 subjects has been added to the study.		

Amendment 1			
Sections Changed and Reasons	**Initial Protocol (Change From)**	**Modified Protocol (Changed To)**	**Impact on Subjects (Risk/Benefit)**
Section 7.1 Overall Study Design	The 2 dose cohorts from the Parent study that will be enrolled into this extension study include the following doses: • Cohort 2 (mid-range dose arm): 0.10 mg suprachoroidal injection of CLS-AX. • Cohort 3 (high-range dose arm): 0.30 mg suprachoroidal injection of CLS-AX.	The ~~3~~**2** dose cohorts from the Parent study that will be enrolled into this extension study include the following doses: • Cohort 2 (**low**-mid-~~range~~ dose arm): 0.10 mg suprachoroidal injection of CLS-AX. • Cohort 3 (high-**mid**-~~range~~ dose arm): 0.5~~3~~0 mg suprachoroidal injection of CLS-AX. • **Cohort 4 (high dose arm): 1.0 mg suprachoroidal injection of CLS-AX.**	Potentially increased risk to subjects mitigated by lack of dose limiting toxicities in cohorts 1 and 2 (0.03 and 0.1 mg/eye respectively), SMC review for dose limiting toxicities prior to initiation of each cohort, and a human equivalent NOAEL of 2.2 mg/eye in monkeys.
Reason for Change	The dosage of Cohort 3 has been increased from 0.3 mg to 0.5 mg. A fourth cohort has been added to the study. Cohort 4 includes a single dose of CLS-AX 1.0 mg. These doses are supported by the lack of dose limiting toxicity in cohorts 1 and 2 (0.03 and 0.1 mg/eye respectively), as well as a human equivalent NOAEL of 2.2 mg/eye in monkeys (with a 2X scaling factor based on 2 mL and 4 mL vitreous volume in monkeys and humans, respectively).		
Section 7.2.1 Primary Endpoint	The primary endpoint for evaluating the continued tolerability of the two dose cohorts will be based on the number of subjects experiencing treatment-emergent (TEAEs), and serious adverse events (SAEs).	The primary endpoint for evaluating the continued tolerability of the **three**~~two~~ dose cohorts will be based on the number of subjects experiencing treatment-emergent (TEAEs), and serious adverse events (SAEs).	None.

Amendment 1			
Sections Changed and Reasons	**Initial Protocol (Change From)**	**Modified Protocol (Changed To)**	**Impact on Subjects (Risk/Benefit)**
Reason for Change	A fourth cohort of approximately 5 subjects has been added to the study.		
Section 7.2.2 Secondary Endpoint	Secondary endpoints for evaluating the tolerability and the effect of the two dose cohorts will include: • Counts and percentages and/or descriptive statistics of changes from Baseline in safety parameters including: intraocular pressure, slit-lamp biomicroscopy outcomes, ophthalmoscopy outcomes, and imaging parameters in the study eye; and vital signs at Visits 6, 7 and 8 (Weeks 16, 20 and 24). • Number and percentage of subjects meeting the additional therapy criteria in the study eye at Visits 6, 7 and 8 (Week 16, 20 and 24). • Number and percentage of subjects receiving additional therapy in the study eye at Visits 5, 6, 7 and 8 (Weeks 12, 16. 20 and 24). • Mean change from Baseline in best corrected visual acuity letter score in the study eye at Visits 6, 7 and 8 (Weeks 16, 20 and 24).	Secondary endpoints for evaluating the tolerability and the effect of the **three**~~two~~ dose cohorts will include: • Counts and percentages and/or descriptive statistics of changes from Baseline in safety parameters including: intraocular pressure, slit-lamp biomicroscopy outcomes, ophthalmoscopy outcomes, and imaging parameters in the study eye; and vital signs at Visits **3, 4, 5,** 6, 7 and 8 (Weeks **4, 8, 12,** 16, 20 and 24). • Number and percentage of subjects meeting the additional therapy criteria in the study eye at Visits **3, 4, 5,** 6, 7 and 8 (Week **4, 8, 12,** 16, 20 and 24). • Number and percentage of subjects receiving additional therapy in the study eye at Visits **3, 4,** 5, 6, 7 and 8 (Weeks **4, 8,** 12, 16. 20 and 24). • Mean change from Baseline in best corrected visual acuity letter score in the study eye at Visits **3, 4, 5,** 6, 7 and 8 (Weeks **4, 8, 12,** 16, 20 and 24).	None.

Amendment 1			
Sections Changed and Reasons	**Initial Protocol (Change From)**	**Modified Protocol (Changed To)**	**Impact on Subjects (Risk/Benefit)**
	• Mean change from Baseline in central subfield retinal thickness (CST) in the study eye at Visits 6, 7 and 8 (Weeks 16, 20 and 24).	• Mean change from Baseline in central subfield retinal thickness (CST) in the study eye at Visits **3, 4, 5,** 6, 7 and 8 (Weeks **4, 8, 12,** 16, 20 and 24).	
Reason for Change	A fourth cohort of approximately 5 subjects has been added to the study. Changes to the visits to be included in the analysis necessary to be consistent with the planned statistical analysis of the data.		
Section 7.3 Number of Subjects	The study population will include up to approximately 10 subjects (up to approximately 5 subjects each from Cohorts 2 and 3) that successfully complete and exit the Parent study without receiving prohibited medication.	The study population will include **a maximum of 19** ~~up to approximately 10~~ subjects (up to approximately 5 subjects each from Cohorts 2**, 3** and ~~4~~**3**) that successfully complete and exit the Parent study without receiving prohibited medication.	None.
Reason for Change	A fourth cohort of approximately 5 subjects has been added to the study.		
Section 8.1 Subject Inclusion Criteria First bullet	Enrolled in and completed the Parent study, CLS1002-101, as part of Cohort 2 or Cohort 3	Enrolled in and completed the Parent study, CLS1002-101, as part of Cohort 2**, Cohort 3,** or Cohort ~~4~~**3**.	None.
Reason for Change	A fourth cohort of approximately 5 subjects has been added to the study.		
Section 8.4.1 General Procedures	The final visit of the extension study occurs at Visit 8 (Week 24). If the subject's study eye qualifies for additional therapy at the final visit (Visit 8) of the extension study and receives additional therapy as a result, data of the treatment administered will be collected.	The final visit of the extension study occurs at Visit 8 (Week 24). If the subject's study eye qualifies for additional therapy at the final visit (Visit 8) of the extension study and receives additional therapy as a result, data of the	None.

Amendment 1			
Sections Changed and Reasons	**Initial Protocol (Change From)**	**Modified Protocol (Changed To)**	**Impact on Subjects (Risk/Benefit)**
		treatment administered will be collected **whenever possible**.	
Reason for Change	Recognition that capturing this information may not be possible but is still desirable.		
Section 11.2.1.1 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, drug delivery system (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). 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, drug delivery 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.	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** ~~drug delivery system~~ (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). 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** ~~drug delivery 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.	None.
Reason for Change	To provide clarity regarding the definition of adverse events.		
Section 11.2.2.2 Assessment of Causality	The Investigator is responsible for making an assessment of the causal relationship between the AE and the study drug, drug delivery	The Investigator is responsible for making an assessment of the causal relationship between the AE and the study drug, **SCS**	None.

Amendment 1			
Sections Changed and Reasons	**Initial Protocol (Change From)**	**Modified Protocol (Changed To)**	**Impact on Subjects (Risk/Benefit)**
	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.	**Microinjector**~~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, **SCS Microinjector**~~drug delivery system~~, and/or study procedure.	
Reason for Change	To provide clarity regarding the determination of causality of an adverse event.		
Section 11.2.3 Recording Adverse Events	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.	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, **SCS Microinjector** ~~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.	None.
Reason for Change	To provide clarity regarding the recording of adverse events.		
Section 11.2.4 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	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, **SCS Microinjector** ~~drug delivery system~~, and/or	None.

Amendment 1			
Sections Changed and Reasons	**Initial Protocol (Change From)**	**Modified Protocol (Changed To)**	**Impact on Subjects (Risk/Benefit)**
	discovered by the Investigator at any time after the study should be reported. 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.	study procedure and discovered by the Investigator at any time after the study should be reported. Investigators will also be notified of all unexpected, serious, drug-related events, **SCS Microinjector** ~~drug delivery system~~ related events and study procedure related events (7/15 Day Safety Reports) that occur during the clinical trial.	
Reason for Change	To provide clarity regarding the reporting of adverse events.		
Section 11.2.5 Follow-up of AEs and SAEs	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. **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	Subjects will be followed for any treatment-related, **SCS Microinjector** ~~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. **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	None.

Amendment 1			
Sections Changed and Reasons	**Initial Protocol (Change From)**	**Modified Protocol (Changed To)**	**Impact on Subjects (Risk/Benefit)**
	the drug delivery system, and/or study procedure, should be reported to the Sponsor.	the **SCS Microinjector**~~drug delivery system~~, and/or study procedure, should be reported to the Sponsor.	
Reason for Change	To provide clarity regarding follow-up of adverse events and serious adverse events.		
Section 11.2.7 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. • Returning a Study drug/ drug delivery system for investigation when directed by Clearside.	Clearside collects product complaints on study drugs and **SCS Microinjectors**~~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. • Returning a Study drug/ **SCS Microinjector** ~~drug delivery system~~ for investigation when directed by Clearside.	None.
Reason for Change	To provide clarity regarding complaint handling.		
Section 12. Statistics	The analysis will include all subject data collected in the Parent study and this extension study for all subjects included in the Safety Population (Section 12.4.1) and will be limited to the endpoints collected in this extension study.	The analysis will include all subject data collected in the Parent study and this extension study for all subjects included in the Safety Population (Section 12.4.1). **Safety data to be summarized** ~~and~~ will be limited to the endpoints collected in this extension study.	None.
Reason for Change	To clarify what data will be included in the safety analysis.		
Section 12.2 Determination of	Sample size is not statistically driven as this is an extension study of Cohorts 2 and 3 of the	Sample size is not statistically driven as this is an extension study of Cohorts 2**, 3** and ~~43~~ of the	None.

Amendment 1			
Sections Changed and Reasons	**Initial Protocol (Change From)**	**Modified Protocol (Changed To)**	**Impact on Subjects (Risk/Benefit)**
Sample Size and Level of Significance	Parent study, CLS1002-101. In the Parent study, it is planned to enroll a total of approximately 15 subjects (approximately 5 subjects (Visit 2, Baseline)) in each of the 3 dose cohorts. Approximately 10 subjects from the Parent study (approximately 5 each in Cohorts 2 and 3) are expected to be eligible to enroll into this extension study.	Parent study, CLS1002-101. In the Parent study, it is planned to enroll a total of approximately **20 to 25~~15~~** subjects (approximately 5 subjects (Visit 2, Baseline)) in each of the **~~4~~3** dose cohorts. **A maximum of 19~~Approximately 10~~** subjects from the Parent study (approximately 5 each in Cohorts 2**, 3** and **~~4~~3**) are expected to be eligible to enroll into this extension study.	
Reason for Change	A fourth cohort of approximately 5 subjects has been added to the study.		
Section 12.4.1 Safety Population	The Safety Population will include all enrolled subjects who are administered CLS-AX in the Parent study, and from whom at least one post-Enrollment Day visit safety measurement is obtained.	The Safety Population will include all ~~enrolled~~ subjects who are administered CLS-AX in the Parent study, **who have provided informed consent for participating in the Extension study,** and from whom at least one ~~post-Enrollment Day visit~~ safety measurement is obtained **after the subject has provided informed consent**.	None.
Reason for Change	To clarify those subjects to be included in the Safety population.		
Section 12.5.1 Schedule of Analyses	Analyses of study data for evaluating each dose cohort will be performed after all subjects enrolled into the dose cohort have completed Visit 8 (Week 24) of the extension (or have been discontinued from the study prior to this visit) and the data has been locked.	Analyses of study data for evaluating **Cohort 2** ~~each dose cohort~~ will be performed after all subjects enrolled into the dose cohort have completed Visit 8 (Week 24) of the extension (or have been discontinued from the study prior to this visit) and the data has been locked.	None.

Amendment 1			
Sections Changed and Reasons	**Initial Protocol (Change From)**	**Modified Protocol (Changed To)**	**Impact on Subjects (Risk/Benefit)**
	Analyses of study data for comparing across dose cohorts will be performed after all subjects enrolled into cohort 3 have completed Visit 8 (Week 24) of the extension (or have been discontinued from the study prior to this visit) and the data has been locked.	**Analyses of study data for evaluating Cohort 3 and for comparison between Cohorts 2 and 3 will be performed after all subjects enrolled into Cohort 3 have completed Visit 8 (Week 24) of the extension (or have been discontinued from the study prior to this visit) and the data has been locked.** Analyses of study data for **evaluating Cohort 4 and for comparisons between all** ~~comparing across~~ dose cohorts will be performed after all subjects enrolled into **C**~~e~~ohort ~~4~~**3** have completed Visit 8 (Week 24) of the extension (or have been discontinued from the study prior to this visit) and the data has been locked.	
Reason for Change	To provide clarity into the purpose of each scheduled analysis. A fourth cohort of approximately 5 subjects has been added to the study.		
Appendix A Time and Events Schedule Header	Enrollment Day Week 12 Day 85 ± 3	Enrollment Day Week 12 Day 85 ± ~~5~~**3**	None.
Reason for Change	To provide needed flexibility in enrolling subjects into the Extension study.		

Project:	1002
Compound Number/Name:	CLS-AX (axitinib injectable suspension)
Protocol Number:	CLS1002-102
IND Number:	132228
Phase:	Non-Interventional
Protocol Title:	EXTENSION STUDY TO EVALUATE THE LONG-TERM OUTCOMES OF SUBJECTS FOLLOWING CLS-AX ADMINISTRATION FOR AGE-RELATED MACULAR DEGENERATION IN THE CLS-AX CLS1002-101 STUDY
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 1 Date:	26 January 2022
Issue Date:	20 July 2021

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 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 CLS1002-102 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
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 Reading Center for Fundus Photographs, Fluorescein Angiograms and Spectral Domain Optical Coherence Tomography	Merit CRO, Inc. 6527 Normandy Lane #100 Madison, Wisconsin 53719 USA

REVISION HISTORY

Table 3: Revision History

Version Number	Date	Revision summary
1.0	20 July 2021	Initial release of protocol.
2.0	26 Jan 2022	Protocol Amendment 1.

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:
Extension study to evaluate the long-term outcomes of subjects following CLS-AX administration for age-related macular degeneration in the CLS-AX CLS1002-101 study

Study center(s): Multi-center

Principal Investigator: Multi-Center

Studied period: 12 Week Duration Estimated date first patient enrolled: Oct 2021 Estimated date last patient completed: December 2022	**Phase of development:** Non-interventional study

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.

All subjects entering this trial will have received CLS-AX at Visit 2 (Baseline, Day 1) of the Parent study, CLS1002-101, as investigational product. The objective of the Parent study is to evaluate the safety and tolerability of a single dose of suprachoroidally administered CLS-AX in subjects with nAMD who show stable visual acuity following 3 or more injections with an intravitreal anti-VEGF therapy in the preceding 5 months.

Characterization of the durability of safety and tolerability of a single dose of suprachoroidally administered CLS-AX will be evaluated in this 12-week, non-interventional extension study of nAMD subjects who participated in and completed the Parent study.

Objectives:

The purpose of this study is to continue characterization of the durability of the safety and tolerability of a single dose of suprachoroidally administered CLS-AX, axitinib injectable suspension, (administered at Visit 2 (Baseline, Day 1) of the Parent study, CLS1002-101), for the treatment of neovascular age-related macular degeneration in subjects participating in and completing the Parent study. This study will be an open-label, non-interventional extension of the Parent study.

Primary: To assess the safety and tolerability of a single dose of CLS-AX in subjects with neovascular age-related macular degeneration up to 24 weeks following administration of CLS-AX at Visit 2 (Baseline, Day 1) in the Parent study.

Secondary: To evaluate the effect of a single dose of CLS-AX on visual function and ocular anatomy and the need for additional treatment for symptoms of nAMD up to 24 weeks following administration of CLS-AX at Visit 2 (Baseline, Day 1) in the Parent study.

Study Design:

This is an open-label, non-interventional extension study of up to 12 weeks in duration in subjects completing Cohorts 2, 3 and 4 of the Parent study, CLS1002-101. The Parent study is a 12-week, Phase 1/2a, multicenter study designed to assess the safety and tolerability of a single dose of CLS-AX administered suprachoroidally in subjects with nAMD who show stable visual acuity following 3 or more injections with an intravitreal (IVT) anti-VEGF therapy in the preceding 5 months.

This extension study includes 4 clinic visits over a maximum of 12 weeks. To ensure subjects have adequate time to evaluate and provide informed consent to participate in the extension study, consent may be obtained prior to, as part of, or after Visit 5 (no later than within 48 hours) of the Parent study. Subject eligibility will be established on the Enrollment Day which will be on the same day as the final visit (Visit 5) of the Parent study after the subject has exited the Parent study or no later than within 48 hours of exiting the Parent Study. Subjects return for safety and tolerability assessments, visual function and ocular anatomy assessments, and the evaluation of the need for additional treatment at Visits 6, 7 and 8 (Weeks 16, 20 and 24 after CLS-AX administration). [redacted]

The 3 cohorts from the Parent study will include subjects who received the following doses:

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

Each cohort will be assessed for safety and tolerability as well as for effects on visual function and ocular anatomy as outlined in the time and events schedule (Section 20).

Number of patients (planned): A maximum of 19 subjects.

Diagnosis and main criteria for inclusion:

Subject eligibility will be determined on the Enrollment Day which will be on the same day as the final visit (Visit 5) of the Parent study after the subject has exited the Parent study, or no later than within 48 hours of exiting the Parent Study.

Inclusion criteria:

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

1. Enrolled in and completed the Parent study, CLS1002-101, as part of Cohort 2, Cohort 3 or Cohort 4.
2. 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.
3. 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:

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

1. [redacted]
2. Enrolled in the Parent study CLS1002-101 as part of Cohort 1.
3. Females of childbearing potential who are pregnant and or lactating.

Investigational product, dosage, and mode of administration:

No investigational product will be administered in this study.

Reference therapy, dosage, and mode of administration: None.

Criteria for evaluation:

Primary: Number of subjects experiencing adverse events and serious adverse events, grouped by organ class and preferred term, relatedness to study treatment, and severity.

Secondary: Incidence/descriptive statistics of changes in ocular safety parameters, visual function and ocular anatomy, and the need for additional treatment for nAMD.

Statistical methods:

This is an open-label, non-interventional, extension 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 at Visit 2 (Day 1) in the Parent study. The Safety Population will include all enrolled subjects who are administered CLS-AX in the Parent study, and from whom at least one post-Enrollment Day visit safety measurement is obtained. The analysis will include all subject data collected in the Parent and extension studies for all subjects included in the Safety Population and will be limited to the endpoints collected in this extension study.

Sample size is not statistically driven as this is an extension study of [redacted].

Study Suspension:

The study enrollment will be immediately suspended, and no additional subjects will be enrolled upon suspension of the Parent study.

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 and the Safety Monitoring Committee have agreed to the course of action to be taken in the Parent study and the IRB /IEC has been notified.

During the period of suspension of enrollment, provided the Investigator determines that it is in the subjects' best interest to continue in the study, subjects currently enrolled in the extension study will continue with the protocol specified visit schedule. The Sponsor's preference is to retain enrolled subjects in the extension study until the final study visit (Visit 8, Week 24).

Additional therapy criteria:

Subjects will be assessed for [redacted]

[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
ADL	Activities of daily living
AE	Adverse event
AMD	Age-related macular degeneration
Baseline	Visit 2 (Baseline, Day 1) of the Parent study, CLS1002-101
BCVA	Best corrected visual acuity
BSS	Balanced saline solution
CNV	Choroidal neovascularization
CRF	Case report form
CST	Central subfield retinal thickness
CTCAE	Common Terminology Criteria for Adverse Events
ETDRS	Early Treatment Diabetic Retinopathy Study
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
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)
LLOQ	Lower Limit of Quantification
LOC III	Lens Opacities Classification System III
nAMD	Neovascular age-related macular degeneration
NCI	National Cancer Institute
MedDRA	Medical Dictionary for Regulatory Applications
Parent study	OASIS, CLS1002-101 Study
PD	Pharmacodynamics
PDGFR	Platelet-derived growth factor receptor

Table 4: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
PK	Pharmacokinetics
PRN	Pro re nata; "when necessary"
RPE	Retinal pigment epithelial
SAE	Serious adverse event
SC	Suprachoroidal
SCS	Suprachoroidal space
SD-OCT	Spectral Domain Optical Coherence Tomography
SOC	Systemic organ class
TEAE	Treatment-emergent adverse event
TK	Toxicokinetic
TKI	Tyrosine kinase inhibitor
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

5. INTRODUCTION

In developed countries, neovascular age-related macular degeneration (nAMD) is the leading cause of irreversible central blindness (Congdon, 2004, The Eye Diseases 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 of 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") 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 (triamcinolone acetonide injectable suspension, CLS-TA). 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 B4 (IB4) signal. This analysis revealed that eyes treated with CLS-AX had significantly lower IB4 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- Good Laboratory Practice (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.

Results from Cohort 1 of the open label, dose-escalation Parent study, CLS1002-101, support the rationale for conducting an extension of follow-up of subjects receiving CLS-AX in cohorts 2, 3 and 4. A total of 6 subjects were enrolled into Cohort 1 of the Parent study. Of these subjects, 2 subjects completed the study without meeting the pre-specified criteria for the administration of additional therapy, demonstrating at least 3 months durability of the effect of CLS-AX on BCVA and central subfield retinal thickness assessed via optical coherence tomography. Without longer follow-up, a more comprehensive assessment of durability will not be possible. Given the anticipated similar or longer durability of effect, a longer duration of follow-up is justified for cohorts 2, 3 and 4, to more fully assess long-term safety, tolerability and effects on visual function and ocular anatomy.

All subjects entering this trial will have received CLS-AX at Visit 2 (Baseline, Day 1) of the Parent study, CLS1002-101, as investigational product. The objective of the Parent study is to evaluate the safety and tolerability, over 12 weeks of follow-up, of a single dose of suprachoroidally administered CLS-AX in subjects with nAMD who show stable visual acuity following 3 or more injections with an intravitreal anti-VEGF therapy in the preceding 5 months.

[redacted]

6. TRIAL OBJECTIVES AND PURPOSE

[redacted] his study will be an open-label, non-interventional 12-week extension of the Parent study.

6.1. Primary Objective

To assess the safety and tolerability of a single dose of CLS-AX in subjects with neovascular age-related macular degeneration up to 24 weeks following administration of CLS-AX at Visit 2 (Baseline, Day 1) in the Parent study.

6.2. Secondary Objectives

To evaluate the effect of a single dose of CLS-AX on visual function and ocular anatomy and the need for additional treatment for symptoms of nAMD up to 24 weeks following administration of CLS-AX at Visit 2 (Baseline, Day 1) in the Parent study.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is an open-label, non-interventional extension study of up to 12 weeks in duration in subjects participating in and completing Cohorts 2, 3 and 4 of the Parent study, CLS1002-101.

[redacted] The Parent study design includes 4 dose cohorts of approximately 5 enrolled subjects in each cohort. 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), followed by a suprachoroidal injection of CLS-AX at Visit 2, Baseline (Day 1) upon enrollment. [redacted]

This extension study includes 4 clinic visits (Enrollment Day, and Visits 6, 7 and 8; Weeks 12, 16, 20 and 24) over a maximum of 12 weeks, for a total of up to 24 weeks follow-up from the time of CLS-AX administration at Visit 2 (Baseline, Day 1) in the Parent study. [redacted] To ensure subjects have adequate time to evaluate and provide informed consent to participate in the extension study, consent may be obtained prior to, as part of, or after Visit 5 (no later than within 48 hours) of the Parent study. Eligibility assessments will only be performed after consent has been obtained and after all the Visit 5 assessments of the Parent study have been completed and the subject has exited the Parent study. [redacted] Post additional treatment assessment of the study eye will be conducted.

Ideally, Enrollment Day assessments should occur on the same day as Visit 5 of the Parent study especially for those subjects who met additional therapy criteria at Visit 5 of the Parent study and were administered additional therapy, so that post therapy assessments may be performed as part of this extension study's Enrollment Day. If due to time constraints, it is not possible to conduct post therapy assessments on the same day as the injection of the additional therapy after exiting Visit 5 of the Parent study, the assessments should occur no later than within 48 hours of having received the additional therapy, upon exiting the Parent study at Visit 5.

The 3 dose cohorts from the Parent study that will be enrolled into this extension study include the following doses:

- [redacted]

Subjects enrolled into this extension study will participate in three monthly follow-up visits (Visits 6, 7 and 8; Weeks 16, 20 and 24) [redacted] he determination whether additional treatment is needed will include reference to data collected during the Parent study (Section 9.4.1).

Criteria for the early termination or suspension of the study are described in Section 7.5.

See Section 20 for the Time and Events Schedule.

7.2. Endpoints

In this extension study, Baseline will be defined as the last non-missing value prior to CLS-AX administration at Visit 2 (Day 1) in the Parent study, CLS1002-101.

7.2.1. Primary Endpoint

The primary endpoint for evaluating the continued tolerability of the three dose cohorts will be based on the number of subjects experiencing treatment-emergent (TEAEs), and serious adverse events (SAEs). Treatment-emergent adverse events are defined as an event that emerges following treatment with CLS-AX (administered at Visit 2 (Baseline, Day 1) of the Parent study, CLS1002-101), 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 three dose cohorts will include:

- [redacted]

7.3. Number of Subjects

The study population will include a maximum of 19 subjects (up to approximately 5 subjects each from Cohorts 2, 3 and 4) that successfully complete and exit the Parent study without receiving prohibited medication. Medications prohibited in the Parent study will continue to be prohibited in this extension study and are defined in Section 9.5.1.

The expected duration of participation in the extension study is up to 12 weeks from study entry. The complete inclusion and exclusion criteria are presented in Section 8.

7.4. Treatment Assignment

This is an open-label, non-interventional extension study of the Parent study, CLS1002-101. There will be no investigational product dispensed or administered in this study.

7.5. Criteria for Study Termination

7.5.1. 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, and subjects will be asked to complete study assessments at Visit 8 (Study Exit, Week 24). The Investigator should promptly notify the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of the termination and of the reasons.

7.5.2. Suspension of the Study

The study enrollment will be immediately suspended, and no additional subjects will be enrolled upon suspension of the Parent study.

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 and the Safety Monitoring Committee have agreed to the course of action to be taken in the Parent study and the IRB/IEC has been notified.

During the period of suspension of enrollment, provided the Investigator determines that it is in the subjects' best interest to continue in the study, subjects currently enrolled in the extension study will continue with the protocol specified visit schedule. The Sponsor's preference is to retain enrolled subjects in the extension study until the final study visit (Visit 8, Week 24).

8. SELECTION AND WITHDRAWAL OF SUBJECTS

Subject eligibility will be determined on Enrollment Day which may be the same day as the final visit (Visit 5) of the Parent study after the subject has exited the Parent study or within no later than 48 hours of exiting the Parent Study.

8.1. Subject Inclusion Criteria

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

1. Enrolled in and completed the Parent study, CLS1002-101, as part of Cohort 2, Cohort 3, or Cohort 4.
2. 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.
3. 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

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

1. [redacted]
2. Enrolled in the Parent study CLS1002-101 as part of Cohort 1.
3. Females of childbearing potential who are pregnant and or lactating.

8.3. Subject Withdrawal Criteria

Subjects may withdraw from the study at any time and for any reason without obligation. Subjects may be removed from the study at the Investigator's discretion or if they require additional therapy due to disease progression that warrants further treatment. 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 9.5.1.

Subjects who withdraw prematurely from the study will be asked to complete Visit 8 (Study Exit) study assessments. For subjects who withdraw consent, no further related activities will be conducted. If an SAE is unresolved at the time of the subject's final study visit, the Investigator should make every attempt to follow up until the SAE is resolved or stabilized, the subject is lost to follow-up, or there is some other resolution of the event.

8.4. Visit Procedure Description

8.4.1. General Procedures

The study will consist of 4 study visits over approximately 12 weeks. Subjects are expected to attend all study visits.

Written informed consent will be obtained for each subject before any study-specific assessments are performed. To ensure subjects have adequate time to evaluate and provide informed consent to participate in the extension study, consent may be obtained prior to, as part of, or after Visit 5 (no later than within 48 hours) of the Parent study. Subject eligibility will be established on the Enrollment Day which may be on the same day as the final visit (Visit 5) of the Parent study after the subject has exited the Parent study or no later than within 48 hours of exiting the Parent Study. If a subject was assessed to have met additional treatment criteria at Visit 5 of the Parent study, data of the additional treatment given will be collected at Enrollment Day.

Ideally, Enrollment Day assessments should occur on the same day as Visit 5 of the Parent study especially for those subjects who met additional therapy criteria at Visit 5 of the Parent study and were administered additional therapy, so that post therapy assessments may be performed as part of this extension study's Enrollment Day. If due to time constraints, it is not possible to conduct post therapy assessments on the same day as the injection of the additional therapy after exiting Visit 5 of the Parent study, the assessments should occur no later than within 48 hours of exiting the Parent study at Visit 5.

[redacted]

Additional safety follow-up visits will occur approximately every 4 weeks through Week 24 (Visits 6, 7 and 8; Weeks 16, 20 and 24, respectively). At Visits 6, 7 and 8 subjects will be evaluated to determine any need for additional treatment based on pre-defined criteria (Section 9.4.1). [redacted]

If the subject's study eye qualifies for additional therapy at the final visit (Visit 5) of the Parent study or Visits 6 or 7 (Weeks 16 or 20) and receives additional therapy as a result, then ocular safety will be assessed in the study eye only following administration of the additional therapy.

The final visit of the extension study occurs at Visit 8 (Week 24). If the subject's study eye qualifies for additional therapy at the final visit (Visit 8) of the extension study and receives additional therapy as a result, data of the treatment administered will be collected whenever possible.

Intraocular pressure will be collected in both eyes at all visits during the extension study. Data from other ocular assessments at Visits 6 and 7 (Weeks 16 and 20) will be collected for the study eye only. All ocular assessments at Visit 8 (Week 24) will be performed on both eyes. Ocular assessment performed after the administration of additional therapy after exiting the Parent study at Visit 5 (Week 12) or Visits 6 and 7 (Weeks 16 and 20) of this extension study will be collected for the study eye only.

8.4.2. Enrollment Day (0 – 48 hours post Visit 5)

Subject eligibility will be determined on the Enrollment Day which will be the same day as the final visit (Visit 5) of the Parent study after the subject has exited the Parent study or no later than within 48 hours of exiting the Parent Study.

1. Written informed consent will be documented for each subject before any study-specific assessments are performed. To ensure subjects have adequate time to evaluate and provide informed consent to participate in the extension study, consent may be obtained prior to, as part of, or after Visit 5 (no later than 48 hours) of the Parent study.
2. Confirm subject meets all the inclusion and none of the exclusion criteria.
3. Confirm study eye (Section 9.2).
4. Collect urine and perform pregnancy test in females of childbearing potential.

Subjects satisfying the additional therapy criteria at the final visit (Visit 5) of the Parent study may receive additional therapy in the study eye. Data of therapy administered will be collected.

8.4.2.1. Enrollment Day - Additional Therapy

If the subject's study eye qualifies for additional therapy at the final visit (Visit 5) of the Parent study, then additional therapy, consisting of an [redacted]

8.4.2.2. Enrollment Day - Post Administration of Additional Therapy

The following assessments must be performed on the study eye after administration of additional therapy if the subject's study eye qualifies for additional therapy at the final visit (Visit 5) of the Parent study and receives additional therapy as a result.

1. Assess adverse events (AEs).

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.

8.4.3. Visits 6 and 7 (Weeks 16 and 20)

At Visit 6 (Week 16) and Visit 7 (Week 20) additional therapy may be administered in the study eye only as needed based on pre-defined criteria described in Section 9.4.1 after the following procedures have been performed.

1. Confirm the study eye (Section 9.2).
2. Assess AEs.
3. Review changes in medical and ocular history.
4. Review changes to medications.
5. Obtain vital signs by performing resting heart rate (resting 5 minutes) and blood pressure measurements.
6. Perform ophthalmic assessments on the study eye only, unless otherwise designated:

[redacted]

7. Perform photographic evaluations on the study eye only: *

[redacted]

8. Determine if the subject's study eye qualifies for the additional therapy according to the Additional Therapy Criteria listed in Section 9.4.1. If the pre-defined criteria are met, then additional therapy consisting of [redacted]

NOTE:

* All images (SD-OCT, fundus photographs and fluorescein angiography) should be uploaded to the Central Reading Center.

8.4.3.1. Visits 6 and 7 (Weeks 16 and 20) - Additional Therapy

If the subject's study eye qualifies for additional therapy according to the Additional Therapy Criteria listed in Section 9.4.1, then additional therapy, consisting of [redacted]

8.4.3.2. Visits 6 and 7 (Weeks 16 and 20) - Post Administration of Additional Therapy

The following assessments must be performed on the study eye after administration of additional therapy if the subject's study eye met Additional Therapy Criteria listed in Section 9.4.1 and receives additional therapy as a result.

1. Assess AEs.
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.

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

Visit 8 (Week 24) is the final study visit. Subjects who prematurely discontinue from the study should also complete all Visit 8 assessments.

1. Confirm study eye (Section 9.2).
2. Assess AEs.
3. Review changes to concomitant medications.
4. Obtain vital signs by performing [redacted]
5. Assess for changes to medical and ocular history.
6. Perform a review of body systems.
7. Collect urine and perform pregnancy test in females of childbearing potential.
8. Perform ophthalmic assessments on both eyes:
   [redacted]

[redacted]

9. Perform photographic evaluations on both eyes:

   [redacted]

10. 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 8 (Week 24) will complete all Visit 8 assessments per protocol, exit the study and revert to standard of care as determined by the Investigator. Data of the additional therapy administered will be collected whenever possible. Subjects will then be released to the physician's care.

NOTE:

[redacted]

8.4.5. 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 8 assessments and the visit documented as such.

9. TREATMENT OF SUBJECTS

9.1. Treatment Regimen, Dosing, and Duration

No study drug will be dispensed or administered as part of this non-interventional extension study (Section 7.1).

9.2. Study Eye Determination

The study eye will be the study eye designated within the Parent study as having received CLS-AX at Visit 2 (Baseline, Day 1) of the Parent study and confirmed at subsequent visits including Visit 5 (Week 12, Study Exit) of the Parent study.

9.3. Fellow Eye Treatment

Subjects may have bilateral nAMD, but only the study eye from the parent study will continue enrollment into this extension study.

[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 6 (Week 16), Visit 7 (Week 20) and Visit 8 (Week 24) of this extension study, subjects will be evaluated for the need for additional therapy for nAMD in the study eye based on the following criteria:

- [redacted]

If the pre-defined criteria are met at Visits 6 and/or 7 (Weeks 16 and/or 20), then additional therapy consisting of an IVT injection of aflibercept 2 mg (0.05 mL), ranibizumab 0.5 mg (0.05 mL), bevacizumab 1.25 mg (0.05 mL), or brolucizumab 6 mg (0.05 mL), as determined by the Investigator, may be administered; even if additional therapy is given, the subjects will remain in the study and will be followed until Visit 8 (Study Exit). Subjects satisfying the additional therapy criteria at Visit 8 (Study Exit) will complete all Visit 8 assessments per protocol, exit the study and revert to standard of care as determined by the Investigator. Data of the additional therapy administered will be collected whenever possible.

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:

- [redacted]

In cases where there is anticipated need for any of the treatments listed here during the study (post Visit 5), 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. Any use of a prohibited medication will be documented as a protocol deviation.

9.6. Treatment Compliance

No study medication will be dispensed or administered to subjects during this extension study; therefore, an assessment of subject treatment compliance is not applicable.

Study medication will only be administered by trained study Investigators in the Parent study.

9.7. Randomization and Masking

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

This is non-interventional extension study. Subjects will remain in the dose cohort they participated under during the Parent study.

10. STUDY DRUG MATERIALS AND MANAGEMENT

This is an open-label, non-interventional extension of the Parent study, CLS1002-101. No study drug will be dispensed or administered to the subjects as part of this protocol. Additional treatments administered during this study will be recorded as concomitant and/or rescue medications. Storage of permitted additional treatments should be according to the Prescribing Information for the individual treatment(s) and is the responsibility of the Investigator.

11. ASSESSMENT OF SAFETY

Measurements obtained from the assessments of safety will be recorded in the subject's source document(s) and the CRF.

11.1. Safety Variables

Safety assessments will include [redacted] In-office urine pregnancy assessment will be performed on females of childbearing potential. All safety assessments will be assessed at visits as specified in the Time and Events Schedule in Section 20.

The determination whether additional treatment is needed will include reference to data collected during the Parent study (Section 9.4.1).

11.1.1. 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 performed in the study eye at Visits 6 and 7 (Weeks 16 and 20) and in both eyes at Visit 8 (Week 24).

11.1.2. 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]

11.1.3. 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.

If the subject's study eye qualifies for additional therapy at the final visit (Visit 5) of the Parent study and receives additional therapy as a result, following enrollment into this extension study, IOP will be measured in the study eye 10 to 30 minutes after treatment is administered if at Enrollment Day or any time during Enrollment Day if administered prior. IOP will be measured at Visits 6, 7 and 8 (Weeks 16, 20 and 24) in both eyes. If additional therapy is administered

PRN at Visits 6 and/or 7, then IOP will be measured twice: in both eyes before treatment and in the study eye 10 to 30 minutes after treatment is administered. Tonometers must be calibrated for accuracy before the first subject visit at that site and according to the manufacturer specifications during the study, until the last subject has exited the study at that site.

11.1.4. 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 biomicroscopy will be assessed at all visits.

If the subject's study eye qualifies for additional therapy at the final visit (Visit 5) of the Parent study and receives additional therapy as a result, following enrollment into this extension study, then slit-lamp biomicroscopy will be performed in the study eye after treatment is administered at Enrollment Day or any time during Enrollment Day if administered prior. Slit-lamp biomicroscopy will be performed in the study eye at Visits 6 and 7 (Weeks 16 and 20) and in both eyes at Visit 8 (Week 24). If additional therapy is administered PRN at Visits 6 and/or 7, then slit-lamp biomicroscopy will be performed twice in the study eye: before treatment and after treatment is administered.

11.1.4.1. 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.

11.1.4.2. 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 5 (SUN, 2005).

Table 5: Anterior Chamber Cells Grading Scale

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

Table 5: Anterior Chamber Cells Grading Scale (Continued)

Score	Cells in Field
4+	>50

11.1.4.3. 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 6 (SUN, 2005).

Table 6: 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)

11.1.5. 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.

If the subject's study eye qualifies for additional therapy at the final visit (Visit 5) of the Parent study and receives additional therapy as a result, following enrollment into this extension study, then indirect ophthalmoscopy will be performed in the study eye after treatment is administered at Enrollment Day or any time during Enrollment Day if administered prior. Indirect ophthalmoscopy will be performed in the study eye at Visits 6 and 7 (Weeks 16 and 20) and in both eyes at Visit 8 (Week 24). If additional therapy is administered PRN at Visits 6 and/or 7, then indirect ophthalmoscopy will be performed twice in the study eye: before treatment and after treatment is administered.

11.1.5.1. 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 7 (Nussenblatt, 1985 as modified in Lowder, 2011).

Table 7: Scale for Determining Degree of Vitreous Haze

Score	Description
0	No inflammation

Table 7: Scale for Determining Degree of Vitreous Haze (Continued)

Score	Description
+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

11.1.6. Fluorescein Angiography

[redacted]

11.1.7. Fundus Photography

[redacted]

11.1.8. Vital Signs

[redacted]

11.1.9. Review of Body Systems (Physical Examination)

[redacted]

11.1.9.1. Pregnancy Screen

Urine pregnancy tests will be performed on all females of childbearing potential on Enrollment Day and at Visit 8 (Week 24).

11.2. Adverse and Serious Adverse Events

11.2.1. Definition of Adverse Events

11.2.1.1. 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 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.

11.2.1.2. Abnormal Clinical Assessments as Adverse Events and Serious Adverse Events

Abnormal assessments (e.g., ocular assessments 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. Abnormal clinical assessments and any clinically significant abnormal laboratory findings 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.

11.2.1.3. 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.

11.2.2. Evaluating Adverse Events

11.2.2.1. 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 11.2.1.3. 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 8: CTCAE Intensity Grades

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Table 8: CTCAE Intensity Grades (Continued)

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

11.2.2.2. Assessment of Causality

The Investigator is responsible for making an assessment of the causal relationship between the AE and the study drug, SCS Microinjector, 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, SCS Microinjector, 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.

11.2.3. 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, SCS

Microinjector, 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.

11.2.4. 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, SCS Microinjector, 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, SCS Microinjector 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.

11.2.5. 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, SCS Microinjector 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 SCS Microinjector, 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.

11.2.6. 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.

11.2.7. Complaint Handling

Clearside collects product complaints on study drugs and SCS Microinjectors 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 48 hours to Clearside at the following address: complaints.QA@clearsidebio.com.
- Returning a Study drug/ SCS Microinjector for investigation when directed by Clearside.

12. 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 has completed the study.

The analysis will include all subject data collected in the Parent study and this extension study for all subjects included in the Safety Population (Section 12.4.1). Safety data to be summarized will be limited to the endpoints collected in this extension study.

12.1. Randomization

Not applicable.

12.2. Determination of Sample Size and Level of Significance

Sample size is not statistically driven as this is an extension study of Cohorts 2, 3 and 4 of the Parent study, CLS1002-101. In the Parent study, it is planned to enroll a total of approximately 20 to 25 subjects (approximately 5 subjects (Visit 2, Baseline)) in each of the 4 dose cohorts. A maximum of 19 subjects from the Parent study (approximately 5 each in Cohorts 2, 3 and 4) are expected to be eligible to enroll into this extension study.

This is an open-label non-interventional study; therefore, no formal statistical testing of the endpoints will be conducted. [redacted]

12.3. Subject Disposition and Demographic and Baseline Characteristics

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

12.4. Analysis Populations

12.4.1. Safety Population

The Safety Population will include all subjects who are administered CLS-AX in the Parent study, who have provided informed consent for participating in the Extension study, and from whom at least one safety measurement is obtained after the subject has provided informed consent.

In the safety analysis, all subject data from both the Parent and extension studies will be used; no data will be excluded due to protocol deviations.

All safety analyses will be based on the Safety Population.

12.5. Analysis Methods

Analyses of all safety data will be performed on the Safety Population. All safety outcomes from both the Parent and extension studies 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.

12.5.1. Schedule of Analyses

The study duration will consist of 12 weeks of additional follow-up after the subject has completed participation in the Parent study CLS1002-101.

Analyses of study data for evaluating Cohort 2 will be performed after all subjects enrolled into the dose cohort have completed Visit 8 (Week 24) of the extension (or have been discontinued from the study prior to this visit) and the data has been locked.

Analyses of study data for evaluating Cohort 3 and for comparison between Cohorts 2 and 3 will be performed after all subjects enrolled into Cohort 3 have completed Visit 8 (Week 24) of the extension (or have been discontinued from the study prior to this visit) and the data has been locked.

Analyses of study data for evaluating Cohort 4 and for comparison between all dose cohorts will be performed after all subjects enrolled into Cohort 4 have completed Visit 8 (Week 24) of the extension (or have been discontinued from the study prior to this visit) and the data has been locked.

12.5.2. 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 (Visit 2, Day 1) 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.

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.

12.5.3. 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 and concomitant medications. Summaries will be provided for each dose cohort.

12.5.4. Subgroup Analysis

No subgroup analyses are planned.

12.5.5. Interim Analysis

Analysis of all safety data will be performed at the completion of each dose cohort. 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.

12.5.6. Pharmacodynamic Analysis

Not applicable.

12.5.7. Pharmacokinetic Analysis

Not applicable.

12.5.8. 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.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

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 continue to 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.
- 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 recorded in the CRF or reported to IRB and/or 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.

13.2. 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.

13.3. 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.

14. 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, study records, 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.

15. ETHICS

15.1. 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.

15.2. Ethical Conduct of the Study

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

15.3. 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.

16. DATA HANDLING AND RECORDKEEPING

16.1. 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.

16.2. 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 drug storage area(s) to confirm continued acceptability and inventory of additional therapy and rescue medication(s), subject charts and study source documents, and any other records relative to study conduct.

16.3. 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.

17. FINANCING AND INSURANCE

17.1. Finance

This study is supported by Clearside Biomedical, Inc.

17.2. Insurance

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

18. PUBLICATION POLICY

All information concerning CLS1002-102 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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20. APPENDICES

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