LIGHT-ACTIVATED AU-011

PROTOCOL AU-011-101

NCT03052127

A PHASE 1B/2 OPEN-LABEL, ASCENDING SINGLE AND REPEAT DOSE CLINICAL TRIAL DESIGNED TO EVALUATE THE SAFETY AND EFFICACY OF LIGHT-ACTIVATED AU-011 FOR THE TREATMENT OF SUBJECTS WITH SMALL PRIMARY CHOROIDAL MELANOMA

Rev-15 21 February 2020

Aura Biosciences, Inc.

85 Bolton Street

Cambridge, MA 02140

INVESTIGATOR'S AGREEMENT

Study title: A Phase 1b/2 open-label, ascending single and repeat dose clinical trial designed to evaluate the safety and efficacy of Light-activated AU-011 for the treatment of subjects with small primary choroidal melanoma.

My signature confirms that I have carefully read, and that I understand this protocol. I agree to follow the study procedures as outlined in this protocol in compliance with current Good Clinical Practice and all other regulatory requirements.

This protocol contains confidential information with respect to products and clinical trials. I agree to hold this information in confidence and not to disclose it to any third parties unless and until this information becomes a matter of public knowledge, or until a formal agreement for that purpose has been entered into by the parties.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

AURA BIOSCIENCES SIGNATURE PAGE

Title: A Phase 1b/2 open-label, ascending single and repeat dose clinical trial designed to evaluate the safety and efficacy of Light-activated AU-011 for the treatment of subjects with small primary choroidal melanoma.

Version/Date Rev-15 21 February 2020

Protocol Approvers: [redacted]

Signature:

Date:

[redacted]

Signature:

Date:

[redacted]

Signature:

Date:

1. SYNOPSIS

Name of Sponsor/Company: Aura Biosciences, Inc.

Name of Investigational Product: Light-activated AU-011

Name of Active Ingredient: AU-011

Title of Study: A Phase 1b/2 open-label, ascending single and repeat dose clinical trial designed to evaluate the safety and efficacy of light-activated AU-011 for the treatment of subjects with small primary choroidal melanoma.

Number of Subjects (planned): Approximately 60 adult subjects

Number of Study Sites: Up to 15 clinical sites

Phase of Development: Phase 1b/2

Objectives:

The primary objective of this study is to evaluate the safety of IVT administration of one of 3 dose levels, repeat dose regimens and one or two laser applications of Light-activated AU-011 given in one or two treatment cycles in the treatment of subjects with small primary choroidal melanoma.

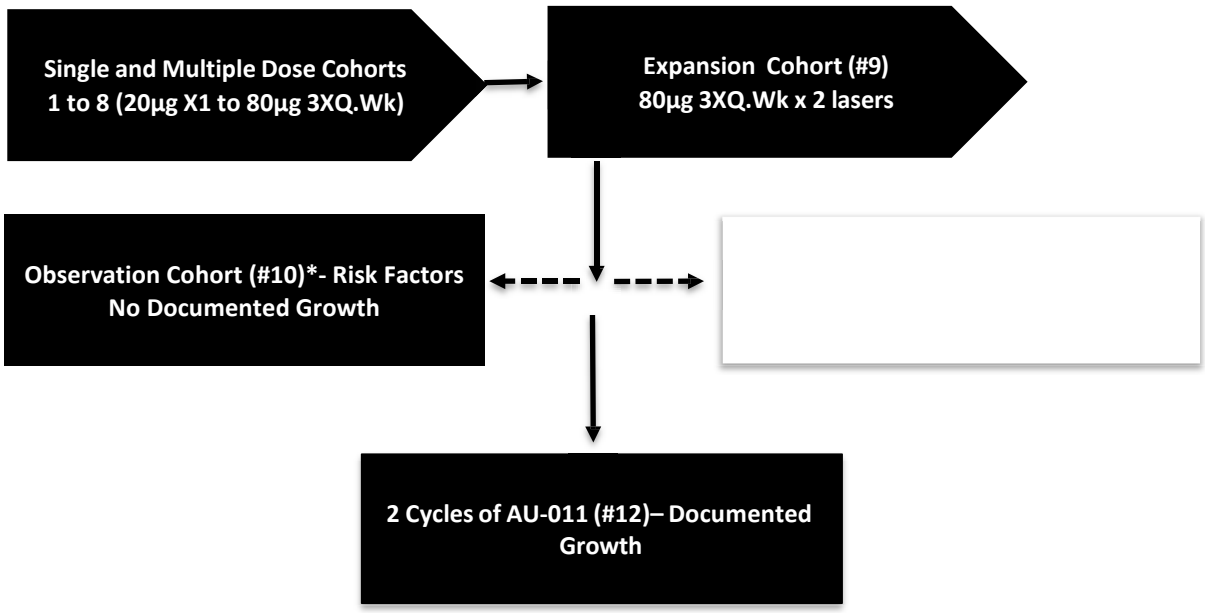
Secondary objectives include evaluating:

- Efficacy of AU-011 with one or two cycles of treatment with the maximum safe and feasible dose
- Efficacy and safety of AU-011 in subjects with documented growth
- The immunogenicity of AU-011
- A-scan amplitudes of the internal reflectivity of the lesion at sites with diagnostic probes
- Optical coherence tomography angiography (OCTA) image changes at sites with OCTA imaging systems for Cohorts 6 through 9

Study Design:

This is an open-label, ascending single and repeat dose and cycle, multicenter study designed to evaluate the safety and efficacy of Light-activated AU-011 at three dose levels and repeat dose regimens and cycles of Light-activated AU-011 and one or two laser applications in subjects with small primary choroidal melanoma (CM). The dose escalation design is shown in the figure below.

Dose Escalation Schematic



*Alternating enrollment; enrollment in Cohorts 10 and 11 closed following approval of protocol revision 11 (Rev-11) at each site and subjects will be enrolled in Cohort 12.

Single Ascending Dose (SAD) Cohorts

Three subjects will receive a single intravitreal (IVT) injection of Light-activated AU-011 low dose (20 µg in [redacted] µL). The injection is followed 6 to 8 hours later by exposure to 689 nm laser light. No more than one subject may be treated per day, and the treated subject must complete the 24-hour post-treatment visit with no safety issues before the next subject in a given cohort may be treated.

If all 3 subjects in the low dose group complete treatment without any dose limiting toxicity (DLT), escalation to the medium dose level group will be initiated. If a DLT is observed in 1 subject in the low dose group, this group will be expanded to 6 subjects. Dose escalation will not be allowed if 2 or more subjects in the low dose group experience a treatment-related DLT. Instead, if 2 or more subjects in the low dose group experience a treatment-related DLT, dose reduction to 10 µg in [redacted]µL may be considered for enrolling an additional 3 subjects.

One week after the last subject in the low dose group completes treatment, the study medical monitor and an independent ocular oncologist will review safety data for all subjects in the low dose group. After review and confirmation that the data support proceeding to treatment with the medium dose group, three subjects will receive a single intravitreal injection of Light-activated AU-011 medium dose (40 µg in [redacted]µL). The injection is followed 6 to 8 hours later by exposure to 689 nm laser light.

If all 3 subjects in the medium dose group complete treatment without any dose limiting toxicity (DLT), escalation to the high dose level group will be initiated. If a DLT is observed in 1 subject in the medium dose group, this group will be expanded to 6 subjects. If 2 or more subjects in the medium dose group experience a DLT after their treatment, this will confirm that the lower dose level is the maximum feasible dose (due to formulation limits).

One week after the last subject in the medium dose group completes treatment, the study medical monitor and an independent ocular oncologist will review safety data for all subjects in the medium dose group. After review and confirmation that the data support proceeding to treatment with the high dose group, 3 subjects will receive a single dose of Light-activated AU-011 high dose (80 µg administered as 2 injections of [redacted] µg in [redacted] µL not more than 2 hours apart). The second injection is followed 6 to 8 hours later by exposure to 689 nm laser light. If a DLT is observed in 1 subject in the high dose group, this group will be expanded to 6 subjects. If 2 or more subjects in the high dose group experience a DLT after their treatment, this will confirm that the medium dose level is the maximum feasible dose and the dose chosen for the repeat dose phase of the study will drop to one dose below the maximum feasible dose of 40 µg and the lower dose of 20 µg will be given as repeat doses.

Multiple Ascending Dose (MAD) Cohorts

One day after the last subject in the high dose group completes treatment, the study medical monitor and independent ocular oncologist will review safety data for all subjects and identify the maximum feasible dose for evaluation in the repeat dose phase of the study. After review and confirmation that the data support proceeding to a repeat dose regimen, 3 subjects will receive an intravitreal injection of 40 µg in [redacted] µL of Light-activated AU-011 as 2 repeat doses one week apart. Each injection is followed 6 to 8 hours later by exposure to 689 nm laser light.

If all 3 subjects in this 2 repeat 40 µg dose group complete treatment without any dose limiting toxicity (DLT) after 2 injections, then this regimen of Light-activated AU-011 may be investigated further in subsequent studies. If a DLT is observed in 1 subject in this 2 repeat 40 µg dose group, this group will be expanded to 6 subjects. If 2 or more subjects in this 2 repeat 40 µg dose group experience a DLT after their treatment, this will confirm that a lower dose repeat regimen should be investigated.

One day after the last subject in the 2 repeat 40 µg dose group completes treatment, the study medical monitor and independent ocular oncologist will review safety data for all subjects and identify whether it is safe to evaluate 3 repeat 40 µg doses in the next cohort of the study.

After review and confirmation that the data support proceeding to a 3 repeat 40 µg dose regimen, 3 subjects will receive an intravitreal injection of 40 µg in [redacted] µL of Light-activated AU-011 as 3 repeat doses 1 week apart. Each injection is followed 6 to 8 hours later by exposure to 689 nm laser light.

If all 3 subjects in this 3 repeat 40 µg dose group complete treatment without any dose limiting toxicity (DLT) after 3 injections, escalation to the next dose cohort will be initiated. If a DLT is observed in 1 subject in this 3 repeat 40 µg dose group, this group will be expanded to 6 subjects. If 2 or more subjects in this 3 repeat 40 µg dose group experience a DLT after their treatment, this will confirm that a fewer number of repeat administrations, or a lower dose at each administration should be investigated.

One day after the last subject in the 3 repeat 40 µg dose group completes treatment, the study medical monitor and independent ocular oncologist will review safety data for all subjects and identify the maximum feasible dose for continued evaluation in the repeat dose phase of the study. After review and confirmation that the data support proceeding, an 80 µg single dose repeat laser regimen will be initiated. Three subjects will receive intravitreal administration of 80 µg of Light-activated AU-011 administered as 2 injections of 40 µg in [redacted] µL (not more than 2 hours apart) followed by two 689

nm laser applications 30 minutes (± 10 minutes) apart, with the first of the 2 laser applications occurring 6 to 8 hours after the second injection.

If all 3 subjects in this 80 µg single dose followed by 2 laser applications dose group complete treatment without any dose limiting toxicity (DLT), then the study may progress to the next cohort. If a DLT is observed in 1 subject in this 2 repeat laser applications following 80 µg single dose group, this group will be expanded to 6 subjects. If 2 or more subjects in this 2 repeat laser applications following 80 µg single dose group experience a DLT after their treatment, this will confirm that a lower dose followed by repeat laser regimen, or a repeat dose followed by single laser application should be investigated further.

One day after the last subject in the 2 repeat laser applications following 80 µg single dose group completes treatment, the study medical monitor and independent ocular oncologist will review safety data for all subjects and identify whether it is safe to evaluate repeat laser applications after each of 3 repeat doses of 80 µg in the study.

After review and confirmation that the data support proceeding to the 3 repeat 80 µg dose regimen followed by a single laser application, 3 subjects will receive an intravitreal administration of 80 µg of Light-activated AU-011 administered as 2 injections of [redacted]µg in [redacted] µL (not more than 2 hours apart) as 3 repeat doses one week apart. Each administration is followed 6 to 8 hours (after the second injection) later by exposure to 689 nm laser light.

One day after the last subject in the 3 repeat 80 µg dose group followed by a single laser application completes treatment, and 4 weeks after the last subject in the 80 µg single dose followed by 2 laser applications dose group complete treatment, the study medical monitor and independent ocular oncologist will review safety data for all subjects and identify whether it is safe to evaluate 3 repeat doses of 80 µg, each followed by 2 repeat laser applications, in the next cohort of the study.

After review and confirmation that the data support proceeding to repeat laser applications after each of 3 repeat 80 µg doses, 3 subjects will receive an intravitreal administration of 80 µg of Light-activated AU-011 administered as 2 injections of [redacted]µg in [redacted] µL (not more than 2 hours apart) as 3 repeat doses one week apart. Each administration is followed 6 to 8 hours (after the second injection) later by 2 exposures to 689 nm laser light 30 minutes (± 10 minutes) apart.

If all 3 subjects in this group, who receive 3 repeat 80 µg doses, each followed by 2 repeat laser applications, complete treatment and have been followed for 4 weeks without any dose limiting toxicity (DLT) after 3 weekly administrations, then this dose and regimen will be considered the maximum feasible dose and investigated in the expanded cohort. If a DLT is observed in 1 subject in this 3 repeat 80 µg dose with 2 repeat laser applications group, this group will be expanded to 6 subjects. If 2 or more subjects in this 3 repeat 80 µg dose with 2 repeat laser applications group experience a DLT after their treatment, this will confirm that a fewer number of repeat administrations of either Light-activated AU-011 or laser, or both, or a lower dose of Light-activated AU-011 at each administration should be investigated further.

Four weeks after the final treatment of the final subject in this cohort, a review of the safety data (including EDI-OCT) by the study medical monitor and independent ocular oncologist will occur. If safety is confirmed, the 3 repeat 80 µg dose with 2 repeat laser applications will be considered the maximum feasible and tolerated dose and this regimen will be expanded by up to 12 additional subjects in Cohort 9.

Efficacy will be assessed at all study visits from Week 12 onwards.

Repeat Cycle and Observation Cohorts

Once the last subject in the expansion cohort has been enrolled and safety of the maximum safe and feasible dose is confirmed, approximately 6 additional subjects, who fulfil the criteria for the clinical diagnosis of CM, but without documented growth, will be enrolled into an observation cohort (Cohort 10). These subjects will be assessed every 3 months (ie, 90 day (+/- 7 days) intervals from the Screening Visit) until tumor growth of the CM lesion is established (as defined in Section 8.3.4.) and at which time will then receive treatment with AU-011, as 3 repeat 80 µg doses, each followed by 2 repeat laser applications and move to the same visit schedule as subjects entering the trial and receiving treatment with AU-011 immediately. These subjects will receive Cycle 2 of AU-011 administered as 3 repeat 80 µg doses, each followed by 2 repeat laser applications no earlier than the Week 12 Visit and after resolution of any inflammation resulting from the first cycle or when the inflammation is minimal and decreasing based on investigator judgement. Cycle 2 should be administered as soon as reasonably possible after inflammation has resolved or is minimal and decreasing based on investigator judgement. If the fovea is near the tumor edge, an adjustment to the laser procedure should be performed on each treatment day of both cycles as outlined in section 8.2.2 and the Injection and Laser Procedure Manual.

In addition, approximately 6 additional subjects, who meet the criteria for a clinical diagnosis of CM, with or without documented growth, will enter Cohort 11 and receive two cycles of AU-011 treatment (each cycle will be comprised of 3 repeat 80 µg doses, each followed by 2 repeat laser applications). Cycle 2 of AU-011 will be administered as 3 repeat 80 µg doses, each followed by 2 repeat laser applications no earlier than the Week 12 Visit and after resolution of any inflammation resulting from the first cycle or when the inflammation is minimal and decreasing based on investigator judgement. Cycle 2 should be administered as soon as reasonably possible after inflammation has resolved or is minimal and decreasing based on investigator judgement. If the fovea is near the tumor edge, an adjustment to the laser procedure should be performed on each treatment day of both cycles as outlined in section 8.2.2 and the Injection and Laser Procedure Manual.

The intention is to alternate the enrollment of Cohorts 10 and 11. If during the enrollment of these subjects, a subject has just been enrolled into Cohort 11 and a subject with documented growth presents, then that subject may instead be enrolled into Cohort 11 rather than Cohort 10 for which they would not be eligible due to the presence of documented growth and instead will be assigned to receive the first of 2 cycles of AU-011.

If 2 subjects experience a DLT during treatment with Cycle 2, as defined in Section 8.4.1., then no further subjects will receive Cycle 2 of AU-011 until discussed with the independent ocular oncologist and medical monitor and continuation of enrollment is confirmed.

Subjects with Documented Growth

Enrollment in Cohorts 10 and 11 was closed following approval of protocol revision 11 (Rev-11) at each site. An additional cohort, Cohort 12, of subjects with minimum defined levels of documented growth will be initiated to allow assessment of safety and efficacy of 2 cycles of AU-011 treatment in this key subgroup of subjects with CM. Since Cohort 12 has the same dose as Cohort 11 no additional safety review will be required prior to initiating this cohort.

Up to 15 subjects, who meet the criteria for a clinical diagnosis of CM with documented growth as defined in Inclusion Criteria 5C, will enter Cohort 12 and receive two cycles of AU-011 treatment (each cycle will be comprised of 3 repeat 80 µg doses, each followed by 2 repeat laser applications). Cycle 2 of AU-011 will be administered as 3 repeat 80 µg doses, each followed by 2 repeat laser applications no earlier than the Week 12 Visit and after resolution of any inflammation resulting from the first cycle or when the inflammation is minimal and decreasing based on investigator judgement. Cycle 2 should be administered as soon as reasonably possible after inflammation has resolved or is minimal and decreasing based on investigator judgement. If the fovea is near the tumor edge, an adjustment to the laser procedure should be performed on each treatment day of both cycles as outlined in section 8.2.2 and the Injection and Laser Procedure Manual.

If 2 subjects experience a DLT during treatment with Cycle 2, as defined in Section 8.4.1., then no further subjects will receive Cycle 2 of AU-011 until discussed with the independent ocular oncologist and medical monitor and continuation of enrollment is confirmed.

Study Methods:

Subjects will be screened for enrollment into the study after providing written informed consent between Day -28 and Day 1. Screening procedures include medical history, ophthalmic assessments, vital signs, and safety laboratory analyses. To be eligible for enrollment, subjects will have a small CM of ≥ 2.0 and ≤ 3.0 mm in thickness, and largest basal diameter ≤ 13.0 mm, OR tumor thickness of ≥ 1.2 and ≤ 3.0 mm with documented growth and largest basal diameter ≤ 13.0 mm. To be eligible for enrollment in Cohort 12, subjects will have clinically diagnosed primary CM with tumor thickness of ≥ 0.5 mm and ≤ 3.0 mm on B-scan ultrasound, a largest basal diameter of ≤ 13.0 mm on fundus photos with an estimated tumor volume ≤50 mm^3 associated with documented tumor growth, defined as ≥ 0.4 mm based on intersite measurements (clinical site and referring center) or ≥ 0.3 mm based on within site measurements on tumor thickness within 2 years of screening.

Qualified subjects will be enrolled into one of twelve cohorts and treated as described above. Each subject in the first 3 cohorts and in cohort 6 will receive a single IVT treatment with Light-activated AU-011, subjects in Cohort 4 will receive 2 repeat doses, and subjects in Cohorts 5, 7, 8, 9, 10, 11 and 12 will receive 3 repeat doses. After administration of Light-activated AU-011, the CM is exposed to 689 nm laser light. Subjects in Cohorts 6, 8, 9, 10, 11 and 12 will receive 2 laser applications 30 minutes (± 10 minutes) apart at 6 to 8 hours after each intravitreal administration (after the second injection for these 80 µg cohorts), while the remaining cohorts will receive a single laser application at 6 to 8 hours after each intravitreal administration (after the second injection in the 80 µg cohorts). In addition, Cohorts 10, 11 and 12 will receive Cycle 2 of AU-011 at the same dose and regimen no earlier than the Week 12 Visit and after resolution of any inflammation resulting from the first cycle or when the inflammation is minimal and decreasing based on investigator judgement. Cycle 2 should be administered as soon as reasonably possible after inflammation has resolved or is minimal and decreasing based on investigator judgement. If the fovea is near the tumor edge, an adjustment to the laser procedure should be performed on each treatment day of both cycles as outlined in section 8.2.2 and the Injection and Laser Procedure Manual.

If subjects are discharged during daylight hours, appropriate sun protection, e.g., sunglasses and a hat, will be required.

Study subjects will be required to return for ocular assessments 24 hours (± 4 hours) following intravitreal administration of study drug and on Day 8, Day 15, Day 29, Week 6, Week 8, Week 12,

Week 26, Week 39, Week 52, Week 78, and Week 104. In addition, subjects in both the 2 and 3 repeat Light-activated AU-011 administration cohorts will have an additional safety visit on Day 9. Subjects in the 3 repeat Light-activated AU-011 administration cohorts will have an additional safety visit at Day 16. Subjects in the observation cohort (Cohort 10) will be seen every 3 months (ie, 90 day (+/- 7 days) intervals from the Screening Visit) until tumor growth is established and then seen at the schedule described in Section 10 and Appendix 1 until the time of receiving Cycle 2, when they will then follow the schedule described in Appendix 4. Subjects in the observation cohort in whom tumor growth is not observed during the 2 year study period will exit the study at Week 104. Subjects in the repeat cycle of AU-011 cohorts (Cohorts 11 and 12) will also follow the schedule described in Section 10 and Appendix 1 until the time they receive the second cycle of AU-011, when they will then follow the schedule described in Appendix 4.

If the second cycle of AU-011 occurs after Visit 15 (Week 78), subjects will be followed for 26 weeks post-treatment and then may be rolled into the long-term follow-up study pending subject consent. Details regarding the follow-up visit schedule after the second cycle of AU-011 can be found in Appendix 4.

All subjects' study participation will be for a minimum of 2 years and all subjects in this study may then be rolled into the long-term follow-up study pending consent.

Ocular assessments include:

- Best Corrected Visual Acuity (BCVA)
- Slit lamp biomicroscopy
- Intraocular pressure (IOP)
- Fundoscopy
- Color fundus photography (fundus photos)
- Fluorescein angiography (FA)
- B-scan ultrasound (B-scan)
- A-scan ultrasound (A-scan) as a separate sub-study at sites with diagnostic probes
- Enhanced depth imaging optical coherence tomography (EDI-OCT)
- Optical coherence tomography angiography (OCTA) as a separate sub-study at sites with OCTA imaging systems for Cohorts 6 through 9
- Visual field
- Tumor size will be evaluated during the study.
- Hematology, serum chemistry and anti-drug antibodies (ADA)
- Concomitant medications and adverse events (AEs) will be reviewed through 30 days following the study treatment. After 30 days, for Cohorts 1 to 9, only AEs or SAEs determined by the Investigator to be related to study product and/or study procedures are to be reported. For Cohort 10, 11 and 12 subjects concomitant medications and all adverse events will be reviewed through their last study visit.

- If peri-tumoral whitening/pigmentary changes are seen during the study, additional assessments as outlined in Section 10.3.10 should be conducted.

Section 10 provides further details on the conduct of the study, study visits, and assessments. Ocular imaging, including B-scan ultrasound (B-scan), A-scan ultrasound (A-scan), fundus photos, FA, EDI-OCT, and OCTA will be read by a centralized Independent Reading Center (IRC)

Eligibility Criteria:
Inclusion Criteria

Subjects must:

1. Be at least 18 years of age of either gender or any race.
2. Have been informed about the nature and requirements of the study, voluntarily agreed to participate in the study, and documented this by signing the Informed Consent Form (ICF) before participating in any study-related activities.
3. Be willing and able to follow all instructions and attend all study visits.
4. Per the expert opinion of the Investigator, have clinically diagnosed primary CM with no known metastatic disease.
5. Have clinically diagnosed primary CM:
   A. with tumor thickness of ≥ 1.2 mm and ≤ 3.0 mm on B-scan ultrasound and with a largest basal diameter of ≤ 13.0 mm on fundus photos associated with tumor growth,

      OR

   B. with tumor thickness of ≥ 2.0 mm and ≤ 3.0 mm on B-scan ultrasound and with a largest basal diameter of ≤ 13.0 mm on fundus photos associated with the presence of subretinal fluid by OCT AND at least one of the following:

      a. Overlying orange pigment (lipofuscin) on fundus photos
      b. Vision loss
      c. Flashes or floaters

      OR

   C. **Criteria for Cohort 12**: with tumor thickness of ≥ 0.5 mm and ≤ 3.0 mm on B-scan ultrasound, a largest basal diameter of ≤ 13.0 mm on fundus photos with an estimated tumor volume ≤50 mm^3 associated with tumor growth within 2 years of screening (defined as ≥ 0.4 mm increase based on intersite measurements or ≥ 0.3 mm based on within site measurements on tumor thickness)

   NOTE: ***Whenever available at the investigative site or referring site, historical images (B-scans and/or color fundus photos) for all subjects should be provided to the Independent Reading Center at the time of entry to the study. The investigative site should make all reasonable efforts to obtain this information from referring sites.***
6. In the opinion of the treating physician, the subject could be managed by interventional therapy, or by cautious observation.
7. Be treatment-naïve for their primary CM.

8. Have a tumor for which the entire extent must be able to be imaged on required fundus photography in a single frame and treated by the laser.
9. If female and capable of becoming pregnant, agree to have pregnancy testing performed at screening (must be negative) and if required at Visit 2 (must be negative); must not be lactating; and must agree to use a medically acceptable form of birth control before administration of the investigational product and for three months after administration of the investigational product. Women considered capable of becoming pregnant include all females who have experienced menarche and have not experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) or have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy).
10. For women of childbearing potential and for males with sexual partners of childbearing potential: Acceptable forms of birth control are spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of partner. For non-sexually active females and males, abstinence will be considered an acceptable form of birth control.
11. Be otherwise in good general health, with no significant or uncontrolled medical conditions, as determined by the Investigator.
12. Be able and willing to avoid all prohibited medications for the appropriate washout period.

Exclusion Criteria

Subjects must not:

1. Have known contraindications or sensitivities to IRDye®700DX phthalocyanine-based dye, or laser in the study eye.
2. Have any ocular condition in the study eye that, in the Investigator's opinion, could affect the subject's safety or trial parameters.
3. Have a CM that invades or encompasses the optic nerve that precludes treatment, as determined by the investigator and/or shows extraocular extension.
4. Have metastatic disease confirmed by abdominal and chest imaging within three months prior to screening.
5. Have undergone vitrectomy at any time or have undergone any ocular surgical intervention in the study eye within three months before Visit 1, or are planning/will require ocular surgery in the study eye prior to the study drug administration. If the subject is likely to require cataract surgery in the study eye at any time prior to the Week 104 visit, he/she should not be enrolled.
6. Have a history of rhegmatogenous retinal detachment, diabetic retinopathy, or other active retinal disease in the study eye unrelated to the CM.
7. Have any active ocular disease in the study eye (other than CM) that may progress during the study and result in a change in vision or loss in vision (e.g., clinically significant corneal dystrophies, keratoconus, glaucoma or clinically significant retinal or macular disease).
8. Have an active ocular infection (bacterial, viral or fungal).

9. Use or require use of heparin or low molecular weight heparins within one week of treatment.
10. Use or require use of immunosuppressive or antineoplastic medications within five half-lives of Visit 1. Steroids, including inhalation steroids, are permitted.
11. Have previously received human papillomavirus (HPV) vaccination.
12. Any active malignancies other than CM, or squamous or basal cell skin cancer. If there is evidence of clinical remission for at least one year, the subject's eligibility may be discussed with the medical monitor.
13. Have any significant illness (e.g., an uncontrolled autoimmune disease, severe cardiovascular disease [confirmed by a cardiologist], active infection, etc.) that the Investigator determines could interfere with study participation or safety, or put the subject at any unnecessary risk.
14. Have planned or will require systemic surgery during the active study treatment period.
15. Have used an investigational drug or medical device within 30 days or 5 half-lives of Visit 1 or be concurrently enrolled in another investigational product trial.

Additional Therapy with AU-011

Subjects may receive additional therapy with AU-011 at the maximum tolerated and feasible dose which is 3 repeat doses of 80 µg each followed by two laser applications (treatment regimen) as outlined in Section 8.3.3 of the protocol. Also, as outlined in Section 8.2.2 and the Injection and Laser Procedure Manual, if the fovea is near the tumor edge, an adjustment to the laser procedure should be performed on each treatment day.

Investigational product, dosage and mode of administration:

The investigational treatment is Light-activated AU-011, a combination product consisting of a drug (AU-011) and a laser (Aura Photoactivation System) that delivers 689 nm light to activate the drug once it is bound to the tumor cells. AU-011 drug substance is a modified human papillomavirus-derived, empty viral like particle (VLP) conjugated to approximately 200 molecules of a phthalocyanine-based photosensitizer IRDye®700DX (the "Dye").

AU-011 is administered by intravitreal injection. Laser light (689 nm) is applied to the CM from 6 hours to 8 hours after administration.

Statistical Methods:

Since this is an open-label, exploratory study, no formal hypothesis testing will be performed. Efficacy will be assessed at the Week 12, 26, 39, 52, 78 and 104 visits for any potential tumor response and changes in ETDRS best corrected visual acuity (BCVA). This will include change from baseline at each visit in tumor thickness by ultrasound and largest basal diameter by digital fundus photography. The proportion of subjects who meet the definition of stable disease (do not meet the definition of disease progression) will also be reported for each visit using change in tumor thickness and changes in largest basal diameter. Change from baseline in ETDRS BCVA letter score at Week 12 and at each subsequent visit and the proportion of subjects who lose or gain 5, 10 or 15 letters will also be evaluated.

Exploratory analyses will be performed for change in internal reflectivity of tumors by A-scan ultrasound at each visit and macular changes (foveal avascular zone and capillary density) by OCTA at each visit.

Background and demographic characteristics will be presented. Continuous variables will be summarized by descriptive statistics (sample size, mean, standard deviation, median, minimum and maximum). Discrete variables will be summarized by frequencies and percentages.

Efficacy and safety will be analyzed at various intervals after the first 2 cohorts have completed 12 months of follow-up and then at further intervals as subsequent cohorts reach similar milestones. Specific details of the timing of such analyses will be included in the Statistical Analysis Plan.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 1 Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADA	Anti-drug antibodies
ADL	Activities of Daily Living
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
A-scan	A-scan ultrasonography
AU-011	A modified human papillomavirus-derived, empty viral like particle (VLP) conjugated to approximately 200 molecules of photosensitizer IRDye® 700DX
BCVA	Best corrected visual acuity
BP	Blood pressure
B-scan	B-scan ultrasonography
CBC	Complete blood count
CM	Choroidal melanoma
CMP	Comprehensive metabolic panel
CRO	Contract research organizations
dL	Deciliter
DLT	Dose limiting toxicity
eCRF	Electronic case report form
EDI-OCT	Enhanced Depth Imaging Optical Coherence Tomography
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HPV	Human papillomavirus
HSPG	Heparan sulfate proteoglycan
ICF	Informed consent form
ICH	International Conference on Harmonization
IND	Investigational New Drug application

Abbreviation or Specialist Term	Explanation
IOP	Intraocular pressure
IRB	Institutional Review Board
IRC	Independent Reading Center
J	Joules
LBD	Largest basal diameter
Min	Minute
mg	Milligram
mL	Milliliter
µg	Microgram
µL	Microliter
N	Number (refers to subjects)
nm	Nanometer
OCTA	Optical coherence tomography angiography
PHI	Protected health information
PI	Principal Investigator
PK	Pharmacokinetic
PV	Papillomavirus
SAE	Serious adverse event
SGOT	Serum glucose-oxaloacetic transaminase
SGPT	Serum glucose-pyruvic transaminase
SOP	Standard operating procedure
TEAE	Treatment emergent adverse event
UM	Uveal melanoma
US	United States of America
VLP	Viral like particle

4. INTRODUCTION

4.1. Uveal Melanoma

The most common primary malignancy of the eye is uveal melanoma (UM)., or more precisely, choroidal melanoma (CM) (Bell 2004). The neoplasm is most commonly manifested in the choroid (90% of cases) followed by the ciliary body (7%), or iris (2%). It is more common in Caucasian adults of northern European descent, who have blue or green eyes and fair skin with a tendency to sunburn, though a definitive link between sun exposures and UM has not been proven (Shields 2014). There are some who believe that blue-eyed persons with extensive sun exposure have higher risk for melanoma (Schmidt-Pokrzywniak 2009). Nevi on the skin have been shown to have an association with increased risk for development of CM (Shah 2005; Singh 2012; Weis 2009). The condition rarely appears in pediatric populations (Shields 2012).

Intraocular tumors present with general visual symptoms, but some patients are asymptomatic with tumors detected as an incidental finding on routine ophthalmologic examination. Visual symptoms include persistent photopsia, floaters, visual field loss, or visual acuity loss (Shields 2014). Diagnosis is based on fundoscopic examination by an experienced clinician using noninvasive testing techniques such as ultrasound, fluorescein angiography (FA) and ocular coherence tomography (OCT). This trial will utilize enhanced depth imaging optical coherence tomography (EDI-OCT) which is more sensitive in assessing disease findings in choroidal melanoma than standard spectral domain optical coherence tomography (SD-OCT). CM is believed to result from transformation of benign choroidal nevi or develop as a *de novo* malignancy. Though early detection can be challenging, there are clinical features that suggest a lesion is "at-risk" for transforming into melanoma and these include lesion thickness over 2 mm, presence of orange pigment, ≤ 3 mm distance from the optic nerve, subretinal fluid accumulation, hollowness on ultrasound, and absence of halo (Shields 2014). Poor prognosis depends on several clinical factors including large tumor size, involvement with the ciliary body, increased age, and extraocular extension.

Because CM is less prevalent than other cancers, is often asymptomatic in early phases, and is slow-growing, detection and prompt diagnosis have complicated treatment studies. In the absence of new therapies and efficacy trials, historical treatment focused on local control of tumor growth, most often through radiation treatments (both plaque brachytherapy and proton beam radiotherapy) or a surgery called enucleation (complete removal of the affected globe). Even with radical treatment such as enucleation; however, metastatic growth – most often and always fatally to the liver – has been widely reported (Collaborative Ocular Melanoma Study Group [COMS] 2004; Bishop 2014).The Collaborative Ocular Melanoma Study (COMS 1998), which recruited 3,217 patients with primary ciliary body or choroidal melanoma in the US from 1987 to 1998, was commissioned to address the paucity of data regarding prospective evaluation of CM treatment, and it has subsequently produced a large body of data regarding CM. This 3-arm study included two multicenter randomized clinical trials. One arm compared the effectiveness of brachytherapy (also known as plaque brachytherapy, plaque radiotherapy or simply, plaque) to enucleation for treatment of medium-size (≥2.5 mm to ≤10.00 mm) choroidal melanomas. The second arm compared the effectiveness of enucleation with and without preoperative external-beam radiotherapy for large choroidal melanomas (>10.00 mm). The third arm was an observational study of small (<2.5 mm) choroidal melanomas.

Cumulative rates of metastases at 5 and 10 years after treatment have been reported at 25% and 34%, respectively (COMS 2005). The most frequently reported sites of metastases include the liver (90%), lungs (24%), and bone (16%) (COMS 2001a; COMS 2004). Patients with metastases that do not involve the liver have longer survival (19–28 months) (Eskelin 2000).

The median survival for a patient with hepatic metastasis is 6 months (estimated survival of 15–20% at 1 year; 10% at 2 years), irrespective of treatment (Bedikian 2006; COMS 2005). Asymptomatic patients at the time of diagnosis of metastases have a slightly longer survival in relation to symptomatic patients (Kim 2010).

COMS provides excellent historical control data for melanoma treatments, and has refined standard CM treatment protocols. For example, COMS showed no difference in 5- or 10- year mortality for large- and medium-sized UMs whether treated with plaque brachytherapy or enucleation (COMS 2001b); nor was there improved survival with preoperative radiation for large choroidal melanomas. Consequently, plaque has remained the standard of care treatment, while enucleation is reserved for patients with the most symptomatic and recurrent CM. The data also steer the direction of optimal treatment to secondary outcomes, such as preservation of visual acuity, instead of solely focusing on mortality and tumor growth.

It is hypothesized that since Light-activated AU-011 treatment is both potent and highly targeted to the tumor that healthy ocular tissues will be preserved.

4.2. Existing Therapies for Choroidal Melanoma

CM is commonly treated according to size (or thickness) of the neoplasm (small ≤ 2.4 mm, medium = 2.5-10 mm, and large > 10 mm according to thickness as measured by ultrasound), documented growth rate, and location (COMS 2004b; Shields 2014). Currently, the most widely used first line treatment options are radiation therapy and enucleation. Management of small suspicious nevi that are at high risk of evolving into CM and small neoplasms is not standardized. Depending on a number of clinical judgment factors, including patient choice and rate of tumor growth, the patient may be treated immediately or followed further before being treated.

There are two main types of radiation therapy: plaque brachytherapy (using iodine-125, ruthenium-106, or palladium-103) and external beam radiation therapy applied as proton beam radiotherapy (Laver 2010). Both of these radiation-based therapies require surgical procedures. In plaque brachytherapy, surgery is required to place the plaque, and in proton beam radiotherapy, surgery is required to enable localization of the tumor. In addition, radiation therapy lacks tumor tissue specificity. As such, it is usually accompanied by irreversible radiation damage to the retina and other ocular structures and results in up to a 6 line or more vision loss at 24 months (COMS 2001c; Bianciotto 2010). In 4% of cases, enucleation is performed after radiation therapy due to blindness, painful eyes or uncontrolled tumor growth (COMS 2001c).

Alternatives to radiation therapy that are not standard of care but have been explored include transpupillary thermotherapy and photodynamic therapy. These therapies are not targeted and may offer limited benefit or may be appropriate for only a subset of patients (e.g., amelanotic tumors), and are not without risks, such as retinal bleeding or vision loss shortly after treatment

(Shields 2002; Pereira 2013). Larger scale tumors cannot be treated by radiation therapies and require enucleation.

4.3. Viruses as Anti-Cancer Agents

The use of viruses as anti-cancer agents has been considered for many years. Initially, the use of viruses in cancer therapy has been towards cancer cell lysis, as many viruses undergo a lytic phase in their life cycle. For instance, the Herpes Simplex Virus-1 is an oncolytic virus that has been developed for anti-cancer therapy as talimogene laherparepvec (T-VEC; Imlygic®) (Andtbacka 2013), and the FDA has approved T-VEC for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery, based on results from the Phase III OPTiM study (Andtbacka 2013, Broderick 2015). It utilizes the property of tumor lysis as a result of viral replication within the tumor as its mechanism of action. Other similar therapies based on other oncolytic virus types (Reovirus, Vaccinia virus) are also in clinical trials (Alemany 2013; Vacchelli 2013). However, the limitation of oncolytic virus based anti-cancer therapy is that of tumor targeting, and as such, T-VEC must be administered by direct intra-lesional injection. Additionally, the tumor cytotoxicity is dependent upon the active replication of the viral agent within the tumor, which may limit its efficacy and increase the risk of toxicity after multiple administrations.

A novel approach to anti-cancer therapy is the use of viral like particles or pseudo-viruses as drug delivery vehicles for targeted therapy. The use of these novel viral-derived structures presents advantages over using full replicating viruses. VLPs and pseudo-viruses are comprised of the outer protein capsid of a virus without any of its genetic material and can be used to deliver drugs efficiently to tumors without relying on viral replication and as such, overcomes the limitations of oncolytic technologies.

In particular, the papillomavirus (PV) has a simple two protein outer shell structure that self-assembles into 55 nM VLPs without incorporating the viral genome. Papillomaviruses have a unique tropism towards cancer cells that is mediated by the binding of the viral capsid to specific modifications of heparan sulfate proteoglycans (HSPGs) on the surface of the cancer cell (Handisurya 2012).

In a number of nonclinical studies, it has been found that PV can bind cancer cells with high selectivity both *in vitro* and *in vivo* through a mechanism of action that involves the initial binding to HSPGs on the tumor cell membrane as well as the basement membrane (Handisurya 2012). HSPGs interact with many proteins, playing a role in cell signaling via growth factors and chemokines modulating cell growth, motility, adhesion and differentiation. Up-regulation of HSPGs can be found on tumors, which can lead to unregulated autocrine signaling loops promoting tumorigenesis and angiogenesis (Blackhall 2001; Perrimon 2000; Schlessinger 2000; Yu 2002).

4.4. Light Activated AU-011 for the Treatment of Choroidal Melanoma

Though several treatment options exist for CM, no treatment both reliably controls tumor growth and preserves vision. Since Light-activated AU-011 therapy is extremely potent and highly targeted to the tumor itself, this therapy has great potential to preserve healthy ocular tissues.

The investigational treatment is Light-activated AU-011, a combination product consisting of a drug (AU-011) and a laser (Aura Photoactivation System) that delivers 689 nm light to activate the drug once it is bound to the tumor cells. AU-011 drug substance is a modified human papillomavirus-derived, empty viral like particle conjugated to approximately 200 molecules of a phthalocyanine-based photosensitizer IRDye® 700DX (the "Dye").

Figure 1 Structure of AU-011

The VLP is composed of two modified viral capsid proteins that self-assemble into an empty proteinaceous sphere of approximately 55 nM in diameter. Each VLP comprises 72 capsomeres, which are made of ~5 molecules of viral capsid protein L1 and ~1 molecule of capsid protein L2. The native amino acid sequence of the L1 protein FG loop which harbors the major epitopes for immune recognition has been altered to minimize an immunogenic response (Fleury 2014).

The Dye molecule is a phthalocyanine that is derivatized with hydrophilic chains for aqueous application on one end and with a labile succinimido group on the other. The labile succinimido moiety covalently cross-links to proteins via the primary amine of lysyl residues. An aliphatic chain acts as a spacer to relieve steric hindrance between the protein and the phthalocyanine core for subsequent activation with light at 689 nm. Upon light activation at 689 nm, the phthalocyanine core acts as a photosensitizer. When targeted to the CM via the AU-011 VLP component, the photosensitizer activity of the Dye results in the selective cell necrosis of the CM tumor cells while sparing healthy cells (Mitsunaga 2012, Kines 2018). A second laser application will also be investigated in this study to ensure that maximum tumor cell necrosis occurs with each administration of Light-activated AU-011. This will ensure selection of the maximum feasible dose in terms of drug dose, number of treatments and number of laser applications.

4.5. Nonclinical Studies of AU-011

The nonclinical program for AU-011 consists of pharmacology (pharmacodynamic), pharmacokinetic, and toxicology studies. The results of these studies support the clinical development of Light-activated AU-011 for the treatment of primary CM. Refer to the IB for additional information.

4.5.1. Pharmacodynamic Studies

In vitro and *in vivo* pharmacology or pharmacodynamic studies with AU-011 were undertaken to demonstrate the following attributes of AU-011:

- AU-011 binding to ocular melanoma cells and the dependence of this binding on the interaction of AU-011 with HSPGs on the tumor cell surface.
- AU-011 killing of uveal tumor cells as a function of AU-011 concentration or dose and the amount of light delivered.
- Additionally, efficacy in orthotopic xenograft, animal models of UM after systemic and IVT administration of AU-011.

Additional information on the AU-011 pharmacodynamic studies conducted to date is provided in the IB.

4.5.2. Pharmacokinetics

After IVT administration in a rabbit orthotopic xenograft model of UM, AU-011 was able to penetrate the tumor and was evenly distributed throughout the tumor. Studies in a rabbit orthotopic xenograft model demonstrated that detectable and quantifiable AU-011 concentrations were seen in tumor tissue at 30 minutes and 8 hours and less so at 16 and 24 hours.

In separate studies in naïve rabbits, AU-011 was readily detectable in the vitreous and retina/choroid samples at 24 hours after IVT injection, and at 96 hours, AU-011 vitreous and retina/choroid concentrations were no longer detectable. No detectable concentrations of AU-011 were found in the lens, and results showed that the systemic concentrations of AU-011 were near or below the limit of detection.

4.5.3. Toxicology

AU-011 was administered as a single dose *via* IVT injection at doses of 5, 20, or 40 µg/eye followed by laser photoactivation to dogs; after dosing, animals were observed for 7 days (Study Day 8, terminal sacrifice) or 35 days (Study Day 29, recovery sacrifice) to assess the reversibility, persistence, or delayed occurrence of effects (AU-TOX-020). No AU-011-related organ weight, macroscopic, or microscopic findings occurred at any of the doses and the No-Observable-Adverse-Effect Level (NOAEL) was considered to be 40 µg/eye of AU-011 delivered as a single IVT dose with a corresponding laser treatment of 50 J/cm^2.

Additional information on the AU-011 toxicology studies conducted to date is provided in the Investigator's Brochure (IB).

4.6. Rationale for the Phase 1b/2 Clinical Trial of Light-Activated AU-011 in Choroidal Melanoma

Light-activated AU-011 is being developed for the treatment of primary CM. This treatment is designed as a targeted tumor killing agent that has the potential to preserve healthy ocular tissues while controlling the tumor. This mechanism of action addresses a significant unmet medical need in patients with CM where vision loss is a common side effect of current therapies. If AU-011 treatment controls tumor growth successfully without the concomitant loss of vision associated with radiotherapy or complete loss of vision following enucleation, earlier treatment

of CM may become the standard of care for these patients. Because AU-011 specifically targets tumor cells, the response of tumors after treatment may be different than that following plaque radiotherapy, which is less selective and will cause death, not only to the melanoma tumor cells, but also the benign choroidal nevus cells, the vascular cells and even the sclera within the treatment area. The number of malignant tumor cells versus benign nevus cells in small melanomas is currently unknown. Some clinical trials (Singh 2005) presume that all melanomas arise from transdifferentiated nevi whereas others presume a portion of these lesions will occur spontaneously or '*de novo*.' Despite the possibility of a different tumor response with a targeted therapy like AU-011 versus radioactivity, all tumors being treated with AU-011 should meet the definition of stable disease as a result of the selective necrosis of the tumor cell component of the lesion.

The first expansion cohort (Cohort 9) is designed to establish the preliminary efficacy of AU-011 delivered at the highest dose that is safe and well tolerated from the escalation phase of the trial. Cohort 10 is designed to provide estimates of growth rates in observation subjects and Cohort 11 is designed to demonstrate the safety and tolerability of administering two 3-week treatment cycles of AU-011. Cohort 12 is designed to evaluate the efficacy and safety of AU-011 in subjects with documented growth who are similar to the planned Phase 3 population.

5. TRIAL OBJECTIVES AND PURPOSE

5.1. Primary Objective

The objective of this study is to evaluate the safety of IVT administration of one of 3 dose levels, repeat dose regimens and one or two laser applications of Light-activated AU-011 given in one or two treatment cycles in the treatment of subjects with small primary choroidal melanoma.

5.2. Secondary and Exploratory Objectives

Secondary objectives include evaluating:

- Efficacy of AU-011 with one or two treatment cycles with the maximum safe and feasible dose
- Efficacy and safety of AU-011 in subjects with documented growth
- The immunogenicity of AU-011
- A-scan amplitudes of the internal reflectivity of the lesion at study sites with diagnostic probes
- Optical coherence tomography angiography (OCTA) image changes at study sites with OCTA imaging systems for Cohorts 6 through 9

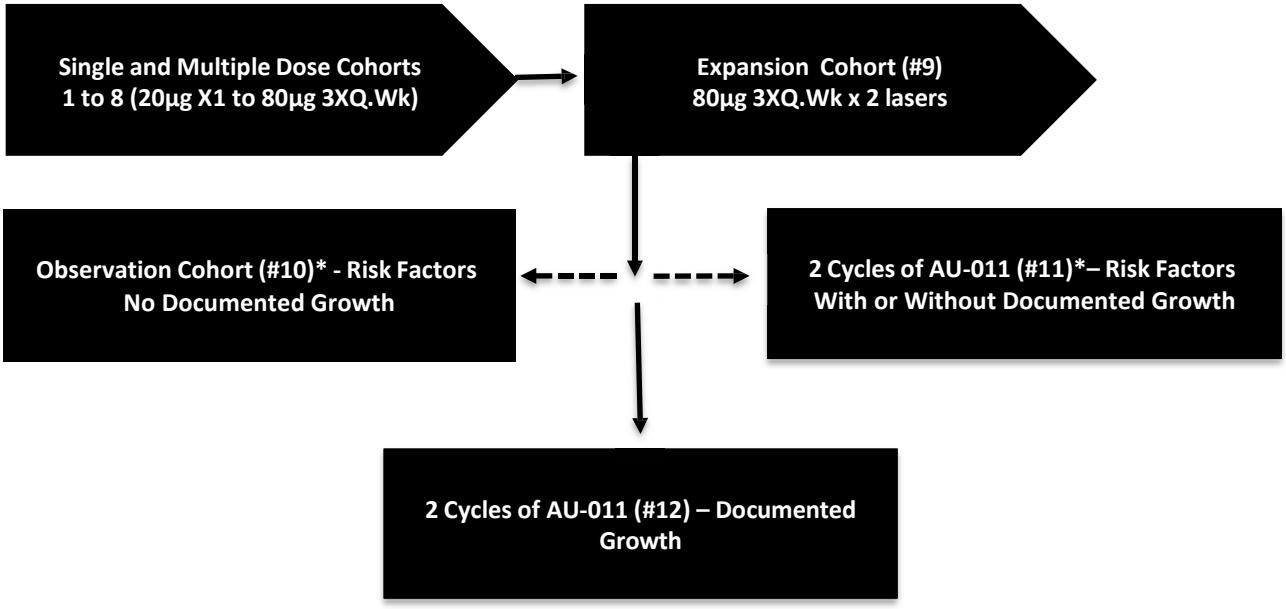
6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

Study Design:

This is an open-label, ascending single and repeat dose and cycle, multicenter study, designed to evaluate the safety, immunogenicity and efficacy of Light-activated AU-011 at 3 dose levels and single and 2 repeat dose regimens and cycles of Light-activated AU-011 and up to two laser applications in approximately 60 subjects with primary CM. The dose escalation design is shown in the figure below. Safety assessments will take place at all study visits and the efficacy assessments will commence at the Week 12 visit.

Figure 2 Dose Escalation Schematic



*Alternating enrollment; enrollment in Cohorts 10 and 11 closed following approval of protocol revision 11 (Rev-11) at each site and subjects will be enrolled in Cohort 12.

Single Ascending Dose (SAD) Cohorts

Three subjects will receive a single IVT injection of Light-activated AU-011 low dose (20 µg in 50 µL). The injection is followed 6 to 8 hours later by exposure to 689 nm laser light. No more than one subject may be treated per day, and the treated subject must complete his/her 24-hour post-treatment visit with no safety issues before the next subject in a given cohort may be treated.

If all 3 subjects in the low dose group complete treatment without any dose limiting toxicity (DLT), escalation to the medium dose level (40 µg in [redacted] µL) group will be initiated. If a DLT is observed in 1 subject in the low dose group, this group will be expanded to 6 subjects. Dose escalation will not be allowed if 2 or more subjects in the low dose group experience a treatment-related DLT. Instead, if 2 or more subjects in the low dose group experience a treatment-related DLT, dose reduction to 10 µg in [redacted] µL may be considered for enrolling an additional 3 subjects.

One week after the last subject in the low dose group completes treatment, the study medical monitor and independent ocular oncologist will review safety data for all subjects in the low dose group. After review and confirmation that the data support proceeding to treatment with the medium dose group, three subjects will receive a single IVT injection of Light-activated AU-011 medium dose (40 µg in [redacted] µL). The injection is followed 6 to 8 hours later by exposure to 689 nm laser light. If all 3 subjects in the medium dose group complete treatment without any dose limiting toxicity (DLT), escalation to the high dose level group will be initiated. If a DLT is observed in 1 subject in the medium dose group, this group will be expanded to 6 subjects. If 2 or more subjects in the medium dose group experience a DLT after their treatment, this will confirm that the low dose level is the maximum feasible dose (due to formulation limits).

One week after the last subject in the medium dose group completes treatment, the study medical monitor and an independent ocular oncologist will review safety data for all subjects in the medium dose group. After review and confirmation that the data support proceeding to treatment with the high dose group, three subjects will receive a single dose of Light-activated AU-011 high dose (80 µg administered as 2 injections of 40 µg in [redacted] µL not more than two hours apart). The second injection is followed 6 to 8 hours later by exposure to 689 nm laser light. If a DLT is observed in 1 subject in the high dose group, this group will be expanded to 6 subjects. If 2 or more subjects in the high dose group experience a DLT after their treatment, this will confirm that the medium dose level is the maximum feasible dose and the dose chosen for the repeat dose phase of the study will drop to one dose below the maximum feasible dose of 40 µg and the lower dose of 20 µg will be given as repeat doses.

Multiple Ascending Dose (MAD) Cohorts

One day after the last subject in the high dose group completes treatment, the study medical monitor and independent ocular oncologist will review safety data for all subjects and recommend proceeding to the repeat dose phase of the study.

After review and confirmation that the data support proceeding to repeat dose regimens, 3 subjects will receive an intravitreal injection of 40 µg in [redacted] µL of Light-activated AU-011 as 2 repeat doses 1 week apart. Each injection is followed 6 to 8 hours later by exposure to 689 nm laser light.

If all 3 subjects in this 2 repeat 40 µg dose group complete treatment without any dose limiting toxicity (DLT) after 2 injections, then this regimen may be investigated further in subsequent studies. If a DLT is observed in 1 subject in this 2 repeat 40 µg dose group, this group will be expanded to 6 subjects. If 2 or more subjects in this 2 repeat 40 µg dose group experience a DLT after their treatment, this will confirm that a lower repeat dose regimen should be investigated.

One day after the last subject in the 2 repeat 40 µg dose group completes treatment, the study medical monitor and independent ocular oncologist will review safety data for all subjects and identify whether it is safe to evaluate 3 repeat 40 µg doses in the next cohort of the study.

After review and confirmation that the data support proceeding to 3 repeat 40 µg dose regimen, 3 subjects will receive an intravitreal injection of 40 µg in [redacted] µL of Light-activated AU-011 as 3 repeat doses 1 week apart. Each injection is followed 6 to 8 hours later by exposure to 689 nm laser light.

If all 3 subjects in this 3 repeat 40 µg dose group complete treatment without any dose limiting toxicity (DLT) after 3 injections, escalation to the next dose cohort will be initiated. If 2 or more subjects in this 3 repeat 40 µg dose group experience a DLT after their treatment, this will confirm that a fewer number of repeat administrations, or a lower dose at each administration should be investigated.

One day after the last subject in the 3 repeat 40 µg dose group completes treatment, the study medical monitor and independent ocular oncologist will review safety data for all subjects and identify the maximum feasible dose for continued evaluation in the repeat dose phase of the study. After review and confirmation that the data support proceeding, an 80 µg single dose repeat laser regimen will be initiated. Three subjects will receive intravitreal administration of 80 µg of Light-activated AU-011 administered as 2 injections of 40 µg in [redacted] µL (not more than 2 hours apart) followed by two 689 nm laser applications 30 minutes (± 10 minutes) apart, with the first of the 2 laser applications occurring 6 to 8 hours after the second injection.

If all 3 subjects in this 80 µg single dose followed by 2 laser applications dose group complete treatment without any dose limiting toxicity (DLT), then the study may progress to the next cohort. If a DLT is observed in 1 subject in this 2 repeat laser applications following 80 µg single dose group, this group will be expanded to 6 subjects. If 2 or more subjects in this 2 repeat laser applications following 80 µg single dose group experience a DLT after their treatment, this will confirm that a lower dose followed by repeat laser regimen, or a repeat dose followed by single laser application, should be investigated further.

One day after the last subject in the 2 repeat laser applications following 80 µg single dose group completes treatment, the study medical monitor and independent ocular oncologist will review safety data for all subjects and identify whether it is safe to evaluate repeat laser applications after each of 3 repeat doses of 80 µg in the study.

After review and confirmation that the data support proceeding to the 3 repeat 80 µg dose regimen followed by a single laser application, 3 subjects will receive an intravitreal administration of 80 µg of Light-activated AU-011 administered as 2 injections of 40 µg in [redacted] µL (not more than 2 hours apart) as 3 repeat doses one week apart. Each administration is followed 6 to 8 hours (after the second injection) later by exposure to 689 nm laser light.

One day after the last subject in the 3 repeat 80 µg dose group, followed by a single laser application, completes treatment and 4 weeks after the last subject in the 80 µg single dose followed by 2 laser applications dose group complete treatment, the study medical monitor and independent ocular oncologist will review safety data for all subjects and identify whether it is safe to evaluate 3 repeat doses of 80 µg, each followed by 2 repeat laser applications, in the next cohort of the study.

After review and confirmation that the data support proceeding to repeat laser applications after each of 3 repeat 80 µg doses, 3 subjects will receive an intravitreal administration of 80 µg of Light-activated AU-011 administered as 2 injections of 40 µg in [redacted] µL (not more than 2 hours apart) as 3 repeat doses one week apart. Each administration is followed 6 to 8 hours (after the second injection) later by 2 exposures to 689 nm laser light 30 minutes (± 10 minutes) apart.

If all 3 subjects in this group, who receive 3 repeat 80 µg doses, each followed by 2 repeat laser applications, complete treatment and have been followed for 4 weeks without any dose limiting toxicity (DLT) after 3 weekly administrations, then this dose and regimen will be considered the

maximum feasible dose and investigated in the expanded cohort. If a DLT is observed in 1 subject in this 3 repeat 80 µg dose with 2 repeat laser applications group, this group will be expanded to 6 subjects. If 2 or more subjects in this 3 repeat 80 µg dose with 2 repeat laser applications group experience a DLT after their treatment, this will confirm that a fewer number of repeat administrations of either Light-activated AU-011 or laser, or both, or a lower dose of Light-activated AU-011 at each administration should be investigated further.

Four weeks after the final treatment of the final subject in this cohort, a review of the safety data (including EDI-OCT) by the study medical monitor and independent ocular oncologist will occur. If safety is confirmed, the 3 repeat 80 µg dose with 2 repeat laser applications will be considered the maximum feasible and tolerated dose and this regimen will be expanded by up to 12 additional subjects in Cohort 9.

Repeat Cycle and Observation Cohorts

Once the last subject in the expansion cohort has been enrolled and safety of the maximum safe and feasible dose is confirmed, approximately 6 additional subjects, who fulfil the criteria for the clinical diagnosis of CM, but without documented growth, will be enrolled into an observation cohort (Cohort 10). These subjects will be assessed every 3 months (ie, 90 day (+/- 7 days) intervals from the Screening Visit) until tumor growth of the CM lesion is established (as defined in Section 8.3.4.) and at which time will then receive treatment with AU-011, as 3 repeat 80 µg doses, each followed by 2 repeat laser applications and move to the same visit schedule as subjects entering the trial and receiving treatment with AU-011 immediately. These subjects will receive Cycle 2 of AU-011 administered as 3 repeat 80 µg doses, each followed by 2 repeat laser applications no earlier than the Week 12 Visit and after resolution of any inflammation resulting from the first cycle or when the inflammation is minimal and decreasing based on investigator judgement. Cycle 2 should be administered as soon as reasonably possible after inflammation has resolved or is minimal and decreasing based on investigator judgement. If the fovea is near the tumor edge, an adjustment to the laser procedure should be performed on each treatment day of both cycles as outlined in section 8.2.2 and the Injection and Laser Procedure Manual.

In addition, approximately 6 further subjects, who meet the criteria for a clinical diagnosis of CM, with or without documented growth, will enter Cohort 11 and receive two cycles of AU-011 treatment (each cycle will be comprised of 3 repeat 80 µg doses, each followed by 2 repeat laser applications). Cycle 2 of AU-011 will be administered as 3 repeat 80 µg doses, each followed by 2 repeat laser applications no earlier than the Week 12 Visit and after resolution of any inflammation resulting from the first cycle or when the inflammation is minimal and decreasing based on investigator judgement. Cycle 2 should be administered as soon as reasonably possible after inflammation has resolved or is minimal and decreasing based on investigator judgement. If the fovea is near the tumor edge, an adjustment to the laser procedure should be performed on each treatment day of both cycles as outlined in section 8.2.2 and the Injection and Laser Procedure Manual.

The intention is to alternate the enrolment of Cohorts 10 and 11. If during the enrollment of these subjects, a subject has just been enrolled into Cohort 11 and a subject with documented growth presents, then that subject may instead be enrolled into Cohort 11 rather than Cohort 10 for which they would not be eligible due to the presence of documented growth and instead will be assigned to receive the first of 2 cycles of AU-011.

If 2 subjects experience a DLT during treatment with Cycle 2, as defined in Section 8.4.1., then no further subjects will receive Cycle 2 of AU-011 until discussed with the independent ocular oncologist and medical monitor and continuation of enrollment is confirmed.

Subjects with Documented Growth

Enrollment in Cohorts 10 and 11 was closed following approval of protocol revision 11 (Rev-11) at each site. An additional cohort, Cohort 12, of subjects with minimum defined levels of documented growth will be initiated to allow assessment of safety and efficacy of 2 cycles of AU-011 treatment in this key subgroup of subjects with CM. Since Cohort 12 has the same dose as Cohort 11 no safety review will be required.

Up to 15 subjects, who meet the criteria for a clinical diagnosis of CM with documented growth as defined in Inclusion Criteria 5C, will enter Cohort 12 and receive two cycles of AU-011 treatment (each cycle will be comprised of 3 repeat 80 µg doses, each followed by 2 repeat laser applications). Cycle 2 of AU-011 will be administered as 3 repeat 80 µg doses, each followed by 2 repeat laser applications no earlier than the Week 12 Visit and after resolution of any inflammation resulting from the first cycle or when the inflammation is minimal and decreasing based on investigator judgement. Cycle 2 should be administered as soon as reasonably possible after inflammation has resolved or is minimal and decreasing based on investigator judgement. If the fovea is near the tumor edge, an adjustment to the laser procedure should be performed on each treatment day of both cycles as outlined in section 8.2.2 and the Injection and Laser Procedure Manual.

If 2 subjects experience a DLT during treatment with Cycle 2, as defined in Section 8.4.1., then no further subjects will receive Cycle 2 of AU-011 until discussed with the independent ocular oncologist and medical monitor and continuation of enrollment is confirmed.

Study Methods

Subjects will be screened for enrollment into the study after providing written informed consent between Day -28 and Day 1. Screening procedures include medical history, ophthalmic assessments, vital signs, and safety laboratory analyses. To be eligible for study enrollment, subjects will have a small CM of ≥ 2.0 and ≤ 3.0 mm in thickness, and largest basal diameter ≤ 13.0 mm, OR tumor thickness of ≥ 1.2 and ≤ 3.0 mm with documented growth and largest basal diameter ≤ 13.0 mm. To be eligible for enrollment in Cohort 12, subjects will have clinically diagnosed primary CM with tumor thickness of ≥ 0.5 mm and ≤ 3.0 mm on B-scan ultrasound, a largest basal diameter of ≤ 13.0 mm on fundus photos with an estimated tumor volume ≤50 mm^3 associated with documented tumor growth, defined as ≥ 0.4 mm based on intersite measurements (clinical site and referring center) or ≥ 0.3 mm based on within site measurements on tumor thickness within 2 years of screening.

Qualified subjects will be enrolled into one of the 12 Cohorts described above. Each subject in the first three Cohorts 1-3 and in Cohort 6 will receive a single intravitreal treatment with Light-activated AU-011, subjects in Cohort 4 will receive 2 repeat doses, and subjects in Cohorts 5, 7, 8, 9, 10, 11 and 12 will receive 3 repeat doses. After administration of Light-activated AU-011, the CM is exposed to 689 nm laser light. Subjects in Cohorts 6, 8, 9, 10, 11 and 12 will receive 2 laser applications 30 minutes (± 10 minutes) apart at 6 to 8 hours after each IVT administration (after the second injection for these 80 µg cohorts), while the remaining cohorts will receive a single laser application at 6 to 8 hours after each IVT administration (after the second injection in

the 80 µg cohorts). In addition, Cohorts 10, 11 and 12 will receive Cycle 2 of AU-011 at the same dose and regimen no earlier than the Week 12 Visit and after resolution of any inflammation resulting from the first cycle or when the inflammation is minimal and decreasing based on investigator judgement. Cycle 2 should be administered as soon as reasonably possible after inflammation has resolved or is minimal and decreasing based on investigator judgement. If the fovea is near the tumor edge, an adjustment to the laser procedure should be performed on each treatment day of both cycles as outlined in section 8.2.2 and the Injection and Laser Procedure Manual.

If subjects are discharged during daylight hours, appropriate sun protection, e.g., sunglasses and a hat, will be required.

Study subjects will be required to return for an ocular examination 24 hours ± 4 hours following intravitreal administration, followed by 11 visits (Day 8, Day 15, Day 29, Week 6, Week 8, Week 12, Week 26, Week 39, Week 52, Week 78, and Week 104). At these visits, subjects will be monitored with systemic and ophthalmic assessments. In addition, subjects in both the 2 and 3 repeat Light-activated AU-011 administration cohorts will have an additional safety visit on Day 9. Subjects in the 3 repeat Light-activated AU-011 administration cohorts will have an additional safety visit at Day 16. Subjects in the observation cohort (Cohort 10) will be seen every 3 months (ie, 90 day (+/- 7 days) intervals from the Screening Visit) until tumor growth is established and then seen at the schedule described in Section 10 and Appendix 1 until the time of receiving Cycle 2, when they will then follow the schedule described in Appendix 4. Subjects in the observation cohort in whom tumor growth is not observed during the 2 year study period will exit the study at Week 104. Subjects in the repeat cycle of AU-011 cohorts (Cohorts 11 and 12) will also follow the schedule described in Section 10 and Appendix 1 until the time they receive the second cycle of AU-011, when they will then follow the schedule described in Appendix 4.

If the second cycle of AU-011 occurs after Visit 15 (Week 78), subjects will be followed for 26 weeks post-treatment and then may be rolled into the long-term follow-up study pending subject consent. Details regarding the follow-up visit schedule after the second cycle of AU-011 can be found in Appendix 4.

All subjects' study participation will be for a minimum of 2 years and all subjects in this study may then be rolled into the long-term follow-up study pending consent.

Ocular assessments including Best Corrected Visual Acuity (BCVA) by Early Treatment Diabetic Retinopathy Study method (ETDRS), slit lamp biomicroscopy, intraocular pressure (IOP), fundoscopy, color fundus photography (FP), fluorescein angiography (FA), B-scan ultrasound (B-scan), A-scan ultrasound (A-scan), enhanced depth imaging optical coherence tomography (EDI-OCT), optical coherence tomography angiography (OCTA), and visual fields will be evaluated during the study. Phlebotomy will be performed at various time points for hematology, serum chemistry and anti-drug antibodies (ADA). Concomitant medications and adverse events (AEs) will be reviewed through 30 days following the study treatment. After 30 days, for Cohorts 1 to 9, only AEs or SAEs determined by the Investigator to be related to study product and/or study procedures are to be reported. For Cohort 10, 11 and 12 subjects, concomitant medications and all adverse events will be reviewed through their last study visit. If peri-tumoral whitening/pigmentary changes are seen during the study, additional assessments as outlined in Section 10.3.10 should be conducted. Further treatment (additional therapy) for CM

will be documented throughout the study. Section 10 provides further details on the conduct of the study, study visits, and assessments.

Ocular imaging, including B-scan, A-scan, FP, FA, EDI-OCT, and OCTA will be read by a centralized Independent Reading Center (IRC) to provide consistency and reliability in data generated for each subject at each study site. At least two independent readers at the IRC will review required screening B-scan images for determination of eligibility and at the predefined time points.

6.2. Criteria for Study Termination

The Sponsor may suspend or terminate the study at any time for any reason. If the Investigator suspends or terminates the study at their site, the Investigator will promptly inform the Sponsor and the Institutional Review Board (IRB) and provide them with a detailed written explanation. The Investigator will also return all study drug and other materials to the Sponsor as required. Upon study completion, the Investigator will provide the IRB with notice of closure.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

To be eligible for this clinical study, subjects must provide written informed consent and meet all of the inclusion criteria and none of the exclusion criteria.

7.1. Subject Inclusion Criteria

Subjects must:

1. Be at least 18 years of age of either gender or any race.
2. Have been informed about the nature and requirements of the study, voluntarily agreed to participate in the study, and documented this by signing the Informed Consent Form (ICF) before participating in any study-related activities.
3. Be willing and able to follow all instructions and attend all study visits.
4. Per the expert opinion of the Investigator, have clinically diagnosed primary CM with no known metastatic disease.
5. Have clinically diagnosed primary CM:

   A. with tumor thickness of ≥ 1.2 mm and ≤ 3.0 mm on B-scan ultrasound and with a largest basal diameter of ≤ 13.0 mm on fundus photos associated with tumor growth,

   OR

   B. with tumor thickness of ≥ 2.0 mm and ≤ 3.0 mm on B-scan ultrasound and with a largest basal diameter of ≤ 13.0 mm on fundus photos associated with the presence of subretinal fluid by OCT AND at least one of the following:

      a. Overlying orange pigment (lipofuscin) on fundus photos
      b. Vision loss
      c. Flashes or floaters

   OR

   C. Criteria for Cohort 12: with tumor thickness of ≥ 0.5 mm and ≤ 3.0 mm on B-scan ultrasound, a largest basal diameter of ≤ 13.0 mm on fundus photos with an estimated tumor volume ≤50 mm^3 associated with tumor growth within 2 years of screening (defined as ≥ 0.4 mm increase based on intersite measurements or ≥ 0.3 mm based on within site measurements on tumor thickness)

   NOTE: ***Whenever available at the investigative site or referring site, historical images (B-scans and/or color fundus photos) for all subjects should be provided to the Independent Reading Center at the time of entry to the study. The investigative site should make all reasonable efforts to obtain this information from referring sites.***

6. In the opinion of the treating physician, the subject could be managed by interventional therapy, or by cautious observation.
7. Be treatment-naïve for their primary CM.

8. Have a tumor for which the entire extent must be able to be imaged on required fundus photography in a single frame and treated by the laser.
9. If female and capable of becoming pregnant, agree to have pregnancy testing performed at screening (must be negative) and if required at Visit 2 (must be negative); must not be lactating; and must agree to use a medically acceptable form of birth control before administration of the investigational product and for three months after administration of the investigational product. Women considered capable of becoming pregnant include all females who have experienced menarche and have not experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) or have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy).
10. For women of childbearing potential and for males with sexual partners of childbearing potential: Acceptable forms of birth control are spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of partner. For non-sexually active females and males, abstinence will be considered an acceptable form of birth control.
11. Be otherwise in good general health, with no significant or uncontrolled medical conditions, as determined by the Investigator.
12. Be able and willing to avoid all prohibited medications for the appropriate washout period (See Section 8.3.2).

7.2. Subject Exclusion Criteria

Subjects must not:

1. Have known contraindications or sensitivities to IRDye®700DX phthalocyanine-based dye, or laser in the study eye.
2. Have any ocular condition in the study eye that, in the Investigator's opinion, could affect the subject's safety or trial parameters.
3. Have a CM that invades or encompasses the optic nerve that precludes treatment, as determined by the investigator and/or shows extraocular extension.
4. Have metastatic disease confirmed by abdominal and chest imaging within three months prior to screening.
5. Have undergone vitrectomy at any time or have undergone any ocular surgical intervention in the study eye within three months before Visit 1, or are planning/will require ocular surgery in the study eye prior to the study drug administration. If the subject is likely to require cataract surgery in the study eye at any time prior to the Week 104 visit, he/she should not be enrolled.
6. Have a history of rhegmatogenous retinal detachment, diabetic retinopathy, or other active retinal disease in the study eye unrelated to the CM.
7. Have any active ocular disease in the study eye (other than CM) that may progress during the study and result in a change in vision or loss in vision (e.g., clinically significant

corneal dystrophies, keratoconus, glaucoma or clinically significant retinal or macular disease).

8. Have an active ocular infection (bacterial, viral, or fungal).
9. Use or require use of heparin or low molecular weight heparins within one week of treatment.
10. Use or require use of immunosuppressive or antineoplastic medications within five half-lives of Visit 1. Steroids, including inhalation steroids, are permitted.
11. Have previously received HPV vaccination.
12. Any active malignancies other than CM, or squamous or basal cell skin cancer. If there is evidence of clinical remission for at least one year, the subject's eligibility may be discussed with the medical monitor.
13. Have any significant illness (e.g., an uncontrolled autoimmune disease, severe cardiovascular disease [confirmed by a cardiologist], active infection, etc.) that the Investigator determines could interfere with study participation or safety, or put the subject at any unnecessary risk.
14. Have planned or will require systemic surgery during the active study treatment period.
15. Have used an investigational drug or medical device within 30 days or 5 half-lives of Visit 1 or be concurrently enrolled in another investigational product trial.

7.3. Withdrawal of Subjects

7.3.1. Subject Discontinuation

Subject participation is voluntary; any subject may discontinue participation in the study without prejudice or may be withdrawn from the study by the Investigator or Sponsor for the following reasons:

- Pregnancy
- Intolerable toxicity thought to be related to study drug
- Subject request
- Inability to comply with trial requirements
- Conditions requiring treatment intervention not permitted by protocol
- Intercurrent illness (Investigator's discretion)
- Non-compliance/lost to follow-up
- Discontinuation by Sponsor

If the subject wishes to withdraw study consent, every effort will be made to encourage the subject to return to the study site for a final visit prior to withdrawing consent.

7.3.2. Loss to Follow-up

The study sites will attempt to follow-up on subjects who do not return for scheduled study examinations. Sites must make a minimum of three documented attempts via telephone, email, or regular mail to contact the subject. If the subject does not reply to any of these attempts, the site must send a letter by certified mail (with a request for notification of receipt of delivery) to the

subject. If a subject is non-responsive to these follow-up attempts, he/she will be considered to be lost to follow-up and the electronic case report form (eCRF) will be updated to note lost to follow-up as the reason for discontinuation.

7.3.3. Early Subject Termination or Subject Withdrawal

Subjects who discontinue from the study early for any reason will be asked to undergo Week 104/Early Termination assessments. If termination occurs before Visit 11 (Week 12), then all ophthalmic assessments, **including imaging** should be performed on both eyes at the Early Termination Visit.

All subjects who discontinue from the study early will be followed for up to 30 days after their last administration of study medication for the development of new AEs.

7.3.4. Follow-up of Subjects with Adverse Events

If any study subject has an AE at the time of completion, termination, or withdrawal, the subject should be followed until the event has resolved, returned to baseline, or in case of permanent impairment, until the condition stabilizes. If in the opinion of the Investigator, the AE or laboratory abnormality/ies are not likely to improve because of the underlying disease, the Investigator must record his or her reasoning for this decision in the subject's medical record and on the eCRF.

8. TREATMENT OF SUBJECTS

8.1. Description of Study Drug

Light-activated AU-011 is a combination product consisting of a drug (AU-011) and a laser (Aura Photoactivation System) that delivers 689 nm light to activate the drug once it is bound to the tumor cells. AU-011 drug substance is a modified human papillomavirus-derived, empty viral like particle conjugated to approximately 200 molecules of a phthalocyanine-based photosensitizer IRDye®700DX. AU-011 will be administered via intravitreal injection as a low dose (20 µg) [redacted] intravitreal injection ([redacted] µL injection), a medium dose (40 µg) per intravitreal injection ([redacted] µL injection), or a high dose (80 µg) per intravitreal injection ([redacted] µL injections with interim IOP assessment). Refer to Section 4.4. Additional information can be found in the IB.

8.2. AU-011 Treatment

8.2.1. Administration of AU-011

In this clinical trial, AU-011 study drug will be administered by IVT injection and will be followed by laser light application (689 nm) to the CM 6 to 8 hours after intravitreal administration of AU-011. The maximum concentration of the current AU-011 formulation is 40 µg in [redacted] µl and as a result, the maximum feasible dose is 80 µg administered as 2 injections of 40µg in [redacted] µl.

Subjects in Cohorts 1 (20 µg single dose), 2 (40 µg single dose) and 3 (80 µg single administration given as 2 injections of 40 µg in [redacted] µl) will receive one treatment followed by a single laser application, subjects in Cohort 4 (40 µg two repeat doses) will receive 2 injections one week apart followed by a single laser application, subjects in Cohort 5 (40 µg three repeat doses) will receive 3 injections one week apart followed by a single laser application, subjects in Cohort 6 (80 µg single dose followed by 2 laser applications) will receive a single dose administered as 2 injections of 40 µg in [redacted] µl followed by 2 laser applications, subjects in Cohort 7 (80 µg three repeat doses followed by a single laser application) will receive 3 doses each administered as 2 injections of 40 µg in [redacted] µl one week apart followed by a single laser application, and subjects in Cohorts 8 and 9 (80 µg three repeat doses followed by two laser applications) will receive 3 doses each administered as 2 injections of 40 µg in [redacted] µl one week apart followed by 2 laser applications. Subjects in cohorts 3, 6, 7, 8 and 9 receiving 80 µg doses given as 2 injections of 40 µg in [redacted] µl will have their IOP measured prior to and after each injection. IOP must be 21 mm Hg or less before each injection can be given and **the maximum interval between the two injections is 2 hours**. IOP must also be 21 mm Hg or less before the patient is discharged from the clinic.

Subjects enrolled in the observation cohort and after exhibiting tumor growth (Cohort 10), and repeat cycle cohorts (Cohorts 11 and 12) will receive 2 cycles of AU-011 at the highest feasible and tolerated dose of 3 repeat 80 µg doses, each followed by 2 repeat laser applications. The second cycle of AU-011 will be administered no earlier than the Week 12 Visit and after resolution of any inflammation resulting from the first cycle or when the inflammation is minimal and decreasing based on investigator judgement. Cycle 2 should be administered as soon as reasonably possible after inflammation has resolved or is minimal and decreasing based

on investigator judgement. However, if 2 subjects experience a DLT during treatment with Cycle 2, as defined in Section 8.4.1, then no further subjects will receive Cycle 2 of AU-011 until discussed with the independent ocular oncologist and medical monitor and continuation of enrollment is confirmed. If the fovea is near the tumor edge, an adjustment to the laser procedure should be performed on each treatment day of both cycles as outlined in section 8.2.2 and the Injection and Laser Procedure Manual.

All subjects will be monitored with systemic and ophthalmic assessments. If subjects are discharged during daylight hours, appropriate sun protection, e.g., sunglasses and a hat, will be required. Study subjects will be required to return for an ocular examination 24 hours ± 4 hours following administration of AU-011 for slit lamp biomicroscopy, IOP, fundoscopy, assessment of any changes in their vision, and AE and concomitant medications review. Cohort 1, 2, and 3 subjects only will also have B-scan ultrasound performed 24 ± 4 hours following administration of AU-011.

Procedures for intravitreal injection, which will be administered by an ophthalmologist, are provided in the study procedures binder.

8.2.2. Laser Activation of AU-011

This study will use the Aura Photoactivation System which will deliver light at 689 nm to the CM 6 to 8 hours after the intravitreal administration (after the **second** intravitreal injection for the subjects receiving 80 µg doses) of study drug AU-011. A second laser application will also be investigated in this trial to ensure that maximum tumor cell necrosis occurs with each administration of Light-activated AU-011.

The Injection and Laser Procedure Manual provides detailed instructions on the procedures for laser application for this study including tumor margin, laser spot size, foveal treatment, and specific high-risk tumor situations including but not limited to:

Subfoveal tumors

Tumor edge ≤1.0mm from the fovea

Tumor edge >1.0mm to 2.0mm from the fovea

Tumor edge >2.0mm to 3.0mm from the fovea

Tumor edge >3.0mm from the fovea

Suggested treatment patterns and estimated number of treatment spots for several tumor size examples have been updated in the Injection and Laser Procedure Manual in conformance to the instructions provided.

8.3. Concomitant Medications

All concomitant medications taken by the study subjects within seven days prior to the first dose of study drug will be documented. Additionally, through 30 days after the completion of study treatment, the Investigator or study staff will ask the subject about any new medications he/she is taking or has taken after the start of the study drug and this information will be documented in the study eCRF. For Cohort 10, 11 and 12 subjects, concomitant medications will be documented through their last study visit. Further treatment (additional therapy) for CM will be documented throughout the course of the study.

The safety committee may, at its discretion, decide to mandate prophylactic use of topical and/or systemic corticosteroids at any point in this dose and frequency escalation study if the severity and/or time course of ocular inflammation suggests that doing so would be in the best interest of study subjects. If any diabetic subjects are prescribed systemic steroids, the site should ensure that the subject is willing to check their blood pressure and fasting glucose levels on a daily basis during treatment and to inform the study physician immediately of any signs or symptoms that suggest either are abnormal.

Artificial tears may be administered within the immediate 24-hour period prior to study treatment and following the study treatment. However, a new, unopened bottle or vial must be used.

8.3.1. Concomitant Steroid Treatment

On study Day 1, ie, day of first administration of AU-011 treatment and before the first laser administration, the Investigator should begin topical 1% prednisone acetate or difluprednate 0.05% topical eye drops and an oral prednisone taper or periocular steroid injection. Subtenon's injection of triamcinolone acetonide (40mg/ml) can be given with up to 1 ml delivered as tolerated. Oral prednisone starting at 60 mg/day and tapering off (for example, over six to eight weeks) can also be used.

These regimens are intended to be a minimum treatment regimen and the Investigator can treat with higher doses than proposed in the guidelines in order to minimize the severity and duration of posterior segment inflammation and allow Cycle 2 of AU-011 therapy to be administered at 12 weeks or as soon as possible thereafter.

If posterior synechiae develop, the Investigator can also start mydriatric agents like mydriacyl, cyclogyl or atropine and miotic inhibitors like phenylephrine.

In the event of any potential breakthrough inflammation, the Investigator may restart clinically appropriate levels of oral prednisone treatment. Additionally, the Investigator may choose to taper subjects more quickly than described above.

If a subject continues to show inflammation during the active treatment period, the Investigator should determine the necessity of increasing the oral prednisone dose to 80 mg daily with slow taper or hospital admission with 250 mg intravenous methylprednisolone 4 times per day over 3 days to protect the eye and vision.

When Cycle 2 or additional therapy of AU-011 is administered, topical prednisone acetate 1% or difluprednate 0.05% topical eye drop taper and periocular steroid injection or oral steroid use should be instituted on the day of the first AU-011 treatment and before the first laser application. The topical steroid eye drop can be tapered and discontinued at the discretion of the Investigator. The periocular or oral steroid may consist of a periocular triamcinolone acetonide (40mg/ml) injection up to 1 ml as tolerated or an oral steroid taper similar to the oral taper described for Cycle 1 of therapy above. These regimens are intended to be a minimum treatment regimen and the Investigator can treat with higher doses than proposed in the guidelines, but not with lower doses.

8.3.2. Prohibited Concomitant Medications

Heparins or low molecular weight heparins are prohibited within one week prior to AU-011 intravitreal injections. Immunosuppressive or antineoplastic medications are prohibited within 5 half-lives of Visit 1. Steroids, including inhalation steroids, are permitted.

8.3.3. Additional Therapy

Additional therapy with AU-011 at the maximum tolerated and feasible dose of 3 repeat doses of 80 µg each followed by two laser applications (treatment regimen) can be provided to:

- ensure that all subjects are able to receive the maximum tolerated and feasible dose, particularly for subjects that were treated with lower doses previously
- allow additional treatment regimens in subjects that have stable disease (treatment extension)
- allow retreatment in subjects that meet the protocol definition of disease progression

If the fovea is near the tumor edge, an adjustment to the laser procedure should be performed on each treatment day as outlined in section 8.2.2 and the Injection and Laser Procedure Manual. Subjects may be considered for additional therapy with AU-011 (defined above) after Visit 11 (Week 12) and only after inflammation from the previous treatment has resolved or when the inflammation is minimal and decreasing based on investigator judgement. **Additional therapy with AU-011 must be approved by the Sponsor on a case-by-case basis prior to the initiation of therapy.** Alternatively, also after Visit 11 (Week 12 Visit), standard of care therapy, including plaque brachytherapy, proton beam radiotherapy or enucleation may be used if the subject meets the protocol definition of disease progression or the Investigator judges that the disease is progressing per their clinical judgement for increases in tumor thickness or LBD that are less than the protocol definition of disease progression. Before additional therapy is performed, the following protocol assessments must be collected in the study eye unless otherwise noted: ETDRS BCVA (both eyes), slit lamp biomicroscopy, IOP measurement, fundoscopy, Fundus photos, EDI-OCT, B-scan ultrasound, A-scan ultrasound, OCTA (Cohorts 6 to 9 only) and a visual field examination. If these assessments have not been performed at the most recent study visit, an unscheduled visit is required to be performed to obtain these assessments.

The criteria for implementing additional therapy due to disease progression is as follows:

- An increase on B-scan ultrasound of >0.5 mm in melanoma thickness from baseline, not due to intralesional hemorrhage/inflammation

  OR

- An increase on digital fundus photos of >1.0 mm in melanoma diameter from baseline, not due to intralesional hemorrhage/inflammation or pigmentary changes

If additional therapy with AU-011 occurs after Visit 15 (Week 78), subjects will be followed for 26 weeks post retreatment and then may be rolled into the long-term follow-up study pending subject consent. Details regarding the follow-up visit schedule after additional therapy with AU-011 can be found in Appendix 4.

The Investigator may offer fine needle aspiration biopsy of the melanoma for genetic analysis before initiating additional therapy.

Any progression of the subject's condition and subsequent treatment must be recorded on the appropriate eCRF.

Details about concomitant steroid treatment for management of anterior and posterior segment inflammation are provided in section 8.3.1 and in the study procedures manual.

At the discretion of the PI, cycloplegic/mydriatic agents may be administered as part of the treatment of anterior ocular inflammation.

8.3.4. AU-011 Treatment Criteria for Observation Cohort

Once tumor growth is established in the observation cohort as described below, subjects will receive the first of 2 cycles of AU-011 treatment and the visit schedule for treatment and follow-up is described in Section 10 and Appendix 1 of this protocol until Cycle 2 is administered, at which time the visit schedule in Appendix 4 will be followed.

The criteria for confirming tumor growth in subjects in the observation cohort are as follows:

- A growth rate of 0.5 mm per year (with a minimum detectable increase of 0.15 mm over a minimum period of 3 months) in melanoma thickness from baseline or an absolute increase of ≥ 0.5 mm during the study period

  OR

- A growth rate of 1.0 mm per year (with a minimum detectable increase of 0.6 mm over a minimum period of 3 months) in melanoma LBD from baseline or an absolute increase of ≥ 1.5 mm during the study period

8.4. Dose Escalation Design and Toxicity

8.4.1. DLT Definition

Dose limiting toxicity[ies] (DLT[s]) is defined as a treatment-related safety event (related to drug and/or laser), severe enough to limit dose escalation (increase of dose or frequency of dosing) of AU-011.

8.4.2. Dose Escalation / Termination

Dose escalation to the next higher dose level, repeat dose group, repeat laser application or repeat cycle will be implemented only if less than 2 subjects in the prior cohort complete the treatment without a DLT.

9. STUDY DRUG

9.1. Study Drug

AU-011 drug product is a sterile, [redacted] aqueous solution supplied at a concentration of [redacted] mg per mL of buffered isotonic solution (pH 6.5). Each vial contains [redacted] mL. Additional information is provided in the study pharmacy manual.

9.2. Study Drug Packaging, Labeling, and Storage

AU-011 is supplied in a [redacted] mL, high density plastic, single-use vial; each vial contains a fill volume of [redacted] mL. AU-011 will be shipped to clinical sites on dry ice. Once the site receives the study drug, it should be immediately stored at frozen temperature (-[redacted] °C ± [redacted] °C).

All study drug must be kept in a secure place under appropriate storage conditions. The Sponsor or its representatives must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

9.3. Study Drug Preparation

The designated site personnel will prepare AU-011 per the manual provided by the Sponsor. The ophthalmologist will administer the study drug as specified in the injection and laser procedure, located in the study procedures manual.

9.4. Study Drug Accountability

Each clinical site is responsible for accountability of all used and unused study drug supplies at the site.

The Sponsor or designee will verify receipt of the study drug at the site during monitoring visit(s), and will conduct an inventory of remaining clinical trial supplies at the site close-out visit. All study drug inventories must be made available for inspection by the monitor, Sponsor, or representatives of the aforementioned and regulatory agencies upon request.

Dispensation and destruction of study drug will be recorded in the source document and drug accountability records. Clinical trial supplies must not be returned or destroyed unless the Sponsor or its representative has granted prior approval. Refer to the study pharmacy manual for additional details.

9.5. Laser System

The Sponsor will be providing the Aura Photoactivation System to the study sites. The Aura Photoactivation System (supplied by a contract manufacturer in accordance with Aura's specification) consists of a laser console and a compatible slit lamp adaptor. The Sponsor will also provide each site with a compatible standard slit lamp biomicroscope and a table for the equipment. The laser photoactivation system has been tested for compliance to applicable FDA laser standards.

The laser system will be labeled "For investigational use only." Refer to the laser user manual for additional information.

10. CONDUCT OF STUDY AND STUDY ASSESSMENTS

10.1. Conduct of Study

10.1.1. Screening and Informed Consent

All subjects will receive a written ICF describing this study and providing sufficient information to make an informed decision about participating in this study. Written informed consent must be obtained before any protocol specific procedures are performed.

The Investigator is responsible for ensuring that a careful and thorough informed consent procedure is implemented before a subject enters the study and at any time during the study should ICF changes be introduced. This includes, but is not limited to: (1) providing a quiet place for the subject to read the ICF and allowing ample time for this review; (2) ensuring that qualified medical personnel are available to directly answer questions that a subject may have; (3) ensuring that each potential study subject understands that his or her medical treatment will not be otherwise affected based on the decision whether or not to participate in the study, that his or her participation is completely voluntary, and that he or she can opt to stop participation in the study at any time for any reason; and (4) ensuring that a full copy of the signed ICF is given to the subject to take home for his or her medical records. The process for obtaining informed consent should also be noted in the subject's source documentation.

In addition, whenever available, historical B-scans and/or color fundus photographs, either from the investigative site or the referring site, should be provided to the Independent Reading Center for subjects at the time of entry to the study. The investigative site should make all reasonable efforts to obtain this information from referring sites.

Appendix 1 and the sections below describe the procedures that will be performed at each visit.

Additionally, for the observation cohort visits every 3 months (ie, 90 day (+/- 7 days) intervals from the Screening Visit), which occur prior to evidence of tumor growth, the same procedures outlined for Visit 6 (Day 15) will be performed with the exception of OCTA and Anti-drug Antibody (ADA) testing which is not required.

10.1.2. Screening (Visit 1 [Day -28 to Day 1])

After providing written informed consent, the following procedures will be performed:

- Demographic information
- Eligibility criteria
- Medical and ophthalmic history
- Concomitant medication review

ALL OPHTHALMIC ASSESSMENTS WILL BE PERFORMED ON BOTH EYES AT SCREENING AND THEREAFTER ON THE STUDY EYE ONLY THROUGHOUT THE STUDY, UNLESS OTHERWISE INDICATED.

- Vital signs (blood pressure [BP] and pulse) recorded
- Serum pregnancy test for women of childbearing potential

- BCVA using ETDRS performed prior to dilating eyes (BCVA)
- Slit lamp biomicroscopy
- IOP measured by applanation or tonopen
- Fundoscopy
- Fundus photos
- FA
- EDI-OCT of the macular region and in the region of the tumor
- B-scan
- A-scan (for sites with diagnostic probes only) – study eye only
- OCTA of the macular region and in the region of the tumor (Cohorts 6 through 9 only)
- Visual field examination
- Laboratory assessments: Complete Blood Count (CBC) with differential and Comprehensive Metabolic Panel (CMP)
- Blood sample for Anti-drug Antibody (ADA) testing

10.1.3. Single Light-activated AU-011 Administration (or Initial for Repeat) Study Treatment (Visit 2 [Day 1])

During Visit 2, the following procedures will be performed:

- Eligibility criteria review
- Vital signs
- BCVA (Both Eyes)
- Slit lamp biomicroscopy
- IOP
- Fundoscopy
- Fundus photos
- EDI-OCT
- OCTA (Cohorts 6 through 9 only)
- B-scan
- Urine pregnancy test for women of childbearing potential (only if Visit 2 occurs more than 7 days after Visit 1)
- Laboratory assessments: CBC with differential and CMP (only if Visit 2 occurs more than 7 days after Visit 1)
- Administration of Light-activated AU-011 treatment

- Intravitreal injection of AU-011 study drug (Subjects in cohorts 3, 6, 7, 8, 9, 10 [after observation of growth], 11 and 12 receiving 80 µg doses administered as 2 injections of 40 µg in [redacted] µl will have their IOP measured prior to and after each injection. IOP must be 21 mm Hg or less before each injection can be given and **the maximum interval between the two injections is 2 hours**. IOP must also be 21 mm Hg or less before the patient is discharged from the clinic).
- Laser treatment (single laser applications for cohorts 1, 2, 3, 4, 5 and 7, and two laser applications for cohorts 6, 8, 9, 10 [after observation of growth], 11 and 12 given 6 to 8 hours after intravitreal administration of AU-011). For subjects in cohorts 3, 6, 7, 8, 9, 10 [after observation of growth], 11 and 12 receiving 80 µg doses administered as 2 injections of 40 µg in [redacted] µl, laser treatment is 6 to 8 hours after the second injection. If the fovea is near the tumor edge, an adjustment to the laser procedure should be performed as outlined in section 8.2.2 and the Injection and Laser Procedure Manual. Subjects should remain at the study site after intravitreal injection until approximately ½ hour after laser treatment.
- If subjects are discharged during daylight hours, appropriate sun protection, e.g., sunglasses and a hat, will be required.
- Subjects must return to the study site for additional assessments 24 hours (± 4 hours) after AU-011 intravitreal administration, refer to Section 10.1.4.

- Record AEs
- Record concomitant medications

If Visit 1 and Visit 2 are within 7 days, the following procedures do not need to be repeated prior to AU-011 study drug injection, unless clinically indicated:

- BCVA (Both Eyes)
- Fundus photos
- EDI-OCT
- OCTA (Cohorts 6 through 9 only)
- B-scan

10.1.4. Visit 3 (Day 2, 24 hours [± 4 hours] Post-Injection Follow-up)

Twenty-four hours (± 4 hours) following intravitreal administration of AU-011 study drug, subjects are required to return to the study site for the following assessments:

- Vital signs
- BCVA (Both Eyes)
- Slit lamp biomicroscopy
- IOP
- Fundoscopy

- Fundus photos
- EDI-OCT
- OCTA (Cohorts 6 through 9 only)
- B-scan (Cohort 1, 2, and 3 subjects only)
- Record AEs
- Record concomitant medications

10.1.5. Visit 4 (Day 8 to Day 9)

During Visit 4, the following procedures will be performed:

- Vital signs
- BCVA (Both Eyes)
- Slit lamp biomicroscopy
- IOP
- Fundoscopy
- Fundus photos
- EDI-OCT
- OCTA (Cohorts 6 through 9 only)
- B-scan
- A-scan (for sites with diagnostic probes only)
- Laboratory assessments: CBC with differential and CMP
- Blood sample for ADA testing (Pre-dose for 2 and 3 repeat Light-activated AU-011 administration cohort subjects)
- Record AEs
- Record concomitant medications

FOR 2 AND 3 REPEAT LIGHT-ACTIVATED AU-011 ADMINISTRATION COHORTS ONLY:

- Administration of Light-activated AU-011 treatment
  - Intravitreal injection of AU-011 study drug (Subjects in cohorts 7, 8, 9, 10 [after observation of growth], 11 and 12 receiving 80 µg doses administered as 2 injections of 40 µg in [redacted] µl will have their IOP measured prior to and after each injection. IOP must be 21 mm Hg or less before each injection can be given and **the maximum interval between the two injections is 2 hours**. IOP must also be 21 mm Hg or less before the patient is discharged from the clinic).
  - Laser treatment (single laser applications for cohorts 4, 5 and 7, and two laser applications for cohorts 8, 9, 10 [after observation of growth], 11 and 12 given 6

to 8 hours after intravitreal administration of AU-011). For subjects in cohorts 7, 8, 9, 10 [after observation of growth], 11 and 12 receiving 80 µg doses administered as 2 injections of 40 µg in [redacted] µl, laser treatment is 6 to 8 hours after the second injection. If the fovea is near the tumor edge, an adjustment to the laser procedure should be performed as outlined in section 8.2.2 and the Injection and Laser Procedure Manual. Subjects should remain at the study site after intravitreal injection until approximately ½ hour after laser treatment.

- If subjects are discharged during daylight hours, appropriate sun protection, e.g., sunglasses and a hat, will be required.
- Subjects must return to the study site for additional assessments 24 hours (± 4 hours) after AU-011 intravitreal administration, refer to Section 10.1.4.

10.1.6. Visit 5 (Day 9 to Day 10, 24 hours [± 4 hours] Post-Injection Follow-up for 2 and 3 Repeat Light-activated AU-011 Administration Cohorts

Twenty-four hours (± 4 hours) following intravitreal administration of AU-011 study drug, subjects are required to return to the study site for the following assessments:

- Vital signs
- BCVA (Both Eyes)
- Slit lamp biomicroscopy
- IOP
- Fundoscopy
- Fundus photos
- EDI-OCT
- OCTA (Cohorts 6 through 9 only)
- Record AEs
- Record concomitant medications

10.1.7. Visit 6 (Day 15 to Day 16)

During this Visit, the following procedures will be performed:

- Vital Signs
- BCVA (Both Eyes)
- Slit lamp biomicroscopy
- IOP
- Fundoscopy
- Fundus photos
- EDI-OCT

- OCTA (Cohorts 6 to 9 only)
- B-scan
- Blood sample for ADA testing (Performed pre-dose and required for 3 repeat Light-activated AU-011 administration cohort subjects only)
- Record AEs
- Record concomitant medications

FOR 3 REPEAT LIGHT-ACTIVATED AU-011 ADMINISTRATION COHORTS ONLY:

- Administration of Light-activated AU-011 treatment
  - Intravitreal injection of AU-011 study drug (Subjects in cohorts 7, 8, 9, 10 [after observation of growth], 11 and 12 receiving 80 µg doses administered as 2 injections of 40 µg in [redacted] µl given as [redacted] µl injections will have their IOP measured prior to and after each injection. IOP must be 21 mm Hg or less before each injection can be given **and the maximum interval between the two injections is 2 hours.** IOP must also be 21 mm Hg or less before the patient is discharged from the clinic).
  - Laser treatment (single laser applications for cohorts 5 and 7, and two laser applications for cohorts 8, 9, 10 [after observation of growth], 11 and 12 given 6 to 8 hours after intravitreal administration of AU-011). For subjects in cohorts 7, 8, 9, 10 [after observation of growth], 11 and 12 receiving 80 µg doses administered as 2 injections of 40 µg in [redacted] µl, laser treatment is 6 to 8 hours after the second injection. If the fovea near the tumor edge, an adjustment to the laser procedure should be performed as outlined in section 8.2.2 and the Injection and Laser Procedure Manual. Subjects should remain at the study site after intravitreal injection until approximately ½ hour after laser treatment.
  - If subjects are discharged during daylight hours, appropriate sun protection, e.g., sunglasses and a hat, will be required.
  - Subjects must return to the study site for additional assessments 24 hours (± 4 hours) after AU-011 intravitreal administration, refer to Section 10.1.4.

10.1.8. Visit 7 (Day 16 to Day 17, 24 hours [± 4 hours] Post-Injection Follow-up for 3 Repeat Light-activated AU-011 Administration Cohorts only)

Twenty-four hours (± 4 hours) following intravitreal administration of AU-011 study drug, subjects are required to return to the study site for the following assessments:

- Vital signs
- BCVA (Both Eyes)
- Slit lamp biomicroscopy
- IOP

- Fundoscopy
- Fundus photos
- EDI-OCT
- OCTA (Cohorts 6 through 9 only)
- Record AEs
- Record concomitant medications

10.1.9. Follow-up Visit 8 (Day 29 ± 1 day)

During this Visit, the following procedures will be performed:

- Vital signs
- BCVA (Both Eyes)
- Slit lamp biomicroscopy
- IOP
- Fundoscopy
- Fundus photos
- EDI-OCT
- OCTA (Cohorts 6 through 9 only)
- B-scan
- A-scan (for sites with diagnostic probes only)
- Laboratory assessments: CBC with differential and CMP
- Blood sample for ADA testing
- Record AEs
- Record concomitant medications

10.1.10. Follow-up Visit 9 (Week 6 ± 3 days)

During this Visit, the following procedures will be performed:

- BCVA (Both Eyes)
- Slit lamp biomicroscopy
- IOP
- Fundoscopy
- Fundus photos
- EDI-OCT
- OCTA (Cohorts 6 through 9 only)

- Record AEs (For single Light-activated AU-011 administration cohort subjects, only study product and/or study procedure related AEs. For 2 and 3 repeat Light-activated AU-011 administration cohort subjects, any AE)
- Record concomitant medications (For 2 and 3 repeat Light-activated AU-011 administration cohort subjects only)

10.1.11. Follow-up Visit 10 (Week 8 ± 3 days)

During this Visit, the following procedures will be performed:

- BCVA (Both Eyes)
- Slit lamp biomicroscopy
- IOP
- Fundoscopy
- Fundus photos
- EDI-OCT
- OCTA (Cohorts 6 through 9 only)
- B-scan
- A-scan (for sites with diagnostic probes only)
- Record AEs (For single and 2 repeat Light-activated AU-011 administration cohort subjects, only study product and/or study procedure related AEs. For 3 repeat Light-activated AU-011 administration cohort subjects, any AE.)
- Record concomitant medications (For 3 repeat Light-activated AU-011 administration cohort subjects only)

10.1.12. Follow-up Visit 11 (Week 12 ± 3 days)

During this Visit, ALL OCULAR ASSESSMENTS WILL BE PERFORMED ON BOTH EYES UNLESS INDICATED OTHERWISE):

- BCVA
- Slit lamp biomicroscopy
- IOP
- Fundoscopy
- Fundus photos
- FA
- EDI-OCT
- OCTA (Cohorts 6 through 9 only)
- B-scan

- A-scan (for sites with diagnostic probes only) – study eye only
- Visual field examination
- Blood sample for ADA testing
- Record study product and/or study procedure related AEs. Record all AEs and concomitant medications for Cohort 10, 11 and 12 subjects.
- If applicable, the Investigator may offer fine needle aspiration biopsy of the melanoma for genetic analysis before initiating additional therapy.

10.1.13. Follow-up Visit 12 (Week 26 ± 7 days)

During this Visit, the following procedures will be performed:

- BCVA (Both Eyes)
- Slit lamp biomicroscopy
- IOP
- Fundoscopy
- Fundus photos
- EDI-OCT
- OCTA (Cohorts 6 through 9 only)
- B-scan
- A-scan (for sites with diagnostic probes only)
- Record study product and/or study procedure related AEs. Record all AEs and concomitant medications for Cohort 10, 11 and 12 subjects.
- If applicable, the Investigator may offer fine needle aspiration biopsy of the melanoma for genetic analysis before initiating additional therapy.

10.1.14. Follow-up Visit 13 (Week 39 ± 7 days)

During this Visit, the following procedures will be performed:

- BCVA (Both Eyes)
- Slit lamp biomicroscopy
- IOP
- Fundoscopy
- Fundus photos
- EDI-OCT
- OCTA (Cohorts 6 through 9 only)
- B-scan

- A-scan (for sites with diagnostic probes only)
- Record study product and/or study procedure related AEs. Record all AEs and concomitant medications for Cohort 10, 11 and 12 subjects.
- If applicable, the Investigator may offer fine needle aspiration biopsy of the melanoma for genetic analysis before initiating additional therapy.

10.1.15. Follow-up Visit 14 (Week 52 ± 7 days)

During this Visit, the following procedures will be performed:

- Vital signs
- BCVA (Both Eyes)
- Slit lamp biomicroscopy
- IOP
- Fundoscopy
- Fundus photos
- FA
- EDI-OCT
- OCTA (Cohorts 6 through 9 only)
- B-scan
- A-scan (for sites with diagnostic probes only)
- Visual field examination
- Blood sample for ADA testing
- Record study product and/or study procedure related AEs. Record all AEs and concomitant medications for Cohort 10, 11 and 12 subjects.
- If applicable, the Investigator may offer fine needle aspiration biopsy of the melanoma for genetic analysis before initiating additional therapy.

10.1.16. Follow-up Visit 15 (Week 78 ± 7 days)

During this Visit, the following procedures will be performed:

- BCVA (Both Eyes)
- Slit lamp biomicroscopy
- IOP
- Fundoscopy
- Fundus photos
- EDI-OCT

- OCTA (Cohorts 6 through 9 only)
- B-scan
- A-scan (for sites with diagnostic probes only)
- Record study product and/or study procedure related AEs. Record all AEs and concomitant medications for Cohort 10, 11 and 12 subjects.
- If applicable, the Investigator may offer fine needle aspiration biopsy of the melanoma for genetic analysis before initiating additional therapy.

10.1.17. Follow-up Visit 16 (Week 104 ± 7 days), End of Study or Early Termination

During this Visit (End of Study) or an Early Termination Visit, the following procedures will be performed (If Early Termination Visit occurs before Visit 11 (Week 12), then all ophthalmic assessments, including imaging should be performed on both eyes):

- Vital signs
- BCVA (Both Eyes)
- Slit lamp biomicroscopy
- IOP
- Fundoscopy
- Fundus photos
- FA
- EDI-OCT
- OCTA (Cohorts 6 through 9 only)
- B-scan
- A-scan (for sites with diagnostic probes only)
- Visual field examination
- Record study product and/or study procedure related AEs. Record all AEs and concomitant medications for Cohort 10, 11 and 12 subjects.
- If applicable, the Investigator may offer fine needle aspiration biopsy of the melanoma for genetic analysis before initiating additional therapy.
- If Early Termination Visit occurs ≤ 30 days following the study treatment: Record any AE and record concomitant medications

10.2. Safety Assessments

10.2.1. History and Vital Signs

A medical history will be recorded at Screening. Vital signs (BP seated and pulse) will be recorded at Visit 1 (Screening), Visit 2 (Day 1), Visit 3 (Day 2), Visit 4 (Day 8), Visit 6 (Day

15), Visit 8 (Day 29), Visit 14 (Week 52), and Visit 16 (Week 104) and at any Early Termination Visit. For both **2 and 3 repeat Light-activated AU-011 administration cohort subjects only**, vital signs will also be recorded at Visit 5 (Day 9) and for the **3 repeat Light-activated AU-011 administration cohort subjects only**, vital signs will also be recorded at Visit 7 (Day 16).

10.2.2. Laboratory Assessments

This study will use a central laboratory for analyzing and reporting hematology (CBC with differential), CMP, and ADA results.

If a situation arises in which the Investigator needs results more quickly than the central laboratory can accommodate, the Investigator may use a local laboratory in parallel, e.g., pregnancy test results for confirming subject eligibility.

10.2.2.1. Hematology and Differential Panel

CBC plus differential panel that includes hemoglobin, hematocrit, red blood cells (RBC), white blood cells (WBC), WBC differential, and platelets will be performed at Visit 1 (Screening), at Visit 2 (Day 1) if Visit 2 occurs more than 7 days after Visit 1, Visit 4 (Day 8), and Visit 8 (Day 29).

10.2.2.2. Comprehensive Metabolic Panel (CMP) and Electrolyte Panel

A CMP includes the following: total bilirubin, direct bilirubin, alkaline phosphatase, ALT (SGPT), AST (SGOT), GGT, LDH, blood urea nitrogen (BUN), creatinine, glucose, uric acid, calcium, phosphorus (or phosphate), total protein, albumin, globulin, triglycerides, cholesterol, CK, sodium, potassium, bicarbonate, chloride, and magnesium. Blood samples for a CMP and Electrolyte Panel will be performed at Visit 1 (Screening), Visit 2 (Day 1) if Visit 2 occurs more than 7 days after Visit 1, Visit 4 (Day 8), and Visit 8 (Day 29).

10.2.2.3. Pregnancy Test and Contraception Requirements

For women of childbearing potential, serum pregnancy test will be performed at Visit 1 (Screening). A central laboratory will be used for analyzing and reporting serum pregnancy results. If Visit 2 (Day 1) occurs more than 7 days after Visit 1, urine pregnancy test will be performed at Visit 2. If the pregnancy test(s) is positive, the subject will be screen failed.

Women of childbearing potential and males with sexual partners of childbearing potential must agree to use a medically acceptable form of birth control before the first single administration of the investigational product and for three months after the last administration of Light-activated AU-011 treatment. Women considered capable of becoming pregnant include all females who have experienced menarche and have not experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) or have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy).

Acceptable forms of birth control are spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of partner. For non-sexually active females and males, abstinence will be considered an acceptable form of birth control.

10.2.2.4. Anti-Drug Antibodies (ADA)

Anti-drug antibody (ADA) blood samples will be taken at Visit 1 (Screening), Visit 4 (Day 8), Visit 8 (Day 29), Visit 11 (Week 12), and Visit 14 (Week 52). For 3 repeat Light-activated AU-011 administration cohort subjects only, also performed at Visit 6 (Day 15).

Study staff will record the visit numbers and dates, and exact times of AU-011 injections and blood samples taken in source documents. A central laboratory will be used for analyzing and reporting ADA data.

10.2.3. Safety Monitoring

The safety and tolerability of Light-activated AU-011 treatment will be assessed through the collection and analysis of AEs, vital signs, ocular examinations, and laboratory tests. All safety assessments and protocol specified tests, including occurrence of AEs, intensity/severity, relationship to study drug, and treatment or action taken to resolve the event, will be performed by qualified study personnel and/or the evaluating physicians.

For the purposes of safety monitoring, baseline is defined as the pre-dose value at Visit 2 (Day 1) or, if no pre-dose Visit 2 (Day 1) result is available, it is the pre-dose test performed closest to Visit 2 (Day 1).

The study medical monitor and independent ocular oncologist will review SAEs and AEs on a monthly basis for the early part of the study and thereafter every six months during the follow up phase for any trends within and between the cohorts.

The study data, including any adverse and/or serious adverse events, together with any determinations of DLTs and decisions on dose reductions, or dose escalations, will be reviewed by the study medical monitor and independent ocular oncologist.

10.2.3.1. Definitions of Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes, but is not limited to, the following:

Any clinically significant worsening of a pre-existing condition other than CM is considered to be an AE. However, worsening of CM is considered to be “disease progression” or “lack of efficacy” and need not be reported as an AE unless it or the signs and symptoms associated with CM are more severe than expected for the subject’s condition.

An AE occurring from overdose (i.e., a dose higher than that indicated in the protocol) of a study drug, whether accidental or intentional.

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms
- Test result requires additional diagnostic testing
- Test result requires significant additional concomitant drug treatment, or other therapy or intervention
- Test result leads to a change in trial dosing or discontinuation of study drug
- Test result is considered to be an AE by the Investigator or Sponsor

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

A clinical diagnosis, rather than the changes in laboratory or other assessment should be recorded on the eCRF as appropriate (e.g., anemia versus low hemoglobin value, bundle branch block rather than abnormal electrocardiogram (ECG)).

For Cohorts 1 to 9, from the time the subject receives the single administration (or initial for repeat) study treatment until 30 days after the subject completes the study treatment, protocol-related events should be recorded as well. For Cohort 10, 11 and 12 subjects, these should be recorded until the last study visit for the subject. A protocol-related AE is an AE occurring during a clinical study that is not related to the study product, but is considered by the Investigator or medical monitor to be related to the research conditions. For example, a protocol-related AE may be an event related to a medical procedure required by the protocol.

10.2.3.2. Serious Adverse Events

Any adverse experience occurring at any dose that results in any of the following outcomes is classified as a serious adverse event (SAE).

- Results in death
- Life threatening (see below for definition)
- Results in persistent or significant disability/incapacity (see below for definition)
- Requires subject hospitalization or prolongs subject hospitalization (see below for definition)
- Results in a congenital anomaly/birth defect in a neonate/infant

Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious AEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Life-threatening refers to immediate risk of death as the event occurred per the reporter. A life-threatening experience does not include an experience, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death.

For example, an allergic reaction resulting in angioedema of the face would not be life threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

Hospitalization is official admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes criteria for an AE to be serious; however, it is not in itself considered a SAE. In the absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported by the PI. This is the case in the following situations:

- The hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (e.g., stent removal after surgery, or other elective procedures). This should be recorded in the study file.
- Hospitalization for survey visits or annual physicals falls in the same category.

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

10.2.3.3. Adverse Event Recording and Reporting

Serious Adverse Events (SAEs) should be reported from the time the subject signs the informed consent to 30 days after the subject completes the study treatment. Adverse Events (AE) should be reported from the time the subject receives the single Light-activated AU-011 administration (or initial for repeat) study treatment to 30 days after the subject completes the study treatment. After 30 days, for Cohorts 1 to 9, only AEs or SAEs determined by the Investigator to be related to study product and/or study procedures are to be reported. Relatedness to Light-activated AU-011 treatment and/or study procedures is determined by the Investigator. For Cohort 10, 11 and 12 subjects, all SAEs and AEs will be reported from the time the subject signs the informed consent through their last study visit. All AEs, regardless of severity and whether or not they are ascribed to the study treatment, will be recorded in the source documents. All AEs and SAEs for subjects who are not screen failures will be recorded on the eCRF.

Study Investigators must follow-up on all AEs, SAEs, and other reportable events until the events have resolved, returned to baseline, or in case of permanent impairment, until the condition stabilizes. If, in the opinion of the Investigator, the AE or laboratory abnormality/ies are not likely to improve because of the underlying disease, the Investigator must record his or her reasoning for this decision in the subject's source documentation and on the eCRF. Any medication or other intervention necessary for the treatment of an AE must be recorded on the concomitant medication eCRF.

All AEs will be characterized by the following criteria:

- Event term
- Intensity or severity
- Relationship to study treatment
- Outcome
- Treatment or action taken.

Whenever possible, recognized medical terms should be used when recording AEs. Colloquialisms and/or abbreviations should not be used.

If more than one distinct AE occurs, each event should be recorded separately. However, if known at the time of reporting, a diagnosis (i.e., disease or syndrome) should be recorded on the eCRF rather than individual signs and symptoms (e.g., record congestive heart failure rather than dyspnea, rales, and cyanosis). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as a separate AE. A diagnosis that is subsequently established should be reported as follow-up information. However, signs and symptoms that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs (e.g., if congestive heart failure and severe headache are observed at the same time, each event should be recorded as an individual AE).

AEs occurring secondary to other events (e.g., sequelae) should be identified by the primary cause; a "primary" event, if clearly identifiable, should represent the most accurate clinical term to record as the AE event term. For example:

> Orthostatic hypotension ➔fainting and fall to floor➔head trauma➔neck pain
>
> The primary event is orthostatic hypotension and the sequelae are fainting, fall, head trauma and neck pain.

10.2.3.4. Classification of Adverse Events by Intensity/Severity

All AEs should be graded by Investigators using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (Appendix 3). If the AE is not specifically listed in the CTC toxicity criteria (for instance posterior segment inflammation, as opposed to uveitis), use the following grades:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)
  - Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

There is a distinction between the severity and the seriousness of an AE. Severity is a measurement of intensity; thus, a severe reaction is not necessarily a SAE. For example, a

headache may be severe in intensity, but would not be serious unless it met one of the criteria for SAEs.

Expectedness

All AEs considered related to Light-activated AU-011 will be evaluated as to whether they are expected or unexpected, and related to Light-activated AU-011, the laser, and/or both. Expectedness will be determined by the Sponsor.

Expected (anticipated): An AE is expected when the nature, severity, or degree of incidence was previously described in the IB.

Unexpected (unanticipated): An AE is unexpected when the nature, severity, or degree of incidence was not previously described in the IB.

Relatedness

The Investigator will determine the assessment of the causal relationship of the AE to the study product and/or laser treatment. The following terms for assessment of the causality to study product or study procedures are to be used:

- Not related: An event that does not follow a reasonable temporal sequence from administration of the study product or procedure, does not follow a known or expected response pattern to the suspect product or procedure and that could be reasonably explained by the known characteristics of the subject's clinical state.
- Related: An event that follows a reasonable temporal sequence from administration of the study product or procedure, follows a known or expected response pattern to the suspected product or procedure and that could not be reasonably explained by the known characteristics of the subject’s clinical state.

Outcome

The clinical outcome of an AE will be characterized as follows:

- Ongoing
- Resolved
- Resolved with sequelae
- Death
- Unknown

Action Taken with Study Drug or Procedure

- None
- Study product or procedure interrupted
- Study product or procedure discontinued

10.2.3.5. Serious Adverse Event Reporting

Serious Adverse Events (SAE) must be reported to the Sponsor as soon as possible and no later than 24 hours after the Investigator first learns of the event. The SAE form is to be completed

and submitted by email to Aura Biosciences. For initial reports, Investigators should record all case details that can be gathered within the reporting timeframe. Relevant follow-up information should be submitted to the Sponsor as soon as it becomes available and/or upon request. For some events, the Sponsor or designee or the medical monitor may follow up with the site by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the event (e.g., hospital discharge summary, consultant report, or autopsy report). Reports relating to the subject's subsequent medical course must be submitted to the Sponsor until the event has resolved or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.

SAE reporting timelines should be followed when reporting a pregnancy or symptomatic overdose.

The SAE report should be sent to the medical monitor and Aura Biosciences via e-mail – Safety@aurabiosciences.com. The following contact information (during both business and non-business hours) is also available:

- Medical Monitor, [redacted]:
  [redacted]
- Aura Biosciences, [redacted]

Study personnel are free to contact the medical monitor, [redacted] by phone at [redacted], or by email at [redacted] regarding any SAE or medical concerns.

Transmission of the SAE report should be confirmed by the site personnel submitting the report. Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the Sponsor as soon as it is available; these reports should be submitted using the SAE Report Form. Non-serious AEs that become serious should be reported to the Sponsor within 24 hours and recorded on the SAE Report Form.

10.3. Ophthalmic Assessments

10.3.1. Best Corrected Visual Acuity (BCVA)

The study's independent visual acuity consultants will certify the visual acuity equipment, examination rooms, and examiners before the study begins at each site. Manifest refraction and BCVA measurement will be performed according to the standard ETDRS refraction and visual acuity testing protocol in **both eyes at all visits**.

10.3.2. Intraocular Pressure (IOP)

IOP will be measured using applanation or tonopen in the study eye at every study visit and in **both eyes** at Visit 1 (Screening) and Visit 11 (Week 12), and at any Early Termination Visit that occurs before Visit 11 (Week 12). In addition, for all 80 µg dose cohorts, IOP must be 21 mm Hg or less before each injection and before discharge from the clinic.

10.3.3. Slit Lamp Biomicroscopy and Fundoscopy

Slit lamp biomicroscopy and fundoscopy will be performed in the study eye at every study visit except at Visit 1 (Screening) and Visit 11 (Week 12), and at any Early Termination Visit that

occurs before Visit 11 (Week 12), where Slit Lamp Biomicroscopy and Fundoscopy will be measured in **both eyes**.

10.3.4. Fluorescein Angiography (FA) and Color Fundus Photography (Fundus Photos)

FA will be performed at Visit 1 (Screening), Visit 11 (Week 12), Visit 14 (Week 52), and Visit 16 (Week 104), and at any Early Termination Visit. Fundus photos will be performed in **both eyes** at Visit 1 (Screening) and Visit 11 (Week 12), and at any Early Termination Visit if that occurs before Visit 11 (Week 12). Fundus photos will be taken for the study eye only at all other visits including Early Termination that occurs after Visit 11 (Week 12). All FAs and fundus photos will be performed using digital fluorescein photography equipment and cameras certified by the IRC. The IRC will certify all photographers performing FA and fundus photos before they perform any imaging on study subjects. The IRC will provide each site with the protocol for image acquisition and transfer.

The largest basal diameter (LBD) of the CM will be measured on the Fundus Photos at baseline and all visits described above. The greatest basal area (GBA) of tumor will also be measured on Fundus Photos at the same visits and tumor volume will be derived using the GBA and the maximum tumor thickness (measured by B-scan ultrasound) using the formula $\pi r^2 h/3$ where r is the radius derived from the GBA and h is the maximum tumor thickness. The criteria to classify tumor response (diameter) on Fundus Photos will be:

Tumor Control:

- Regression = Any reduction > 0.5 mm in the largest basal diameter (LBD) of the CM from baseline
- Stable Disease (SD) = Maximum LBD of the CM is within ≥ -0.5 mm to ≤ +1.0 mm change in diameter from baseline

Tumor Progression:

- Progression = Any increase > 1.0 mm in the LBD of the CM from baseline not judged by the Investigator to be due to inflammation/swelling, hemorrhage or pigmentary changes

10.3.5. Enhanced Depth Imaging Optical Coherence Tomography (EDI-OCT)

The study's IRC will certify the EDI-OCT machine and technician(s) before the study begins at each site. EDI-OCT will be performed in **both eyes** at Visit 1 (Screening) and Visit 11 (Week 12), and at any Early Termination that occurs before Visit 11 (Week 12) and in the study eye only at all other visits including Early Termination that occurs after Visit 11 (Week 12). All images will be sent to the IRC for assessment throughout the study and in accordance with the IRC-provided protocol.

10.3.6. Optical Coherence Tomography Angiography (OCTA)

OCTA will be recorded at sites with OCTA imaging systems in Cohorts 6 through 9. The study's IRC will certify the OCTA machine and technician(s) before the study begins at each site. OCTA will be performed in **both eyes** at Visit 1 (Screening) and Visit 11 (Week 12), and at any Early Termination that occurs before Visit 11 (Week 12) and in the study eye only at all other visits

including Early Termination that occurs after Visit 11 (Week 12). All images will be sent to the IRC for assessment throughout the study and in accordance with the IRC-provided protocol.

10.3.7. B-scan Ultrasound

B-scan ultrasound (B-scan) will be performed in **both eyes** at Visit 1 (Screening) and Visit 11 (Week 12), and at any Early Termination Visit if that occurs before Visit 11 (Week 12) and in the study eye only at Visit 2 (Day 1), Visit 3 (Day 2) for cohorts 1, 2 and 3 only, Visit 4 (Day 8), Visit 6 (Day 15), Visit 8 (Day 29), Visit 10 (Week 8), Visit 12 (Week 26), Visit 13 (Week 39), Visit 14 (Week 52), Visit 15 (Week 78), Visit 16 (Week 104), and at any Early Termination that occurs after Visit 11 (Week 12). Ultrasound technicians will be certified by the IRC prior to study initiation based on adherence to IRC provided imaging acquisition and transfer protocols. Tumor thickness eligibility for the study is determined by B-scan measurement.

Criteria to classify tumor response (thickness) on B-scan will be:

Tumor Control:

- Complete Response (CR) = Entire tumor is a flat lesion and of equal (or less) thickness to the surrounding choroid
- Regression = Any reduction > 0.5 mm in the maximum thickness of the CM from baseline
- Stable Disease (SD) = Maximum thickness of the CM is within ≥ -0.5 mm to ≤ +0.5 mm change from baseline

Tumor Progression:

- Progression = Any increase > 0.5 mm in the maximum thickness of the CM from baseline not judged by the Investigator to be due to inflammation/swelling or hemorrhage

10.3.8. A-scan Ultrasound

A-scan ultrasound (A-scan) will be recorded in the study eye at sites with diagnostic probes. The amplitude of the internal reflectivity of the lesion will be recorded at Visit 1 (Screening), Visit 4 (Day 8), Visit 8 (Day 29), Visit 10 (Week 8), Visit 11 (Week 12), Visit 12 (Week 26), Visit 13 (Week 39), Visit 14 (Week 52), Visit 15 (Week 78), Visit 16 (Week 104), and at any Early Termination Visit. Ultrasound technicians will be certified by the IRC prior to enrollment of subjects in to the sub-study, based on adherence to IRC provided imaging acquisition and transfer protocols.

10.3.9. Visual Field Examination

Visual field assessment will be performed using automated perimetry testing (e.g., Humphrey 24-2 SITA standard). Visual field examinations will be performed in **both eyes** at Visit 1 (Screening) and Visit 11 (Week 12), and at any Early Termination Visit that occurs before Visit 11 (Week 12) and in the study eye only at Visit 14 (Week 52), Visit 16 (Week 104), and any Early Termination Visit that occurs after Visit 11 (Week 12).

10.3.10. Additional Assessments

If peri-tumoral whitening/pigmentary changes are seen at any time during the study, the Investigators should notify the sponsor and the additional assessments outlined below should be conducted if the required equipment is available at the Investigational site:

1. Wide field fundus autofluorescence (FAF) over lesion and extent of whitening
2. Single line scan OCT images oversampled at least 50 times with EDI on, including normal retina, whitening and tumor
3. Indocyanine green (ICG) angiography
4. OCTA in the area of retinal whitening

These assessments should be conducted at the visit that the changes are first observed and at scheduled visits through 26 weeks (as outlined in Appendix 1) from the last treatment day for that cycle. If changes were seen with the first cycle of treatment and there are further changes/increases observed during the second cycle, the additional assessments should be conducted at the visit when observed and at scheduled visits through 26 weeks (as outlined in Appendix 4) from the last treatment day of second cycle.

10.4. General Methodology

Since this is an exploratory study, no formal hypothesis testing will be performed. Descriptive statistics will be used to tabulate and summarize efficacy and safety outcomes. Background and demographic characteristics will be presented. Continuous variables will be summarized by descriptive statistics (sample size, mean, standard deviation, median, minimum and maximum). Discrete variables will be summarized by frequencies and percentages.

Safety assessments will be made at all study visits and both safety and tolerability will be evaluated by assessing the incidence of DLTs (as defined in Section 8.4.1), AEs and the incidence of SAEs.

AEs, SAEs, and other findings will be summarized by presenting the percentages of subjects with each event for each treatment group. When relevant, the time course of AEs will be presented.

All safety analyses will be presented by dose group and over all subjects. Safety analyses will summarize subjects by the treatment received.

The safety analysis will summarize ocular treatment-emergent AEs (TEAEs) in the study eye for all treated subjects using discrete summaries at the subject- and event-level by system organ class and preferred term. A TEAE will be defined as occurring on or after the day that treatment is initiated. An additional analysis will investigate ocular AEs for the non-study eye. Non-ocular TEAEs will be summarized using discrete summaries at the subject- and event-level by system organ class and preferred term. Treatment-related ocular and non-ocular TEAEs will be summarized similarly. Ocular and non-ocular TEAEs will also be summarized by severity or toxicity grade. Additionally, TEAEs will be summarized by treatment schedule as deemed necessary to better understand the safety profile.

The presence or absence of anti-drug antibodies will be summarized by treatment group.

10.5. Efficacy

Since this is a single arm, exploratory study, no formal hypothesis testing will be performed. Efficacy will be assessed at the Week 12, 26 39, 52, 78 and 104 visits for any potential tumor response and changes in ETDRS best corrected visual acuity (BCVA). This will include change from baseline at each visit in tumor thickness by ultrasound and largest basal diameter by digital fundus photography. The proportion of subjects who meet the definition of stable disease (do not meet the definition of disease progression) will also be reported for each visit using change in tumor thickness and for changes in largest basal diameter. Change from baseline in ETDRS BCVA at Week 12 and at each subsequent visit will include changes in letter score and the proportion of subjects who lose or gain 5, 10 or 15 letters.

Exploratory analyses will be performed for change in internal reflectivity of tumors by A-scan ultrasound at each visit and macular changes (foveal avascular zone and vessel density) by OCTA at each visit.

Background and demographic characteristics will be presented. Continuous variables will be summarized by descriptive statistics (sample size, mean, standard deviation, median, minimum and maximum). Discrete variables will be summarized by frequencies and percentages.

Efficacy and safety will be analyzed at various intervals after the first 2 cohorts have completed 12 months of follow-up and then at further intervals as subsequent cohorts reach similar milestones. Specific details of the timing of such analyses will be included in the Statistical Analysis Plan.

11. SOURCE DATA/DOCUMENTS

11.1. Study Monitoring

The Investigator will permit monitoring, quality audits, and inspections by the government regulatory authorities, and the Sponsor or its representative(s) of all study related documents (e.g., source documents, regulatory documents, data collection instruments, eCRFs).

Study monitoring involves the following elements:

- Aura Biosciences personnel, or designee, may meet with Investigators prior to the initiation of the study in order to review the adequacy of the subject population, facilities, and equipment with respect to the needs of the study, and to familiarize the Investigator and support staff with the study protocol.
- Aura Biosciences personnel, or designee, may meet with the Investigators at the time enrollment is initiated in order to ensure that subjects are being properly selected, that the methods described in the study protocol are thoroughly understood by the Investigator, and that study data are being correctly recorded.
- Aura Biosciences personnel, or designee, may visit the clinical site at any time during the course of the study to review and/or collect completed eCRFs. Additionally, telephone consultation will occur as necessary during the course of the study to ensure the proper progress and documentation of the study findings.
- Aura Biosciences personnel will review protocol deviations regularly.

11.2. Audits and Inspections

Authorized representatives of Aura Biosciences, a regulatory authority, an Independent Ethics Committee, or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. The Investigator should contact Aura Biosciences immediately if contacted by a regulatory agency about an inspection.

11.3. Institutional Review Board (IRB)

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

12. QUALITY CONTROL AND QUALITY ASSURANCE

The eCRFs will be reviewed by Aura Biosciences or designee. All data on eCRFs will be 100% source-verified by office-based monitoring and during site visits for accuracy and completeness by a clinical monitor. All data captured by the EDC system will be transferred through an electronic interface into a study database for management, analysis, and reporting. Any other data (eg, laboratory results) will also be transferred into the database. Upon completion of data collection, the database will receive a quality assurance (QA) check to ensure acceptable accuracy and completeness.

13. ETHICS

13.1. IRB Review

The study protocol, subject information and consent form, the IB, any subject diary card or written instructions to be given to the subject, available safety information, subject recruitment procedures (e.g., study website), information about payments and compensation available to the subjects and documentation evidencing the Investigator's qualifications should be submitted to the IRB for review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment. The Investigator must submit and, where necessary, obtain IRB and/or Sponsor approval for all subsequent protocol amendments and changes to the ICF or changes of the investigational site, facilities or personnel. The Investigator should notify the IRB of protocol deviations or SAEs occurring at the site and other AE reports received from the Sponsor in accordance with local procedures.

Safety updates for Light-activated AU-011 will be prepared by the Sponsor or its representative as required, for submission to the relevant IRB.

13.2. Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, principles set forth in the Declaration of Helsinki (1998 version applicable for study sites in the EU), ICH Guideline E6 for GCP (CPMP/ICH/135/95 Jan 1997), and the U.S. Code of Federal Regulations (CFR) Title 21, parts 50, 54 56, and 312.

Appendix 2 provides more detail about the Sponsor's commitments to clinical research and to this study.

13.3. Written Informed Consent

Informed consent is a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated ICF.

The ICF will be submitted for approval to the IRB that is responsible for review and approval of the study. Each consent form must include all of the relevant elements currently required by the national regulatory body, as well as local county authority or state regulations.

Before recruitment and enrollment into the trial, each prospective candidate will be given a full explanation of the trial. Once the essential information has been provided to the prospective candidate, and the Investigator is sure that the individual candidate understands the implications of participating in this trial, the candidate will be asked to give consent to participate in the trial by signing an ICF. A notation that written informed consent has been obtained will be made in the subject's medical record. A copy of the ICF, to include the subject's signature, will be provided by the Investigator to the subject.

If an amendment to the protocol substantially alters the trial design or the potential risks to the subjects, the subject's consent to continue participation in the trial should be obtained.

13.4. Subject Confidentiality

Confidentiality of subject's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and national data protection laws, as applicable. HIPAA regulations require that, in order to participate in the trial, a subject must sign an authorization from the trial that he or she has been informed of following:

- What protected health information (PHI) will be collected from subjects in this trial;
- Who will have access to that information and why;
- Who will use or disclose that information;
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws;
- The information collected about the research trial will be kept separate from the subject's medical records, but the subject will be able to obtain the research records after the conclusion of the trial;
- Whether the authorization contains an expiration date; and
- The rights of a research subject to revoke his or her authorization.

In the event that a subject revokes authorization to collect or use his or her PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled trial period.

In compliance with ICH GCP guidelines, it is a requirement that the Investigator and institution permit authorized representatives of Sponsor, the regulatory authorities and the IRB direct access to review the subject's original medical records at the site for verification of trial-related procedures and data.

Measures to protect confidentiality include: only a unique trial number and initials will identify subjects on the eCRF or other documents submitted to the Sponsor. This information, together with the subject's date of birth, will be used in the database for subject identification. Subject names or addresses will not be entered on the eCRF or in the database. No material bearing a subject's name will be kept on file by the Sponsor. Subjects will be informed of their rights within the ICF.

14. DATA HANDLING AND RECORDKEEPING

14.1. Data Collection

The eCRF is the primary data collection instrument for the trial. eCRFs will be kept current to enable the monitor to review the subjects' status throughout the course of the trial. In order to maintain confidentiality, only the study number, subject number and date of birth will identify the subject on the eCRF. All data requested on the eCRF must be supported by and be consistent with the subject's source documentation.

Source documents are the original documents, data, records and certified copies of original records of clinical findings, observations and activities from which the subject's eCRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the field was "Not Done" or "Unknown". For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The Principal Investigator will sign and date the subject eCRF casebook indicating that the data on the eCRF have been assessed, once all data for that subject is final.

14.2. Study Documentation and Retention of Records

All study-related records must be maintained for at least 2 years after a marketing application is approved for the drug; or if an application is not approved for the drug, until at least 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA/health authorities or regulatory agencies have been notified. The Sponsor will notify the principal Investigator when records are no longer needed. The Investigator will not discard any records without notifying the Sponsor. If the Investigator moves from the current investigational site, the Sponsor should be notified in writing or by email of the name of the person who will assume responsibility for maintenance of the records at the investigational site or the new address at which the records will be stored. The Investigator will notify the Sponsor as soon as possible in the event of accidental loss or destruction of any study documentation.

14.3. Amendments to the Protocol

Amendments to the protocol shall be planned, documented, and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor (or its representative). The written amendment must be reviewed and approved by the Sponsor, and submitted to the IRB for approval.

Amendments specifically involving change to trial design, risk to subject, increase to dosing or exposure, subject number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the appropriate IRB.

The amendment will be submitted formally to regulatory authorities by the Sponsor as applicable, after IRB approval and specifically when an increase to dosing or subject exposure and/or subject number has been proposed; or, when the addition or removal of an Investigator is necessitated.

15. DISCLOSURE AND PUBLICATION POLICY

All information provided regarding the trial, as well as all information collected/documented during the course of the trial, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the trial. Results from the trial will be published/presented as per the Sponsor's publication strategy.

Inclusion of the Investigator in the authorship of any multi-center publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the trial. The Investigator acknowledges that the trial is part of a multi-center trial and agrees that any publication by the Investigator of the results of the trial conducted at his/her research site shall not be made before the first multi-center publication. In the event there is no multi-center publication within fifteen (15) months after the trial has been completed or terminated at all trial sites, and all data has been received, the Investigator shall have the right to publish its results from the trial, subject to the notice requirements described herein and subject to acknowledgement of the Sponsor as appropriate. Investigator shall provide the Sponsor thirty (30) days to review a manuscript or any poster presentation, abstract or other written or oral material which describes the results of the trial for the purpose only of determining if any confidential or patentable information is disclosed thereby. If the Sponsor requests in writing, the Investigator shall withhold any publication or presentation an additional sixty (60) days solely to permit the Sponsor to seek patent protection.

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17. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS

	Screening	Active Period						Follow-up Period								End of Study or Early Termination
Assessment	**Visit 1 D -28 to 1**	**Visit 2 D1**	**Visit 3 D2 ± 4H**	**Visit 4 D8 + 1D**	**Visit 5 D9 ± 4H**	**Visit 6 [o] D15 + 1D**	**Visit 7 D16 ± 4H**	**Visit 8 D29± 1D**	**Visit 9 W6 ± 3D**	**Visit 10 W8 ± 3D**	**Visit 11 W12 ± 3D**	**Visit 12 W26 ± 7D**	**Visit 13 W39 ± 7D**	**Visit 14 W52 ± 7D**	**Visit 15 W78 ± 7D**	**Visit 16 W104 ± 7D or Early Termination**
Informed consent	X															
Eligibility review	X	X														
Demographics	X															
Medical and ophthalmic history	X															
Vital signs[a]	X	X	X	X	X[j]	X	X[k]	X						X		X
Pregnancy test	X	X[b]														
Laboratory assessments (CBC with differential and CMP)	X[c]	X[c]		X[c]				X[c]								
Light-activated AU-011 treatment		X[d]		X[j]		X[k]										
ADA samples	X			X		X[k]		X			X			X		
BCVA	X	X [e]	X	X	X[j]	X	X[k]	X	X	X	X	X	X	X	X	X
Slit lamp biomicroscopy[f]	X	X	X	X	X[j]	X	X[k]	X	X	X	X	X	X	X	X	X
IOP[f]	X	X	X	X	X[j]	X	X[k]	X	X	X	X	X	X	X	X	X
Fundoscopy[f]	X	X	X	X	X[j]	X	X[k]	X	X	X	X	X	X	X	X	X
Fundus photos[f]	X	X[e]	X	X	X[j]	X	X[k]	X	X	X	X	X	X	X	X	X
FA[f]	X										X			X		X
EDI-OCT[f]	X	X[e]	X	X	X[j]	X	X[k]	X	X	X	X	X	X	X	X	X
OCTA[f, p]	X	X[e]	X	X	X[j]	X	X[k]	X	X	X	X	X	X	X	X	X
B-scan[f]	X	X[e]	X[l]	X		X		X		X	X	X	X	X	X	X
A-scan (study eye only)	X			X				X		X	X	X	X	X	X	X
Visual field exam[f]	X										X			X		X
AE review[q]	X[q]	X	X	X	X[j]	X	X[k]	X	X[m]	X[n]	X[h,q]	X[h,q]	X[h,q]	X[h,q]	X[h,q]	X[h,i,q]
Concomitant medication review[q]	X	X	X	X	X[j]	X	X[k]	X	X[j]	X[k]	X[q]	X[q]	X[q]	X[q]	X[q]	X[g,q]

[a]Vital signs include BP seated and pulse.
[b]Serum pregnancy test will be performed at Visit 1. If Visit 2 occurs more than 7 days after Visit 1, then urine pregnancy test will be performed at Visit 2.
[c]CBC with differential includes hemoglobin, hematocrit, red blood cells (RBC), white blood cells (WBC), WBC differential, and platelets. CMP includes total bilirubin, direct bilirubin, alkaline phosphatase, ALT (SGPT), AST (SGOT), GGT, LDH, blood urea nitrogen (BUN), creatinine, glucose, uric acid, calcium, phosphorus (or phosphate), total protein, albumin, globulin, triglycerides, cholesterol, CK, sodium, potassium, bicarbonate, chloride, and magnesium. If Visit 2 occurs more than 7 days after Visit 1, then laboratory assessments will be repeated at Visit 2.
[d]Subjects should remain at the study site following intravitreal injection until approximately ½ hour after laser treatment. If subjects are discharged during daylight hours, appropriate sun protection, e.g., sunglasses and a hat, will be required.
[e]If Visit 1 and Visit 2 are within 7 days, the following procedures do not need to be repeated prior to AU-011 study drug injection, unless clinically indicated: BCVA, fundus photos, EDI-OCT, OCTA, and B-scan.
[f]FA and Fundus photos, EDI-OCT, OCTA, B-scan, Visual Field, IOP, Slit lamp and Fundoscopy will be performed in both eyes at Visit 1 (Screening) and Visit 11 (Week 12), and at any Early Termination Visit if that occurs before Visit 11 (Week 12), and in the study eye only at all remaining visits where applicable for each assessment.
[g]If Early Termination Visit occurs ≤ 30 days following study treatment.
[h]Study product and/or study procedure related AEs only for Cohorts 1 to 9.
[i]Any AE for up to 30 days after the last AU-011 treatment if Early Termination Visit occurs ≤ 30 days following study treatment.
[j]For 2 and 3 Repeat Light-activated AU-011 administration cohort subjects only
[k]For 3 Repeat Light-activated AU-011 administration cohort subjects only
[l]For Cohort 1, 2 and 3 subjects only
[m]For Single Light-activated AU-011 administration cohort subjects, only study product and/or study procedure related AEs. For 2 and 3 Repeat Light-activated AU-011 administration cohort subjects, any AE.
[n]For Single Light-activated AU-011 administration cohort and 2 Repeat Light-activated AU-011 administration cohort subjects, only study product and/or study procedure related AEs. For 3 Repeat Light-activated AU-011 administration cohort subjects, any AE.
[o]For the observation cohort (Cohort 10) every 3 month visits (i.e. 90 day (+/- 7 days) intervals from the Screening Visit) prior to evidence of tumor growth, all procedures outlined for Visit 6 (Day 15) will be performed with the exception of OCTA and Anti-drug Antibody (ADA) testing which is not required.
[p]For Cohort 6, 7, 8, and 9 subjects only
[q]For Cohort 10, 11, and 12 subjects, all SAEs and AEs and concomitant medications will be reported from the time the subject signs the informed consent through their last study visit.

APPENDIX 2. SPONSOR'S COMMITMENTS

The Sponsor is committed to:

1. Complying with all applicable health authority regulations governing the conduct of clinical research studies, including the U.S. Food and Drug Administration.
2. Protecting the rights, health, safety and welfare of study subjects.
3. Informing the clinical Investigators of any new information about the study which may affect the health, safety or welfare of the subjects, or may influence their decision to continue participation in the study.
4. Providing the clinical Investigators with the study protocol, and access to electronic CRFs on which to document the study evaluation variables for each subject entered into the study.
5. Providing the statistical analysis and study report writing resources necessary to complete reporting of the study results.
6. Ensuring equity of consideration among all Investigators in multicenter studies in all matters of publications, meeting presentations, etc.
7. Certifying that IRB/EC approval of the protocol and Investigator's Agreement will be completed prior to treatment at an investigational site.

APPENDIX 3. COMMON TECHNICAL CRITERIA FOR ADVERSE EVENTS (CTCAE)

Refer to CTCAE, Version 4, published May 28, 2009 (v4.03: June 14, 2010)

Online resources are available at http://evs.nci.nih.gov/ftp1/CTCAE/About.html and include the following documents provided in different formats:

- The file named "CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf" provides the most recent release of core terminology and is available as a PDF document in traditional small booklet format.
- The file name "CTCAE4.03_2010-06-14_QuickReference_8.5x11.pdf" provides the most recent release of core terminology and is available as a PDF document in letter-sized format.

APPENDIX 4. AU-011 ADDITIONAL THERAPY AND SECOND CYCLE (COHORTS 10, 11 & 12) VISIT SCHEDULE

If the Investigator elects to give additional therapy with AU-011 as outlined in Section 8.3.3 then the following visit schedule and assessments must be performed. Similarly, the same visit schedule will be used for the second cycle of AU-011 for Cohorts 10, 11 and 12. Concomitant steroid treatment as outlined in section 8.3.1 should be administered with additional therapy or second cycle of AU-011. Prior to additional therapy and second cycle with AU-011, subjects must have provided informed consent and women of child-bearing potential must undergo a urine pregnancy test.

Subjects will be assessed for safety 24 hours after each AU-011 administration and at 2 weeks, 4 weeks, 12 weeks, and 26 weeks after completion of additional therapy with AU-011. Additional unscheduled visits may occur at the discretion of the investigator. If a protocol defined visit is scheduled to occur within 1 week of either the 4 week, 12 week or 26 week post additional therapy or second cycle follow-up visit, only one visit is required and the visit should be recorded as the protocol defined visit and all the assessments of that visit should be performed. After the 26 week post additional therapy or second cycle follow-up visit, remaining study visits will be conducted per the visit schedule in Section 10 and Appendix 1. If any post additional therapy, or second cycle follow-up visit will occur after the planned Week 104 End of Study Visit, the 26 week post additional therapy, or second cycle follow-up visit should be recorded as the Week 104 End of Study Visit.

AU-011 Additional Therapy or Second Cycle 1, 2 & 3

The following procedures will be performed:

- Informed Consent Form Amendment Review and Consent
- Vital signs
- BCVA (Both Eyes)
- Slit lamp biomicroscopy
- IOP
- Fundoscopy
- Fundus photos
- EDI-OCT
- OCTA (Cohorts 6 through 9 only)
- B-scan
- Blood sample for ADA testing (prior to AU-011 administration)
- Urine pregnancy test for women of childbearing potential (prior to first AU-011 administration)
- Administration of Light-activated AU-011 treatment

- Intravitreal injection of AU-011 study drug (Highest established safe dose at the time of the retreatment request will be offered). The subject will receive 80 µg doses administered as 2 injections of 40 µg in [redacted] µl and the subject's IOP will be measured prior to and after each injection. IOP must be 21 mm Hg or less before each injection can be given and **the maximum interval between the two injections is 2 hours**. IOP must also be 21 mm Hg or less before the patient is discharged from the clinic).
- Laser treatment (Highest safe regimen at the time of the retreatment request will be offered and given 6 to 8 hours after intravitreal administration of AU-011). As the subject will receive 80 µg doses administered as 2 injections of 40 µg in [redacted] µl, the two laser treatments will be administered 6 to 8 hours after the second injection 30 minutes (±10 minutes) apart. If the fovea is near the tumor edge, an adjustment to the laser procedure should be performed on each treatment day as outlined in section 8.2.2 and the Injection and Laser Procedure Manual. Subjects should remain at the study site after intravitreal injection until approximately ½ hour after laser treatment.
- If subjects are discharged during daylight hours, appropriate sun protection, e.g., sunglasses and a hat, will be required.

- Record AEs
- Record concomitant medications

24 hour Post Additional Therapy or Second Cycle Follow-Up (1 Day after AU-011 treatment)

The following procedures will be performed:

- Vital Signs
- BCVA (Both Eyes)
- Slit lamp biomicroscopy
- IOP
- Fundoscopy
- Fundus photos
- EDI-OCT
- OCTA (Cohorts 6 through 9 only)
- Record AEs
- Record concomitant medications

2-Week Post Additional Therapy or Second Cycle Follow-Up (14 to 15 days after last AU-011 treatment)

The following procedures will be performed:

- BCVA (Both Eyes)
- Slit lamp biomicroscopy
- IOP
- Fundoscopy
- Fundus photos
- EDI-OCT
- OCTA (Cohorts 6 through 9 only)
- B-scan
- Blood sample for ADA testing
- Record AEs
- Record concomitant medications

4-Week Post Additional Therapy or Second Cycle Follow-Up (4 weeks +/- 1 day after last AU-011 treatment)

The following procedures will be performed:

- BCVA (Both Eyes)
- Slit lamp biomicroscopy
- IOP
- Fundoscopy
- Fundus photos
- EDI-OCT
- OCTA (Cohorts 6 through 9 only)
- B-scan
- Blood sample for ADA testing
- Record AEs
- Record concomitant medications

12-Week Post Additional Therapy or Second Cycle Follow-Up (12 weeks +/- 3 days after last AU-011 treatment)

The following procedures will be performed:

- BCVA (Both Eyes)

- Slit lamp biomicroscopy
- IOP
- Fundoscopy
- Fundus photos
- EDI-OCT
- OCTA (Cohorts 6 through 9 only)
- B-scan
- Blood sample for ADA testing
- Record study product and/or study procedure related AEs. Record all AEs and concomitant medications for Cohort 10, 11 and 12 subjects.

26 Week Post Additional Therapy or Second Cycle Follow-Up (26 weeks +/- 7 days after last AU-011 treatment)

The following procedures will be performed:

- BCVA (Both Eyes)
- Slit lamp biomicroscopy
- IOP
- Fundoscopy
- Fundus photos
- EDI-OCT
- OCTA (Cohorts 6 through 9 only)
- B-scan
- Blood sample for ADA testing
- Record study product and/or study procedure related AEs. Record all AEs and concomitant medications for Cohort 10, 11 and 12 subjects.

After the 26 week post additional therapy or second cycle follow-up visit, remaining study visits will be conducted per the visit schedule in Section 10 and Appendix 1. If additional therapy or second cycle with AU-011 occurs after Visit 15 (Week 78), subjects will be followed for 26 weeks post treatment and then may be rolled into the long-term follow-up study pending subject consent.

AU-011 Additional Therapy or Second Cycle Schedule of Assessments

Assessment	Treatment 1	24 Hr Post Treatment Follow-up	Treatment 2	24 Hr Post Treatment Follow-up	Treatment 3	24 Hr Post Treatment Follow-up	2-Week Post Treatment Follow up	4-Week Post Treatment Follow up	12-Week Post Treatment Follow up	26-Week Post Treatment Follow up
Informed consent	X[c]									
Vital signs	X	X	X	X	X	X				
Pregnancy test	X[a]									
Light-activated AU-011 treatment	X		X		X					
ADA samples	X		X		X		X	X	X	X
BCVA	X	X	X	X	X	X	X	X	X	X
Slit lamp biomicroscopy	X	X	X	X	X	X	X	X	X	X
IOP	X	X	X	X	X	X	X	X	X	X
Fundoscopy	X	X	X	X	X	X	X	X	X	X
Fundus photos	X	X	X	X	X	X	X	X	X	X
EDI-OCT	X	X	X	X	X	X	X	X	X	X
OCTA	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]
B-scan	X		X		X		X	X	X	X
AE review[e]	X	X	X	X	X	X	X	X	X[b,e]	X[b,e]
Concomitant medication review[e]	X	X	X	X	X	X	X	X	X[e]	X[e]

[a]In women of child bearing potential only.
[b]Record study product and/or study procedure related AEs only for subjects in Cohorts 1 to 9.
[c]If informed consent not previously obtained on protocol amendment Rev-7 or later
[d]Cohorts 6 through 9 only
[e]For Cohort 10, 11, and 12 subjects, all SAEs and AEs and concomitant medications will be reported from the time the subject signs the informed consent through their last study visit.