ALLEGRO OPHTHALMICS, LLC
PROTOCOL: DRY AMD STUDY 101

A PHASE IIa RANDOMIZED, CONTROLLED, DOUBLE-MASKED, CROSSOVER CLINICAL TRIAL DESIGNED TO EVALUATE THE SAFETY AND EXPLORATORY EFFICACY OF 1.0 mg LUMINATE® (ALG-1001) AS A TREATMENT FOR NON-EXUDATIVE MACULAR DEGENERATION

Rev. 1.6 January 29, 2019

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Protocol Approval

A PHASE IIa RANDOMIZED CONTROLLED, DOUBLE-MASKED, CROSSOVER CLINICAL TRIAL DESIGNED TO EVALUATE THE SAFETY AND EXPLORATORY EFFICACY OF 1.0 mg LUMINATE® (ALG-1001) AS A TREATMENT FOR NON-EXUDATIVE MACULAR DEGENERATION

The following individuals approve this protocol dated January 29, 2019. Any changes to this version of the protocol must have an amendment or administrative letter.

Allegro Approvals:

Hampar Karageozian Chief Executive Officer	Date
Vicken Karageozian, MD Chief Medical Officer	Date
Melvin Sarayba, MD Medical Monitor	Date

Signature Page for Investigator:

Product: LUMINATE® (ALG-1001)

Study No: Dry AMD Study 101

Title:

A PHASE IIa RANDOMIZED CONTROLLED, DOUBLE-MASKED, CROSSOVER CLINICAL TRIAL DESIGNED TO EVALUATE THE SAFETY AND EXPLORATORY EFFICACY OF 1.0 mg LUMINATE® (ALG-1001) AS A TREATMENT FOR NON-EXUDATIVE MACULAR DEGENERATION

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with all relevant local regulations, the current International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice (GCP), and with the principles of the most recent version of the Declaration of Helsinki.

Investigator Name [PRINT IN BLOCK CAPITAL LETTERS]	Signature	Date

Institution Name and Address

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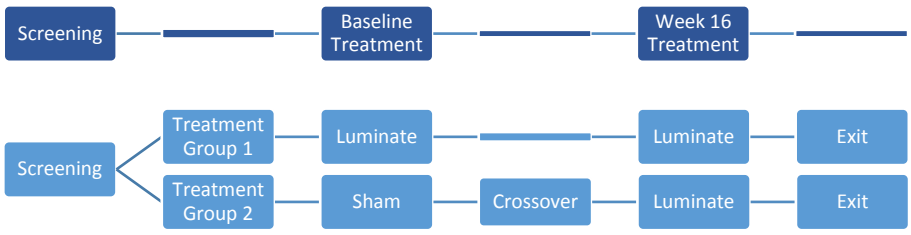
LIST OF ABBREVIATIONS

ACD	Anterior Chamber Depth
AE	Adverse Event
AMD	Age-related Macular Degeneration
BCVA	Best Corrected Visual Acuity
CRA	Clinical Research Associate
CRF	Case Report Form
EC	Ethics Committee
ERG	Electroretinography
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IOP	Intraocular Pressure/Tonometry
IRB	Institutional Review Board
OCT	Optical Coherence Tomography
OD	Right Eye
OS	Left Eye
PI	Principal Investigator
PVD	Posterior Vitreous Detachment
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SC	Study Coordinator
SOP	Standard Operating Procedure
USP	United States Pharmacopeia

PROTOCOL SYNOPSIS

Study Title:	A Phase IIa randomized, controlled, double-masked, crossover clinical trial designed to evaluate the safety and exploratory efficacy of 1.0 mg Luminate® (ALG-1001) as a treatment for Non-Exudative Macular Degeneration
Study Objectives:	To evaluate the safety and exploratory efficacy of 1.0mg of Luminate® in patients with Intermediate Non-Exudative Macular Degeneration
Study Population	1. Subjects with symptomatic decrease of VA in the last 12 months 2. Subjects without evidence of wet AMD 3. Subjects with moderate areas of RPE disturbances and/or drusen in the macula 4. Subjects with BCVA of 20/40 – 20/200 5. Evidence of reasonably well-preserved areas of RPE and photoreceptors by OCT examination in the central macula
Study Design:	Approximately 40 eligible subjects who have been diagnosed with intermediate Non-Exudative AMD, that require treatment will be enrolled and randomized (1.7:1) to one of 2 treatment groups: Treatment Group 1: 25 Non-Exudative AMD subjects with BCVA of 20/40 – 20/200 will be **injected intravitreally with 1.0mg of Luminate®** Treatment Group 2: 15 Non-Exudative AMD subjects with BCVA of 20/40 – 20/200 will be **treated with a sham injection** At the 16-week visit, the study will be unmasked to the sponsor and injecting investigator (observing investigators will remain masked). Subjects in the treatment group will receive a 2nd dose of Luminate®. Subjects in the control group will be offered the opportunity to crossover to treatment with a single dose of Luminate®. 
Investigational Drug:	1.0 mg Luminate® solution for intravitreal injection in 0.05cc isotonic saline solution
Control:	Sham Injection
Key Inclusion Criteria:	**Key General Inclusion Criteria:** 1. Male or female patients, 50 to 85 years of age at screening visit 2. Subject has signed the Informed Consent form **Key Ocular Inclusion Criteria (Study Eye):** 1. Subjects with Non-Exudative AMD having ETDRS BCVA between 33 and 72 letters read (equivalent to 20/40 – 20/200 on Snellen Chart) with the level of vision caused by the non-exudative AMD and no other factor/s

	2. Subjects with symptomatic decrease in visual acuity in the last 12 months 3. Subjects with combination of areas of RPE disturbances (hyper or hypopigmentation) and/or ≥ 1 large druse(n) (>125 microns) and/or multiple intermediate drusen (62-124 microns) in the macula as confirmed by the central reading center 4. Subjects with evidence of reasonably well-preserved areas of RPE by clinical examination and well-defined RPE and outer segment ellipsoid line by OCT examination in the central 1 mm of the macula as confirmed by the central reading center. More specifically, reasonably well- preserved central 1 mm of the macula means: a. The RPE and outer retinal layers throughout the central 1 mm are intact b. No signs of NVAMD such as intraretinal or sub retinal fluid, or sub retinal hyper-reflective material c. No serous pigment epithelium detachments >100 microns in height
Key Exclusion Criteria:	**Key General Exclusion Criteria:** 1. Females who are pregnant, nursing, planning a pregnancy during the study or who are of childbearing potential not using a reliable method of contraception and/or not willing to maintain a reliable method of contraception during their participation in the study. Women of childbearing potential with a positive urine pregnancy test administered at baseline are not eligible to receive study drug. 2. Participation in an investigational drug or device study within 90 days of screening **Key Ocular Exclusion Criteria:** 1. Subjects with active exudative AMD in the fellow eye 2. Subjects who had anti-VEGF IVT in either eye in the past 90 days **Key Ocular Exclusion Criteria (Study Eye):** 1. Subjects with pigment epithelium detachments 2. Subjects with active exudative AMD 3. Subjects with any prior retina surgery 4. Subjects with pathology that could prevent observation and follow-up of macular structures and measurement of BCVA (i.e. advanced primary open angle glaucoma, any stage of normal tension glaucoma and corneal opacification) 5. Subjects that are likely to require cataract surgery in the opinion of the investigator within the study protocol period

Study Outcomes	**<u>Primary Efficacy Endpoint</u>:** 1. Percentage of population with ≥ 8 letters (1 ½ lines) BCVA gain in the Luminate group (Treatment group 1 that received 2 doses of Luminate) from baseline to study week 28 vs the Sham control group from baseline to study week 12

	Secondary Efficacy Endpoints: 1. Percentage of population with ≥ 8 letters (1 ½ lines) BCVA gain from baseline to study week 12 (Luminate vs Sham control group) 2. Percentage of population in the Sham → Luminate crossover population with ≥ 8 letters (1 ½ lines) BCVA gain from baseline to study week 12 vs from study visit week 16 to study visit week 28 3. Percentage of population with ≥ 10 letters (2 lines) BCVA gain in the Luminate group (Treatment group 1 that received 2 doses of Luminate) from baseline to study week 28 vs the Sham control group from baseline to study week 12 4. Percentage of population with ≥ 10 letters (2 lines) BCVA gain from baseline to study week 12 (1.0mg Luminate vs Sham control) 5. Percentage of population in the Sham → Luminate crossover population with ≥ 10 letters (2 lines) BCVA gain from baseline to study week 12 vs from study visit week 16 to study visit week 28 6. Mean observed changes in ETDRS BCVA between groups at week 12 7. Mean observed changes in ETDRS BCVA between 1.0mg Luminate at week 28 vs Sham at week 12 8. Mean observed changes in ETDRS BCVA between groups at week 12 in the subset of study subjects with a ≥ 8 letters (1 ½ lines) BCVA gain from baseline 9. Mean observed changes in ETDRS BCVA between 1.0mg Luminate at week 28 vs Sham at week 12 in the subset of study subjects with a ≥ 8 letters (1 ½ lines) BCVA gain from baseline 10. Maximum observed changes in ETDRS BCVA between 1.0 mg Luminate and Sham 11. Percent of population that convert from non-exudative to exudative AMD **Exploratory Endpoints:** 1. Percentage of population with ≥ 7 and ≥ 9 letters BCVA gain in the Luminate group (Treatment group 1 that received 2 doses of Luminate) from baseline to study week 28 vs the Sham control group from baseline to study week 12 2. Improvement in anatomy (by OCT) 3. Improvement in multi-focal ERG 4. Improvement in color vision test 5. Improvement in perimetry 6. Improvement in microperimetry 7. Improvement in fundus autofluorescence 8. Improvement in low luminance visual acuity **Safety Endpoints:** 1. Adverse events 2. Complete ocular examination including: an external examination of the eye and adnexa, slit lamp biomicroscopy, dilated direct and indirect ophthalmoscopy, and IOP, OCT, Fundus photo and autofluorescence.

Statistical Methodology	No formal hypothesis testing is planned; descriptive statistics will be used to summarize the study outcomes.

A Phase IIa RANDOMIZED, CONTROLLED, DOUBLE-MASKED, CROSSOVER CLINICAL TRIAL DESIGNED TO EVALUATE THE SAFETY AND EXPLORATORY EFFICACY OF 1.0 mg LUMINATE® (ALG-1001) AS A TREATMENT FOR NON-EXUDATIVE MACULAR DEGENERATION

1.0 BACKGROUND AND RATIONALE

Integrins are heterodimeric transmembrane proteins and are important for cell-cell and cell-matrix interactions, which act as transmembrane linkers between their extracellular ligands and the cytoskeleton. Through the transmembrane links, integrins provide modulation of various outside-in and inside-out signaling pathways essential in the biological functions of cells such as: cell migration, differentiation, survival during embryogenesis, angiogenesis, wound healing, immune and non-immune defense mechanism, hemostasis and oncogenic transformation (Hynes RO., 2002).

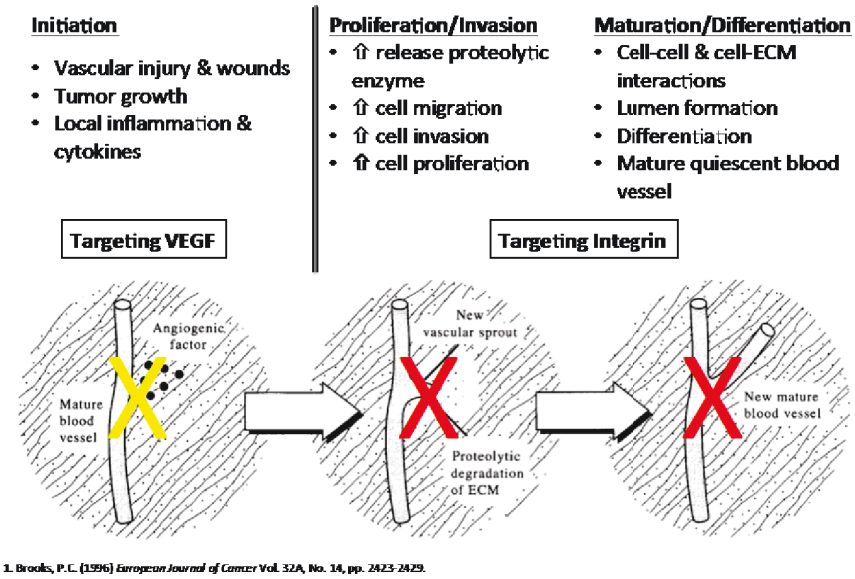


Figure 1

The molecular events involved in the development of NV and CNV have not been fully elucidated; however, while VEGF has been shown to play a major role in the development of NV and CNV (Umeda et. al., 2006; Friedlander et. al., 1996), integrins $\alpha_5\beta_1$, $\alpha_v\beta_3$, and $\alpha_v\beta_5$ are also implicated in the angiogenic process, and are known to be expressed in neovascular ocular tissue from patients with

Wet AMD and proliferative DR (Umeda et. al., 2006; Friedlander et. al., 1996). As shown in **Figure 1 above**, targeting integrin works against proliferation and invasion, as well as maturation and differentiation (Brooks et. al., 1996).

Allegro has discovered a peptide sequence, in either linear or cyclic form, that effectively binds to $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins. These integrin receptors have been found to be intimately involved in the angiogenesis associated with Wet AMD, DME and proliferative DR. More recent evidence in the literature has demonstrated the neuroprotective effects of $\alpha_v\beta_3$ integrin targeting agents in the central nervous system. (Han et al, 2013).

Recent genomics and proteomics work from Cal Tech and Johns Hopkins has shown potential neuroprotective effects of Luminate® therapy in the eye. Further research has shown Luminate® to be neuroprotective in several cultured mouse retina models in vitro. In addition to this, in-vivo testing in a rat optic nerve crush model has also demonstrated pre-treatment with Luminate® to be highly protective of the ganglion cell layer. It is based on this data and the large breadth of safety data in humans to date that this study was contemplated.

2.0 STUDY OBJECTIVE

To evaluate the safety and exploratory efficacy of 1.0 mg of Luminate® in treating patients with Intermediate Non-Exudative Macular Degeneration

3.0 STUDY DESIGN

Potential study participants will be asked to sign an informed consent document prior to screening. Screening will be conducted from -28 days to -2 days prior to randomization and treatment.

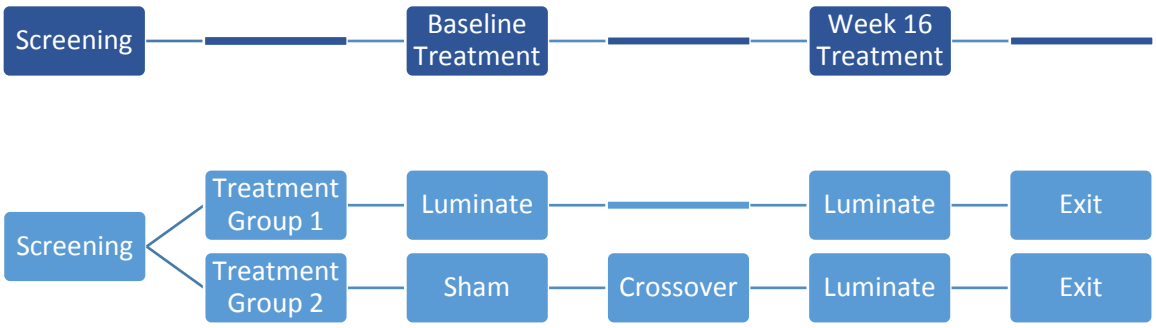
This will be a double-masked study. The injecting unmasked investigator will administer 1.0mg of Luminate®/50µL, or Sham injection by intravitreal injection into the study eye. The assessing investigator will be masked.

Eligible subjects who have been diagnosed with intermediate non-exudative AMD, that require treatment will be enrolled and randomized (1.7:1) to one of 2 treatment groups. Twenty-five (25) study subjects will receive 1.0mg/50µL of Luminate®, and fifteen (15) study subjects will receive Sham injection at the clinical site, the masked examiner will perform ocular examinations as well as IOP, BCVA, OCT, Multi-Focal ERG, and color vision testing assessments.

All study subjects will return for examination after 4 weeks, and thereafter after each month, through 32-week visit. The visits and parameters to be evaluated at each study visit are displayed in Table 2 Section .

At the 16-week visit, the study will be unmasked to the sponsor and injecting investigator (observing investigators will remain masked). Subjects in Group 1 will receive a second dose of Luminate®. Subjects in Group 2 will be offered the opportunity to crossover to an open-label treatment with a single dose of Luminate®. All study subjects will continue to be followed through 32 weeks of follow-up.

The safety and efficacy of Luminate® 1.0mg/50µL and sham injection will be evaluated over the course of this 32-week study. Since this is Phase IIa clinical trial, no formal hypothesis testing is planned; descriptive statistics will be used to summarize the study outcomes.



Approximately 40 subjects from up to 15 sites will be enrolled in this study.

***Study Treatment Group*:**

- Treatment Group 1: Non-Exudative AMD subjects with a BCVA of 20/40 – 20/200 will be administered an intravitreal injection of 1.0 mg Luminate® at Day 0 and Week 16

***Control*:**

- Treatment Group 2: Non-Exudative AMD subjects with a BCVA of 20/40 – 20/200 will be administered a sham injection at Day 0

Sham Crossover:

- Open-label administration of an intravitreal injection of 1.0 mg Luminate® at Week 16 to sham control patients

Blood Sample for Genetic Analysis::

A blood sample will be retained for exploratory genetic analysis that may provide insight into Dry AMD and an individual subject's response to Luminate®.

Table 1 Dry AMD STUDY 101 TREATMENT SCHEDULE

	Visit -1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
	Day -28 to Day -2	Week 0 (Injection)	Week 4 (post injection)	Week 8 (post injection)	Week 12 (post injection)	Week 16 (post injection	Week 20 (post injection)	Week 24 (post injection)	Week 28 (post injection)	Week 32 (post injection)
Group 1										
Luminate® 1.0mg BCVA 20/40 – 20/200	---	✓	---	---	---	✓	---	---	---	---
Group 2							---	---	---	---
Sham Injection BCVA 20/40 – 20/200	---	✓	---	---	---	---	---	---	---	---
Luminate® 1.0mg(crossover injection) BCVA 20/40 – 20/200	---	---	---	---	---	✓	---	---	---	---

✓ = study treatments

4.0 STUDY OUTCOMES

4.1 EFFICACY

PRIMARY ENDPOINT

1. Percentage of population with ≥ 8 letters (1 ½ lines) BCVA gain in the Luminate group (Treatment group 1 that received 2 doses of Luminate) from baseline to study week 28 vs the Sham control group from baseline to study week 12

SECONDARY ENDPOINTS

1. Percentage of population with ≥ 8 letters (1 ½ lines) BCVA gain from baseline to study week 12 (Luminate vs Sham control group)
2. Percentage of population in the Sham → Luminate crossover population with ≥ 8 letters (1 ½ lines) BCVA gain from baseline to study week 12 vs from study visit week 16 to study visit week 28
3. Percentage of population with ≥ 10 letters (2 lines) BCVA gain in the Luminate group (Treatment group 1 that received 2 doses of Luminate) from baseline to study week 28 vs the Sham control group from baseline to study week 12
4. Percentage of population with ≥ 10 letters (2 lines) BCVA gain from baseline to study week 12 (1.0mg Luminate vs Sham control)
5. Percentage of population in the Sham → Luminate crossover population with ≥ 10 letters (2 lines) BCVA gain from baseline to study week 12 vs from study visit week 16 to study visit week 28
6. Mean observed changes in ETDRS BCVA between groups at week 12
7. Mean observed changes in ETDRS BCVA between 1.0mg Luminate at week 28 vs Sham at week 12
8. Mean observed changes in ETDRS BCVA between groups at week 12 in the subset of study subjects with a ≥ 8 letters (1 ½ lines) BCVA gain from baseline
9. Mean observed changes in ETDRS BCVA between 1.0mg Luminate at week 28 vs Sham at week 12 in the subset of study subjects with a ≥ 8 letters (1 ½ lines) BCVA gain from baseline
10. Maximum observed changes in ETDRS BCVA between 1.0 mg Luminate and Sham
11. Percent of population that convert from non-exudative to exudative AMD

EXPLORATORY ENDPOINTS

1. Percentage of population with ≥ 7 and ≥ 9 letters BCVA gain in the Luminate group (Treatment group 1 that received 2 doses of Luminate) from baseline to study week 28 vs the Sham control group from baseline to study week 12
2. Improvement in anatomy (by OCT)
3. Improvement of multi-focal ERG
4. Improvement in color vision test

5. Improvement in perimetry
6. Improvement in microperimetry
7. Improvement in fundus autofluorescence
8. Improvement in low luminance visual acuity

4.2 SAFETY

1. Adverse events
2. Complete ocular examination including: an external examination of the eye and adnexa, slit lamp biomicroscopy, dilated direct and indirect ophthalmoscopy, and IOP, OCT, Fundus photo and autofluorescence.

5.0 STUDY POPULATION

Approximately 40 patients with a diagnosis of Intermediate Non-Exudative Macular Degeneration will be recruited into the study.

5.1 INCLUSION CRITERIA

General Inclusion Criteria:

1. Male or female, between 50 - 85 years of age at screening visit.
2. Subject has signed the Informed Consent form

Ocular Inclusion Criteria (Study Eye):

1. Subjects with non-exudative AMD having ETDRS BCVA between 33 and 72 letters read (equivalent to 20/40 – 20/200 on Snellen Chart) with the level of vision caused by the non-exudative AMD and no other factor/s
2. Subjects with symptomatic drop in visual acuity in the last 12 months
3. Subjects with combination of areas of RPE disturbances (hyper or hypopigmentation) and/or ≥ 1 large druse(n) (>125 microns) and/or multiple intermediate drusen (63-124 microns) in the macula as confirmed by the central reading center
4. Subjects with evidence of reasonably well-preserved areas of RPE by clinical examination and well-defined RPE and outer segment ellipsoid line by OCT examination in the central 1 mm of the macula as confirmed by the central reading center. More specifically, reasonable well-preserved central 1 mm of the macula means:
    a. The RPE and outer retinal layers throughout the central 1 mm are intact
    b. No signs of NVAMD such as intraretinal or sub retinal fluid, or sub retinal hyper-reflective material
    c. No serous pigment epithelium detachments >100 microns in height

5.2 EXCLUSION CRITERIA

General Exclusion Criteria:

1. Females who are pregnant, nursing, planning a pregnancy during the study or who are of childbearing potential not using a reliable method of contraception and/or not willing to maintain a reliable method of contraception during their participation in the study. Women of childbearing potential with a positive urine pregnancy test administered at baseline are not eligible to receive study drug
2. Participation in an investigational drug or device study within 90 days of screening

Key Ocular Exclusion Criteria:

1. Subjects with active exudative AMD in the fellow eye
2. Subjects who had anti-VEGF IVT in either eye in the past 90 days

Key Ocular Exclusion Criteria (Study Eye):

1. Subjects with serous pigment epithelium detachments
2. Subjects with active exudative AMD
3. Subjects with any retina surgery
4. Subjects with pathology that could prevent observation and follow-up of macular structures and measurement of BCVA (i.e. primary open angle glaucoma, any stage of normal tension glaucoma and corneal opacification).
5. Subjects that are likely to require cataract surgery in the opinion of the investigator within the study protocol period

6.0 STUDY METHODS

6.1 SUBJECT SCREENING

Subjects will be screened by the investigator based upon the following criteria that are detailed in the case report forms to be utilized for the screening visit:

1. Informed consent
2. Inclusion/Exclusion
3. For women ages <60, negative urine pregnancy test at screening
4. Demographic information
5. Medical/Ophthalmic History
6. List of concomitant medications
7. Refraction with ETDRS BCVA at 4/1 meters in the study eye
8. Low luminance visual acuity
9. Lanthony D-15 Color Vision Test
10. Slit-lamp biomicroscopy
11. Humphrey 10-2 Threshold Perimetry
12. Microperimetry (if available)
13. IOP
14. Indirect ophthalmoscopy/ dilated fundus exam

15. Fundus Photo
16. Fundus autofluorescence (if available)
17. Spectral-domain OCT with appropriate cuts for respective machine
18. Multi-Focal ERG – (if available)
19. Prophylactic antibiotic drops (when applicable)

Subjects will be cleared for enrollment by the Sponsor.

Once all the study requirements for enrollment are satisfied, all screening documents must be forwarded to the Sponsor for review and determination that the eligibility criteria have been met.

Upon receipt of the screening documents for a given screened subject, the Sponsor or designee will notify the investigator in writing or via email whether the subject has been cleared for enrollment in the study. The screening window is from -28 to -2 days prior to enrollment/injection to allow 3 days of pre-injection antibiotics at doctor's discretion.

6.2 SUBJECT ENROLLMENT

Upon enrollment in the study, the study subject will be randomly assigned to one of the two treatment groups, i.e., Luminate® group or Sham group.

6.3 INVESTIGATIONAL MATERIALS

The investigational materials will be labeled by Allegro Ophthalmics, LLC, and will be provided to the investigational site. The medications will be identified as an investigational compound and will carry the following statement: *"CAUTION: NEW DRUG – LIMITED BY FEDERAL LAW TO INVESTIGATIONAL USE ONLY"*. The study code and subject number will be identified on the label of the medication bottles, along with the batch number, expiration date and storage requirements for the study drug.

During the study, the investigator must maintain an inventory of all study supplies in stock, as well as those dispensed and administered to study subjects. The study drug must be stored in a secure area to prevent unauthorized distribution. The investigational drug is to be administered only to subjects entered into the study, in accordance with the conditions specified in the protocol.

At the end of the study, and following a full accounting and recording of all study medications, unused supplies of the investigational products will either be returned to the Sponsor (or its designee) or disposed of under the direction of the Sponsor or designee. The sponsor may authorize disposal of unused supplies of the investigational drug provided this alternative disposition does not expose humans to risks from the drug.

6.4 INSTRUCTIONS FOR USE AND ADMINISTRATION OF INVESTIGATIONAL PRODUCT

6.4.1 INTRAVITREAL INJECTION PREPARATION – LUMINATE® 1.0MG/50µL SOLUTION OR SHAM INJECTION

The study drugs are supplied in a 0.30 mL conical-shaped glass vial as a sterile liquid product ready for injection. Prior to the injection, the investigator should confirm that the vial to be used matches the vials that have been specifically assigned to the particular study subject. Luminate® should be stored at refrigerated temperature.

6.4.2 INTRAVITREAL INJECTION PROCEDURE

The injection and post-injection procedures below are guidance and sites may use the standard of care procedure at their institution.

The subject is placed in a SITTING position and the procedure explained again to the subject in lay terms prior to beginning.

- Apply one drop of IOP lowering agent (investigators choice) ophthalmic drops to the eye to be injected.
- Apply two (2) drops of proparacaine on the surface to be injected, followed by two (2) drops of antibiotic.
- To disinfect the periocular skin, eyelids, and lashes use 5% povidone iodine swabs in a systemic fashion.
- The investigator wears gloves and a sterile drape is placed on the eye, then the lid speculum is placed over the drape.
- The injection location is at the investigator's discretion; however, the inferior temporal or superior temporal location is preferred.
- Expel two (2) drops of 5% povidone iodine on the ocular surface. Wait 90 seconds. Saturate a sterile cotton tip with proparacaine drops and place over the injection site. Bleed any bubbles out of the syringe and expel any excess drug so that 0.05 mL remains in the syringe just prior to injection.
- Insert the needle (30 or 31-gauge needle) 3.5 to 4.0 mm posterior to the limbus avoiding the horizontal axis. Inject slowly INTO THE CENTRAL VITREOUS (neither anterior nor posterior) and remove the needle from the eye slowly to avoid loss of drug. Use the cotton swab as a tamponade to avoid loss of drug at injection site.
- After injection, the investigator will observe the subject for several minutes to ensure that untoward complications have not occurred.
- Check vision with finger counting and if vision is worse for more than 1 minute, an anterior chamber paracentesis with a 30 or 31-gauge needle should be performed. The IOP can be taken at regular intervals, at the investigator's discretion, until the IOP has stabilized and the investigator has determined that the subject is safe to leave the clinic.

6.5 CONCOMITANT MEDICATIONS

Subjects will receive pre-injection and post-injection antibiotic eye drops at the discretion of the principal investigator at each site. It is recommended that study subjects receive antibiotic eye drops three days pre-injection and up to one week post-injection.

Any systemic medications that are considered necessary for the subject's welfare may be used. Additionally, topical anti-inflammatories, antibiotics, steroids, intraocular pressure agents, and/or cycloplegics to treat or assess the ocular condition may be used at the discretion of the investigator. All medications administered shall be reported in the appropriate section of the source document and case report form (CRF).

7.0 STUDY VISITS AND PROCEDURES:

Demographic, medical and medication history of all subjects will be recorded, and the following ophthalmic examinations will be conducted and recorded during the course of the study: inclusion/exclusion criteria, demographics, medical and ophthalmic history, list of current medications, slit-lamp biomicroscopy, refraction and BCVA examinations, tonometry for intraocular pressure (IOP), indirect ophthalmoscopy, dilated fundus exam, and Spectral-domain OCT (SD-OCT), multi-focal ERG, and color vision test . Subjects will be queried for adverse events at each visit and adverse events must be reported in the appropriate section of the CRF.

The blood sample for the genetic analysis can be collected at any visit between Visit 2/Week 0 and Visit 10/Week 32.

INSTRUCTIONS FOR PATIENTS ENROLLMENT INTO THE STUDY

- After signing of ICF, Investigator assigns the patient screening number
- Investigator performs screening procedures as described in section 7.1
- Allegro approves the patient

7.1 VISIT 1 - SCREENING VISIT (-28 TO -2 DAYS) [BOTH EYES]

All screening/baseline procedures will be reviewed by the Sponsor or designee to ensure the subject is appropriate for enrollment and injection. After review of the inclusion and exclusion criteria for appropriateness of the subject, the following information/procedures will be performed on both eyes:

1. Informed Consent
2. Inclusion/Exclusion Criteria
3. Demographics
4. Medical and Ophthalmic History
5. Concomitant medications
6. Urine Pregnancy Test
7. Non-Dilated Assessments
    a. Refraction and Best-Corrected Visual Acuity

b. Low luminance visual acuity
c. Lanthony D-15 Color Vision Test
d. Slit-Lamp Biomicroscopy
e. Humphrey 10-2 Threshold Perimetry
f. Microperimetry (if available)
g. Tonometry (IOP) (applanation or tonopen)

8. Dilated Assessments
    a. Indirect Ophthalmoscopy/dilated fundus exam
    b. Fundus Photo
    c. Fundus Autofluorescence (if available)
    d. Spectral-Domain OCT
    e. Multi-Focal ERG – (if available)

7.2 VISIT 2 – WEEK 0 INTRAVITREAL INJECTION CONCOMITANT MEDICATIONS

1. Non-Dilated Assessments
    a. Refraction and Best-Corrected Visual Acuity (Both Eyes)
    b. Slit-Lamp Biomicroscopy (Study Eye only)
    c. Tonometry (IOP) (applanation or tonopen) (Study Eye only)
2. Dilated Assessments
    a. Indirect Ophthalmoscopy/ dilated fundus exam (Study Eye only)
3. Study treatment administered (Intravitreal Injection)
4. Assess adverse events

7.3 VISIT 3 – WEEK 4 (± 3 DAYS)

1. Concomitant medications
2. Non-Dilated Assessments
    a. Refraction and Best-Corrected Visual Acuity (Both Eyes)
    b. Slit-Lamp Biomicroscopy (Study Eye only)
    c. Tonometry (IOP) (applanation or tonopen) (Study Eye only)
3. Dilated Assessments
    a. Indirect Ophthalmoscopy/dilated fundus exam (Study Eye only)
4. Assess adverse events

7.4 VISIT 4 – WEEK 8 (± 3 DAYS)

1. Concomitant medications
2. Non-Dilated Assessments
    a. Refraction and Best-Corrected Visual Acuity (Both Eyes)
    b. Slit-Lamp Biomicroscopy (Study Eye only)
    c. Tonometry (IOP) (applanation or tonopen) (Study Eye only)
3. Dilated Assessments
    a. Indirect Ophthalmoscopy/dilated fundus exam (Study Eye only)
4. Assess adverse events

7.5 VISIT 5 – WEEK 12 (± 3 DAYS)

1. Concomitant medications

2. Non-Dilated Assessments
    a. Refraction and Best-Corrected Visual Acuity (Both Eyes)
    b. Low luminance visual acuity (Study Eye only)
    c. Lanthony D-15 Color Vision Test (Study Eye only)
    d. Slit-Lamp Biomicroscopy (Study Eye only)
    e. Humphrey 10-2 Threshold Perimetry (Study Eye only)
    f. Microperimetry – if available (Study Eye only)
    g. Tonometry (IOP) (applanation or tonopen) (Study Eye only)
3. Dilated Assessments
    a. Indirect Ophthalmoscopy/dilated fundus exam (Study Eye only)
    b. Fundus Photo (Study Eye only)
    c. Fundus Autofluorescence – if available (Study Eye only)
    d. Spectral-Domain OCT (Study Eye only)
    e. Multi-Focal ERG - if available (Study Eye only)
4. Assess adverse events

7.6 VISIT 6 – WEEK 16 (± 3 DAYS)

1. Concomitant medications
2. Non-Dilated Assessments
    a. Refraction and Best-Corrected Visual Acuity (Both Eyes)
    b. Slit-Lamp Biomicroscopy (Study Eye only)
    c. Tonometry (IOP) (applanation or tonopen) (Study Eye only)
3. Dilated Assessments
    a. Indirect Ophthalmoscopy/dilated fundus exam (Study Eye only)
4. Study treatment administered (Intravitreal Injection)
5. Assess adverse events

7.7 VISIT 7 – WEEK 20 (± 3 DAYS)

1. Concomitant medications
2. Non-Dilated Assessments
    a. Refraction and Best-Corrected Visual Acuity (Both Eyes)
    b. Slit-Lamp Biomicroscopy (Study Eye only)
    c. Tonometry (IOP) (applanation or tonopen) (Study Eye only)
3. Dilated Assessments
    a. Indirect Ophthalmoscopy/dilated fundus exam (Study Eye only)
4. Assess adverse events

7.8 VISIT 8 – WEEK 24 (± 3 DAYS)

1. Concomitant medications
2. Non-Dilated Assessments
    a. Refraction and Best-Corrected Visual Acuity (Both Eyes)
    b. Slit-Lamp Biomicroscopy (Study Eye only)
    c. Tonometry (IOP) (applanation or tonopen) (Study Eye only)
3. Dilated Assessments
    a. Indirect Ophthalmoscopy/dilated fundus exam (Study Eye only)
4. Assess adverse events

7.9 VISIT 9 – WEEK 28 (± 3 DAYS)

1. Concomitant medications
2. Non-Dilated Assessments
    a. Refraction and Best-Corrected Visual Acuity (Both Eyes)
    b. Slit-Lamp Biomicroscopy (Study Eye only)
    c. Tonometry (IOP) (applanation or tonopen) (Study Eye only)
3. Dilated Assessments
    a. Indirect Ophthalmoscopy/dilated fundus exam (Study Eye only)
4. Assess adverse events

7.10 VISIT 10 – WEEK 32 (± 3 DAYS)

1. Concomitant medications
2. Non-Dilated Assessments
    a. Refraction and Best-Corrected Visual Acuity (Both Eyes)
    b. Low luminance visual acuity (Study Eye only)
    c. Lanthony D-15 Color Vision Test (Study Eye only)
    d. Slit-Lamp Biomicroscopy (Study Eye only)
    e. Humphrey 10-2 Threshold Perimetry (Study Eye only)
    f. Microperimetry – if available (Study Eye only)
    g. Tonometry (IOP) (applanation or tonopen) (Study Eye only)
3. Dilated Assessments
    a. Indirect Ophthalmoscopy/dilated fundus exam (Study Eye only)
    b. Fundus Photo (Study Eye only)
    c. Fundus Autofluorescence – if available (Study Eye only)
    d. Spectral-Domain OCT (Study Eye only)
    e. Multi-Focal ERG - if available (Study Eye only)
4. Assess adverse events

7.11 TABLE 2: SCHEDULE OF VISITS FOR DRY AMD STUDY 101

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
	Screening Day (-28 to -2 days)	Intravitreal Injection day Week 0 (Day 0 ±1)	Week 4 Post Injection (±3 Days)	Week 8 Post Injection (±3 Days)	Week 12 Post Injection (±3 days)	Week 16 Post Injection (±3 days)	Week 20 Post Injection (±3 days)	Week 24 Post Injection (±3 days)	Week 28 Post Injection (±3 days)	Week 32 Post Injection (±3 days)
Informed consent	✓									
Inclusion & exclusion criteria	✓									
Demographic Information	✓									
Medical and ophthalmic history	✓									
Concomitant medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Urine Pregnancy Test(if applicable)	✓									
Refraction – BCVA	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Low luminance BCVA	✓				✓					✓
Lanthony D-15 Color Vision Test	✓				✓					✓
Slit-Lamp biomicroscopy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Humphrey 10-2 Threshold Perimetry	✓				✓					✓
Microperimetry – if available	✓				✓					✓
IOP	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Indirect ophthalmoscopy/ dilated fundus exam	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Fundus Photo	✓				✓					✓
Fundus Autofluorescence	✓				✓					✓
OCT- Spectral Domain	✓				✓					✓
Multi-Focal ERG – if available	✓				✓					✓
Blood Sample for Genetic Analysis[1]										
Study Treatment administered		✓				✓				
Assess Adverse Events		✓	✓	✓	✓	✓	✓	✓	✓	✓

1 = Blood sample for Genetic Analysis can be collected at any visit between Visit 2/Week 0 and Visit 10/Week 32.

8.0 STUDY COMPLETION

8.1 SUBJECT COMPLETION

Subjects are considered to have completed the study if they have completed all required examinations through week 32. The study is considered to be completed when all subjects have completed the trial.

8.2 SUBJECT DISCONTINUATION

Reasons for discontinuing a subject from a study include non-compliance with the required visits or with the treatment regimen. Subjects have the right to withdraw from participation in the study at any time, for any reason without prejudice to further treatment. The investigator may elect to discontinue any subject for reasons unrelated to the study product. The following may be justifiable reasons for the Investigator to withdraw a subject from the study:

- A subject is uncooperative, or misses two or more consecutive follow-up visits.
- A subject was erroneously included in the study.
- A subject develops an exclusion criterion or concurrent disease.
- The Sponsor terminates the study.

Details of a subject's exit from the study should be recorded in the subject's clinical records.

The study subject may be discontinued by an investigator or by the sponsor. Should an investigator decide to discontinue the study subject, based on clinical observations, this should be reported to the sponsor with reasons for the discontinuation. Appropriate notification will be provided to the sponsor within approximately five working days.

8.3 EARLY EXIT VISIT

A study subject may exit from the study prior to completion in the following situations:

- The principal investigator determines that it is not in the best interest of the subject to continue participation
- The study subject wishes to withdraw from the study for any reason.

The Sponsor must be contacted prior to exiting the study subject. Every effort should be made to have the subjects return to the site for completion of exit visit procedures.

The study exit assessments are as follows:

1. Concomitant medications
2. Urine pregnancy test
3. Non-Dilated Assessments
    a. Refraction and Best-Corrected Visual Acuity
    b. Low luminance visual acuity
    c. Lanthony D-15 Color Vision Test
    d. Slit-Lamp Biomicroscopy
    e. Humphrey 10-2 Threshold Perimetry

f. Microperimetry – if available
g. Tonometry (IOP) (applanation or tonopen)

4. Dilated Assessments
    a. Indirect Ophthalmoscopy/ dilated fundus exam
    b. Fundus Photo
    c. Fundus Autofluorescence – if available
    d. Spectral-Domain OCT
    e. Multi-Focal ERG - if available
6. Assess adverse events

9.0 ADVERSE EVENT REPORTING

An adverse event is any untoward and unintended sign, symptom or disease temporally associated with the use of an investigational drug or other protocol-imposed intervention whether or not considered drug-related.

All treatment-emergent adverse events/adverse reactions occurring during the study should be recorded, regardless of the assumption of causal relationship. If a subject has an ongoing adverse events/adverse reactions at the time of study completion, the ongoing adverse events/adverse reactions must be followed-up and provided appropriate medical care until the signs and symptoms have remitted or stabilized.

Conditions or diseases that are chronic but stable should not be recorded on AE pages of the CRF. Changes in a chronic condition of disease that are consistent with natural disease progression are NOT adverse events and should not be recorded on the AE pages of the CRF.

9.1 Adverse Event Definitions

The following definitions of terms apply to this section:

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether considered drug related or not.

Life-threatening adverse event or life-threatening suspected adverse reaction. An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or suspected adverse reaction. An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Results in death.
- Is life-threatening.

- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Requires inpatient hospitalization.
- Prolongs inpatient hospitalization.
- Is a congenital anomaly/birth defect.
- Is a significant medical event (i.e., one that may jeopardize the subject or may require intervention to prevent one or more of the other outcomes listed above).

Sight-threatening adverse events include the following:

- It caused a decrease in visual acuity of 30 ETDRS letters (compared with the last assessment of visual acuity prior to the most recent treatment) lasting >1 hour.
- It caused a decrease in visual acuity to the level of Light Perception or worse lasting >1 hour.
- It required surgical intervention (e.g., conventional surgery, vitreous tap or biopsy with intravitreal injection of anti-infectives, or laser or retinal cryopexy with gas) to prevent permanent loss of sight.
- It is associated with severe intraocular inflammation (i.e., 4+ anterior chamber cell/flare or 4+ vitritis).
- In the opinion of the investigator, it may require medical intervention to prevent permanent loss of sight.

Sight-threatening events (as defined above) should be reported as SAEs.

A non-serious adverse event is any AE that does not meet the definitions for SAEs as described above.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event or unexpected suspected adverse reaction. An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator brochure or is not listed at the specificity or severity that has been observed.

9.2 Classification of Adverse Events by Relationship, Severity and Action Taken

The study medication relationship for each adverse event/adverse reaction should be determined by the Investigator using these explanations:

- **Not Related:** The event is clearly related to other factors such as subject's clinical condition, therapeutic interventions, concomitant disease, therapy administered or accidental trauma of the subject and does not follow a known response pattern to the product.
- **Possibly Related:** The event follows a reasonable, temporal sequence from the time of study medication administration and/or follows a known response pattern to the study medication, but could have been produced by other factors such as the subject's clinical state, therapeutic interventions or concomitant therapy administered to the subject.
- **Related:** The event follows a reasonable, temporal sequence from the time of study medication administration or placement and/or follows a known response pattern to the study medication and cannot be reasonably explained by other factors such as subject's clinical state, therapeutic interventions or concomitant therapy administered to the subject, and either occurs immediately following study medication administration, or improves on stopping the study medication, or reappears on repeat exposure, or there is a positive reaction at the application site.

Intensity (severity) of an adverse event is defined as a qualitative assessment of the level of discomfort of an adverse event as is determined by the Investigator or reported to him/her by the subject. The assessment of intensity is made irrespective of study medication relationship or seriousness of the event and should be evaluated according to the following scale:

1 = Mild: present, but not distressing, and no disruption of normal daily activity
2 = Moderate: discomfort sufficient to reduce or affect normal daily activity
3 = Severe: incapacitating, with inability to work or perform normal daily activity

A change in severity for a reported AE will require a stop date for the previous severity and a new start and stop date for the new severity. For example, a change in severity may go from mild to severe or from severe to moderate. In either case, the start and stop dates should be recorded.

Action taken in response to an adverse event is coded as:

1=None
2=Test Article interrupted
3=Test Article discontinued
4=Non-drug therapy
5=New OTC or Rx drug added
6=Hospitalized (≥24 hours)

Outcome of an adverse event is coded as:

1=Recovered without sequelae
2=Recovered with sequelae
3=Stable and ongoing
4=Ongoing
5=Death
6=Unknown/ Lost to follow-up

Please note: the term "severe" is used to describe the intensity (severity, see above) of an event/reaction; the event/reaction itself may be of relatively minor medical significance (such as severe headache). This is not the same as a "Serious" Adverse Event, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to the subject's life or vital functions. "Serious" (NOT severity) serves as a guide for defining regulatory reporting obligations.

9.3 Adverse Events Requiring Expedited Reporting

Serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) require expedited reporting to the Sponsor or designee regardless of relationship to study Insert or study procedure.

All SAEs and SUSARs must be reported to the study Sponsor or designee by telephone and e-mail or fax within 48 hours of knowledge of the event and to the IRB within the required reporting window of each IRB. Information on whether or not the event is considered drug related, or whether there is a reasonable possibility that the drug caused the event should be included with this report.

All reported AEs should be followed until resolution or until the adverse event has stabilized with no further change anticipated. Subjects who have an ongoing SAE or SUSAR at study completion or at discontinuation from the study will be followed by the Investigator or his or her designee until the event is resolved or determined to be irreversible, chronic, or stable by the Investigator.

9.4 Follow-up of Subjects After Adverse Events

If adverse events/adverse reactions occur, the Investigator will institute support and/or treatment as deemed appropriate. If a non-SAE/adverse reaction is unresolved at the time of the last visit, an effort will be made to follow up until the adverse event/adverse reaction is resolved or stabilized, the subject is lost to follow-up, or there is other resolution to the event.

10.0 STATISTICS

10.1 SAMPLE SIZE CONSIDERATIONS

Since this is a Phase IIa exploratory clinical study, no formal hypothesis testing will be performed. The sample size was determined based on establishing a reasonable number of subjects to provide adequate safety and efficacy information to proceed to the next phase of clinical development.

In case of patient drop-out, more subjects may be enrolled to fulfill approximately 40 evaluable subjects with follow-up visits.

10.2 GENERAL CONSIDERATIONS

Descriptive statistics will be used to tabulate and summarize study outcomes. Background and demographic characteristics will be presented. Continuous variables will be summarized by descriptive statistics (sample size, mean and standard deviation, median, minimum and maximum). Discrete variables will be summarized by frequencies and percentages. Adverse events will be summarized by presenting the number and percentage of patients having any adverse event. Any other information collected (such as severity or relationship to study device) will be listed as appropriate. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

10.3 ANALYSIS PLAN

An interim analysis on exploratory efficacy may be performed when all subjects have reached the week 12 visit. The observers and subjects will continue to be masked during the entire course of the study.

10.4 EXPLORATORY GENETIC ANALYSES

For subjects who provide consent for genetic samples, a blood sample will be retained for exploratory genetic analysis that may provide insight into an individual subject's response to the Luminate® treatment.

11.0 ETHICAL AND REGULATORY CONSIDERATIONS

The proposed study is subject to all applicable governmental rules and regulations concerning the conduct of clinical trials on human subjects. This includes, but is not necessarily limited to, the approval of local Institutional Review Board (IRB) or Ethics Review Committee (EC) (where applicable); obtaining prospective informed consent; monitoring of the conduct of the study and the completeness of the CRF by the Sponsor or its designee(s); and appropriate record retention by the Investigator. Applicable institutional review, Investigator/Sponsor obligations, study monitoring and protocol change procedures are detailed in appendices.

12.0 PUBLICATION POLICY

All manuscripts, abstracts or other modes of presentation arising from the results of the study must be reviewed and approved in writing by Allegro in advance of submission. The review is aimed at protecting Allegro's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results or other information, generated or created in relation to the study shall be set out in the agreement between each Investigator and Allegro as appropriate.

13.0 APPENDICES

A EXAMINATION PROCEDURES, TESTS, EQUIPMENT AND TECHNIQUES

B SPONSOR OBLIGATIONS

C INVESTIGATOR OBLIGATIONS

D WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

E STUDY MONITORING

F PROTOCOL CHANGES AND PROCEDURES

G INSTRUCTIONS FOR COMPLETION OF CASE REPORT FORMS

APPENDIX A: EXAMINATION PROCEDURES, TESTS, EQUIPMENT, AND TECHNIQUES

1. VISUAL ACUITY

Visual acuity will be measured using a standard ETDRS chart at 4 meters with a standard test luminance of 85 cd/m^2.

BCVA at screening should be determined with a new refraction done with a phoropter or using trial frames utilizing the ETDRS chart starting at 4 meters.

Measurement Technique

The chart should be at a comfortable viewing angle. The subject should attempt to read each letter, line-by-line, left to right, beginning with line 1 at the top of the chart. The subject should be told that the chart has letters only, no numbers. If the subject reads a number, he or she should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number. The subject should be asked to read slowly, about 1 letter per second, so as to achieve the best identification of each letter. The subject is not to proceed to the next letter until a definite response is given.

If the subject changes a response (e.g., that was a "C" not an "O") before the next letter has been read aloud, then the change must be accepted. If the subject changes a response having read the next letter, then the change is not accepted. The examiner should never point to the chart or to specific letters on the chart during the test.

A maximum effort should be made to identify each letter on the chart. This may include encouraging the subject to guess. If the subject identified a letter as 1 of 2 letters, he or she should be asked to choose one letter and, if necessary, to guess. When it becomes evident that no further meaningful readings can be made, despite encouragement to read or guess, the examiner should stop the test for that eye. However, all letters on the last line should be attempted, as letter difficulties vary and the last may be the only 1 read correctly. The study subject should always try to read the next line down to ensure that they have stopped at the small line possible for them to read. The number of letters missed or read incorrectly should be noted. These values will be used to compute overall number of letters read.

Low luminance visual acuity will be tested with the same methodology as described above except with the addition of a 2.0-log unit neutral density filter placed in front of the correction of the study eye. A 10-minute dark adaptation will be done prior to testing.

2. EXTERNAL EYE EXAMINATION AND SLIT LAMP BIOMICROSCOPY

The physician will examine the eyelid, conjunctiva, cornea, anterior chamber, lens and posterior chamber, both through direct observation and with the aid of a slit lamp biomicroscope. Fluorescein dye will be instilled into the eye studied, to facilitate visualization of the corneal surface. The subject will be seated while being examined and the adjustable chin rest and forehead strap will stabilize the head. Observations will be graded as follows:

None (Normal)..... **0**	Mild .....**+1**
Moderate……..**+2**	Severe .....**+3**

The following examples illustrate the application of the general grading system to the evaluation of various ophthalmic structures.

LID

Erythema

None (0)	Normal, without any redness
Mild (+1).....	A low grade flushed reddish color
Moderate (+2)	Diffused redness encompassing the entire lid margin
Severe (+3).....	Deep, diffused reddish color of lid margins and superior or inferior eyelid

Edema

None (0)	Normal, no swelling of the eyelid tissue
Mild (+1).....	Slight swelling, above normal
Moderate (+2)	General swelling
Severe (+3).....	Extensive swelling of the eyelid(s), with or without eversion of upper and/or lower lids

CONJUNCTIVA (Bulbar and Palpebral)

Congestion

None (0)	Normal. May appear blanched to reddish-pink without perilimbal injection. Conjunctival vessels easily observed.
Mild (+1).....	A flush, reddish color predominantly confined to the palpebral or bulbar conjunctiva
Moderate (+2)	More pronounced red color of the palpebral or bulbar conjunctiva
Severe (+3).....	Definite (bright) redness of the palpebral or bulbar conjunctiva

Edema

None (0)	Normal, no swelling of the conjunctiva
Mild (+1).....	Slight diffuse or regional swelling of the conjunctiva
Moderate (+2)	General swelling of the conjunctiva
Severe (+3).....	Extensive swelling of the conjunctiva

Discharge

None (0)	Normal, no discharge noted
Mild (+1).....	Slight discharge
Moderate (+2)	Obvious mucoid discharge
Severe (+3).....	Obvious mucoid or mucopurulent discharge with crusting and matting of the lid margins.

CORNEA

Staining/Erosion

None (0)	No Fluorescein staining of epithelium, no epithelial defect
Mild (+1).....	Slight staining confined to a small area
Moderate (+2)	Regionally dense staining (1mm or greater in diameter) with underlying structure moderately visible
Severe (+3).....	Marked staining or epithelial loss

Edema

None (0)	Transparent and clear
Mild (+1).....	Slightly dull glass appearance, may include fine isolated droplets
Moderate (+2)	Dull glass appearance with large number of vacuoles
Severe (+3).....	Epithelial bullae and/or stromal edema, localized or diffuse, with or without stromal striae

Endothelial Changes (i.e. pigment, guttata, etc.)

None (0)	Normal
Mild (+1).....	Slight polymorphism / pleomegathism, slight pigment, keratoprecipitates
Moderate (+2)	Moderate polymorphism / pleomegathism, few non-central guttata-like bodies, moderate pigment, keratoprecipitates
Severe (+3).....	Dense pigment, keratoprecipitates, several / many guttata-like bodies involving central cornea, severe polymorphism / pleomegathism

ANTERIOR CHAMBER

Cells

None (0)	No cells seen
Mild (+1).....	Few cells seen (1-5 cells)
Moderate (+2)	Several cells seen (6-25 cells)
Severe (+3).....	Numerous cells seen (26-50 cells)
Hypopyon (+4).....	Obvious purulent formation in the anterior chamber (>50 cells, indicate size of hypopyon)

Flare

None (0)	No Tyndall effect
Mild (+1).....	Tyndall beam in the anterior chamber has a mild intensity
Moderate (+2)	Tyndall beam in the anterior chamber is of strong intensity
Severe (+3).....	Tyndall beam is very intense. The aqueous has a white, milky appearance.

Anterior Synechiae

None (0)	No adhesion of iris to cornea
Mild (+1).....	0-25% of iris adhering to cornea
Moderate (+2)	26-50% of iris adhering to cornea
Severe (+3).....	> 50% of iris adhering to cornea

Posterior Synechiae

None (0)	No adhesion of iris to lens
Mild (+1).....	0-25% of iris adhering to lens
Moderate (+2)	26-50% of iris adhering to lens
Severe (+3).....	> 50% of iris adhering to lens

IRIS

The iris should be observed for atrophy, nodules, and neovascularization. These observations should be qualitatively graded as present or absent.

LENS PATHOLOGY

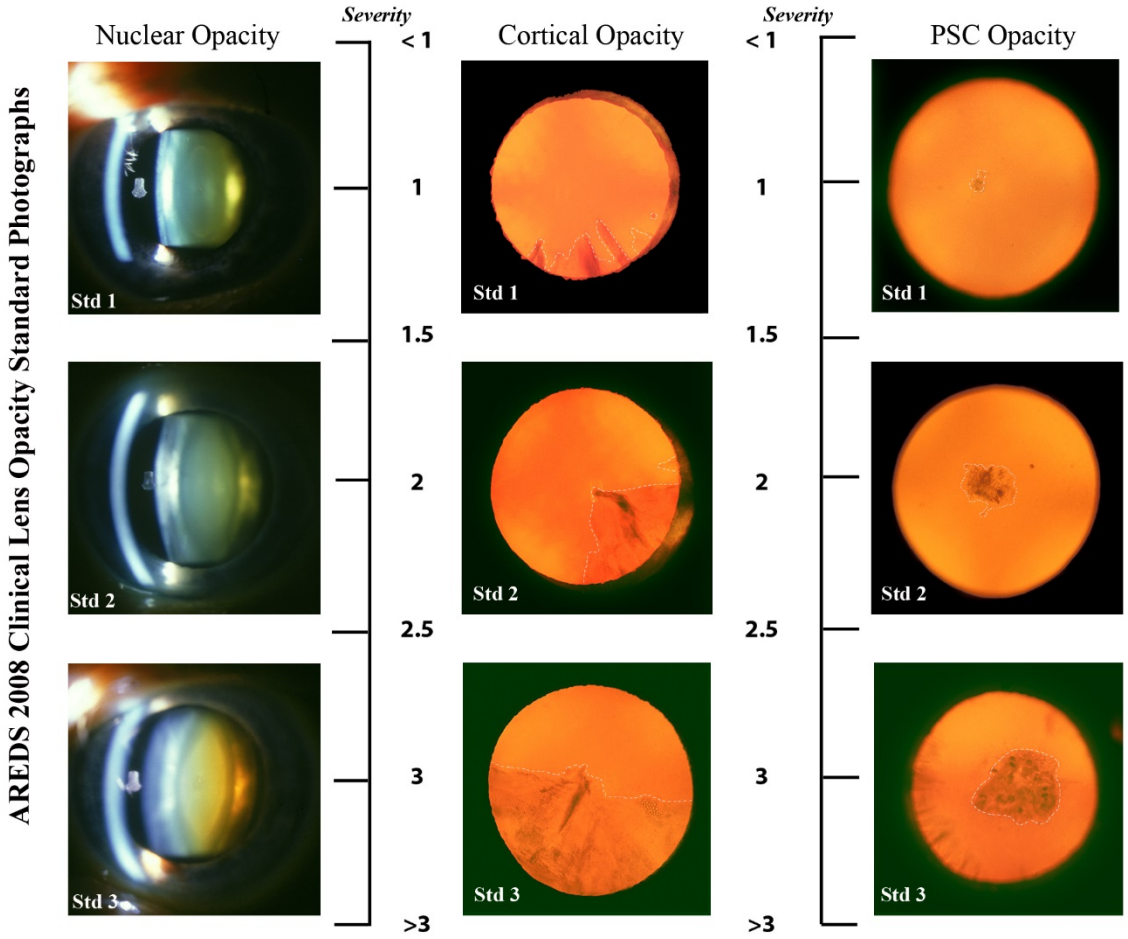
See AREDS 2008 Clinical Lens Opacity Standard Photographs Below

Nuclear Landmarks - In the normal or non-sclerotic lens, the "nucleus" consists of a central dark interval (sulcus), adjacent bean-shaped brighter areas (lentils - 1 anterior and 1 posterior to the sulcus), and brighter curved bands (lamellae or nuclear surface bands). Although nuclear sclerosis Standard 1 shows signs of moderate opalescence, many of these features are visible.

Grading Rules - For grading the severity of nuclear sclerosis, two factors are considered: 1) the optical density (sometimes described as "opalescence") of the nuclear landmarks, especially the sulcus, and 2) the definitions of these structures (contrast between light and dark bands). Optical density is given greater weight. In the early stages of nuclear sclerosis, increased optical density is noticeable only in the normally dark bands, particular the sulcus, but in advanced stages the density of all bands becomes greater. With increasing nuclear sclerosis, the definition of nuclear landmarks decreases, and finally disappears. For grading status, the primary consideration is the degree of reflectance (sometimes termed "opalescence") of the sulcus, with secondary consideration given to the definition of the nuclear features, i.e. contrast of the dark and bright bands.

Slit Lamp Settings - Grading of nuclear opalescence is done with the illuminating beam of the slit lamp angled at 45° to the viewing axis, the slitbeam width set at 0.3 mm ***or a comparable slit lamp width*** and the slitbeam height set at 9 mm.

If you believe the severity of the opacity is between 2 standard photos, estimate the percent of the way between the two standards; e.g., halfway between 1 and 2 would be 1.5. If the severity of the opacity is greater than the last standard, estimate the percent of the way between the last standard and a completely opacified lens, e.g., 3.8 or 3.3.



VITREOUS PATHOLOGY

Vitreous pathology will include an examination of the anterior vitreous that can be visualized with the slit lamp technique. Special notation should be made for hemorrhage, cells, or flare. Each condition is to be noted and graded according to the following scale:

None (Normal) ... **0** Mild .....**+1** Moderate…….....**+2**
Severe .....**+3**

3. INTRAOCULAR PRESSURE MEASUREMENTS

Intraocular pressure will be measured with the aid of a TonoPen™ instrument or Goldmann Tonometer. In either case the intraocular pressure will be recorded in the Case Report forms and the method by which the pressure was obtained will also be recorded.

4. INDIRECT OPHTHALMOSCOPY

Ophthalmoscopy is an examination of the back part of the eyeball (fundus), which includes the retina, optic disc, choroid, and blood vessels.

Indirect ophthalmoscopy and slit-lamp ophthalmoscopy are performed after eye drops are placed to dilate the pupils. Direct ophthalmoscopy can be performed with or without dilation of the pupil.

The examiner performs this examination by holding the eye open. The examiner wears an indirect ophthalmoscope on the head. While holding the eye open each quadrant of the eye will be examined and noted for any pathology utilizing a hand-held lens (preferably 20D). If any pathology is found or suspected in the periphery of the retina a scleral depressed examination will also be performed.

5. DILATED FUNDUS EXAM

All readings will be conducted by the Ophthalmologist at the facility where the study is being conducted.

Pupillary Dilation
It is recommended that all subjects whenever possible be dilated to a minimum of 6 to 8mm. This will allow for better quality imaging and will assist in obtaining high quality stereo images. A proven method is the instillation of 1 drop of 1% Tropicamide (or equivalent) followed by 1 drop of 2.5% Phenylephrine (or equivalent). Subjects with heavily pigmented irises will take longer to achieve full dilation.

6. OPTICAL COHERENCE TOMOGRAPHY (OCT)

Please refer to the device operator's manual and study training manual for complete details on this procedure.

7. MULTI-FOCAL ERG:

Please refer to the device operator's manual and study training manual for complete details on this procedure.

8. FUNDUS PHOTOGRAPHY AND AUTOFLUORESCENCE:

Please refer to the device operator's manual and study training manual for complete details on this procedure.

9. COLOR VISION TEST:

Please refer to the Lanthony D-15 operator's manual and study training manual for complete details on this procedure.

APPENDIX B: SPONSOR'S OBLIGATIONS

Allegro Ophthalmics, LLC is committed to:

1. Complying with the local health authority regulations for the conduct of clinical research studies.
2. Informing the investigator of any new information about the study drug, which may affect the subject's welfare or which may influence the subject's decision to continue participation in the study.
3. Providing to the investigator the most up-to-date editions of the Clinical Investigator's Brochure (for the study medication/products), the protocol, and a full set of Case Report Forms for each subject entered into the study, to document the study evaluation parameters.
4. Providing study medications/products suitably masked/blinded (as applicable), coded and packaged for use with subjects entered into the study.
5. Providing statistical and report writing resources to complete appropriate reporting of study results.
6. Ensuring equity considerations among all investigators in multi center studies, including all matters of publications and meeting presentations, etc.

APPENDIX C: INVESTIGATORS OBLIGATIONS

The Investigator is obligated to:

1. Obtain and submit to the Sponsor a copy of his/her Institutional (Ethical) Review Board's (IRB) approval of the protocol prior to initiating the study.

2. Obtain signed informed consent from each subject or his/her legal guardian, prior to acceptance of the subject into the study, and provide a copy of the signed informed consent to the Sponsor.

3. In the event of a serious, severe or unexpected incident or adverse experience, whether related to the use of the investigational drug or device or not, or the death of a subject, the investigator is responsible for notifying the Sponsor immediately (see Appendix E, Procedures for Handling and Reporting Adverse Reactions).

4. Read, and agree to adhere to the study protocol prior to the initiation of the study. Deviations from the study protocol are not to be implemented without the prior written approval of the Sponsor, unless protection of the safety and welfare of the study subjects requires prompt action. During the study, if the investigator feels that in his/her clinical judgment, it is necessary to promptly terminate one or more subjects from the study, or to promptly implement reasonable alternatives to, or deviations from the protocol in consideration of the safety of study subjects, the Sponsor is to be notified of these terminations, and deviations, and reasons for such changes are to be documented in the study records. The investigator is to also notify any Institutional Review Board to which he/she is responsible of any such changes.

5. Accurately record, at the clinical site, all required data on each subject's Case Report Form. The original Case Report Form will be forwarded to the Sponsor in a manner mutually agreed upon by the investigator and the Sponsor. Copies of the completed Case Report Forms will remain in the investigator's possession. Any change in data made on a Case Report Form by the investigator should be done by marking out the incorrect data with a single line, and dating and initialing the change made, explaining if necessary, without obscuring the original entry. Only Black ink should be used on Case Report Forms and "white-out" is not to be used.

6. Replace subjects who fail to complete the study because they choose to drop out of the investigation, fail to keep their specified appointments, or are discontinued by the investigator for administrative reasons unrelated to the investigational drugs or devices.

7. Keep accurate records of the number of investigational drug or device units received from the Sponsor and dispensed or administered to each subject during the study, and return any unused study drugs or devices to the Sponsor at the completion of the study. Before returning the investigational drugs or devices to the Sponsor, a detailed inventory should be recorded and placed in the investigator's file.

8. Assure that investigational drugs or devices will be dispensed or administered only to subjects under his/her personal supervision, or under the supervision of authorized co-investigators responsible to him/her.

9. Allow a representative of the Sponsor's clinical research team and/or representatives of health regulatory agencies to inspect all Case Report Forms and corresponding portions of each study subject's original office, hospital, and laboratory records at mutually convenient times, at regular intervals during the study, and upon request after the study has been-completed. The purpose of these on-site monitoring visits is to provide the Sponsor the opportunity to evaluate the progress of the study, document compliance with the protocol and with regulatory requirements, verify the accuracy and completeness of subjects' Case Report Forms, resolve any apparent discrepancies or inconsistencies in the study records, and account for all investigational supplies.

10. Provide the Sponsor with a brief (i.e. one to three pages) Investigator's Summary within 90 working days of the study completion.

11. Complete the study within the time limits agreed upon with the Sponsor prior to the initiation of the study. Ensure the accuracy, completeness, legibility and timeliness of the data reported to the sponsor in the case report forms and all required reports.

12. Retain essential documents until at least 2 years after the last approval of a marketing application in the USA and, as applicable, other countries in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product and the appropriate regulatory agencies have been notified. These documents should be retained for a longer period, however, if required by the applicable regulatory bodies, or upon special arrangements with the sponsor. The sponsor will inform the investigator/institution as to when these documents no longer need to be retained.

    If for any reason the investigator withdraws from the responsibility for maintaining the study records, document custody may be transferred to other suitable person or institution, which has the capacity and accept responsibility for safeguarding the records for the remainder of the required time period. The Sponsor is to be notified in writing of any intention to transfer study documentation, at least 30 days before the transfer takes place.

APPENDIX D: WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor, provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

    Whenever the minor child is in fact able to give consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (CLINICAL RESEARCH)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic methods. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (NON-CLINICAL BIOMEDICAL RESEARCH)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers - either healthy persons or subjects for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

APPENDIX E: STUDY MONITORING

1. Member(s) of the Sponsor's clinical research team or designee will meet with the investigator prior to the initiation of the study, to assess the adequacy of the investigator's patient population, facilities, and equipment, and to familiarize the investigator with the protocol.

2. A member of the Sponsor's clinical research team or designee will meet with the investigator after several of the subjects have initiated the study, to ensure that the subjects are being properly selected, that adequate supplies for the study have been provided and that the assignment of medication is properly recorded. In addition, the monitor will verify that the investigator follows the approved protocol and all approved amendments, if any, by reviewing the investigator's regulatory documents, source documents, informed consent forms, and case report forms of study subjects.

3. A member of the Sponsor's clinical research team or designee will meet with the investigator when all subjects have completed the Final Visit of the study, to collect the Case Report Forms, unused drugs, and unused supplies and materials.

4. Interim monitoring visits and telephone consultations will occur as necessary, to ensure the proper progression and documentation of the study.

APPENDIX F: PROTOCOL CHANGES AND PROCEDURES

If the investigator desires to modify the procedure and/or design of the study, he or she must contact and obtain the consent of the Sponsor and, where applicable, local Institutional Review Board, regarding the proposed changes. Any changes to the Study Protocol will only be made in the form of protocol amendments, signed by the Investigator and the authorized Sponsor representative(s), and approved by the Institutional Review Board, prior to their implementation.

APPENDIX G: INSTRUCTIONS FOR COMPLETION OF SOURCE DOCUMENTS AND CASE REPORT FORMS

1. Complete source documents will be supplied to the study sites. The source documents should be filled out using a black ink ball-point pen.

2. At each subject visit, the appropriate source document must be completed. The data will be entered into the CRF. Be sure to provide all information requested including subject identification number and initials, name of investigator, date(s), etc. All applicable questions should be answered and all data requested should be supplied. Those areas, which require a response but are not filled in correctly are considered incomplete or erroneous entries, and will have to be corrected. Supplying all the necessary data the first time saves office time for the investigator during subsequent audits and monitoring visits.

3. If the investigator needs to correct an erroneous entry on the source documents, the only acceptable procedure is to draw a single horizontal line through the incorrect entry, enter the correct data next to it, then initial and date the new entry, explain if necessary, without obscuring the original entry. Even if the correction is made on the same date as at the top of the form, the date must still be supplied next to the correction, since there is no other way of identifying when the correction was made. Correction fluid ("Whiteout"), eraser, or any other correction methods that would obscure the original entry are NOT allowed.

4. All medications used should be recorded on the Concomitant Medication form, with the appropriate start and stop date as applicable.

5. All Adverse Events should be recorded on the Adverse Event form with appropriate event name, start and stop dates, relation to study drug, intensity, and outcome.

6. The completed source documents are to be reviewed and signed by the Principal Investigator or designee.