ALLEGRO OPHTHALMICS, LLC
PROTOCOL DME 202B (Version 2.66)

A PHASE 2 MULTICENTER, RANDOMIZED, CONTROLLED, DOUBLE-MASKED CLINICAL TRIAL DESIGNED TO EVALUATE THE SAFETY AND EXPLORATORY EFFICACY OF LUMINATE® (ALG-1001) AS COMPARED TO AVASTIN® IN THE TREATMENT OF DIABETIC MACULAR EDEMA

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IND : 119548

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Signature Page for Investigator:

Product: LUMINATE® (ALG-1001)

Study No: DME-202B (Version 2.66)

Title:

A PHASE 2 MULTICENTER, RANDOMIZED, CONTROLLED, DOUBLE-MASKED CLINICAL TRIAL DESIGNED TO EVALUATE THE SAFETY AND EXPLORATORY EFFICACY OF LUMINATE® (ALG-1001) AS COMPARED TO AVASTIN® IN THE TREATMENT OF DIABETIC MACULAR EDEMA

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	Signature	Date

[PRINT IN BLOCK CAPITAL LETTERS]

Institution Name and Address

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LIST OF ABBREVIATIONS

ACD	Anterior Chamber Depth
AE	Adverse Event
Allegro	Allegro Ophthalmics, LLC
BCVA	Best Corrected Visual Acuity
CRA	Clinical Research Associate
CRF	Case Report Form
EC	Ethics Committee
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
SAE	Serious Adverse Event
SC	Study Coordinator
SOP	Standard Operating Procedure
USP	United States Pharmacopeia

PROTOCOL SYNOPSIS

Study Title:	A Phase 2 Randomized, Controlled, Double-Masked, Multicenter Clinical trial Designed to Evaluate the Safety and Exploratory Efficacy of Luminate® (ALG-1001) as Compared to Avastin® in the Treatment of Diabetic Macular Edema (DME)
Study Objectives:	This 2-stage study will evaluate the safety and efficacy of Luminate® (ALG-1001) as compared to Avastin® in patients with centrally-involved DME
Study Design:	**Stage 1:** 120 eligible subjects with DME will be enrolled and randomized to one of 4 treatment groups at an allocation ratio of 1:1:1:1, i.e., one of three doses of Luminate intravitreal injection or Avastin intravitreal injection. Subjects will be followed monthly for 24 weeks (6 months). **Stage 2 (select sites):** 75 eligible subjects with DME will be enrolled and randomized to one of 5 treatment groups at an allocation ratio of 1:1:1:1:1. Subjects will be followed monthly for 20 weeks (5 months). The treatment groups are as follows for Stage 2: Group 1 — Week 0 (Baseline): Avastin 1.25 mg IVT Weeks 1, 4 and 8: Luminate 1.0 mg IVT + sham injection Weeks 12 and 16: Sham IVT Group 2 — Week 0 (Baseline); Avastin 1.25 mg IVT Weeks 1, 4 and 8: Luminate 0.5 mg IVT + sham injection Weeks 12 and 16: Sham IVT Group 3 — Week 0 (Baseline): Sham IVT Weeks 1, 4 and 8: Luminate 1.0 mg + Avastin 1.25 mg IVT Weeks 12 and 16: Sham IVT Group 4 — Week 0: Sham IVT Weeks 1, 4 and 8: Luminate 0.5 mg IVT + Avastin 1.25 mg IVT Weeks 12 and 16: Sham IVT Group 5 — Week 0 (Baseline): Sham IVT Weeks 1, 4 and 8: Avastin 1.25 mg + Sham IVT Weeks 12 and 16: Avastin PRN
Investigational Drug:	**Stage 1:** 1.0, 2.0, and 3.0 mg Luminate® solution for intravitreal injection in 0.1cc isotonic saline solution **Stage 2:** 0.5 and 1.0 mg Luminate® solution for intravitreal injection in 0.05cc isotonic saline solution
Control:	1.25 mg Avastin® intravitreal injection

Key Inclusion Criteria:	**Key General Inclusion Criteria:** 1. Male or female, 18 years of age or older 2. Prior diagnosis of diabetes mellitus (Type 1 or 2) **Key Ocular Inclusion Criteria (Study Eye):** 3. Decreased vision due to DME involving central foveal subfield, which is defined as the central 1000 μm from the center of fovea, at screening 4. Best-corrected visual acuity (BCVA) ≤ 73 and ≥ 24 (20/40 to 20/320 Snellen equivalent, respectively) at screening and baseline (prior to treatment), as assessed by the investigator 5. Central retinal thickness (CRT) ≥ 350 μm on spectral-domain optical coherence tomography (SD-OCT) at screening and baseline (prior to treatment), as assessed by the investigator and confirmed by central reading center (CRC) 6. In the investigator's opinion, the patient still has significant intraretinal fluid with room for improvement in both macular edema and BCVA 7. Intraocular pressure (IOP) is under control (i.e., IOP ≤ 25 mmHg)

Key Exclusion Criteria:	**Key General Exclusion Criteria:** 1. Uncontrolled diabetes mellitus as evidenced by a hemoglobin A1c (HbA1c) value > 10% within 3 months of screening visit 2. Uncontrolled blood pressure at screening, as assessed by the investigator 3. 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 4. Participation in any investigational drug (within 60 days) or device study (within 30 days) prior to baseline **Key Ocular Exclusion Criteria (Study Eye):** 5. Treatment with an ocular anti-VEGF medication (eg, pegaptanib sodium, bevacizumab, ranibizumab, aflibercept) within 45 days of baseline 6. Treatment with ocular steroid injections or implants, whether by subconjunctival, periocular, or intravitreal route of administration within 6 months prior to baseline or fluocinolone acetonide implant (Iluvien®) within 36 months prior to baseline 7. Panretinal or macular laser photocoagulation within 3 months prior to baseline 8. Active proliferative diabetic retinopathy (PDR) such as NVE, NVD, vitreous hemorrhage, or neovascular glaucoma 9. Current evidence of retinal detachment as assessed by the investigator to significantly affect central vision prior to baseline

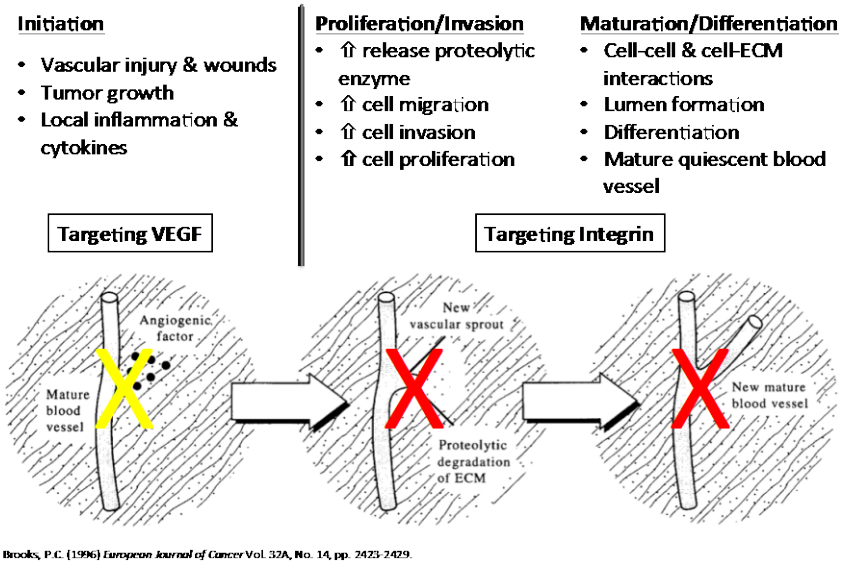
	10. Vitreomacular adhesion/traction or epiretinal membrane evident by ophthalmoscopy and/or by spectral-domain optical coherence tomography (SD-OCT) examinations at screening, as assessed by the investigator to significantly affect central vision and confirmed by central reading center 11. History or evidence of the following procedures at any time unless specified: • vitrectomy • macular surgery • incisional glaucoma surgery • cataract or refractive surgery within 3 months prior to baseline 12. YAG laser treatment in last 30 days prior to study enrollment 13. A history of cataract surgery complications/vitreous loss 14. Congenital eye malformations 15. A history of penetrating ocular trauma 16. High myopia, with a spherical equivalent of > - 8.00D at screening 17. Other ocular pathologies that in the investigator's opinion, would interfere with the subject's central vision **Ocular Exclusion Criterion (Either Eye):** 18. Active ocular/intraocular infection or inflammation at baseline 19. History of recurrent or active uveitis
Study Outcomes	**Efficacy** The efficacy outcomes are BCVA and CRT as assessed with SD-OCT (quantified by the CRC) , as defined in the Study Analysis Plan (SAP). **Safety** Safety parameters to be evaluated include adverse events, BCVA, slit-lamp biomicroscopy, ophthalmoscopy, fundus photography, and post-injection evaluations through the course of this study.
Statistical Methods	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 comparisons that may warrant further consideration.

A PHASE 2 MULTICENTER, RANDOMIZED, CONTROLLED, DOUBLE-MASKED CLINICAL TRIAL DESIGNED TO EVALUATE THE SAFETY AND EXPLORATORY EFFICACYOF LUMINATE® (ALG-1001) AS COMPARED TO AVASTIN® IN THE TREATMENT OF DIABETIC MACULAR EDEMA

1. 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).

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**, targeting integrin works against proliferation and invasion, as well as maturation and differentiation (Brooks et. al., 1996).



1. Brooks, P.C. (1996) *European Journal of Cancer* Vol. 32A, No. 14, pp. 2423-2429.

FIGURE 1
THE ANGIOGENIC CASCADE: TARGETING VEGF VS. INTEGRIN

Allegro has developed an anti-integrin oligopeptide Luminate® as a first in class therapeutic for vascular eye diseases, including wet age-related macular degeneration (Wet AMD), diabetic macular edema (DME) and focal symptomatic vitreomacular traction (VMA). Specifically, Allegro has discovered a peptide sequence, in either linear or cyclic form, that effectively binds to $\alpha_5\beta_1$, $\alpha_v\beta_3$ 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.

DME is the leading cause of blindness in the working age population (www.diabetes.org). In the United States, 10.2 million people over age 40 have been diagnosed with diabetes (www.diabetes.org), of which 4.1 million have some form of diabetic retinopathy (DR). Further, the prevalence of DME in the U.S. approaches 30% in adults who have had diabetes for 20 years or more (Klein et. al., 1984).

DME is the result of thickening of the center part of the retina due to damage of retinal capillaries from diabetes. Application of laser to damaged capillaries within thickened retina has been the mainstay of treatment for over 25 years (EDTRS Study Group, 1985; AAO 2009). Recent results from the Diabetic Retinopathy Clinical Research Network demonstrated that in eyes with reduced visual acuity from DME involving the center of the macula, anti-VEGF therapy with Lucentis in combination with focal/grid laser provides superior vision outcomes and an acceptable safety profile compared with the previous standard treatment of laser (ETDRS Research Group, 1985).

Luminate® solution for intravitreal injection approaches DME by collectively suppressing the production of aberrant blood vessels; reducing the leakage of aberrant blood vessels; and inhibiting the growth of aberrant blood vessels. The most common treatment for DME is currently ranibizumab (Lucentis®), aflibercept (Eylea®) and bevacizumab (Avastin®). All three of these options are anti-VEGF treatments, and are very large antibodies from 20KD to 150KD in size that bind to VEGF receptors. These antibodies must be administered at four to six week intervals for Avastin® and Lucentis® and every eight weeks for Eylea® at substantial inconvenience, cost, and cumulative risk of infection.
The use of Luminate® solution for intravitreal injection has the potential to be both an effective stand-alone product as well as complementary to existing anti-VEGF treatments based on its unique mechanism of action and potentially longer duration of treatment effect as suggested in Phase 1 DME and wet AMD studies.

The purpose of this study is to explore the safety and efficacy of 3 doses of Luminate® in a DME population, as compared to treatment with Avastin.

2. STUDY OBJECTIVE

The objective of this study is to evaluate the safety and efficacy of 4 doses of Luminate in a population of patients with active DME, and to compare the outcomes of Luminate treatment with Avastin treatment.

3. STUDY DESIGN

This is a 2-stage, prospective, randomized, double-masked multicenter, Phase II clinical trial:

Stage 1: One-hundred twenty (120) eligible subjects with active DME will be randomized to one of four treatment groups in a 1:1:1:1 ratio. This includes 3 Luminate treatment groups (1.0 mg, 2.0 mg or 3.0 mg), and an Avastin® group. An active focal laser group was also present in previous versions of this protocol which has since been removed. At the time that this laser group was actively included in randomization, the randomization design had been a 1:1:1:1:1 ratio.

In addition to the study treatment (Luminate or Avastin with the treatments and schedules defined below), during the course of follow-up, prn retreatment will be allowed for any subject with central subfield thickness ≥ 350 μm on SD-OCT exam based on review of the OCT images by the central reading center. Retreatment will be performed using the originally assigned treatment, i.e., Luminate with Luminate and Avastin with Avastin.

Stage 2 (select sites): Seventy five (75) eligible subjects with active DME will be randomized to one of five treatment groups in a 1:1:1:1:1 ratio. These treatment groups consist of 2 Luminate treatment groups (0.5 mg and 1.0 mg), 2 Luminate and Avastin adjunctive treatment groups, and an Avastin® (1.25 mg) group. The Luminate monotherapy arms will also include an Avastin intravitreal injection at Week 0 (Baseline).

In addition to the study treatment, during the course of follow-up for Stage 2, prn Avastin retreatment will be allowed, at Week 12 and Week 16, in the Avastin monotherapy arm for any subject with central subfield thickness ≥ 350 μm on SD-OCT exam based on review of the OCT images by the central reading center.

Rescue treatment can be administered to any study subject who experiences a significant decrease in BCVA, as defined below:

- BCVA loss of > 15 letters from baseline regardless of OCT finding.

  OR

- BCVA loss of > 10 letters from the prior study visit accompanied by an increase in OCT central retinal thickness of > 100 μm as compared to the previous study visit based on the investigator's judgment.

If one of the above criteria is met, rescue treatment may be administered at the discretion of the unmasked investigator but should not involve unmasking the subject or any additional staff.

If a subject meets one of the above criteria and has not received the assigned study treatment in several weeks, Allegro recommends that the first option to be considered by the unmasked investigator for rescue is the originally assigned study treatment. Avastin rescue is another option.

Any subject who receives rescue treatment will continue to be followed for 4 weeks after the rescue therapy for safety evaluations and then will early exit the study after completing exist visit procedures per the protocol.

STAGE 1:

The treatment groups are as follows for stage 1:

Group 1 Luminate 1.0 mg intravitreal injection administered at baseline (Day 0), weeks 4 and 8 with prn Luminate injection at week 20 for a total of at least 3 and no more than 4 Luminate injections. Sham injections will be performed at weeks 12 and 16 and may also be performed at week 20 if prn Luminate is not required.

Group 2 Luminate 2.0 mg intravitreal injection administered at baseline (Day 0), weeks 4 and 8 with prn Luminate injection at week 20 for a total of at least 3 and no more than 4 Luminate injections. Sham injections will be performed at weeks 12 and 16 and may also be performed at week 20 if prn Luminate is not required.

Group 3 Luminate 3.0 mg intravitreal injection administered at baseline (Day 0), weeks 4 and 8 with prn Luminate injection at week 20 for a total of at least 3 and no more than 4 Luminate injections. Sham injections will be performed at weeks 12 and 16 and may also be performed at week 20 if prn Luminate is not required.

Group 4 Avastin 1.25 mg intravitreal injection administered at baseline (Day 0), weeks 4 and 8 with prn Avastin injection at weeks 12, 16, or 20 for a total of at least 3 and up to 6 Avastin injections. Sham injections may be performed at weeks 12, 16, and 20 if prn Avastin is not required.

An active focal laser arm was also present in previous versions of this protocol which has since been removed. Any patients enrolled into the active laser group prior to approval of protocol amendment 2.64 will remain in that group and follow that applicable treatment schedule accordingly. A table showing the four treatment arms and visits is provided below, with the treatments to be administered at each visit.

STAGE 1 Study Visits and Treatments Administered

	Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Groups 1, 2 & 3							
Luminate	✓	✓	✓	-	-	✓prn or sham	-
Sham Injection	-	-	-	✓	✓		-
Group 4							-
Avastin	✓	✓	✓	✓ prn or sham	✓ prn or sham	✓ prn or sham	-
Sham Injection	-	-	-				-

✓ = study treatment
✓ prn = treatment as needed or sham if no active treatment needed per central reading center

All study subjects will be masked to the treatment assignment. Additionally, at each clinical site, masked examiners will perform ocular examinations as well as IOP, BCVA, OCT, FA and fundus photography assessments.

Potential study participants will be asked to sign an informed consent document prior to screening. Screening will be conducted from -20 days to -3 days prior to randomization and treatment during Week 0. This timing is intended to allow OCT images to be reviewed by the central reading center for a determination of eligibility based on CRT ≥ 350 µm. Subjects will be randomized to one of the four treatment groups once the OCT images have been reviewed and the required CRT cut-off being verified by the central reading center.

All study subjects will return for examination every 4 weeks through week-24 (6 months). The visits and parameters to be evaluated at each study visit are displayed in Table 2.1.

The safety and efficacy of 3 doses of Luminate will be evaluated over the course of the 24-week stage. Since this is Phase 2 clinical trial, no formal hypothesis testing is planned; descriptive statistics will be used to summarize the study outcomes.

STAGE 2:

The treatment groups are as follows for stage 2:

Group 1 Week 0 (Baseline): Avastin 1.25 mg IVT
Weeks 1, 4, and 8: Luminate 1.0 mg IVT + sham injection (~30-60 minutes apart)
Weeks 12 and 16: Sham IVT

Group 2 Week 0 (Baseline); Avastin 1.25 mg IVT
Weeks 1, 4, and 8: Luminate 0.5 mg IVT + sham injection (~30-60 minutes apart)
Weeks 12 and 16: Sham IVT

Group 3 Week 0 (Baseline): Sham IVT
Weeks 1, 4 and 8: Luminate 1.0 mg + Avastin 1.25 mg IVT (~30-60 minutes apart)
Weeks 12 and 16: Sham IVT

Group 4 Week 0: Sham IVT
Weeks 1, 4, and 8: Luminate 0.5 mg IVT + Avastin 1.25 mg IVT (~30-60 minutes apart)
Weeks 12 and 16: Sham IVT

Group 5 Week 0 (Baseline): Sham IVT
Weeks 1, 4, and 8: Avastin 1.25 mg + Sham IVT (~30-60 minutes apart)
Weeks 12 and 16: Avastin PRN

STAGE 2 Study Visits and Treatments Administered

	Week 0 (Baseline)	Week 1	Week 4	Week 8	Week 12	Week 16	Week 20
Groups 1							
Luminate 1.0 mg IVT	-	✓	✓	✓	-	-	-
Avastin 1.25 mg IVT	✓	-	-	-	-	-	-
Sham IVT	-	✓	✓	✓	✓	✓	-
Group 2							
Luminate 0.5 mg IVT	-	✓	✓	✓	-	-	-
Avastin 1.25 mg IVT	✓	-	-	-	-	-	-
Sham IVT	-	✓	✓	✓	✓	✓	-

Groups 3							
Luminate 1.0 mg IVT	-	✓	✓	✓	-	-	-
Avastin 1.25 IVT	-	✓	✓	✓	-	-	-
Sham IVT	✓	-	-	-	✓	✓	-
Group 4							
Luminate 0.5 mg IVT	-	✓	✓	✓	-	-	-
Avastin 1.25 mg IVT	-	✓	✓	✓	-	-	-
Sham IVT	✓	-	-	-	✓	✓	-
Group 5							
Avastin 1.25 mg or prn IVT	-	✓	✓	✓	✓ prn or sham	✓ prn or sham	-
Sham IVT	✓	✓	✓	✓			-

✓ = study treatment
✓ prn = treatment as needed or sham if no active treatment needed per central reading center

All study subjects will be masked to the treatment assignment. Additionally, at each clinical site, masked examiners will perform ocular examinations as well as IOP, BCVA, OCT, FA and fundus photography assessments.

Potential study participants will be asked to sign an informed consent document prior to screening. Screening will be conducted from -20 days to -3 days prior to randomization and treatment during Week 0. This timing is intended to allow OCT images to be reviewed by the central reading center for a determination of eligibility based on CRT ≥ 350 µm. Subjects will be randomized to one of the five treatment groups once the OCT images have been reviewed and the required CRT cut-off being verified by the central reading center.

All study subjects will return for examination 1 week after baseline then every 4 weeks through week 20 (5 months). The visits and parameters to be evaluated at each study visit are displayed in Table 2.2.

The safety and efficacy of study treatments will be evaluated over the course of the 20-week study. Since this is a Phase 2 clinical trial, no formal hypothesis testing is planned; descriptive statistics will be used to summarize the study outcomes.

4. STUDY OUTCOMES

4.1 EFFICACY

The efficacy outcomes are change in BCVA and CRT as assessed with SD-OCT (quantified by the CRC), as defined in the Study Analysis Plan (SAP).

4.2 Safety

Safety parameters to be evaluated include BCVA, slit-lamp biomicroscopy, ophthalmoscopy, fundus photography, post-injection evaluations, and adverse events through the study.

5. STUDY POPULATION

Up to 195 eligible subjects (includes stage 1 and 2) with centrally-involved DME who meet the protocol inclusion and exclusion criteria will be enrolled into the study.

5.1 INCLUSION CRITERIA

General Inclusion Criteria:

1. Male or female, 18 years of age or older
2. Prior diagnosis of diabetes mellitus (Type 1 or 2)
3. Patient has completed/signed an informed consent prior to any study-related procedures and examinations and is able to follow study instructions and likely to complete all required visits
4. Patient has provided, at screening, written documentation in accordance with the relevant local privacy requirements (eg, Written Authorization for Use and Release of Health and Research Study Information and written Data Protection consent, as required by regional health authorities)
5. Willing and able to return for all study visits

Ocular Inclusion Criteria (Study Eye):

6. Decreased vision due to DME involving central foveal subfield, which is defined as the central 1000 μm from the center of fovea, at screening
7. Best-corrected visual acuity (BCVA) ≤ 73 and ≥ 24 (20/40 to 20/320 Snellen equivalent, respectively) at screening and baseline (prior to treatment), as assessed by the investigator
8. Central retinal thickness (CRT) ≥ 350 μm on spectral-domain optical coherence tomography (SD-OCT) at screening and baseline (prior to treatment), as assessed by the investigator and confirmed by central reading center (CRC)
9. In the investigator's opinion, the study eye still has significant intraretinal fluid with room for improvement in both macular edema and BCVA
10. Intraocular pressure (IOP) is under control (i.e., IOP ≤ 25 mmHg in the study eye)

5.2 EXCLUSION CRITERIA

General Exclusion Criteria:

11. Uncontrolled diabetes mellitus as evidenced by a hemoglobin A1c (HbA1c) value > 10% within 3 months of screening visit
12. Uncontrolled blood pressure at screening, as assessed by the investigator

13. 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
14. Participation in any investigational drug (within 60 days) or device study (within 30 days) prior to baseline
15. History or current evidence of a medical condition (systemic or ophthalmic disease, metabolic dysfunction, physical examination finding or clinical laboratory finding) that may in the opinion of the investigator preclude the safe administration of study drug, adherence to the scheduled study visits, safe participation in the study or affect the results of the study (eg, autoimmune disease, advanced coronary artery disease, or cerebral vascular disease, other unstable or progressive worsening of a cardiovascular or pulmonary condition, Parkinson's disease, liver failure, cancer, or dementia)
16. History or current evidence of hypersensitivity to any components of the study drug or clinically relevant sensitivity to fluorescein dye or iodine, as assessed by the investigator

Ocular Exclusion Criteria (Study Eye):

17. Treatment with an ocular anti-VEGF medication (eg, pegaptanib sodium, bevacizumab, ranibizumab, aflibercept) within 45 days of baseline
18. Treatment with ocular steroid injections or implants, whether by subconjunctival, periocular, or intravitreal route of administration within 6 months prior to baseline or fluocinolone acetonide implant (Iluvien®) within 36 months prior to baseline
19. Panretinal or macular laser photocoagulation within 3 months prior to baseline
20. Active proliferative diabetic retinopathy (PDR) such as NVE, NVD, vitreous hemorrhage, or neovascular glaucoma
21. Current evidence of retinal detachment as assessed by the investigator to significantly affect central vision prior to baseline
22. Vitreomacular adhesion/traction or epiretinal membrane evident by ophthalmoscopy and/or by spectral-domain optical coherence tomography (SD-OCT) examinations at screening, as assessed by the investigator to significantly affect central vision and confirmed by central reading center
23. History or evidence of the following procedures at any time unless specified:
    - vitrectomy
    - macular surgery
    - incisional glaucoma surgery
    - cataract or refractive surgery within 3 months prior to baseline
24. YAG laser treatment in last 30 days prior to study enrollment

25. A history of cataract surgery complications/vitreous loss
26. Congenital eye malformations
27. A history of penetrating ocular trauma
28. High myopia, with a spherical equivalent of >- 8.00D at screening
29. Other ocular pathologies that in the investigator's opinion, would interfere with the subject's central vision.

Ocular Exclusion Criterion (Either Eye):

30. Active ocular/intraocular infection or inflammation at baseline
31. History of recurrent or active uveitis

6. 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 18 to 60, negative urine pregnancy test at screening
4. Demographic information
5. Medical/Ophthalmic History
6. A screening HbA1c blood test or results within the last 3 months of screening visit
7. List of concomitant medications
8. Refraction with ETDRS BCVA at 4/1 meters in the study eye
9. Afferent Pupillary Defect Assessment
10. Slit-lamp biomicroscopy
11. IOP
12. Indirect ophthalmoloscopy/ dilated fundus exam
13. Fundus photography
14. Spectral-domain OCT with appropriate cuts for respective machine
15. Fluorescein angiography
16. B-scan ultrasound (for participating sites in Stage 1)
17. Prophylactic antibiotic drops (when applicable)

Subjects will be cleared for enrollment by the OCT reading center, which will verify that the OCT meets the inclusion/exclusion criteria of ≥ 350 μm.

Once all of the study requirements for enrollment are satisfied, all screening documents must be forwarded to the Sponsor via the CRO 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 -20 to -3 days prior to enrollment/injection to allow 3 days of pre-injection antibiotics.

6.2 SUBJECT ENROLLMENT

Upon enrollment in the study, the study subject will be randomly assigned to one of the treatment groups, i.e., one of 3 doses of Luminate or Avastin for stage 1 or one of 2 doses of Luminate in conjunction with Avastin for stage 2.

All study subjects will be masked to the treatment assignment. Additionally, at each clinical site, masked examiners will perform ocular examinations as well as IOP, BCVA, OCT, FA, and fundus photography assessments.

6.3 INVESTIGATIONAL MATERIALS

The investigational materials will be labeled by Allegro Ophthalmics, LLC, in a manner consistent with the study design. 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.

The investigator or a qualified designee will be responsible for keeping current and accurate records of the amount of drug received, dispensed, and returned to the study site. During the course of 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 in order 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

The study drug is supplied in a 0.30 mL conical-shaped glass vial as a sterile liquid product ready for injection. Prior to the injection, the unmasked 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 Preparation – Avastin

Avastin® for intravitreal injection is supplied in a 1.0mL tuberculin syringe as a sterile liquid product ready for injection. Prior to the injection, the unmasked investigator should confirm the syringe volume and that the syringe to be used matches the randomization number specifically assigned to the particular study subject.

6.4.3 Intravitreal Injection Procedure

With the exception of the IOP lowering drops pre-injection and cotton swab tamponade post-injection, which are required, the rest of the below injection and post-injection procedures 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 brimonidine or similar IOP lowering agent 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. Expel excess drug to 0.1 mL.
- 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 RETREATMENT CRITERIA

During the course of follow-up, retreatment will be allowed for any subject with central subfield thickness ≥ 350 μm on OCT based on review of the OCT images by the central reading center. Study subjects will be retreated at the study visits outlined in Section 3 Study Design with their respective assigned group (i.e., Luminate with Luminate or Avastin with Avastin).

6.6 RESCUE CRITERIA

At study Weeks 4, 8, 12, 16, and 20 (for Stage 1 ONLY) rescue treatment is available for all groups should there be a significant decrease in BCVA.

Rescue is to be implemented at the discretion of the principal investigator when:

- BCVA loss of > 15 letters from baseline regardless of OCT finding.

  OR

- BCVA loss of > 10 letters from the prior study visit accompanied by an increase in OCT central retinal thickness of > 100 μm as compared to the previous study visit based on the investigator's judgment

If one of the above criteria is met, rescue treatment may be given at the discretion of the unmasked Investigator but should not involve unmasking the subject or any additional staff.

If a subject meets one of the above rescue criteria and has not received the assigned study treatment in several weeks, Allegro recommends that the first option to be considered by the unmasked investigator for rescue is the originally assigned study treatment,

Avastin rescue is another option, however since Avastin is a final option, any other necessary intervention to stabilize the subject should be considered.

Any subject who receives rescue treatment will continue to be followed for 4 weeks after the rescue therapy for safety evaluations and then will early exit the study after completing exist visit procedures per the protocol.

6.7 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.

Clinical sites using antibiotic eye drops will call study subjects three days prior to possible retreatment by intravitreal injection on week 4 and week 8 and instruct them to restart their antibiotic drops in anticipation of an 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 electronic case report form (eCRF). Any intravitreal injections in the study eye must be cleared by the Sponsor prior to administration.

Any intravitreal injections of anti-VEGF agents or intravitreal steroids IN THE NON-STUDY EYE must be administered at least 1 week and preferably 2 weeks after the STUDY EYE treatment or prior to the next scheduled study visit for the STUDY EYE.

7 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 as further detailed in Tables 2.1 and 2.2 and shown below:

- Inclusion/Exclusion criteria
- Demographics
- Medical and ophthalmic history
- List of current medications
- Baseline negative urine pregnancy test during the screening window if female between 18 to 60 years of age.
- Slit-lamp biomicroscopy
- Refraction
- Best-corrected visual acuity determination
- Intraocular pressure (IOP)
- Indirect ophthalmoscopy/Dilated fundus exam
- Spectral-Domain OCT
- APD
- Fluorescein Angiography
- B-scan ultrasound for PVD (sub-study only done for a portion of the study sites/ subjects in stage 1)
- HbA1c

Both eyes will be examined at the screening/baseline visit. Beginning the day of the first injection, only the study eye will be assessed. **In subjects where both eyes qualify for enrollment, the eye with the worse BCVA should be enrolled.** Subjects will return for study visits and be examined as detailed in this section of the protocol.

The treatment window from the Screening visit to the Baseline Visit / Drug injection is 20 days. During this 20-day window screening OCTs must be submitted and the subject deemed eligible by the OCT reading center prior to enrollment. Once the subject is deemed eligible by the OCT reading center the subject's screening documents must be submitted to the sponsor and approved by the sponsor/CRO prior to drug administration.

7.1 STAGE 1 VISIT SCHEDULE

7.1.1 VISIT 0 - SCREENING VISIT (-20 TO -3 DAYS)

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:

1. Inclusion/Exclusion Criteria
2. Demographics
3. Medical and Ophthalmic History
4. List of Current Medications
5. Refraction and Best-Corrected Visual Acuity
6. Afferent Pupillary Defect
7. Slit-Lamp Biomicroscopy
8. Tonometry (IOP) (applanation or tonopen)
9. Indirect Ophthalmoscopy/Dilated Fundus Examination
10. Fundus Photography
11. Spectral-Domain OCT
12. Fluorescein Angiography
13. B-scan ultrasound for PVD (for applicable sites)
14. HbA1c
15. If patient is a female between 18 to 60 years old, needs a negative pregnancy test during the screening window
16. Dispense prophylactic antibiotic medication at investigator discretion

7.1.2 VISIT 1 – WEEK 0 AND DAY OF INJECTION/TREATMENT

When the subject arrives for the baseline visit on the day of first injection, the following procedures will be performed:

1. List of Current Medications
2. Refraction and Best-Corrected Visual Acuity
3. Afferent Pupillary Defect
4. Slit Lamp Biomicroscopy
5. Tonometry (IOP) (applanation or tonopen)
6. Indirect Ophthalmoscopy/Dilated Fundus Examination
7. Spectral-Domain OCT
8. Assess adverse events
9. Intravitreal injection
10. Dispense/continue prophylactic antibiotic medication at investigator discretion

7.1.3 VISIT 2 - STUDY WEEK 4 (± 3 DAYS)

When the subject returns for the 4-week post injection visit, the following procedures will be performed within the visit window:

1. List of Current Medications
2. Refraction and Best-Corrected Visual Acuity
3. Slit-Lamp Biomicroscopy
4. Tonometry (IOP) (applanation or tonopen)
5. Indirect Ophthalmoscopy/Dilated Fundus Examination
6. Spectral-Domain OCT
7. B-scan ultrasound for PVD (for applicable sites)
8. Assess adverse events
9. Dispense/continue prophylactic antibiotic medication at investigator discretion
10. Intravitreal injection

7.1.4 VISIT 3 - STUDY WEEK 8 (± 3 DAYS)

When the subject returns for the 8-week post injection visit, the following procedures will be performed within the visit window:

1. List of Current Medications
2. Refraction and Best-Corrected Visual Acuity
3. Slit-Lamp Biomicroscopy
4. Tonometry (IOP) (applanation or tonopen)
5. Indirect Ophthalmoscopy/Dilated Fundus Examination
6. Spectral-Domain OCT
7. B-scan ultrasound for PVD (for applicable sites)
8. Assess adverse events
9. Dispense/continue prophylactic antibiotic medication at investigator discretion
10. Intravitreal injection

7.1.5 VISIT 4 - STUDY WEEK 12 (± 3 DAYS)

When the subject returns for the 12-week post injection visit, the following procedures will be performed:

1. List of Current Medications
2. Refraction and Best-Corrected Visual Acuity
3. Afferent Pupillary Defect
4. Slit-Lamp Biomicroscopy
5. Tonometry (IOP) (applanation or tonopen)
6. Indirect Ophthalmoscopy/Dilated Fundus Examination
7. Fundus Photography
8. Spectral-Domain OCT
9. Fluorescein Angiography
10. B-scan ultrasound for PVD (for applicable sites)
11. Assess adverse events
12. Dispense/continue prophylactic antibiotic medication at discretion

The procedural assessments (other than OCT) required at Visit 4 may be performed at the Retreatment Visit 4.1 as long as the visit window is followed appropriately per the protocol (-3 to +5 days) and OCT results have been received from Duke Reading Center prior to patient retreatment.

7.1.6 VISIT 4.1 - STUDY WEEK 12 (0 TO +5 DAYS)

All study subjects will return for this retreatment visit. Prior to visit 4.1, the OCT CRT result from Visit 4 is determined by the central reading center, who will notify the sites regarding whether or not the result is ≥ 350 µm. This will allow the site to determine which treatment, per the treatment table on page 14 of the protocol, is to be administered at Visit 4.1. All study subjects will receive some form of treatment at this visit (either active or sham treatment).

7.1.7 VISIT 5 - STUDY WEEK 16 (± 3 DAYS)

When the subject returns for the 16-week post injection visit, the following procedures will be performed:

1. List of Current Medications
2. Refraction and Best-Corrected Visual Acuity
3. Slit-Lamp Biomicroscopy
4. Tonometry (IOP) (applanation or tonopen)
5. Indirect Ophthalmoscopy/Dilated Fundus Examination
6. Spectral-Domain OCT
7. Assess adverse events
8. Dispense/continue prophylactic antibiotic medication at discretion

The procedural assessments (other than OCT) required in Visit 5 may be performed at the Retreatment Visit 5.1 as long as the visit window is followed appropriately per the protocol (-3 to +5 days) and OCT results have been received from Duke Reading Center prior to patient retreatment.

7.1.8 VISIT 5.1 - STUDY WEEK 16 (0 TO +5 DAYS)

All study subjects will return for this retreatment visit. Prior to visit 5.1, the OCT CRT result from Visit 5 is determined by the OCT reading center, who will notify the sites whether or not the result is ≥ 350 µm. This will allow the site to determine which treatment, per the treatment table on page 14 of the protocol, is to be administered at Visit 5.1. All study subjects will receive some form of treatment at this visit (either active or sham treatment).

7.1.9 VISIT 6 - Study Week 20 (± 3 days)

1. List of Current Medications
2. Refraction and Best-Corrected Visual Acuity
3. Slit-Lamp Biomicroscopy
4. Tonometry (IOP) (applanation or tonopen)

5. Indirect Ophthalmoscopy/Dilated Fundus Examination
6. Spectral-Domain OCT
7. Assess adverse events
8. Dispense/continue prophylactic antibiotic medication at discretion

The procedural assessments (other than OCT) required in Visit 6 may be performed at the Retreatment Visit 6.1 as long as the visit window is followed appropriately per the protocol (-3 to +5 days) and OCT results have been received from Central Reading Center prior to patient retreatment.

7.1.10 VISIT 6.1 - STUDY WEEK 20 (0 TO +5 DAYS)

All study subjects will return for this retreatment visit. Prior to visit 6.1, the OCT CRT result from Visit 6 is determined by the OCT reading center, who will notify the sites whether or not the result is ≥ 350 µm. This will allow the site to determine which treatment, per the treatment table on page 14 of the protocol, is to be administered at Visit 6.1. All study subjects will receive some form of treatment at this visit (either active or sham treatment).

7.1.11 VISIT 7 - STUDY WEEK 24 (± 3 DAYS)

1. Medical and Ophthalmic History
2. List of Current Medications
3. Refraction and Best-Corrected Visual Acuity
4. Afferent Pupillary Defect
5. Slit-Lamp Biomicroscopy
6. Tonometry (IOP) (applanation or tonopen)
7. Indirect Ophthalmoscopy/Dilated Fundus Examination
8. Fundus Photography
9. Spectral-Domain OCT
10. Fluorescein Angiography
11. B-scan ultrasound for PVD (for applicable sites)
12. HbA1c
13. Assess adverse events

TABLE 2.1 - SCHEDULE OF VISITS FOR DME-202B STUDY [STAGE 1]

	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 4.1 Retreatment	Visit 5	Visit 5.1 Retreatment	Visit 6	Visit 6.1 Retreatment	Visit 7
	Screening (-20 to -3 days)	Week 0 & Day of Injection	Week 4	Week 8	Week 12	Week 12[1] (0 to +5 days)	Week 16	Week 16[1] (0 to +5 days)	Week 20	Week 20[1] (0 to +5 days)	Week 24
Informed consent	✓										
Inclusion & exclusion criteria	✓										
Urine pregnancy test women < 60 years of age	✓										
Demographic Information	✓										
Medical and ophthalmic history	✓										✓
HbA1c	✓										✓
Concomitant medications	✓	✓	✓	✓	✓		✓		✓		✓
Refraction and ETDRS BCVA	✓	✓	✓	✓	✓		✓		✓		✓
Afferent pupillary defect	✓	✓			✓						✓
Slit-Lamp biomicroscopy	✓	✓	✓	✓	✓		✓		✓		✓
IOP	✓	✓	✓	✓	✓		✓		✓		✓
Indirect ophthalmoscopy/ dilated fundus exam	✓	✓	✓	✓	✓		✓		✓		✓
Fundus photography	✓				✓						✓
OCT- Spectral Domain	✓	✓	✓	✓	✓		✓		✓		✓
Fluorescein Angiography	✓				✓						✓
B-scan (where applicable)	✓		✓	✓	✓						✓
Adverse events		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Study Treatment		✓	✓	✓		✓		✓		✓	
Prophylactic antibiotic medication (if applicable)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

[1] The window for the retreatment visits (4.1, 5.1, 6.1) of 0-5 days is in relation to the expected visits 4, 5 and 6, respectively, based on the randomization date.

TABLE 2.2 - SCHEDULE OF VISITS FOR DME-202B STUDY [STAGE 2]

	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 5.1 Retreatment	Visit 6	Visit 6.1 Retreatment	Visit 7
	Screening (-20 to -3 days)	Week 0 Baseline	Week 1 (-1 day)	Week 4 (+3 days)	Week 8 (± 3days)	Week 12 (± 3days)	Week 12[1] (0 to +5 days)	Week 16 (± 3days)	Week 16[1] (0 to +5 days)	Week 20 (± 3days)
Informed consent	✓									
Inclusion & exclusion criteria	✓									
Urine pregnancy test women < 60 years of age	✓									
Demographic Information	✓									
Medical and ophthalmic history	✓									✓
HbA1c	✓									✓
Concomitant medications	✓	✓	✓	✓	✓	✓		✓		✓
Refraction and ETDRS BCVA	✓	✓	✓	✓	✓	✓		✓		✓
Afferent pupillary defect	✓	✓								✓
Slit-Lamp biomicroscopy	✓	✓		✓	✓	✓		✓		✓
IOP	✓	✓	✓	✓	✓	✓		✓		✓
Indirect ophthalmoscopy/ dilated fundus exam	✓	✓		✓	✓	✓		✓		✓
Fundus photography	✓					✓				✓
OCT- Spectral Domain	✓	✓	✓	✓	✓	✓		✓		✓
Fluorescein Angiography	✓									✓
Adverse events		✓	✓	✓	✓	✓	✓	✓	✓	✓
Study Treatment		✓	✓	✓	✓		✓		✓	
Prophylactic antibiotic medication (if applicable)	✓	✓	✓	✓	✓	✓	✓	✓	✓	

[1] The window for the retreatment visits (4.1, 5.1) of 0-5 days is in relation to the expected visits 4 and 5, respectively, based on the randomization date.

7.2 STAGE 2 VISIT SCHEDULE

7.2.1 VISIT 0 - SCREENING VISIT (-20 TO -3 DAYS)

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:

1. Inclusion/Exclusion Criteria
2. Demographics
3. Medical and Ophthalmic History
4. List of Current Medications
5. Refraction and Best-Corrected Visual Acuity
6. Afferent Pupillary Defect
7. Slit-Lamp Biomicroscopy
8. Tonometry (IOP) (applanation or tonopen)
9. Indirect Ophthalmoscopy/Dilated Fundus Examination
10. Fundus Photography
11. Spectral-Domain OCT
12. Fluorescein Angiography
13. HbA1c
14. If patient is a female between 18 to 60 years old, needs a negative pregnancy test during the screening window
15. Dispense prophylactic antibiotic medication at investigator discretion

7.2.2 VISIT 1 – WEEK 0 AND DAY OF INJECTION/TREATMENT

When the subject arrives for the baseline visit on the day of first injection, the following procedures will be performed:

1. List of Current Medications
2. Refraction and Best-Corrected Visual Acuity
3. Afferent Pupillary Defect
4. Slit Lamp Biomicroscopy
5. Tonometry (IOP) (applanation or tonopen)
6. Indirect Ophthalmoscopy/Dilated Fundus Examination
7. Spectral-Domain OCT
8. Assess adverse events
9. Intravitreal injection
10. Dispense/continue prophylactic antibiotic medication at investigator discretion

7.2.3 VISIT 2 - STUDY WEEK 1 (- 1 DAY)

When the subject returns for the 1-week post baseline visit, the following procedures will be performed within the visit window:

1. List of Current Medications

2. Refraction and Best-Corrected Visual Acuity
3. Tonometry (IOP) (applanation or tonopen)
4. Spectral-Domain OCT
5. Assess adverse events
6. Dispense/continue prophylactic antibiotic medication at investigator discretion
7. Intravitreal injections

7.2.4 VISIT 3 - STUDY WEEK 4 (+ 3 DAYS)

When the subject returns for the 4-week post baseline visit, the following procedures will be performed within the visit window:

1. List of Current Medications
2. Refraction and Best-Corrected Visual Acuity
3. Slit-Lamp Biomicroscopy
4. Tonometry (IOP) (applanation or tonopen)
5. Indirect Ophthalmoscopy/Dilated Fundus Examination
6. Spectral-Domain OCT
7. Assess adverse events
8. Dispense/continue prophylactic antibiotic medication at investigator discretion
9. Intravitreal injections (Week 4 should never occur less than 3 weeks after Week 1, to ensure proper spacing between treatment visits for safety purposes)

7.2.5 VISIT 4 - STUDY WEEK 8 (± 3 DAYS)

When the subject returns for the 8-week post baseline visit, the following procedures will be performed within the visit window:

1. List of Current Medications
2. Refraction and Best-Corrected Visual Acuity
3. Slit-Lamp Biomicroscopy
4. Tonometry (IOP) (applanation or tonopen)
5. Indirect Ophthalmoscopy/Dilated Fundus Examination
6. Spectral-Domain OCT
7. Assess adverse events
8. Dispense/continue prophylactic antibiotic medication at investigator discretion
9. Intravitreal injections

7.2.6 VISIT 5 - STUDY WEEK 12 (± 3 DAYS)

When the subject returns for the 12-week post baseline visit, the following procedures will be performed:

1. List of Current Medications
2. Refraction and Best-Corrected Visual Acuity
3. Slit-Lamp Biomicroscopy
4. Tonometry (IOP) (applanation or tonopen)

5. Indirect Ophthalmoscopy/Dilated Fundus Examination
6. Fundus Photography
7. Spectral-Domain OCT
8. Assess adverse events
9. Dispense/continue prophylactic antibiotic medication at discretion

The procedural assessments (other than OCT) required at Visit 5 may be performed at the Retreatment Visit 5.1 as long as the visit window is followed appropriately per the protocol (-3 to +5 days) and OCT results have been received from Duke Reading Center prior to patient retreatment.

7.2.7 VISIT 5.1 - STUDY WEEK 12 (0 TO +5 DAYS)

All study subjects will return for this retreatment visit. Prior to visit 5.1, the OCT CRT result from Visit 5 is determined by the OCT reading center, who will notify the sites whether or not the result is ≥ 350 µm. This will allow the site to determine which treatment, per the treatment table on page 15 of the protocol, is to be administered at Visit 5.1. All study subjects will receive some form of treatment at this visit (either active or sham treatment).

7.2.8 VISIT 6 - STUDY WEEK 16 (± 3 DAYS)

When the subject returns for the 16-week post baseline visit, the following procedures will be performed:

1. List of Current Medications
2. Refraction and Best-Corrected Visual Acuity
3. Slit-Lamp Biomicroscopy
4. Tonometry (IOP) (applanation or tonopen)
5. Indirect Ophthalmoscopy/Dilated Fundus Examination
6. Spectral-Domain OCT
7. Assess adverse events
8. Dispense/continue prophylactic antibiotic medication at discretion

The procedural assessments (other than OCT) required in Visit 6 may be performed at the Retreatment Visit 6.1 as long as the visit window is followed appropriately per the protocol (-3 to +5 days) and OCT results have been received from Duke Reading Center prior to patient retreatment.

7.2.9 VISIT 6.1 - STUDY WEEK 16 (0 TO +5 DAYS)

All study subjects will return for this retreatment visit. Prior to visit 6.1, the OCT CRT result from Visit 6 is determined by the OCT reading center, who will notify the sites whether or not the result is ≥ 350 µm. This will allow the site to determine which treatment, per the treatment table on page 15 of the protocol, is to be administered at Visit 6.1. All study subjects will receive some form of treatment at this visit (either active or sham treatment).

7.2.10 VISIT 7 - STUDY WEEK 20 (± 3 DAYS)

1. Medical and Ophthalmic History
2. List of Current Medications
3. Refraction and Best-Corrected Visual Acuity
4. Afferent Pupillary Defect
5. Slit-Lamp Biomicroscopy
6. Tonometry (IOP) (applanation or tonopen)
7. Indirect Ophthalmoscopy/Dilated Fundus Examination
8. Fundus Photography
9. Spectral-Domain OCT
10. Fluorescein Angiography
11. HbA1c
12. Assess adverse events

8 STUDY COMPLETION

8.1 SUBJECT COMPLETION

Subjects are considered to have completed the study if they have completed all required examinations through Week 24 for Stage 1 and through Week 20 for Stage 2. The study is considered to be completed when all randomized subjects have either completed or been terminated from the trial.

8.2 SUBJECT DISCONTINUATION

Subjects who experience an unacceptable lack of effectiveness and who have not responded to retreatment (as defined above), or intolerable side effects or adverse reactions should be discontinued at the investigators discretion from the study and should receive appropriate treatment at the discretion of the investigator. Subjects who discontinue from the study within the first month (4 weeks) of participation can be replaced.

Other 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 TERMINATION OF STUDY OR PARTICIPATION BY A CLINICAL SITE OR SPONSOR

The Sponsor or Clinical Site reserves the right to discontinue the study at a single site for safety or administrative reasons at any time. If the Sponsor or Investigator discovers conditions during the study indicating that the study or participation by a clinical site should be terminated, this action may be taken after appropriate consultation between the Sponsor and Investigator.

Conditions that may warrant termination of the study include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
- The decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the study at any time.

Conditions that warrant discontinuation of the study at a specific study site include:

- Failure of the Investigator to enroll subjects into the study at an acceptable rate.
- Failure of the Investigator to comply with the Protocol or pertinent regulations.
- Submission by the Investigator of false information from the research facility to the Sponsor.

Any subject who completes all study visits will be considered to have completed the study.

8.4 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 following assessments must be completed by the investigator prior to exiting the study subject from the study. Furthermore the Sponsor must be contacted prior to exiting the study subject.

1. List of current medications
2. Refraction and BCVA
3. Afferent pupillary defect
4. Slit-lamp biomicroscopy
5. Tonometry (IOP) (applanation or tonopen)
6. Indirect ophthalmoscopy/dilated fundus examination
7. Fundus photography
8. Spectral-domain OCT
9. Fluorescein angiography
10. Assess adverse events

These assessments can be found in the Early Termination Visit schedule in the Case Report Forms.

9 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 also 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 or not considered drug related.

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)
7=Hospitalized (>= 24 hours)

Outcome of an adverse event is coded as:

1=Recovered without sequelae
2=Stable and ongoing
3=Ongoing
4=Death
5=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 an 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 STATISTICS

10.1 SAMPLE SIZE CONSIDERATIONS

Since this is a Phase 2 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.

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 POPULATIONS

The modified Intent to Treat (mITT) data set will include all randomized subjects who receive at least one dose of study drug and have at least one follow-up visit. Last observation carry forward (LOCF) will be used to impute missing data from subjects. If a subject receives rescue therapy, that subject's worst reported value will be imputed for all subsequent visits. Data will be analyzed as randomized.

The Per Protocol (PP) data set will include all subjects who meet all inclusion and none of the exclusion criteria at the eligibility visit, who are compliant with all study requirements and who complete the study through Weeks 20 and 24 (Stage 2 and Stage 1 respectively). Missing data will not be imputed. Data recorded after rescue therapy will be excluded. Data will be analyzed as treated.

The safety dataset will include all subjects who receive study drug. Missing data will not be imputed. Data will be analyzed as treated.

10.4 INTERIM ANALYSES

An interim analysis might be performed to support planning of further clinical development. To maintain the integrity of the ongoing study, individuals who are directly involved in study conduct and data management (eg, personnel at investigational sites, Allegro Medical Safety Physician, Clinical Operations, and Data Management) would remain masked to treatment assignment of individual patients until study completion.

11 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 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.

APPENDICES

A SAMPLE SUBJECT INFORMED CONSENT

B EXAMINATION PROCEDURES, TESTS, EQUIPMENT AND TECHNIQUES

C SPONSOR OBLIGATIONS

D INVESTIGATOR OBLIGATIONS

E WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

F STUDY MONITORING

G PROTOCOL CHANGES AND PROCEDURES

H INSTRUCTIONS FOR COMPLETION OF CASE REPORT FORMS

APPENDIX A: SAMPLE INFORMED CONSENT

An Informed Consent Form will be provided and is to be read by and discussed with each subject prior to initiating the trial. When signed and dated by the subject, it becomes the investigator's record of Informed Consent. The signed informed consent document will be kept on file at the investigational site and a copy should be given to the subject for his or her records.

SUBJECT INFORMATION AND CONSENT FORM (EXAMPLE)

A SAFETY AND EFFICACY STUDY COMPARING LUMINATE®, AVASTIN®, AND FOCAL LASER IN PATIENTS WITH DIABETIC MACULAR EDEMA

PROTOCOL #:	DME – 202B
SPONSOR:	Allegro Ophthalmics, LLC 31473 Rancho Viejo Rd, Suite 204 San Juan Capistrano, CA 92675
PRINCIPAL INVESTIGATOR:	_____
ALLEGRO MEDICAL OFFICER	VICKEN KARAGEOZIAN, MD
ADDRESS(ES):	31473 RANCHO VIEJO ROAD #204 SAN JUAN CAPISTRANO CALIFORNIA, 92675

Purpose of the Subject Information and Consent Form

This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand.

The purpose of this form is to give you information about the research study and, if signed, will give your permission to take part in the study. The form describes the purpose, procedures, benefits, risks, discomforts and precautions of the research study. You should take part in the study only if you want to do so. You may refuse to take part or withdraw from this study at any time without penalty or loss of benefits to which you are otherwise entitled. Please read this Subject Information and Consent Form and ask as many questions as needed. You should not sign this form if you have any questions that have not been answered to your satisfaction.

You will receive a copy of this signed consent form for your records.

Purpose of Study
You have been asked to participate in this research study, sponsored by Allegro Ophthalmics, LLC, to determine whether an new class of drugs to treat bleeding disorders of the eye would be effective as compared to the current standard of care drugs or laser treatments used in treating diabetic macular edema (swelling in the back of the eye from your diabetes). In this study 1.0, 2.0, or 3.0 mg of Luminate® will be compared to the current standards-of-care of 1.25mg Avastin.®

Luminate® is an experimental product which has been tested in both animals and human patients in the past for safety and initial efficacy. In addition, improvements in vision and resolution of macular swelling have been observed in human subjects when the drug has been used alone.

You are being chosen for this study because your treating physician feels that your Diabetic Macular Edema (swelling in the back of the eye from your diabetes) is not resolved with the current standard of care medication (i.e., Avastin®) or without further medical intervention. As the study drug, Luminate®, has a different mechanism of action, meaning it works in a different way than the current standard of care drugs on the market, it has been found in animal and other human studies to provide an additional level of benefit in treating bleeding disorders of the eye above and beyond those benefits in vision or retinal anatomy seen with Avastin® (the current standard of care). Your participation in this study may directly benefit you by further improving the anatomy of the eye and improving your ability to see.

Luminate® is experimental when used in the eye, such as for this use, and has not been approved by the Food and Drug Administration. The safety and efficacy of Luminate® will be evaluated in this study.

Approximately 120 subjects are expected to participate.

Duration of Participation
You will be in this study for approximately six months.

Study Procedures

If you agree to take part in this study, you will first sign this Subject Information and Consent Form before any study-related procedures are performed. Before enrolling into this study, your study doctor or his staff will take your medical history to make sure you have no other medical problems that would interfere with your participation in this study, and are not using any medications which might make your participation unsafe. You will also receive an eye examination. This exam includes:

Slit Lamp Exam is an examination of your eye by the Study Doctor using a special microscope that allows your physician to see both the outside and the inside of your eye under magnification. The doctor will look at your pupil and eye movements. The lens and back of your eye will also be examined after drops have been placed in your eyes to dilate your pupil. This exam will be performed on both eyes at the Screening Visit, but only on the study eye during all remaining visits.

Fundus Exam is an examination with an ophthalmoscope (an instrument with a strong light and a magnifying lens) of the interior lining of the eyeball, including the retina, optic disc (the head of the nerve to the eye), and the macula. This exam will be conducted by your Study Doctor. This exam will be performed on both eyes at the Screening Visit, but only on the study eye during all remaining visits. .

Intraocular Pressure is a measure of the pressure of the fluid inside your eye. This exam will be performed on both eyes at the Screening Visit, but only on the study eye during all remaining visits.

Visual Acuity uses letters projected on a screen to measure how well your eye can see at a specific distance. This exam will be performed on both eyes at the Screening Visit, but only on the study eye during all remaining visits.

Optical Coherence Tomography (OCT) uses light to measure the thickness of the retina. You may be familiar with ultrasound used to obtain pictures of pregnancies. OCT uses light instead of sound to obtain pictures of the inside of your eye. Like ultrasound, it is painless. You will be asked to look into the front of the OCT machine. While the instrument acquires an image, you will see lights of various colors. This exam will be performed on both eyes at the Screening Visit, but only on the study eye during all remaining visits.

Fundus Photography, i.e., photographs of your retina, will be taken. Eye drops will dilate your pupils, allowing for the inside of your eye to be examined. A special camera will then be used to take photographs. The bright flashes used to take the photographs may be annoying, but are not painful and cause no damage to the eye. Photography will be performed on both eyes at the Screening Visit, and on the study eye on follow up visits.

Fluorescein Angiography is a test in which pictures of your retina are taken using a yellow dye. The dye, called fluorescein, will be injected into a vein (blood vessel) in your arm or hand. This dye will travel through your blood vessels to your eyes. The camera will then flash a special light into your eye and will take pictures of your retina; the pictures will show the amount of dye leaking out of the blood vessels into your retina. This test will be performed on both eyes at the Screening Visit, and on the study eye on follow up visits.

Intravitreal Injections will be given in one of your eyes (the "study eye") within 20 days following your screening visit, and at intervals during the course of the study. The pupil of your eye will be dilated, and your eye will be anesthetized (numbed). You will then receive an injection into your eye.

If you are a woman of childbearing potential (under age 60), you must have a negative pregnancy test to participate in this study.

If you are eligible for the study, you will receive injections into your eye of 1.0, 2.0, or 3.0 mg of Luminate®, or 1.25mg of Avastin®.

The study drug will be drawn up into a small syringe and with your eye anesthetized (numbed), the drug will be injected into the white of the eye usually under the upper or lower lid. There will be only a single injection at Baseline.

Following the injections, you will need to return for additional examinations at study weeks 4, 8, 12, 16, 20, and 24. At these visits, you will have an eye examination.

If you decide to participate in the study, it is important that you return to the study site at the scheduled times for observation of your overall well-being.

Risks or Discomforts
Your eye condition may or may not improve or may worsen while participating in this study.

If you experience any side effects during the study, you should tell the study staff.

While there are no known side effects specifically related to the study drug, the potential side effects from an intravitreal injection may include:

- burning/stinging
- headache
- foreign body sensation
- brow-ache
- photophobia (intolerance to light)
- excessive tearing
- eye inflammation
- pain
- lowering of eye pressure
- transient macular edema

What are the possible risks or discomforts?

Risk of Eye Examination and Dilation
As part of the eye exam, drops will be put in your eyes to dilate the pupils. The drops may blur your vision and make you sensitive to light. The drops will wear off over several hours. There is a small risk of an allergic reaction to the drops. There is also a small risk that the drops could cause the eye pressure to rise. If this happens, it will be treated, but there is a very small risk of losing vision from the pressure rise. Due to the blurring effect on your vision and possible light sensitivity, you will be advised not to drive until the drops have worn off and, if necessary, have someone come with you who can drive after the exam.

Risk of Optical Coherence Tomography
The vast majority of people feel no discomfort on exposure to the light source used to obtain the images of the retina. However, as with any bright light source some people may experience photophobia (sensitivity to light).

Risks of Intravitreal Injection with Luminate®

Luminate® has been tested in two previous human clinical trials and has been found to be safe and well tolerated. In this study, you will be examined for the need to receive Luminate® at monthly to quarterly intervals depending on the study arm you are enrolled into.

Prior to injection, your eye is numbed with an eye drop and it may be cleaned with betadine. You may experience redness or swelling of the eye or eyelid, or bleeding, tearing or watering of your eye. You may experience corneal abrasion (scratch on the clear front surface of the eye) if you rub your eye while numb. These events are likely to clear up quickly. You may experience an allergy to the numbing drops or betadine. This is usually treated by antihistamines that are given by mouth or by injection if your symptoms are severe.

In clinical studies conducted with Luminate® to date, the most common eye-related side effects were:

1. Conjunctival hemorrhage (bleeding under the clear covering of the eye)
   - Mild eye pain
   - Vitreous floaters (small specks floating in your field of vision)
2. Transient increased eye pressure
   - Vitreous detachment (a common condition that occurs naturally with the aging of the eye in which the clear gel that fills the space between the lens and the back of the eye separates away from the back of the eye)
   - Intraocular inflammation (swelling and redness inside the eye)
   - Foreign body sensation in eye
   - Eye irritation (redness)

Other Risks

You should be aware that there might be additional risks that are currently unknown and unforeseeable. Your condition may not improve, or may worsen while participating in the study. You may still require the current standard of care treatment Avastin® or focal laser whether you participate in this study or not.

Additionally, there is the risk of the injection procedure that is inherent in any type of injection into the eye. These risks include infection, retinal detachment, bleeding in the vitreous cavity, temporary rise in eye pressure, and cataract formation, any of which could affect your vision in that eye.

If you do not understand what the symptoms of the side effects are, ask your study doctor to explain them to you.

Other possible side effects can occur which may have no symptoms. There may be risks associated with the use of this study drug that are currently unknown.

Reproductive Risks

You must not participate in this study if you are a woman who is breast-feeding, pregnant, considering a pregnancy, or not using effective birth control methods during the study period.

Medically acceptable forms of birth control include:

- IUD (intrauterine device)
- Condom + spermicide
- Diaphragm + spermicide
- Birth control pills, implants (like Norplant), or injections (like Depo-Provera) used with a condom or diaphragm

If you think you are pregnant during the study, you must tell the study doctor immediately. If you become pregnant, you will be removed from the study and your pregnancy will be followed to its outcome.

If you are a female between 18 to 60 years old, you will need a negative urine pregnancy test during the screening window to be eligible for enrollment.

Alternative Treatment

The only currently available definitive treatment option for your condition is focal laser or anti-VEGF treatment such as Avastin®. If you continue to deteriorate despite treatment with to your study designated treatment regime during the study the investigator has the option to perform a "rescue treatment" with one of these alternative treatment options. As you consider your participation in this study, your other alternative is not to participate in this study.

Benefits
Your participation in this study may directly benefit you. Your participation will also help provide information about the safety and effectiveness of Luminate® for treating focal vitreomacular adhesion.

Costs
You will receive the study drug, other medications and the eye examinations free of charge. If travelling to the clinic for treatment and follow up examinations is a burden, travel cost reimbursement is available on an as needed basis.

Compensation for Injury
If you are injured as a result of the study drug or study procedures performed during your participation in this research study, you should seek medical attention at the medical provider of your choice. The Sponsor will cover the medical expenses necessary to treat the injury only to the extent that such costs are not covered by your health insurance policy, by a government program, or by any other third party.

You must follow the directions of the study doctor to be eligible for this coverage.

Neither the Sponsor nor the study doctor has a program in place to provide other compensation in the event of an injury.

Legal Rights
The above section does not restrict your right to seek legal assistance. You do not waive any legal rights by signing this Subject Information and Consent Form.

Voluntary Participation/Withdrawal
YOUR PARTICIPATION IN THIS STUDY IS ENTIRELY VOLUNTARY. YOU MAY REFUSE TO PARTICIPATE OR MAY WITHDRAW FROM THIS STUDY AT ANY TIME AND STILL RECEIVE MEDICAL CARE OR ANY BENEFITS TO WHICH YOU MAY BE ENTITLED AT THIS SITE.

Before withdrawing from this study, notify your study doctor that you wish to withdraw. This notice will allow your study doctor to inform you if there are any potential medical risks of withdrawal. You may be asked to return to the clinic for tests.

Your study doctor, according to his judgment, may stop the study at any time. Allegro Ophthalmics, LLC may also stop the study or your participation at any time with or without your consent.

New Findings
Your study doctor will inform you of any new information about this drug, which might develop during the course of this research and which might influence your willingness to participate in this study.

Confidentiality
Information from this study will be submitted to the sponsor and to the U.S. Food and Drug Administration. It may be submitted to governmental agencies in other countries where the study drug may be considered for approval. Medical records and the consent form signed by you will be inspected by the sponsor or an agent for the sponsor, and may be inspected by the U.S. Food and Drug Administration or Ministry of Health and your physician's Ethics Review Committee.

Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed.

The results of this research project may be presented at meetings or in publications; however, your identity will not be disclosed in those presentations.

Videography/Photography
Your procedure may be photographed, videotaped or observed for medical, scientific or educational purposes. Only your affected eye and the area nearby will be used. Your identity will not be revealed by the pictures or by any descriptive text accompanying them.

Questions
If you have any questions concerning your participation in this study or if at any time you feel you have experienced a research-related injury or reaction to the study drug, contact:

Principal Investigator:
Daytime telephone number(s): _____
24-hour contact number(s): _____

If you have questions about your rights as a research subject, you may contact "_____". An Independent Review Board is a group of scientific and non-scientific individuals who perform the initial and ongoing ethical review of the research study with the study subject's safety and welfare in mind. If you have study-related comments, complaints or concerns, you should first contact the study investigator. Please call the "_____ IRB" if you want to talk to someone other than the study investigator or have difficulty reaching the study investigator. For further information regarding the clinical trials process and your role as a research subject, you may contact "_____ IRB"

Subject's Statement of Consent

DME-202b - A SAFETY AND EFFICACY STUDY COMPARING LUMINATE®, AVASTIN®, AND FOCAL LASER IN HUMAN SUBJECTS WITH DIABETIC MACULAR EDEMA

I have read or have had read to me this consent form. I have been encouraged to ask questions about anything regarding this study or this consent form that I do not understand and I have received satisfactory answers to my questions so far. I voluntarily consent to participate in this study.

I consent to the release of my medical records to the sponsor or its designees, the U.S. FDA or other regulatory agencies, and my physician's Ethics Review Committee.

By signing this consent form, I have not waived any of the legal rights that I otherwise would have as a participant in a research study.

_____

Subject's Signature Date

_____

Printed Name of Subject

_____

Signature of Person Obtaining Consent Date

_____

Printed Name of Person Obtaining Consent

Witness Statement:
I verify that the information in this consent form has been read by the subject or read to the subject, if necessary:

_____

Witness Signature Date

_____

Investigator's Signature Date

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

1. VISUAL ACUITY

Visual acuity will be measured using a standard ETDRS chart at 4 meters.

Visual Acuity Charts

ETDRS BCVA

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.

Please refer to the Study procedure manual for further details.

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 / pleomegathis

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

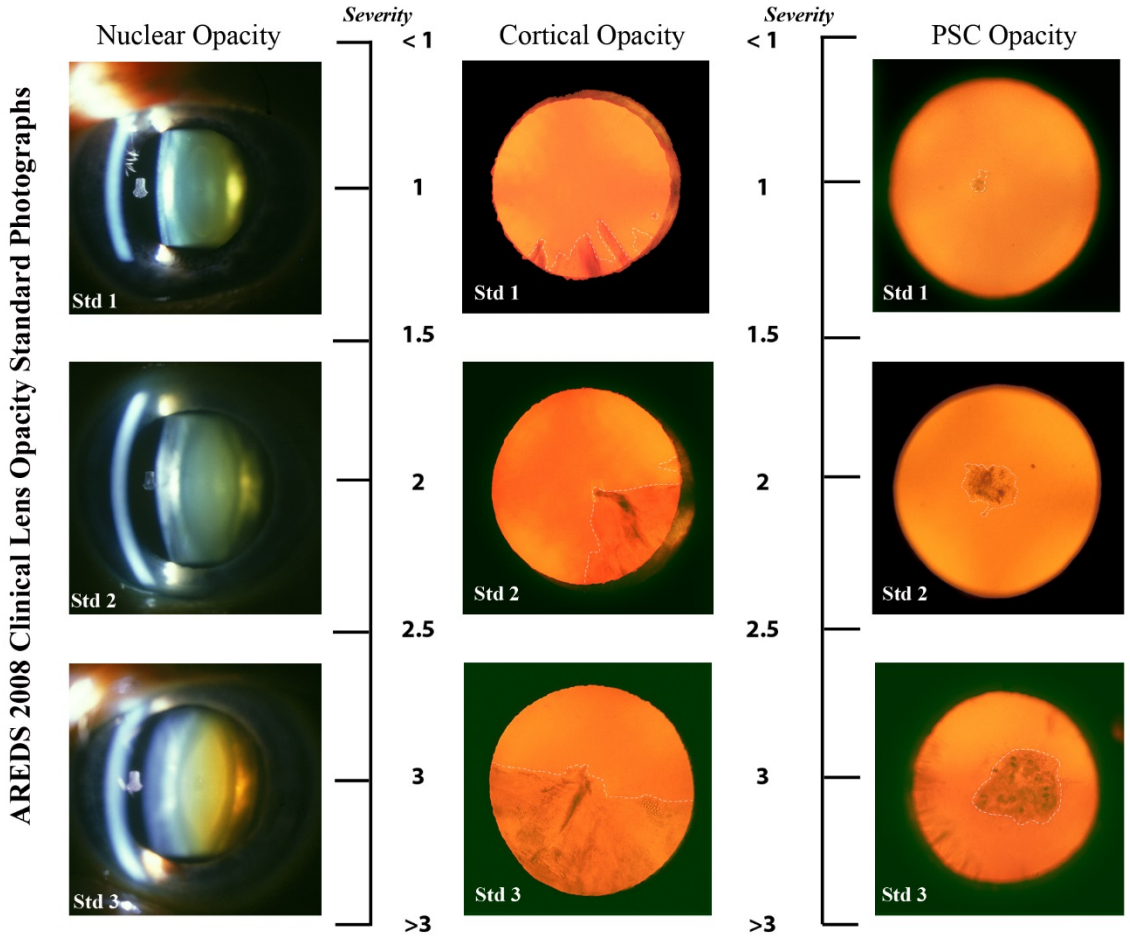
See AREDS 2008 Clinical Lens Opacity Standard Photographs Below

Nuclear Landmarks - In the normal or nonsclerotic 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 study training manual for complete details on this procedure.

7. FLUORESCEIN ANGIOGRAPHY

Please refer to the study training manual for complete details on this procedure.

8. B-SCAN ULTRASOUND FOR PVD

The following b-scan instructions are simply additional guidance. The formal b-scan protocol for site use throughout this study will be provided directly from Duke Reading Center.

Posterior vitreous detachment is a common condition associated with aging. It occurs when the posterior hyaloid detaches or separates from the retina as the vitreous liquefies. B-scan is a useful tool for detecting the presence of a PVD in both opaque and clear ocular media. A summary of this protocol can be found in Exhibit A (page 10).

Instrumentation
The Ellex Innovative Imaging v3 B-scan instrument or similar kinetic B-scan is to be used for B-scan examinations on study subjects. The Ellex machine provides a 10 MHz transducer and allows the storage of both static images (echograms) and video footage (movies) in 10 second increments. The suggested steps to be followed in the use of the v3 machine are listed in Exhibit B (page 13).

B-scan Basics
The B-scan probe contains a transducer surrounded by fluid. The transducer oscillates rapidly back and forth, producing a focused sound beam. The sound beam moves to and from a marker located on the probe housing. Once emitted into the eye, the sound beam is reflected from any acoustic interfaces in its path (e.g., vitreous pathology and the retina) and corresponding echoes are displayed on the display screen of the instrument. The acoustic section obtained is very thin, much like the slice of the knife. Therefore, for a thorough examination of the posterior segment, the sound beam must be moved throughout the vitreous cavity.

Proper interpretation of a B-scan echogram requires knowing where the probe is positioned and where the probe marker is directed. The B-scan echogram is demarcated on the left by the initial line that represents the location of the probe face on the eye. The right side of the echogram corresponds to the portion of the eye located opposite the center of the probe face. The upper aspect of the echogram represents the region of eye where the probe marker is directed. The lower aspect of the echogram corresponds to the region of the eye located opposite the probe marker (Fig 1).

Subject Confidentiality and Naming Convention
Per established HIPAA guidelines, the identity of study subjects must be masked. Therefore, no identifiable subject data should be visible on any study materials.

A naming convention is used to identify the site, subject, and visit on each A- or B-scan image. The four components of the convention, separated by an underscore (_), include the site number, subject number, subject initials, and visit label. These identifiers are recorded as follows: three-digit site number_, three-digit subject number_, three letter subject initials_, and a one-digit visit number (e.g., 001_001_ABC_1). B-scan images must also be labeled according to the area of eye examined (see “Labeling B-scan Images”).

The Visit Schedule for this trial is as follows:

Visit Schedule

Study Visit	Visit Label
0	Screening
2	Week 4
3	Week 8
4	Week 12
7	Week 24

*B-scan examination will be performed per the schedule described above. Should the subject have an unscheduled visit with a B-scan examination, that visit # is 99.

NOTE: Whenever the investigator determines (by clinical exam and B-scan) that a subject has a total PVD, then B-scan examinations will not be performed on the subject at subsequent visits to the site.

B-scan Screening Examination of the Posterior Segment
Before starting the examination, ensure that patient identifiers have been placed on the instrument screen (see "Subject Confidentiality and Naming Convention"). The gain is set at maximum and the screen brightness is adjusted appropriately for the detection of low reflective echoes within the vitreous cavity. An ophthalmic coupling gel is applied to the probe. A preservative free gel (e.g., Gen Teal Gel) is recommended to minimize irritation to the eye.

The patient is positioned comfortably, preferably in a reclined position, with the eye to be examined situated close to the screen display to facilitate hand-eye coordination. Local anesthetic drops are instilled and the room lighting is dimmed. The subject is asked to fixate away from the probe, toward the portion of eye being examined. The examination is conducted with the probe placed directly on the conjunctiva. Placement of the probe on the conjunctiva promotes sound beam penetration and helps determine which area of the eye is being examined.

The posterior segment of the eye is examined systematically using basic screening techniques (i.e., specific transverse and longitudinal scans). The findings of each patient examination are documented with certain echograms and movies.

Longitudinal Scans
In a longitudinal probe position, the sound beam produces a radial section. The beam sweeps perpendicular to the limbus and parallel to a single meridian of the opposite fundus (i.e., one clock hour). For the screening examination, longitudinal scans are performed along the 12:00, 3:00, 6:00, and 9:00 meridians. The sound beam passes through the optic nerve posteriorly and sweeps anteriorly toward the ciliary body (Fig 2). Peripheral aspects of a meridian are best displayed with the probe resting near the fornix.

The probe marker is always directed toward the center of the cornea and the meridian being examined. As the probe is slowly shifted from limbus to fornix, it is simultaneously rocked slightly from side to side to help ensure lesion detection. Longitudinal scans are performed as follows:

- 12:00 meridian; probe is placed at 6:00
- Nasal meridian; probe is placed at 9:00 OD or 3:00 OS
- 6:00 meridian; probe is placed at 12:00
- Temporal meridian; probe is placed at 3:00 OD or 9:00 OS

B-scan Characteristics of a PVD

A total PVD is a complete separation of the posterior hyaloid from the retina. As defined in this protocol, a total PVD can either remain adherent to or can be detached from the optic disc. On B-scan, a total PVD produces an extensive, thin, membranous acoustic interface of low reflectivity that typically exhibits undulating mobility. In many cases, a total PVD can be shown to insert into the vitreous base. Also, a Weiss ring usually can be identified when a total PVD is detached from the optic disc. The Weiss ring produces one or two distinct, bright, point-like echoes within the plane of the PVD, typically located in the vicinity of the optic disc (Fig 3). However, in a highly elevated and/or folded PVD, the

Weiss ring will usually be situated more anteriorly (and not necessarily overlying the optic disc). Therefore, detection of the Weiss ring may be more challenging in this form of total PVD.

A partial PVD is attached to the retina in one or more areas and may still be attached to the macula and optic disc. Insertion of the PVD into the vitreous base is sometimes demonstrated. When limited in extent, a partial PVD typically appears as a smooth, shallow membranous acoustic interface that exhibits little or no mobility. A Weiss ring usually cannot be identified in a partial PVD.

No PVD is detected when the posterior hyaloid is completely attached to both the retina and the optic disc.

Assessment of Mobility

An important aspect of diagnosing an extensive PVD with B-scan is the evaluation of mobility. An extensive or total PVD typically exhibits an undulating motion. The mobility of membranous acoustic interfaces is captured in a movie.

To evaluate mobility, the area of interest is displayed, the probe is held stationary, and the patient is asked to move their eye back and forth two or three times. Sufficient gel is applied to the probe face and a scan is performed with the patient fixating away from the probe, toward the area being examined. **IMPORTANT**: **The area of interest should remain on the screen throughout the procedure. This is accomplished by asking the patient to move their eye in the same direction as the sound beam is oscillating.**

For longitudinal scans (e.g., LM and RM), the patient is asked to move their eye in a radial manner, toward (but not into) the probe face. During this procedure, the optic nerve void is displayed before, during, and following the eye movement. Maintaining display of the optic nerve void provides for the assessment of lesion mobility in relation to the optic disc (and the macula for the LM and RM views).

Documentation of Findings
The presence or absence of a PVD should be clearly documented in both movies and echograms. The purpose of documentation is to record all pertinent findings of the B-scan examination. When any membranous acoustic interfaces are detected, the appearance, location (including any insertions into the fundus), presence of a Weiss ring, and mobility should be well demonstrated. Movies and echograms are initially stored on the internal hard drive of the instrument (see Exhibit B).

To make a movie for the purpose of demonstrating mobility, the first step is to localize the area of interest. Once the pathology is clearly displayed, the probe is held steady, the patient is asked to maintain their fixation, and the image is frozen. The probe is then restarted and the patient is asked to move their eye back and forth two or three times (to fill the 10 second time-frame). By following this procedure, lesion mobility can be captured adequately in the 10 second movie.

Once all findings have been documented, the images should be reviewed for quality and completeness. If the required images fail to demonstrate the examination findings or are of inferior technical quality, they should be replaced. Additional movies are encouraged if necessary to thoroughly document all pertinent findings.

The images stored on the internal hard drive are then archived to a flash drive (see Exhibit C). The final step is to upload the images on the flash drive to a website for grading by the Ultrasound Reading Center (see Uploading B-scan Images to Secure Website).

Baseline Visit
Vitreous status and mobility is captured in the movies. The required images are:

a. Longitudinal macula (LMAC)
i. Probe is placed at the horizontal (nasal) limbus (right eye 3:00, left eye 9:00) with marker pointing temporally towards the center of cornea.
ii. This captures on the monitor as scan (as seem from top of monitor to bottom) the temporal horizontal retina, macula, optic nerve, and nasal periphery on the bottom of the screen.

b. Reverse macula (RMAC)
i. Probe is placed at the horizontal (temporal) limbus (right eye 9:00, left eye 3:00) with marker pointing nasally towards the center of the cornea
ii. This captures on the monitor a scan (as seen from top of monitor to bottom) the nasal horizontal retina, optic nerve shadow, macula and temporal periphery on the bottom of the screen.

c. Longitudinal to 12:00 (L12)
i. Probe is placed at the inferior (6:00) limbus (same location in right and left eye) with marker pointing superiorly to 12:00 towards the center of the cornea.
ii. The eyelids typically need to be held open and the patient should be encouraged to keep their fellow eye open during the exam to help align the study eye
iii. In this protocol, the probe direction needs to be slightly nasally displaced to include the optic nerve in the image
iv. This captures on the monitor (as seen from the top of the monitor to the bottom) the superior retina, optic nerve, and inferior periphery

d. **Longitudinal to 6:00 (L6)**
i. Probe is placed at the superior (12:00) position (same location in the right and left eye) with marker pointing inferiorly to 6:00 towards the center of the cornea
ii. In this protocol, the probe direction needs to be slightly nasally displaced to include the optic nerve in the image
iii. This captures on the monitor (as seen from the top of the monitor to the bottom) the inferior retina, optic nerve, and superior periphery

NOTE: Additional movies and echograms should be obtained, as needed, to adequately demonstrate pertinent findings.

Post Injection Follow-Up Visits
Vitreous status and mobility is captured in the movies. The required images are as stated at Baseline Visit

NOTE: Additional movies and echograms should be obtained, as needed, to adequately demonstrate pertinent findings.

Labeling B-scan Images
For the Baseline visit, movies of the transverse screening procedure are only labeled according to the clock hour examined (i.e., 12, 3, 6 or 9).

Echograms and other movies are labeled according to the area of eye examined. The labeling scheme for these images is described below (see also Fig 4).

Further Details could be found in the procedure manual for B-scan ultrasonography.

EXHIBIT A

I ^{3} SYSTEMv3

Posterior B-scan Procedure

(1) **POWER:** Press the switch on the front panel or the switch on the power strip on the cart; an indicator will light.

(2) **BEGIN: Click** on the user name & enter password (if necessary). The I^3 power-up screen will appear.

(3) **SELECT MODE** from **Mode screen: New Patient** screen will appear.

(4) **SUBJECT ID:** Enter data in **New Patient screen;** press **ENTER;** press **Save.**

(5) **B-SCAN IMAGE:** Appears after **Subject ID** data has been saved; depress **Left Footswitch** to activate scan.

(6) **FREEZE SCAN**: depress **LEFT FOOTSWITCH.**

(7) **MOVIE:** Last 10 seconds of the examination is automatically stored as a movie.

(8) **ADVANCE OR REWIND MOVIE:** Turn **Threshold knob** as desired.

(9) **SAVE MOVIE TO INTERNAL HARD DRIVE**: Press **Shift F11** or click **Save Movie**.

(10) **SAVE ECHOGRAM TO INTERNAL HARD DRIVE**: Press **F12** or **Right Footswitch** or click **Save Frame**.

(11) **LABEL IMAGE: Probe orientation Field** will open; enter label; click **OK** or press **ENTER.**

WARNING: Proper Windows shut down procedure must be followed to turn off the instrument. *Click on the* ***X*** *at the top right of the screen. A box will pop up saying you are logging off; click YES. Once shut down of the application is complete, you will see a Windows screen; click* **TURN OFF COMPUTER,** *then click* ***TURN OFF*** *in the next box…when you see static on the screen it is safe to turn off the power strip.*

Failure to follow this procedure will potentially result in loss of ALL patient data.

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EXHIBIT B

I 3 SYSTEMv3

ARCHIVING IMAGES FROM THE INTERNAL HARD DRIVE
TO THE EXTERNAL HARD DRIVE

1) Click on the **Archive** tab at the top of the screen.
2) Click on **Create Archive** at the bottom of the screen.
    a. A search window will open.
    b. Find your removable drive letter and click it once.
    c. Click **Create new folder** to make a folder.
        i. Rename the new folder by dragging your mouse across the folder name and highlighting it.
        ii. Rename the folder using the appropriate naming convention.
        iii. Press **Enter.**
3) Click **OK.**
4) The subjects will be listed in the upper half of the Archive screen.
5) Select individual subjects or click **Select All** on the middle bar.
    a. Click the **Down Arrow** on the middle bar.
        i. The scans selected will move to the bottom half of the screen.
6) Click **Archive** at the bottom.
7) When Archive is complete a pop-up will ask, "**Delete archived records**? Yes/no
    a. To keep patient data on the internal hard drive press **NO**
    b. To delete patient data from the internal hard drive press **YES**

APPENDIX C: 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 D: 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 E: 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 F: 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, in order 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, in order 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, in order 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 G: 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 H: 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.