NCT03539549

Study ID: 1771-201-008

Title: Evaluation of Abicipar Pegol in Patients with Neovascular Age-Related Macular Degeneration

Protocol Amendment 1 Date: 16 Oct 2018

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EVALUATION OF ABICIPAR PEGOL IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

Protocol Number:	1771-201-008
Phase:	2
Name of Investigational Product:	Abicipar pegol
Sponsor:	Allergan (North America) 2525 Dupont Drive Irvine, California USA 92612 [redacted]
Emergency Telephone Number(s):	Refer to the Study Contacts Page.

[redacted]

Refer to the final page of this protocol for electronic signature and date of approval.

The following information can be found on FDA Form 1572 and/or study contacts page: Name and contact information of Allergan study personnel and Emergency Telephone Numbers; name, address, and statement of qualifications of each investigator; name of each subinvestigator working under the supervision of the investigator; name and address of the research facilities to be used; name and address of each reviewing IRB; US 21 CFR 312.23 section 6(iii)b.

INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR:

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.
- Maintain all information supplied by Allergan in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.
- Ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

I have read this protocol in its entirety and I agree to all aspects.

Investigator Printed Name	Signature	Date

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Protocol Summary

Study Compound(s): Abicipar pegol (hereafter referred to as abicipar)

Phase: 2

Study Objective(s): The primary objective is to evaluate abicipar for safety and treatment effect in patients with neovascular age-related macular degeneration (AMD).

Study Design

Structure: multicenter, open-label, single-arm study

Duration: 28 weeks

Study Treatment Groups: 2 mg abicipar

Controls: not applicable

Dosage/Dose Regimen: intravitreal injections of 2 mg abicipar administered at baseline (Day 1) and Weeks 4, 8, 16, and 24

Randomization/Stratification: None

Visit Schedule: There will be 9 scheduled visits during the study. These include screening (Days -21 to -2); baseline (Day 1); Weeks 4, 8, 12, 16, 20, 24, and 28/Early Exit. For patients at selected sites who participate in pharmacokinetic (PK) blood sampling, there will be 1 additional visit: Day 3.

Study Population Characteristics

Number of Patients: Approximately 100 patients will be enrolled at approximately 40 sites in the US.

Condition/Disease: Patients with neovascular AMD

Key Inclusion Criteria: [redacted]

Key General Inclusion Criteria:

- Male or female patients, 50 years of age or older at the time of informed consent

Key Ocular Inclusion Criteria (study eye):

- [redacted]
- [redacted]
- BCVA ≤ 78 and ≥ 24 letters (20/32 to 20/320 Snellen equivalents, respectively) at screening and baseline (Day 1, prior to treatment)

Key Ocular Inclusion Criterion (Non-study Eye):

- BCVA of 34 letters (Snellen equivalent 20/200) or better at baseline (Day 1, prior to treatment)

Key Exclusion Criteria:

Key Ocular Exclusion Criteria (Either Eye)

- Active periocular, ocular, or intraocular infection at baseline (Day 1)

Key Ocular Exclusion Criteria (Study Eye):

- Previous or concurrent macular laser treatment
  - Cataract or refractive surgery (excluding yttrium aluminum garnet [YAG] laser posterior capsulotomy) within the last 3 months prior to baseline (Day 1)

Response Measures

Efficacy:

- BCVA assessed by Early Treatment of Diabetic Retinopathy Study (ETDRS) letters
- Central retinal thickness (CRT) assessed with spectral-domain optical coherence tomography (SD-OCT)

[redacted]

General Statistical Methods and Types of Analyses:

The safety population, consisting of patients who received at least 1 study treatment, will be used for all analyses. Statistical analysis will be primarily descriptive.

Efficacy: Summary statistics of the following efficacy variables will be provided:

- Proportion of patients with stable vision (ie, patients who lose fewer than 15 letters in BCVA) from baseline
- Mean change from baseline in BCVA
- Proportion of patients with a gain of 15 or more ETDRS letters in BCVA from baseline
- Mean change from baseline in CRT as assessed with SD-OCT

[redacted]

Sample Size Calculation: The study will enroll approximately 100 patients. This sample size is determined empirically and is considered appropriate for the planned assessments.

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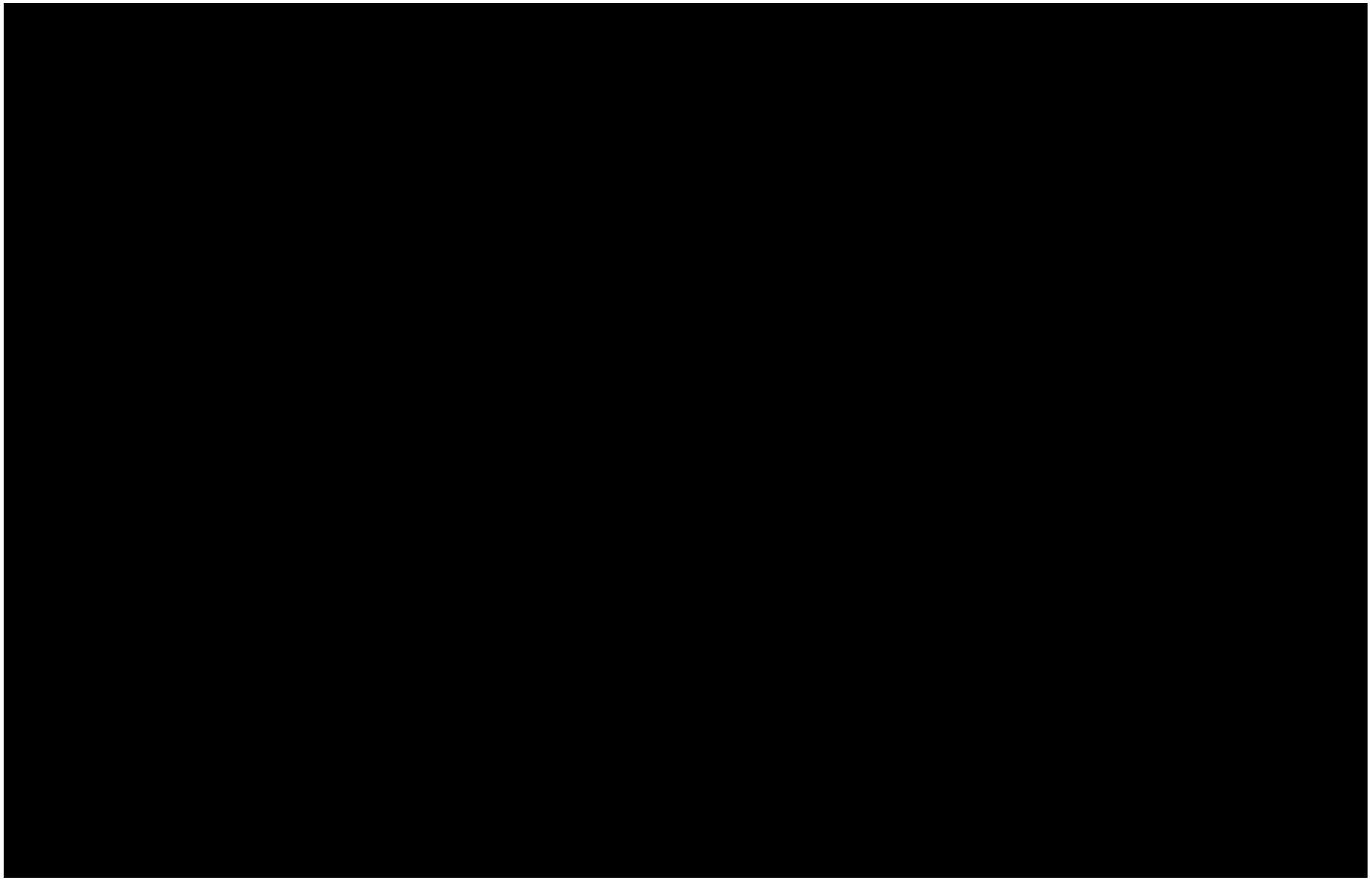


1. Background and Clinical Rationale

Age-related macular degeneration (AMD) is the leading cause of severe vision loss in industrialized countries worldwide (World Health Organization 2013). AMD is a macular disorder characterized by drusen deposits, retinal pigment epithelium (RPE) abnormalities, geographic atrophy, and neovascular maculopathy (Pieramici 2006). The advanced stages of AMD, which are associated with severe loss of vision, consist of either choroidal neovascularization (neovascular AMD) or central geographic atrophy. The majority of severe vision loss due to advanced AMD is attributable to the development of choroidal neovascularization (CNV) (Ferris 1983, Sommer 1991). Neovascular AMD is characterized by the growth of choroidal vessels into the subretinal space. These newly formed vessels have a tendency to leak blood and fluid, causing retinal edema, which is accompanied by metamorphopsia. The new vessels are accompanied by proliferation of fibrous tissue, and the continued growth of this lesion into the macula results in progressive, severe, and irreversible central vision loss (Shah 2007, Shah 2009). Left untreated, neovascular AMD results in severe visual impairment with an average loss of around 4 lines of visual acuity within 2 years of disease onset (Blinder 2003, Wong 2008).

Vascular endothelial growth factor-A (VEGF-A) is implicated in the development and maintenance of neovascularization that characterizes the neovascular form of AMD (Ding 2009). Studies have shown elevated VEGF-A levels in areas of laser-induced CNV in primates, and clinically in patients with AMD. VEGF-A is a potent mitogen for endothelial cells, which causes increased vascular permeability and promotes leukocyte-induced damage to retinal endothelial cells (Grisanti 2008). Degenerated tissues produce and release VEGF-A, which binds to specific receptors located on the endothelial cells of nearby preexisting blood vessels. These endothelial cells then proliferate and migrate out through the diseased tissue. Pericytes, smooth muscle-like cells, provide structural support to these newly formed blood vessel loops and blood flow begins in these vessels. Thus, VEGF-A serves as a rate-limiting step in angiogenesis (Ciulla 2009). It also increases vascular permeability by leukocyte-mediated endothelial cell injury, formation of fenestrae, and the dissolution of tight junctions. This leads to intraretinal fluid accumulation and subsequent distortion of the macula, resulting in decreased visual acuity (Cheung 2013).

The discovery of VEGF-A's role in the pathogenesis of neovascular ocular disease provided a strong rationale for the development of highly specific and targeted anti-vascular endothelial growth factor (VEGF)-based therapies (Ciulla 2009). Three anti-VEGF agents, pegaptanib sodium, ranibizumab, and aflibercept are currently approved in many countries for the treatment of neovascular AMD. In addition, off-label use of a fourth anti-VEGF agent,

bevacizumab, as a treatment option for neovascular AMD, has become common worldwide. These agents are delivered to the vitreal cavity by intravitreal injection. This method is now widely accepted as a safe and effective means of delivering anti-VEGF compounds to the back of the eye.

One drawback with currently approved anti-VEGF treatments is the need to frequently administer intravitreal injections. It would be highly desirable to develop an agent that requires less frequent injections. Not only would this remove a significant treatment burden on patients and their health care providers, but it would decrease the risk of complications associated with frequent intravitreal injections.

Abicipar pegol (hereafter referred to as abicipar) is a pegylated designed ankyrin repeat protein (DARPin) therapeutic with an overall molecular weight of approximately 34 kDa. DARPin therapeutics are a novel class of small, single domain proteins. The protein moiety consists of an alternative scaffold domain to antigen receptors based on ankyrin repeats targeted against human VEGF-A. The targeting sequence is covalently linked to a single molecule of maleimide polyethylene glycol of 20 kDa (mPEG20) through a polypeptide linker and a carboxy-terminal cysteine.

Abicipar binds to and inhibits the biological activity of human VEGF-A. Results of in vitro assays show that abicipar inhibits VEGF-mediated cellular responses in several different assays, generally in the low picomolar range. In vivo pharmacodynamic data demonstrate marked efficacy in 2 ocular animal models relevant to the target indication of neovascular AMD. Abicipar has demonstrated a pharmacodynamic profile that is appropriate for a product being developed for use in the treatment of exudative or ischemic retinal diseases.

In addition, in vivo rabbit ocular studies have been conducted to assess the ocular pharmacokinetics (PK) of abicipar. Data from these studies indicate that abicipar has a vitreal half-life that ranges from approximately 3.9 to 7.5 days, indicating a potential for a longer duration of action compared to marketed anti-VEGF therapies when considering dissociation constant, half-life, and dose.

The abicipar clinical development program for neovascular AMD consists of a completed Phase 1 study (MP0112-CP01), an ongoing Phase 1 clinical pharmacokinetics study (150998-012) and an ongoing Phase 1 clinical pharmacokinetics study (1771-101-008 [to be conducted in Japan]), 3 completed Phase 2 studies (150998-001 [in 3 stages], 150998-002 [conducted in Japan], and 150998-003 [conducted in the United States]), and 2 ongoing global Phase 3 safety and efficacy studies (150998-005 and 150998-006). Abicipar intravitreal injection has been shown to be safe and effective for the treatment of neovascular

AMD in 1 Phase 1 and 3 Phase 2 clinical studies. One Phase 1 study (MP0112-CP01) and 3 Phase 2 studies (150998-001, 150998-002, and 150998-003) have been completed in the neovascular AMD program. Study MP0112-CP01 was a single-ascending-dose study evaluating intravitreal doses of abicipar ranging from 0.04 to 2 mg/eye in patients with neovascular AMD. Study 150998-001 was conducted in 3 stages. Stage 1 was an open-label, single-dose, dose-escalation study to evaluate the safety of abicipar and establish the highest tolerable dose. Stage 1 dose cohorts included 1 mg, 2 mg, 3 mg, and 4.2 mg abicipar given as a single intravitreal injection. Stage 2 was a randomized, double-masked study to assess the safety and efficacy of 3 mg and 4.2 mg abicipar versus ranibizumab 0.5 mg in up to 2 intravitreal injections. Stage 3 was a randomized, double-masked study to evaluate the safety and efficacy of repeat administration of abicipar 1 mg and 2 mg (1 injection at baseline and then every 4 weeks; total 3 injections) versus ranibizumab 0.5 mg (1 injection at baseline and then every 4 weeks; total 5 injections).

Studies 150998-002 and 150998-003 were similarly designed randomized and double-masked studies to evaluate the safety and efficacy of 1 and 2 mg of abicipar following repeat administration (1 injection at baseline and then every 4 weeks; total 3 injections) versus ranibizumab 0.5 mg (1 injection at baseline and then every 4 weeks; total 5 injections) in treatment-naïve Japanese and non-Japanese patients with neovascular AMD, respectively, to support the clinical development in Japan.

Following administration of a 2-mg dose, abicipar was measurable in human serum between baseline (Day 1) and Week 1 postdose, with concentrations falling below the lower limit of quantitation (BLQ) by Week 4. Peak serum concentration after dosing (C_{max}) was observed between 1 and 3 days postdose and ranged from 1.05 to 2.66 nM. These concentrations are 7-fold and 35-fold lower than those observed at the no-observed-adverse-effect level in rabbits and dogs, respectively. Concentrations of abicipar were BLQ by 4 weeks following a single injection (Studies MP0112-CP01 and 150998-001, Stage 1) or 3 repeat injections (Study 150998-001, Stage 3, Study 150988-002, Study 150998-003). The latter data suggest that abicipar does not accumulate in the systemic circulation following 3 monthly injections.

Study 1771-201-008, which follows a new protocol numbering system, is designed to evaluate the safety and treatment effect of abicipar produced using a modified manufacturing process.

2. Study Objectives

The primary objective is to evaluate abicipar for safety and treatment effect in patients with neovascular AMD.

3. Study Design

This is a multicenter, open-label, 28-week study to evaluate abicipar for safety and treatment effect in patients with neovascular AMD. Approximately 100 patients will be enrolled to receive 2 mg abicipar administered at baseline (Day 1) and Weeks 4, 8, 16, and 24.

There will be a total of 9 scheduled visits during the study. These include screening (Days -21 to -2); baseline (Day 1); Weeks 4, 8, 12, 16, 20, 24, and 28/Early Exit. For patients at selected sites who participate in PK blood sampling, there will be 1 additional visit: Day 3.

4. Study Population and Entry Criteria

4.1 Number of Patients

Approximately 100 patients will be enrolled at approximately 40 sites.

4.2 Study Population Characteristics

This study will enroll patients with neovascular AMD.

One eye will be selected as the study eye for the duration of the study. If both eyes are eligible, the eye with the worse best-corrected visual acuity (BCVA), assessed at screening and confirmed at baseline (Day 1), will be selected as the study eye. If both eyes meet all the inclusion/exclusion criteria and BCVA values are identical for both eyes, the patient may choose to select their non-dominant eye for treatment, or else the right eye will be selected as the study eye.

4.3 Inclusion Criteria

The following are requirements for entry into the study:

General Inclusion Criteria

1. Male or female patients, 50 years of age or older at the time of informed consent
2. Patient has completed/signed an informed consent prior to conduct of any study-related procedures or examinations, is able to follow study instructions, and is likely to complete all required visits

3. Patient has provided, at screening, written documentation in accordance with the relevant country and local privacy requirements (eg, Written Authorization for Use and Release of Health and Research Study Information and written Data Protection consent)

Ocular Inclusion Criteria (Study Eye)

[redacted]

6. BCVA ≤ 78 and ≥ 24 letters (20/32 to 20/320 Snellen equivalents, respectively) at screening and at baseline (Day 1, prior to treatment) visits

[redacted]

Ocular Inclusion Criteria (Non-study Eye)

8. BCVA of 34 letters (Snellen equivalent 20/200) or better at baseline (Day 1, prior to treatment)

4.4 Exclusion Criteria

The following are criteria for exclusion from participating in the study:

General Exclusion Criteria

[redacted]

[redacted]

Ocular Exclusion Criteria (Either Eye)

8. Active periocular, ocular, or intraocular infection at baseline (Day 1)

[redacted]

Ocular Exclusion Criteria (Study Eye)

[redacted]

[redacted]

17. Previous or concurrent macular laser treatment

[redacted]

[redacted]

- Cataract or refractive surgery (excluding yttrium aluminum garnet [YAG] laser posterior capsulotomy) within the last 3 months prior to baseline (Day 1)

[redacted]

4.5 Permissible and Prohibited Medications/Treatments

4.5.1 Permissible Medications/Treatments

Therapy considered necessary for the patient's welfare may be given at the discretion of the investigator. All medications must be recorded in the electronic case report form (eCRF). If the permissibility of a specific medication/treatment is in question, please contact Allergan.

- Non-investigational therapies for the non-study eye are permissible at any time, at the investigator's discretion
- Corticosteroids administered via intra-nasal, inhaled, intra-articular, or ocular topical routes are permitted during the study
- If cataract surgery is necessary, attempt to schedule cataract surgery ≥ 7 days after the most recent study treatment. Study treatment may be resumed ≥ 14 days after cataract surgery, assuming an absence of surgical-related complications

4.5.1.1 Definition of Females of (Non-)Childbearing Potential and/or Acceptable Contraceptive Methods

For purposes of this study, females will be considered of childbearing potential unless they are naturally postmenopausal or permanently sterilized (ie, hysterectomy). Natural menopause is defined as the permanent cessation of menstrual periods, determined retrospectively after a woman has experienced 12 months of amenorrhea without any other obvious pathological or physiological cause. For women of childbearing potential who may participate in the study, the following methods of contraception, if properly used, are generally considered reliable: hormonal contraceptives (ie, oral, patch, injection, implant), male condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, vaginal contraceptive ring, intrauterine device, surgical sterilization (bilateral tubal ligation, bilateral salpingectomy), vasectomized partner, or sexual abstinence. For male patients who participate in the study, condoms should be used as method of contraception.

The investigator and each patient will determine the appropriate method of contraception for the patient during the participation in the study.

If a female becomes pregnant during the study, the investigator will notify the sponsor immediately after the pregnancy is confirmed and the patient will be exited from the study after appropriate safety follow-up. The investigator will (1) notify the patient's physician that the patient was being treated with an investigational drug (abicipar), and (2) follow the progress of the pregnancy. The investigator must document the outcome of the pregnancy and provide a copy of the documentation to Allergan.

If a female partner of a male study patient becomes pregnant during the study, the investigator will notify Allergan immediately after the pregnancy is confirmed. The investigator will (1) obtain a consent from the female partner for pregnancy follow-up, and (2) follow the progress of the pregnancy to term. The investigator must document the outcome of the pregnancy and provide a copy of the documentation to Allergan.

4.5.2 Prohibited Medications/Treatments

The decision to administer a prohibited medication/treatment is done with the safety of the study patient as the primary consideration. When possible, it is recommended to notify Allergan before the prohibited medication/treatment is administered.

Use of the following medications are prohibited during the study:

- Any periocular injection or intravitreally administered therapy other than study medication in the study eye
- Verteporfin PDT for treatment of neovascular AMD in the study eye
- Systemic (eg, oral, intravenous, intramuscular) corticosteroids taken within 5 days prior to any study visit
- Systemic (eg, intravenous, oral) anti-VEGF medications (eg, bevacizumab, ziv-aflibercept) or VEGF-receptor inhibitor (eg, sunitinib, sorafenib, pazopanib)

4.5.3 Special Diet or Activities

Patients are not required to fast prior to blood and urine collections for laboratory tests.

5. Study Treatments

5.1 Study Treatments and Formulations

Abicipar is a solution at a concentration of 40 mg/mL provided in sterile single-use glass vial. Abicipar produced using a modified manufacturing process will be utilized in this trial. One single-dose vial will be packaged in a box for each injection. Materials for preparing abicipar for intravitreal injection will also be provided. These include a filter needle, an injection needle, and an injection syringe.

5.2 Control Treatment(s)

Not applicable.

5.3 Methods for Masking

Not applicable.

5.4 Treatment Allocation Ratio and Stratification

Not applicable.

5.5 Method for Assignment to Treatment Groups/Randomization

Prior to initiation of study treatment, each patient who provides informed consent and/or assent will be assigned a patient number that will serve as the patient identification number on all study documents.

This is an open-label, single arm study. No randomization will be performed. Study medication will be labeled with medication kit numbers.

5.6 Treatment Regimen and Dosing

Enrolled patients will receive 2 mg abicipar administered by intravitreal injections at baseline (Day 1) and Weeks 4, 8, 16, and 24.

5.6.1 Treatment Regimen/Dosage Adjustments/Dose Discontinuation

If the study eye develops a treatment-related adverse event at any time during the study, treatment dose may be temporarily held or discontinued and the reason for dose holding or discontinuation will be recorded on the eCRF.

The treatment regimen will be adjusted based on the following criteria:

- Intraocular inflammation: discontinue the dose and exit the patient when the event of intraocular inflammation has been resolved. For more information, refer to Section 6.3.2.
- IOP: hold dose if IOP is ≥ 30 mm Hg in the study eye. Treatment may resume when IOP is < 30 mm Hg, either spontaneously or by treatment, as determined by the evaluating physician.
- New retinal break or retinal detachment: hold dose for the study eye. Treatment may resume after the retinal break/detachment has been successfully treated.
- Ocular and/or periocular infection: hold dose until the infection is resolved in both eyes

The investigator may hold or discontinue study treatment for other safety reasons at his/her discretion.

5.7 Storage of Study Medications/Treatments

The study medication must be stored in a secure area and administered only to patients entered into the clinical study, at no cost to the patient, in accordance with the conditions specified on the study medication kit label and in the procedure manual.

Only assigned individuals authorized by the investigator may have access to study medication.

5.8 Preparation of Study Medications/Treatments

Abicipar must be prepared in a hospital pharmacy or by an investigator or trained assistant in the clinic using aseptic technique. The instructions for preparation of the individual doses are provided in the procedure manual.

5.9 Treatment Administration

Abicipar will be administered by intravitreal injection as specified in the procedure manual. The injection volume is 0.05 mL (50 µL).

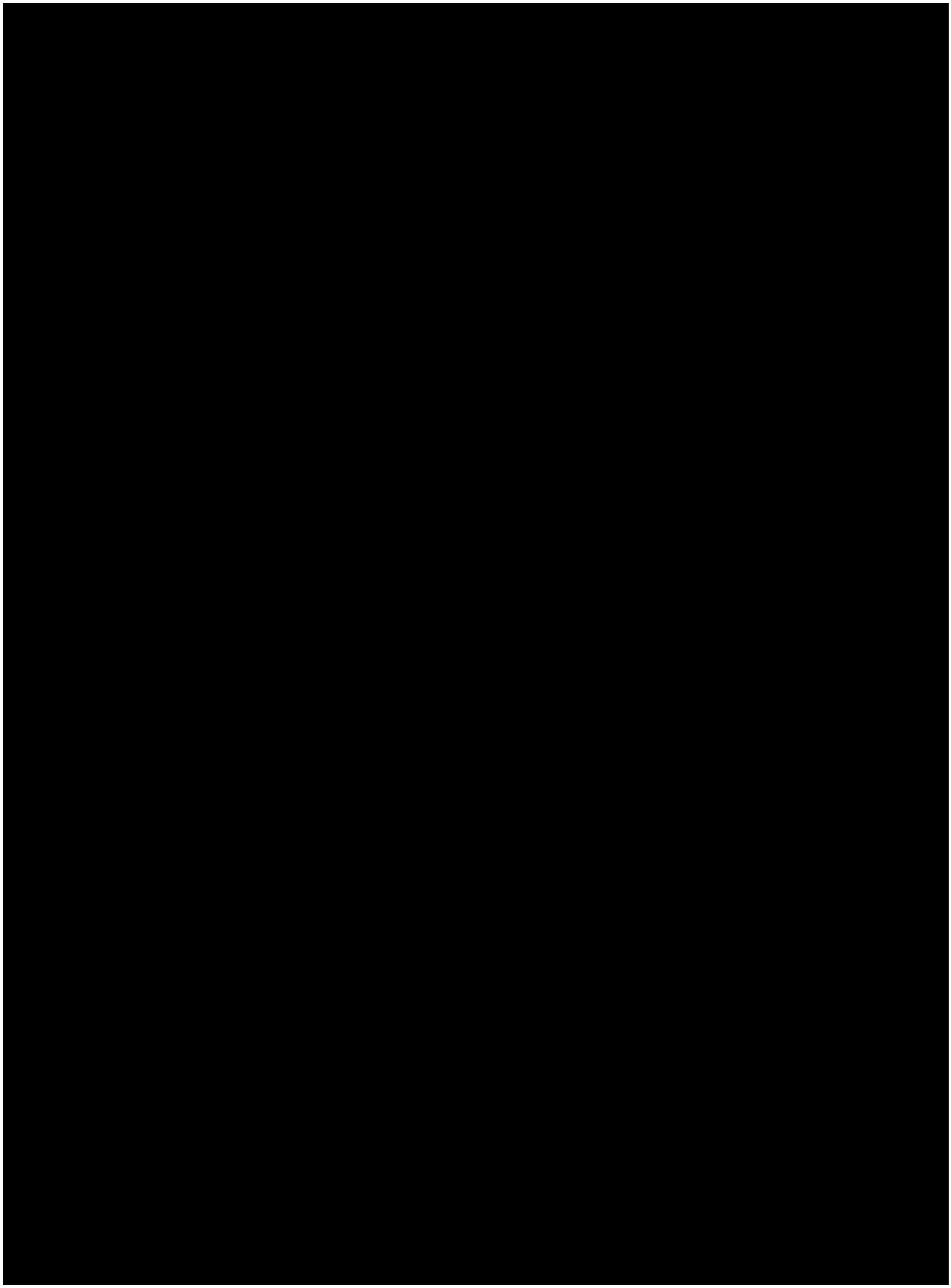
Prior to study treatment, the study eye of each patient will be anesthetized with topical anesthetic and prepared according to the standard protocol detailed in the Procedure Manual. Medication will be injected into the vitreous of the study eye through the pars plana.

6. Response Measures and Summary of Data Collection Methods

6.1 Efficacy Measures

- BCVA assessed using the Early Treatment of Diabetic Retinopathy Study (ETDRS) letters (Age-Related Eye Disease Study [AREDS] Research Group, 2001)
- Central retinal thickness (CRT) assessed with spectral-domain optical coherence tomography (SD-OCT)

[redacted]



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6.4 Examination Procedures, Tests, Equipment, and Techniques

Details for all examination procedures and tests are provided in the corresponding procedure manuals.

6.4.1 Disease Characterization

6.4.1.1 Dilated Color Fundus Photography

A standardized procedure for the collection of fundus digital photographic images of the retina, optic disc, and macula will be followed. Color fundus images are required to be sent to Allergan for evaluation, as necessary.

6.4.1.2 Fluorescein Angiography

A standardized procedure for examining the retinal circulation and vessel permeability using a dye tracing method will be followed. It involves injection of sodium fluorescein into the systemic circulation, and then an angiogram is obtained by digitally photographing the fluorescence emitted after illumination of the retina with blue light at a wavelength of 490 nanometers. Fluorescein angiograms are required to be sent to Allergan for evaluation, as necessary.

6.4.2 Efficacy

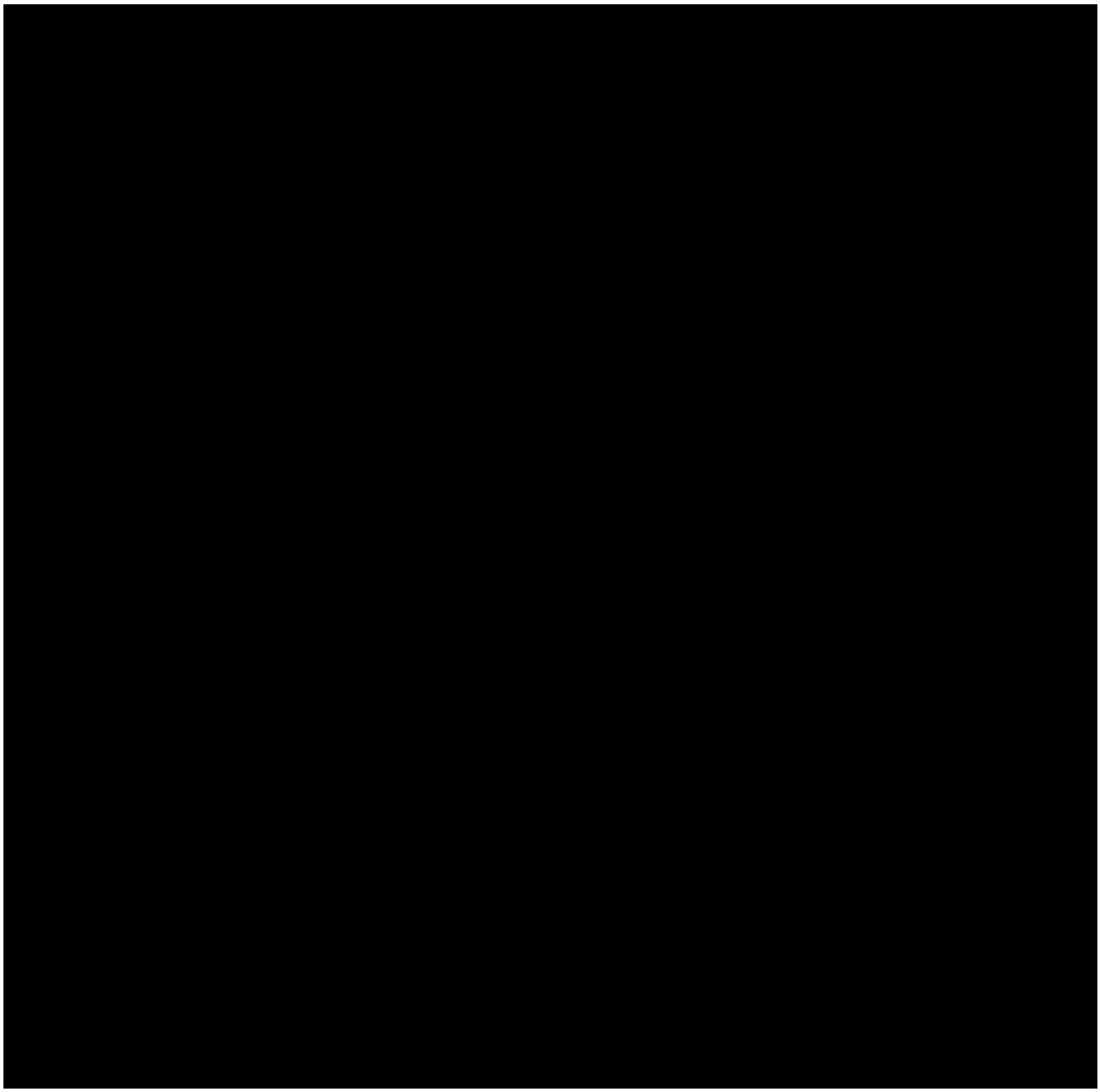
6.4.2.1 Best-corrected Visual Acuity

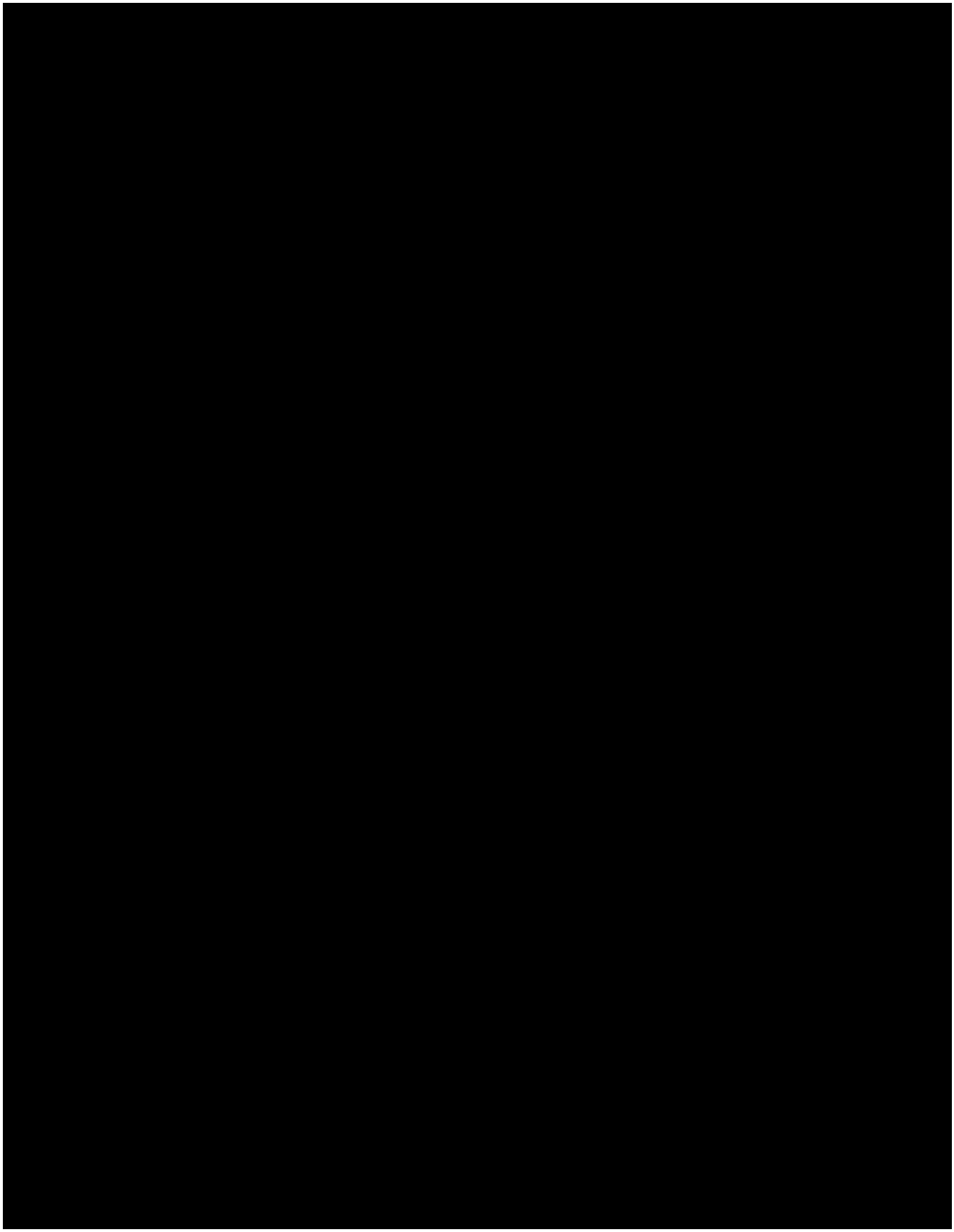
BCVA measures will be quantified using the ETDRS method (AREDS Research Group, 2001). BCVA testing must precede any examination requiring contact with the study eye. BCVA must be performed following manifest refraction and completed according to the procedures outlined in the procedure manual. Certification of the examiners at each investigative site will occur prior to screening any study patients.

6.4.2.2 Optical Coherence Tomography

OCT is a laser-based, non-invasive, diagnostic system providing high-resolution imaging optical sections of the retina. The CRT in the study eye (defined as the central 1000 microns from the center of the fovea) will be captured using SD-OCT.

Electronic OCT images will be assessed at the site and will be used to confirm patient eligibility for study enrollment as well as to monitor disease progression for safety. Images are required to be sent to Allergan. The same OCT system (eg, Spectralis or Cirrus) must be used throughout the study for a given patient. See the procedure manual for further details.





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6.4.3.5 Best-corrected Visual Acuity

All BCVA measures will be used as safety measures to evaluate vision loss over time. BCVA is also used as a measure of efficacy as described in Section 6.4.2.1.

6.4.3.6 Pregnancy Test

Females of childbearing potential will have urine pregnancy tests performed at baseline (Day 1, prior to treatment administration) and study exit. Urine pregnancy test kits will be provided by the site and will be administered at the site according to the instructions provided with the tests. The pregnancy test must be negative for the patient to receive study medication. Additional pregnancy tests may be performed at any time during the study, at the investigator's discretion.

6.4.3.7 Adverse Events

All adverse events will be monitored and reported on an adverse event eCRF, including seriousness, severity, action taken, and relationship to study drug. If adverse events occur, the first concern will be the safety of the study patient.

6.5 Other Study Supplies

Allergan will make provisions (directly or indirectly) to supply the study sites with standard photographs for grading of cataracts, ETDRS supplies (if needed), medications or supplies (anti-infective ophthalmic solution, local anesthetic eyedrop, dilating eyedrop, povidone iodine, syringe, needles, cotton tip swabs, sterile fields, and cellulose sponges), PK blood sampling kits, and immunogenicity (anti-abicipar antibody) blood sampling kits. Tubes for collection of clinical laboratory analysis will be provided by a central laboratory.

6.6 Summary of Methods of Data Collection

Clinical data will be entered into the eCRF using an electronic data capture system. Data entered into the eCRF will correspond to and be supported by source documentation maintained at the sites.

7. Statistical Procedures

This section is a summary of the planned statistical analyses. A detailed statistical analysis plan (SAP) will be developed and finalized before database lock.

7.1 Analysis Populations

The safety population, consisting of patients who received at least 1 study treatment, will be used for all analyses.

7.2 Methods of Analysis

7.2.1 Efficacy Analyses

Efficacy measures will be based on BCVA and CRT measured in the study eye. Efficacy variables include the following:

- Proportion of patients with stable vision (ie, patients who lose fewer than 15 letters in BCVA) from baseline
- Mean change from baseline in BCVA
- Proportion of patients with a gain of 15 or more ETDRS letters in BCVA from baseline

- Mean change from baseline in CRT as assessed with SD-OCT

Efficacy variables will be summarized using descriptive statistics as appropriate.

[redacted]

7.3 Subgroup Analyses

Not applicable.

7.4 Sample Size Calculation

The study will enroll approximately 100 patients. This sample size is determined empirically and is considered appropriate for the planned assessments.

7.5 Interim Analyses

An interim analysis is planned when all patients have completed the Week 12 visit or have exited early from the study.

[redacted]

8.1 Patient Entry Procedures

8.1.1 Overview of Entry Procedures

Prospective patients as defined by the criteria in Sections 4.3 and 4.4 (inclusion/exclusion criteria) will be considered for entry into this study.

8.1.2 Informed Consent and Patient Privacy

The study will be discussed with the patient and a patient wishing to participate must give informed consent prior to any study-related procedures or change in treatment. The patient must also give authorization and other written documentation in accordance with the relevant country and local privacy requirements (where applicable) prior to any study-related procedures or change in treatment.

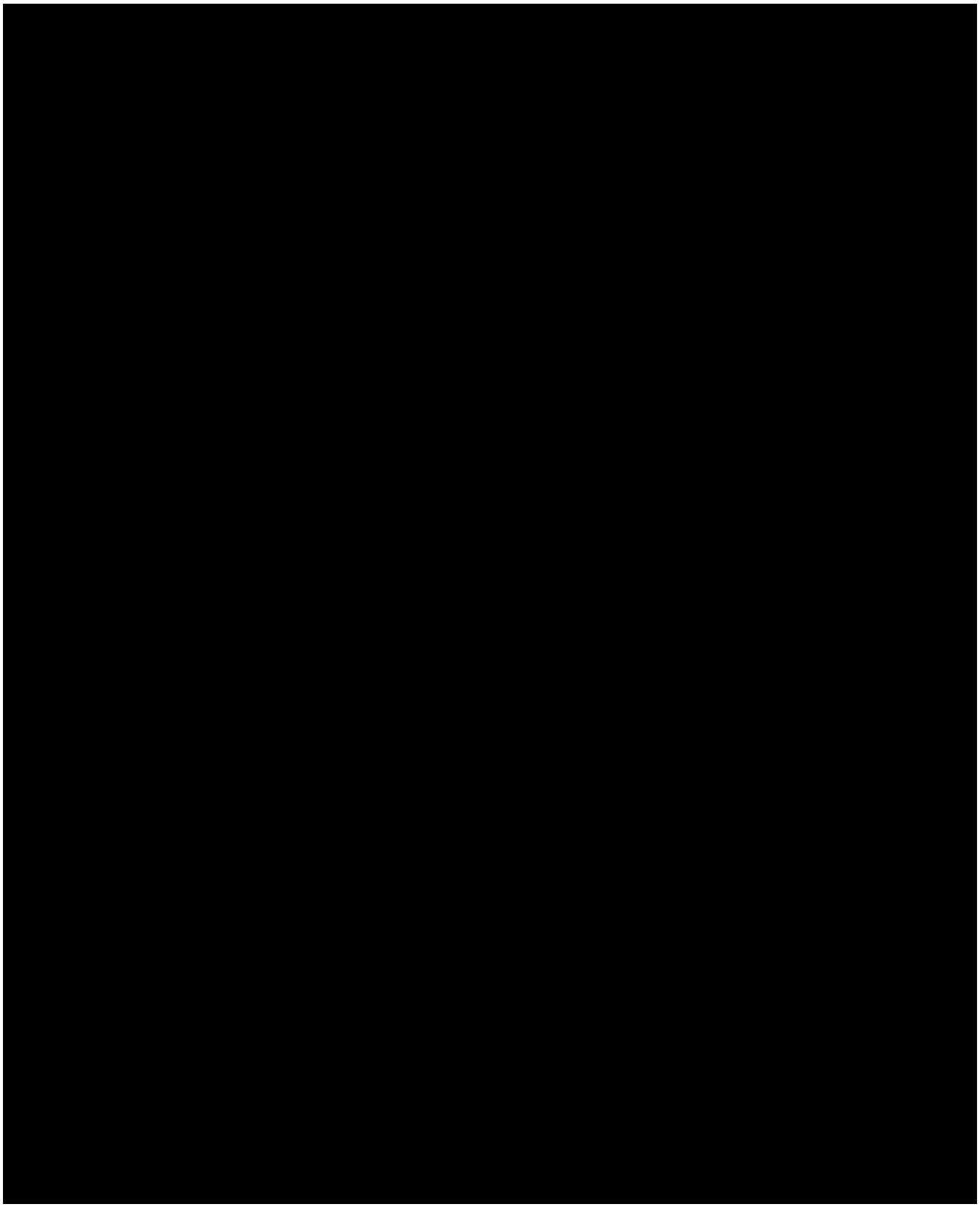
Each patient that provides informed consent and/or assent will be assigned a patient number that will be used on patient documentation throughout the study.

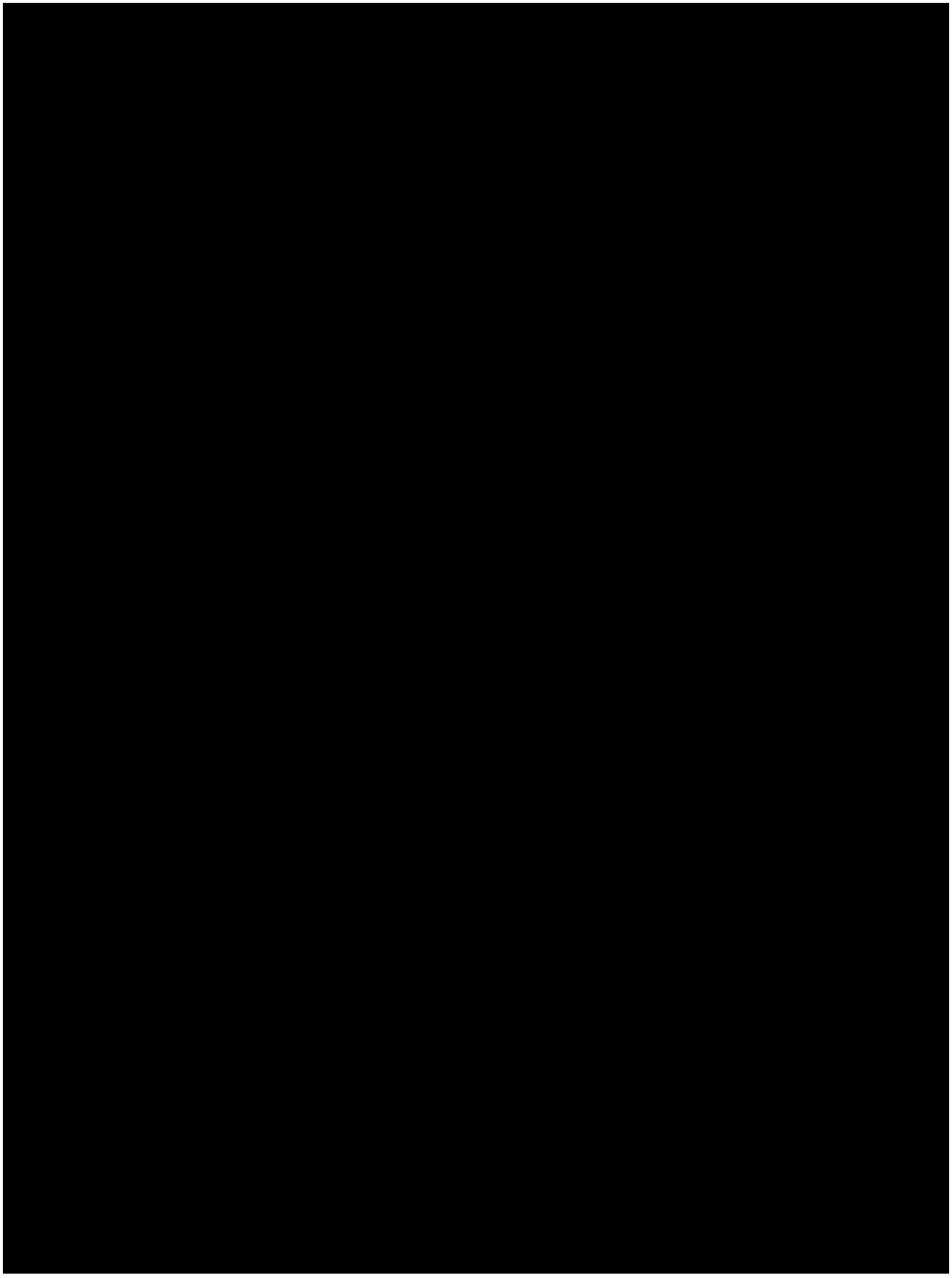
8.2 Procedures for Final Study Entry

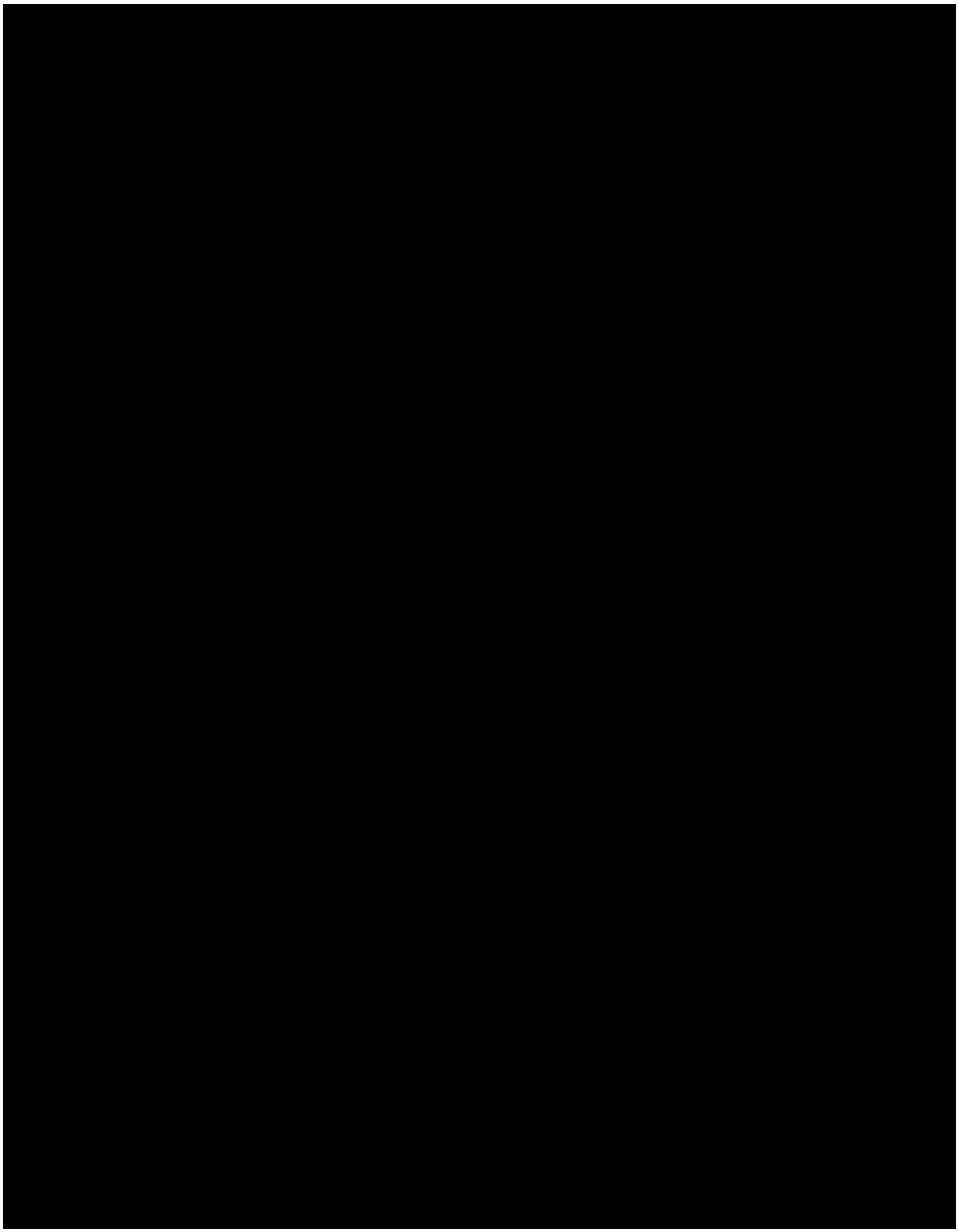
All screening laboratory tests must be performed, and the results must be evaluated and determined to be acceptable to the investigator prior to patient entry into the study. Screening laboratory tests may be repeated once at the discretion of the investigator or Allergan.

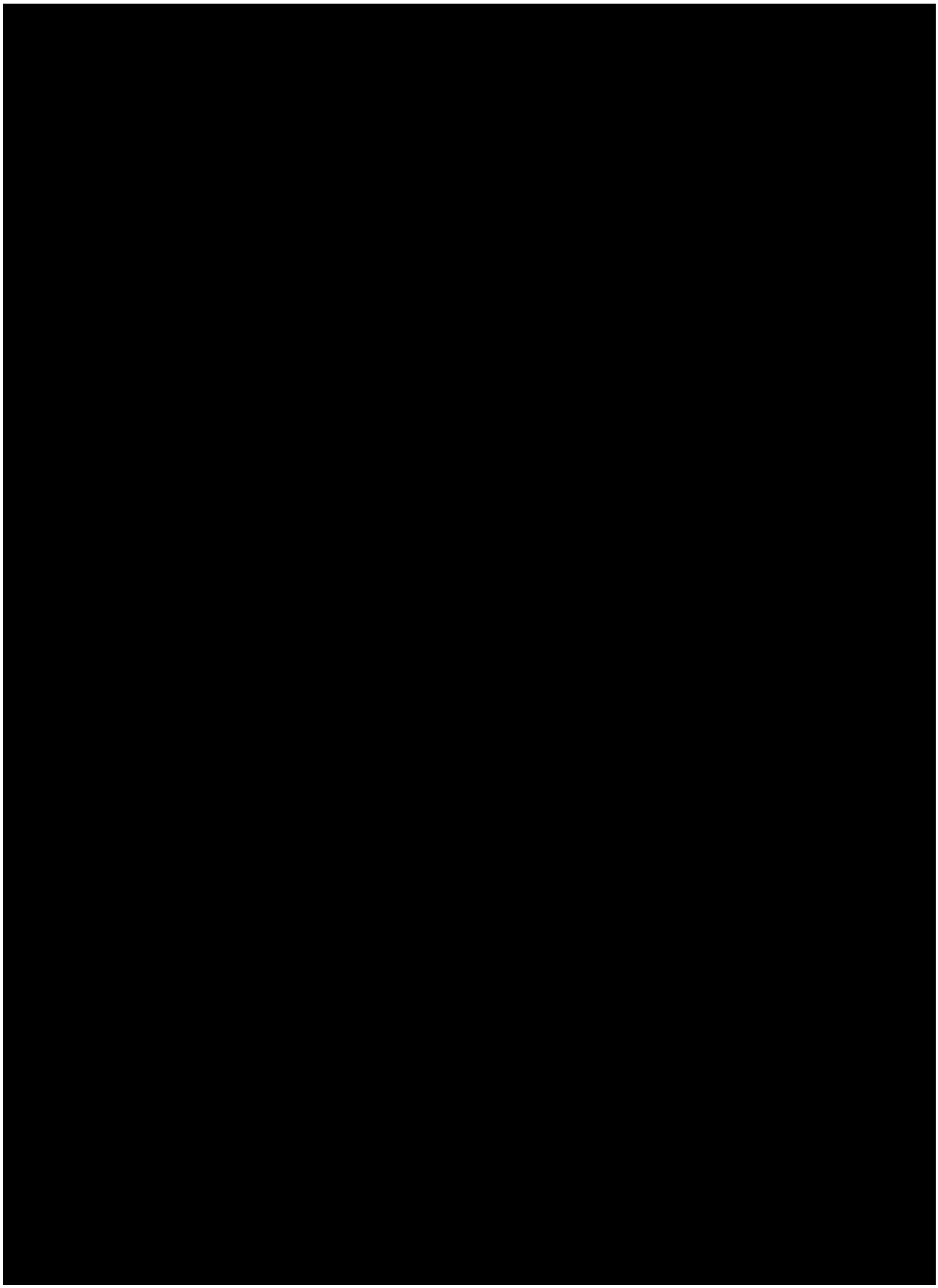
A urine pregnancy test administered to women of childbearing potential at the baseline (Day 1) visit must be negative prior to treatment administration.

A patient is considered to have entered the study at the time of assignment to treatment at the baseline (Day 1) visit. See Section 5.5 for the method for assignment to treatment.









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8.4 Instructions for the Patients

Patients are instructed that they do not need to fast before visits.

Patients are instructed to strictly follow the study visit schedule and to report all changes in condition to the investigative site.

8.5 Unscheduled Visits

Additional examinations may be performed as necessary to ensure the safety and well-being of patients during the study. The eCRFs should be completed for each unscheduled visit.

8.6 Compliance with Protocol

Allergan must be informed of any patients who are inadvertently enrolled despite significant deviation from protocol-specified criteria. A decision regarding the patient's continued participation will be made on a case-by-case basis.

8.7 Early Discontinuation of Patients

Patients may voluntarily withdraw from the study at any time. A patient's participation in the study may be terminated if it is deemed by the investigator or Allergan that it is unsafe for the patient to continue in the study.

Notification of early patient discontinuation from the study and the reason for discontinuation will be made to the sponsor and will be clearly documented on the appropriate eCRF.

For patients who discontinue from the study early due to other reasons, every effort must be made to have these patients return to the clinical center for completion of the Early Exit visit.

8.8 Study Termination

The study may be stopped at his/her study site at any time by the site investigator. Allergan may stop the study (and/or the study site) for any reason with appropriate notification.

9. Adverse Events

Adverse events occurring during the study will be recorded on an adverse event eCRF. If adverse events occur, the first concern will be the safety of the study participants.

9.1 Definitions

9.1.1 Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. In addition, during the screening period, adverse events will be assessed regardless of the administration of a pharmaceutical product.

Note: Adverse events must be collected once informed consent has been obtained, regardless of whether or not the patient has been administered study drug.

Progression of treatment indication including new or worsening of anticipated clinical signs or symptoms, which are collected as clinical efficacy variables and assessed as unequivocally associated with the disease progression and/or lack of efficacy, should NOT be reported as

adverse events unless the disease progression is greater than anticipated in the natural course of the disease.

Adverse events will be assessed, documented, and recorded in the eCRF throughout the study (ie, after informed consent has been obtained). At each visit, the investigator will begin by querying for adverse events by asking each patient a general, non-directed question such as "How have you been feeling since the last visit?" Directed questioning and examination will then be done as appropriate. All reported adverse events will be documented on the appropriate eCRF.

9.1.2 Serious Adverse Event

A serious adverse event is any adverse event occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (See Section 9.3 for procedures for reporting a serious adverse event.)

Allergan considers all cancer adverse events as serious adverse events. In addition, Allergan considers any abortion (spontaneous or nonspontaneous) as a serious adverse event.

Pre-planned surgeries or procedures for pre-existing, known medical conditions for which a patient requires hospitalization is not reportable as a serious adverse event.

Any pre-planned surgery or procedure should be clearly documented in the site source documents by the medically qualified investigator at the time of the patient's entry into the study. If it has not been documented at the time of the patient's entry into the study, then it should be documented as a serious adverse event and reported to Allergan.

9.1.3 Severity

A clinical determination will be made of the intensity of an adverse event. The severity assessment for a clinical adverse event must be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated.
Moderate	Discomfort enough to cause interference with usual activity.
Severe	Incapacitating with inability to work or do usual activity.
Not applicable	In some cases, an adverse event may be an 'all or nothing' finding which cannot be graded.

9.1.4 Relationship to Study Drug or Study Procedure

A determination will be made of the relationship (if any) between an adverse event and the study drug or study procedure, as applicable. A causal relationship is present if a determination is made that there is a reasonable possibility that the adverse event may have been caused by the drug or study procedure.

A study procedure occurring during the screening/baseline period can include a study required diagnostic procedure.

For treatment-related adverse events, the investigator will note on the eCRF whether the event is related to the study medication, and/or the injection procedure.

9.2 Procedures for Reporting Adverse Events

Any adverse event must be recorded on the appropriate eCRF.

All adverse events that are drug-related and unexpected (not listed as treatment-related in the current Investigator's Brochure) must be reported to the governing Institutional Review Board/Independent Ethics Committee (IRB/IEC) as required by the IRB/IEC, local regulations, and the governing health authorities. Any adverse event that is marked 'ongoing' at the exit visit must be followed-up as appropriate.

9.3 Procedures for Reporting a Serious Adverse Event

Any serious adverse event occurring during the study period (beginning with informed consent) and for at least 12 weeks after the last dose of study drug must be immediately reported but no later than 24 hours after learning of a serious adverse event. Serious adverse events must be reported to Allergan (or Agent of Allergan) as listed on the Allergan Study Contacts Page and recorded on the serious adverse event form. All patients with a serious adverse event must be followed up and the outcomes reported. The investigator must supply

the sponsor and the IRB/IEC with any additional requested information (eg, autopsy reports and discharge summaries).

In the event of a serious adverse event, the investigator must:

1. Notify Allergan immediately by fax or email using the serious adverse event form (contact details can be found on page 1 of the serious adverse event form); phone numbers and relevant Allergan personnel contacts are also on the front page of protocol and Study Contacts Page.

2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.

3. Provide Allergan with a complete, written description of the adverse event(s) on the serious adverse event form describing the event chronologically, including any treatment given (eg, medications administered, procedures performed) for the adverse event(s). Summarize relevant clinical information about the event: signs, symptoms, diagnosis, clinical course and relevant clinical laboratory tests, etc. Include any additional or alternative explanation(s) for the causality which includes a statement as to whether the event was or was not related to the use of the investigational drug.

4. Promptly inform the governing IRB/IEC of the serious adverse event as required by the IRB/IEC, local regulations, and the governing health authorities.

9.4 Procedures for Unmasking of Study Medication

This is an open-label study.

10. Administrative Items

This protocol is to be conducted in accordance with the applicable Good Clinical Practice (GCP) regulations and guidelines, eg, the International Conference on Harmonisation (ICH) Guideline on GCP.

10.1 Protection of Human Patients

10.1.1 Compliance with Informed Consent Regulations (US 21 CFR Part 50) and Relevant Country Regulations

Written informed consent is to be obtained from each patient prior to any study-related activities or procedures in the study, and/or from the patient's legally authorized representative.

10.1.2 Compliance With IRB or IEC Regulations

This study is to be conducted in accordance with IRB regulations (US 21 CFR Part 56.103) or applicable IEC regulations. The investigator must obtain approval from a properly constituted IRB/IEC prior to initiating the study and re-approval or review at least annually. Allergan is to be notified immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/IEC correspondence with the investigator should be provided to Allergan.

10.1.3 Compliance With Good Clinical Practice

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

10.1.4 Compliance With Electronic Records; Electronic Signatures Regulations (US 21CFR Part 11)

This study is to be conducted in compliance with the regulations on electronic records and electronic signature.

10.2 Changes to the Protocol

The investigator must not implement any deviation from or changes of the protocol without approval by Allergan and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards to study patients, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers).

10.3 Patient Confidentiality

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the patient's name will not be disclosed in these documents. The patient's name may be disclosed to the Sponsor of the study, Allergan, or the governing health authorities or the FDA if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

10.3.1 Patient Privacy

Written authorization and other documentation in accordance with the relevant country and local privacy requirements (where applicable) is to be obtained from each patient prior to enrollment into the study, and/or from the patient's legally authorized representative in accordance with the applicable privacy requirements (eg, the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information ("HIPAA"), European Union Data Protection Directive 95/46/EC ["EU Directive"]).

In accordance with HIPAA requirements, additional purposes of this study may include publishing of anonymous patient data from the study.

10.4 Documentation

10.4.1 Source Documents

Source documents may include a patient's medical records, hospital charts, clinic charts, the investigator's patient study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the eCRF serves as part of the investigator's record of a patient's study-related data.

The following information should be entered into the patient's medical record:

- Patient's name
- Patient's contact information
- The date that the patient entered the study, patient number, and patient randomization [or medication kit] number
- The study title and/or the protocol number of the study and the name of Allergan

- A statement that informed consent was obtained (including the date). A statement that written authorization or other country and local patient privacy required documentation for this study has been obtained (including the date).
- Dates of all patient visits
- All concurrent medications (List all prescription and non-prescription medications being taken at the time of enrollment. At each subsequent visit, changes to the list of medications should be recorded.)
- Occurrence and status of any adverse events
- Vital signs and general physical examination findings
- The results of pregnancy tests performed by the site
- Copies of the laboratory reports generated by the central laboratory for the analysis of blood and urine samples
- Visual acuity worksheets
- Results of abnormal findings from ophthalmic examination (including slit-lamp biomicroscopy, IOP assessment, and indirect ophthalmoscopy examination)
- SD-OCT imaging files and backup copies of electronic records
- Dilated fundus photography files and backup copies of electronic records
- Fluorescein angiography duplicate and backup copies of the electronic records if a digital system is used
- Procedure notes for the study medication administration procedures must include the following:
    - Date and time the vial is removed from the refrigerator
    - Date and time of the procedure
    - Evaluation of the injection site
    - Location of the injection to the nearest clock hour

- Complications, if any

- The date the patient exited the study, and a notation as to whether the patient completed the study or reason for discontinuation

Source documentation practices must follow Section 4.0 of ICH E6, Good Clinical Practice: Consolidated Guidance and ALCOA, ie, records must be **A**ttributable, **L**egible, **C**ontemporaneous, **O**riginal and **A**ccurate.

10.4.2 Case Report Form Completion

The investigator is responsible for ensuring that data are properly recorded on each patient's eCRFs and related documents. An investigator who has signed the protocol signature page should personally sign for the eCRFs (as indicated in the case report forms) to ensure that the observations and findings are recorded on the eCRFs correctly and completely. The eCRFs are to be submitted to Allergan in a timely manner at the completion of the study, or as otherwise specified by Allergan and will be maintained in a central data repository.

10.4.3 Study Summary

An investigator's summary will be provided to Allergan within a short time after the completion of the study, or as designated by Allergan. A summary is also to be provided to the responsible IRB/IEC.

10.4.4 Retention of Documentation

All study related correspondence, patient records, consent forms, patient privacy documentation, records of the distribution and use of all investigational products, and copies of eCRFs should be maintained on file.

For countries falling within the scope of the ICH guidelines, the sponsor-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

Allergan requires that it be notified in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

10.5 Labeling, Packaging, and Return or Disposal of Study Medications/Treatments

10.5.1 Labeling/Packaging

Study medication will be packaged, labeled, and supplied by Allergan. All study medications will be identified as an investigational compound and will be labeled with the protocol study number and medication kit number. The label will also specify the storage conditions and state that the study medication is limited to investigational use.

10.5.2 Clinical Supply Inventory

The investigator must keep an accurate accounting of the number of investigational units received from Allergan, dispensed or administered to the patients, and the number of units returned to Allergan during and at the completion of the study. A detailed inventory must be completed for the study medication. The study medication must be dispensed or administered only by an appropriately qualified person to patients in the study. The medication is to be used in accordance with the protocol for patients who are under the direct supervision of an investigator. A unit is defined as a single-dose vial.

10.5.3 Return or Disposal of Study Medications/Treatments and/or Supplies

All clinical study medications/treatments and/or supplies will be returned to Allergan or Allergan designee for destruction. Used syringes and needles must be destroyed per local site procedure.

10.6 Monitoring by the Sponsor

A representative of the sponsor will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the study.

Authorized representatives of Allergan or regulatory authority representatives will conduct on-site visits to review, audit and copy study-related documents. These representatives will

meet with the investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

10.7 Handling of Biological Specimens

Samples of blood and urine for evaluation of hematology, chemistries, and urinalysis will be analyzed at a centralized clinical laboratory with certification from a recognized accreditation agency (eg, College of American Pathology [CAP] or Clinical Laboratory Improvement Amendments [CLIA] certification).

Serum samples obtained will be analyzed for abicipar concentrations (free and total) and anti-drug antibodies (binding and neutralizing) by bioanalytical laboratories using validated methods.

Details about the handling, processing, and shipment of all biological specimens are provided in the procedure manual.

All samples will be returned to Allergan or Allergan designee for destruction. Allergan shall have full ownership rights to any biological specimens/samples derived from the study.

10.8 Publications

Allergan as the sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

10.9 Coordinating Investigator

A signatory Coordinating Investigator will be designated prior to the writing of the Clinical Study Report.

11. References

Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS Report No. 8. Arch Ophthalmol. 2001;119:1417-1436.

Blinder KJ, Bradley S, Bressler NM, Bressler SB, Donati G, Hao Y, et al. Effect of lesion size, visual acuity, and lesion composition on visual acuity change with and without verteporfin therapy for choroidal neovascularization secondary to age-related macular degeneration: TAP and VIP Report No.1. Am J Ophthalmol. 2003;136:407-418.

Cheung LK, Eaton A. Age-related macular degeneration. Pharmacotherapy 2013;33(8):838-855.

Ciulla TA, Rosenfeld PJ. Antivascular endothelial growth factor therapy for neovascular age-related macular degeneration. Curr Opin Ophthalmol. 2009;20:158-165.

Ding X, Patel M, Chan CC. Molecular pathology of age-related macular degeneration. Prog Retin Eye Res. 2009;28(1):1-18.

Ferris FL 3rd. Senile macular degeneration: review of epidemiologic features. Am J Epidemiol. 1983 Aug;118(2):132-151.

Grisanti S, Tatar O. The role of vascular endothelial growth factor and other endogenous interplayers in age-related macular degeneration. Prog Retin Eye Res. 2008;27:372-390.

Pieramici DJ, Bressler SB, Koester JM, Bressler NM. Occult with no classic subfoveal choroidal neovascular lesions in age-related macular degeneration: clinically relevant natural history information in larger lesions with good vision from the Verteporfin in Photodynamic Therapy (VIP) Trial: VIP Report No. 4. Arch Ophthalmol. 2006;124:660-664.

Shah AR, Del Priore LV. Natural history of predominantly classic, minimally classic, and occult subgroups in exudative age-related macular degeneration. Ophthalmology. 2009;116:1901-1907.

Shah AR, Del Priore LV. Progressive visual loss in subfoveal exudation in age-related macular degeneration: a meta-analysis using Lineweaver-Burke plots. Am J Ophthalmol. 2007;143:83-89.

Sommer A, Tielsch JM, Katz J, Quigley HA, Gottsch JD, Javitt JC, et al. Racial differences in the cause-specific prevalence of blindness in East Baltimore. N Engl J Med. 1991;325:1412-1417.

Wong TY, Chakravarthy U, Klein R, Mitchell P, Zlateva G, Buggage R, et al. The natural history and prognosis of neovascular age-related macular degeneration: A systematic review of the literature and meta-analysis. Ophthalmology. 2008;115:116-126.

World Health Organization. Priority eye diseases: age related macular degeneration. Prevention of blindness and impairment. Geneva, Switzerland: World Health Organization; 2013.

12. Attachments

12.1 Glossary of Abbreviations

Term/Abbreviation	Definition
A/G	albumin/globulin
ALT	alanine aminotransferase
AMD	age-related macular degeneration
AREDS	Age-Related Eye Disease Study
AST	aspartate aminotransferase
BAB	binding antibodies
BCVA	best-corrected visual acuity
BUN	blood urea nitrogen
BLQ	below the lower limit of quantitation
CAP	College of American Pathology
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	peak serum concentration after dosing
CNV	choroidal neovascularization
CRT	central retinal thickness
DA	disc area
DARPin	designed ankyrin repeat protein
DME	diabetic macular edema
eCRF	electronic case report form
ETDRS	Early Treatment of Diabetic Retinopathy Study
EU	European Union
FA	fluorescein angiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice

GGT	gamma-glutamyl transferase
HbA1c	glycated hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council on Harmonisation
IEC	independent ethics committee
IOP	intraocular pressure
IRB	institutional review board
LDH	lactate dehydrogenase
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
mPEG20	maleimide polyethylene glycol of 20 kDa
NAB	neutralizing antibodies
OCT	optical coherence tomography
OU	both eyes
PDT	photodynamic therapy
PEG	polyethylene glycol
PK	pharmacokinetic
PPV	pars plana vitrectomy
RBC	red blood cell
RPE	retinal pigment epithelium
SAP	statistical analysis plan
SD-OCT	spectral-domain optical coherence tomography
SE	study eye
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
TEAE	treatment-emergent adverse event
US	United States

VEGF	vascular endothelial growth factor
VEGF-A	vascular endothelial growth factor-A
WBC	white blood cell
YAG	yttrium aluminum garnet

12.2 Protocol Amendment Summary Amendment 1

Title: Evaluation of Abicipar Pegol in Patients with Neovascular Age Related Macular Degeneration

Protocol 1771-201-008 Amendment 1

Date of Amendment: October 2018

Amendment Summary

This summary includes changes made to Protocol 1771-201-008 (Approved January 2018).

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
[redacted]	[redacted] ”	Administrative change
Section 4.5.2	Revised as follows: “Systemic (eg, oral, intravenous, intramuscular) corticosteroids taken <u>within 5 days prior to any study visit</u> ~~regularly (defined as exposure for 5 or more consecutive days)~~”	Administrative change

Section	Revision	Rationale
Section 5.6.1	Section title revised as follows: "Treatment Regimen/Dosage Adjustments/Dose Discontinuation" Text revised as follows: "If the study eye develops a treatment-related adverse event at any time during the study, treatment dose may be temporarily held or discontinued and the reason for dose holding or discontinuation will be recorded on the eCRF." First bullet point revised as follows: "Intraocular inflammation: ~~may hold or~~ discontinue the dose and exit the patient when the event of intraocular inflammation has been resolved ~~at the investigator's discretion, eg, if intraocular inflammation is graded as ≥ 2+ as assessed by biomicroscopy in the study eye~~. For more information, refer to Section 6.3.2."	Change made for patient safety
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Note: Stricken text was removed and underlined text was added.

ALLERGAN

Protocol 1771-201-008 Amd 1

[redacted]

Approval Date: 16-Oct-2018