Protocol Title: A Phase 2 Randomized, Open-Label, Multicenter Study Evaluating Administration of Repeated Intravitreal Doses of ICON-1 in Patients with Choroidal Neovascularization Secondary to Age-related Macular Degeneration

Protocol date: 19 January 2018

NCT Number: NCT03452527

CLINICAL STUDY PROTOCOL

PROTOCOL TITLE:	A Phase 2 Randomized, Open-Label, Multicenter Study Evaluating Administration of Repeated Intravitreal Doses of ICON-1 in Patients with Choroidal Neovascularization Secondary to Age-related Macular Degeneration
PROTOCOL NUMBER:	IT-004
PHASE OF DEVELOPMENT:	Phase 2
INVESTIGATIONAL PRODUCT:	human Immuno-conjugate 1 (ICON-1)
INDICATION:	Choroidal Neovascularization Secondary to Age-related Macular Degeneration
IND NUMBER:	102,472
SPONSOR:	Iconic Therapeutics, Inc. 7000 Shoreline Court Suite 270 South San Francisco, CA 94080
DATE OF PROTOCOL:	Original: 19 January 2018

1 SPONSOR SIGNATURE PAGE

This study will be conducted as outlined herein in accordance with current International Council for Harmonisation (ICH) guidelines, Good Clinical Practices (GCPs), the Declaration of Helsinki, and complying with the obligations and requirements of the Sponsor as listed in Title 21 of the United States Code of Federal Regulations.

Approved by:

_____

[redacted]
Medical Monitor

_____
Date

_____

[redacted]
Chief Medical Officer

_____
Date

_____

[redacted]
Biostatistician

_____
Date

2 PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Title:	A Phase 2 Randomized, Open-label, Multicenter Study Evaluating Administration of Repeated Intravitreal Doses of ICON-1 in Patients with Choroidal Neovascularization Secondary to Age-related Macular Degeneration
Protocol Number:	IT-004

I have read and understand all sections of this protocol and commit to conducting the study as outlined herein in accordance with the current International Council for Harmonisation (ICH) guidelines, Good Clinical Practices (GCPs) and the Declaration of Helsinki, and complying with the obligations and requirements of the Clinical Investigator and other requirements as listed in Title 21 of the United States Code of Federal Regulations and other applicable regulations.

I agree to provide the Sponsor with accurate financial information to allow the Sponsor to submit complete and accurate certification and disclosure statements as required by applicable regulations.

Principal Investigator's Name (Printed)

Principal Investigator's Signature

Date

3 KEY ROLES AND CONTACTS

Key roles and contact information may be updated by written notification to the clinical sites without a protocol amendment.

Sponsor:	Iconic Therapeutics, Inc. 7000 Shoreline Court, Suite 270 South San Francisco, CA 94080
Medical Monitor:	[redacted] Medical Monitor
Sponsor's Responsible Medical Officer:	[redacted] Chief Medical Officer

4 PROTOCOL SYNOPSIS

Protocol Title	A Phase 2 Randomized, Open-label, Multicenter Study Evaluating Administration of Repeated Intravitreal Doses of ICON-1 in Patients with Choroidal Neovascularization Secondary to Age-related Macular Degeneration
Protocol Number	IT-004
Study Phase	Phase 2
Study Sites	Up to 10 centers located in the United States
Study Objectives	To evaluate the safety and efficacy of repeated intravitreal injections of ICON-1 0.6 mg administered as maintenance therapy or in combination with aflibercept (Eylea®) in patients with neovascular (wet) age-related macular degeneration (AMD).
Study Design	This is a signal-seeking, Phase 2, randomized, open-label, multicenter study to evaluate the safety and efficacy of repeated intravitreal injections of ICON-1 0.6 mg in patients with wet AMD who are naive to treatment for wet AMD in the selected study eye. Eligible patients will be randomly assigned to one of the following two treatment arms in the selected study eye in a 1:1 ratio: • **ICON-1 Maintenance Therapy:** Aflibercept (Eylea®) monthly during Months 0-2 and ICON-1 0.6 mg monthly during Months 2-4, then aflibercept retreatment up to every 8 weeks as needed during Months 4-8, based on the retreatment criteria. • **ICON-1 + AFL Combination Therapy:** Aflibercept (Eylea®) monthly and ICON-1 0.6 mg monthly (administered 0-7 days after aflibercept) during Months 0-2, then aflibercept retreatment up to every 8 weeks as needed during Months 4-8, based on the retreatment criteria. Patients will receive up to three intravitreal injections in the study eye at each injection visit according to the patient's assigned treatment arm. During Months 4-8, as needed aflibercept retreatment will be administered based on the following pre-specified criteria: • Clinically significant anatomical evidence of increased or persistent CNV activity (e.g., new or persistent fluid on OCT, leakage, hemorrhage on FA) compared to the previous scheduled visit, as determined by the investigator

	Safety will be evaluated by means of occurrence of adverse events, clinical laboratory tests (serum chemistry, hematology, and coagulation), vital signs measurements, slit-lamp biomicroscopy, intraocular pressure (IOP), and dilated ophthalmoscopy. Pharmacodynamic and biological activity will be measured by means of BCVA by ETDRS, spectral-domain optical coherence tomography (sdOCT), optical coherence tomography angiography (OCT-A), color fundus photography (CFP), and fundus fluorescein angiography (FA). Immunogenicity will be evaluated by anti-drug antibodies (ADA). Patients (or their legally authorized representative) may choose to withdraw from the study for any reason at any time without prejudice. Study assessments for an Early Termination Visit should be conducted in the event a subject discontinues from the study prematurely.
Study Duration	Enrollment is anticipated to take approximately 6 months and patient participation will be approximately 10 months including screening, treatment and follow-up.
Number of Patients	Approximately 20 patients will be enrolled and randomized in the study (approximately 10 patients per treatment arm).
Study Population	**Inclusion Criteria** Patients must meet all of the following criteria to be included in the study: 1. Verbal and written informed consent obtained from the subject or the subject's legal representative (as applicable). 2. Males or females of any race, ≥50 years of age. 3. Clinical diagnosis of treatment-naïve, active primary CNV secondary to AMD in the study eye as determined by the Investigator. 4. BCVA of 83 to 24 ETDRS letters (20/25 up to 20/320 Snellen equivalent) in the study eye at Screening. 5. Study eye meets all of the following lesion characteristics at Screening as determined by the Investigator: a) Total lesion size <4 disc areas based on fundus fluorescein angiography (FA) and <10 mm^2 on OCT-A b) CNV area is >50% of total lesion size based on FA 6. Adequate clarity of ocular media and adequate pupillary dilation to permit good quality imaging of fundus in the study eye as determined by the Investigator.

	7. If a woman of childbearing potential (WOCBP) (i.e., not postmenopausal for at least 2 years or not surgically sterile), must have a negative serum pregnancy test at Screening, and must use adequate birth control with their non-surgically sterile male sexual partner throughout the study. Adequate methods of birth control include hormonal contraceptives, intrauterine contraceptive device (IUD), condom with spermicide, contraceptive sponge with spermicide, diaphragm with spermicide and cervical cap with spermicide. **Exclusion Criteria** Patients who meet any of the following criteria will be excluded from the study: 1. Monocular patient or patient with BCVA of ≤35 letters (20/200 or worse Snellen equivalent) in the better seeing eye. 2. CNV secondary to other causes in the study eye as determined by the Investigator. 3. Any prior treatment of CNV or advanced AMD in the study eye (e.g., laser, pharmacological [e.g., anti-VEGF agents] or surgical treatment, or any investigational therapy), except for dietary supplements or vitamins. 4. Presence in the study eye of suspected polypoid choroidal vasculopathy (PCV) and retinal angiomatous proliferation (RAP) lesion components, hemorrhagic pigment epithelial detachment (PED), retinal tears or rips, or vitelliform macular dystrophy as determined by the Investigator. 5. History of recurrent CNV in the study eye as determined by the Investigator. 6. Presence of any of the following lesion characteristics in the study eye as determined by the Investigator: a) Retinal hemorrhage area >50% of total lesion area based on FA b) Fibrosis area >50% of total lesion area based on FA c) Subfoveal scar, fibrosis or atrophy visible on sdOCT 7. Chronic, uncontrolled glaucoma or ocular hypertension in the study eye defined as an IOP >25mmHg regardless of concomitant treatment with IOP-lowering medications. 8. Previous participation in an investigational study of ICON-1. 9. Known serious allergy to fluorescein sodium for injection in angiography.

	10. Known hypersensitivity to aflibercept (Eylea®) or any of the excipients in Eylea®. 11. History of intraocular or ocular surface surgery (including cataract surgery and YAG laser procedures) in the study eye within 3 months prior to Screening. 12. History of vitrectomy in the study eye. 13. For a patient receiving chronic anticoagulant treatment (e.g., patients with a history of cardiovascular/cerebrovascular diseases [events] or hospitalization due to such conditions), the patient is without confirmation of stable clotting time using the appropriate test (Prothrombin Time (PT), International Normalized Ratio (INR) (e.g., Coumadin), or activated partial thromboplastin time (aPTT) (e.g., Pradaxa)) over the last 6 months from the patient's treating physician. Some agents do not require PT/INR/aPTT monitoring (e.g., aspirin, Eliquis (apixaban)). 14. Hereditary or chronic hemorrhagic or coagulopathy conditions (i.e., hemophilia). 15. Use of any investigational product or device within 30 days prior to Screening, or planned use of an investigational product or device during the study. Age-related Eye Disease Study (AREDS)-formulated vitamins (which have been under investigation) are allowed during the study. 16. History or presence of other concurrent conditions deemed by the Investigator to be likely to impact the subject's visual acuity in the study eye or to interfere with the interpretation of the study results, such as optic neuritis or atrophy (related to multiple sclerosis or other neurological disease), uveitis, or retinal vasculitis in the study eye. 17. Presence of any other concurrent medical condition, including mental illness or substance abuse, deemed by the Investigator to be likely to interfere with a subject's ability to provide informed consent, comply with monthly study visits and assessments, or interfere with the interpretation of the study results. 18. Woman who is pregnant or lactating.
Study Eye Determination	The study eye is defined as the eye that meets all of the inclusion criteria and none of the exclusion criteria. If both eyes meet the criteria for entry, the eye with the worst BCVA will be selected as the study eye.

Investigational Product	**Investigational Product** The investigational product is human Immuno-conjugate 1 (ICON-1). ICON-1 is a recombinant fusion protein that targets and binds to Tissue Factor (TF) overexpressing cells and suppresses the aberrant TF signaling that lies at the root of overly vascularized disease states like wet AMD. It is a dimeric antibody-like protein with a molecular weight of 157 kDa; each monomer has two functional domains joined by a linker. The targeting domain of ICON-1 is a mutated FVIIa protein conjugated to an Fc effector moiety of a human IgG1 immunoglobulin.
Test Article Administration	Patients will be randomly assigned to one of two treatment arms in a 1:1 ratio: • **ICON-1 Maintenance Therapy:** Aflibercept (2 mg/50 µL) monthly during Months 0-2 and ICON-1 0.6 mg (two injections of 0.3 mg [300 µg/100 µL]) monthly during Months 2-4, then aflibercept up to every 8 weeks as needed during Months 4-8, based on retreatment criteria. • **ICON-1 + AFL Combination Therapy:** Aflibercept (2 mg/50 µL) monthly and ICON-1 0.6 mg (two injections of 0.3 mg [300 µg/100 µL]) monthly during Months 0-2, then aflibercept up to every 8 weeks as needed during Months 4-8, based on retreatment criteria. Using aseptic technique, ICON-1 or aflibercept will be administered by first withdrawing vial contents through a 5-micron 19-gauge filter needle attached to a 1-cc tuberculin or Luer Lock syringe and then replacing the filter needle with a 30-gauge x ½ inch needle for the intravitreal injection. Adequate topical anesthesia and broad-spectrum microbicide will be given prior to injection. At treatment visits with two injections, both intravitreal injections will be administered on the same day. At treatment visits with three injections, the three intravitreal injections (first injection: aflibercept 2 mg, second injection: ICON-1 0.3 mg, and third injection: ICON-1 0.3 mg) may be administered on the same day OR the three injections may be administered across two separate days up to 7 days apart. If the three injections will be split across two days, the entire 0.6 mg dose of ICON-1 (two injections of 0.3 mg) must be administered on the same day. IOP will be measured before and after each injection. When multiple injections are administered on the same day, the second injection and the third injection (if applicable) will be administered following stabilization of IOP to the pre-injection level (i.e., within 5 mmHg of

	the pre-injection IOP) AND a minimum of 30 minutes after the prior injection.
Study Endpoints	**Primary Endpoint:** • Change in choroidal neovascularization by FA and OCT-A over time **Secondary Endpoints:** [redacted] • Change in Best Corrected Visual Acuity over time • Change in CST by sdOCT over time [redacted] • Time to retreatment during PRN aflibercept retreatment period • Percent of patients receiving PRN aflibercept retreatment over time **Safety Endpoints:** • Occurrence of ocular and systemic serious adverse events and adverse events • Changes in standard clinical laboratory tests (serum chemistry, hematology, coagulation) • Changes in vital signs and ophthalmic examinations • Systemic levels of ADA over time
Statistical Analyses	**Statistical Methods** All patients who receive ICON-1 will be considered evaluable and will be included in the analysis. This study is exploratory and its sample size is not determined by statistical power considerations. As descriptors of the two treatment arms, univariate data summaries will be provided. For ordinal and continuous endpoints, summary statistics will include number of patients, mean, median, standard deviation, minimum, and maximum. For categorical endpoints, summary statistics will include number of patients, frequency, and percentages. This Phase 2 trial is a signal-seeking trial to assess effects of ICON-1 on the biology of the CNV complex. As such, the primary aim for the

	assessment of biological activity in this trial is to delineate the functional and anatomical profiles of ICON-1 in terms of: • Function, as tracked through visual acuity and attendant treatment implications: – temporal changes in BCVA, as measured by actual mean changes in BCVA; percent of patients with BCVA gain post baseline; percent of patients with BCVA >20/40 and <20/200 post baseline; percent of patients who remain within BCVA severity level post baseline; – Signs of CNV activity, as measured by time to re-treatment with aflibercept and percent of patients receiving aflibercept re-treatment • Anatomic, as tracked through physical (qualitative and quantitative) longitudinal changes in the eye that can be imaged through sdOCT, FA, CFP, and OCT-A: – CNV complex changes; – Changes in CST; [redacted] Thus, the data analyses for assessing biological activity in this trial are geared towards descriptive multifactorial summaries. There are no interim analyses planned; however, patient clinical and safety data will be examined on an ongoing basis to ensure patient safety and compliance.

5 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

6 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	anti-drug antibodies
AE	adverse event
AFL	aflibercept
ALT	alanine aminotransferase
AMD	age-related macular degeneration
aPTT	activated partial thromboplastin time
AREDS	Age-related Eye Disease Study
AST	aspartate aminotransferase
BCVA	best-corrected visual acuity
BUN	blood urea nitrogen
CFP	color fundus photography
CNV	choroidal neovascularization
CO_2	carbon dioxide
CPK	creatine phosphokinase
CrCl	creatinine clearance
CRO	Contract Research Organization
CST	central retinal subfield thickness
DMP	Data Management Plan
EC	ethics committee
eCRF	electronic case report form
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fundus fluorescein angiography
Fc	fragment crystallizable
FDA	Food and Drug Administration
FVIIa	activated Factor VII
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
Hct	hematocrit
Hgb	hemoglobin

ICON-1	human Immuno-conjugate 1 (ICON-1)
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Council for Harmonisation
IgG	immunoglobulin G
INR	International Normalized Ratio
IOP	intraocular pressure
IRB	Institutional Review Board
IUD	intrauterine device
IVT	intravitreal
kDa	kilodaltons
LDH	lactic dehydrogenase
MAb	monoclonal antibody
MCV	mean corpuscular volume
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
µg	microgram
mg	milligram
mL	milliliter
MPV	mean platelet volume
NK	natural killer
OCT-A	optical coherence tomography angiography
OTC	over-the-counter
OU	both eyes
PCV	polypoid choroidal vasculopathy
PED	pigment epithelial detachment
PI	Principal Investigator
PK	pharmacokinetics
PRN	*pro re nata*, as needed
PT	Prothrombin Time
RAP	retinal angiomatous proliferation
RBC	red blood cell

RDW	red cell distribution volume
RPE	retinal pigment epithelium
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
sdOCT	spectral-domain optical coherence tomography
SE	study eye
TF	tissue factor
TEAE	treatment emergent adverse event
VEGF	vascular endothelial growth factor
WBC	white blood cell
WOCBP	women of child-bearing potential
YAG	yttrium-aluminum-garnet

In this protocol, Sponsor duties refer to responsibilities that will be performed by the Sponsor, the Sponsor's designee or the Sponsor's designated CRO. In this protocol, Investigator refers to the Principal Investigator or his/her designee who is responsible for performing study evaluations.

7 ETHICS

7.1 Institutional Review Board or Ethics Committee

The protocol, Investigator's Brochure, informed consent form (ICF), advertisements to be used for patient recruitment, and any other written information provided to patients for this study, including all consent forms translated to a language other than the native language of the clinical site must be approved by the Investigator's Institutional Review Board (IRB) or Ethics Committee (EC) before the study is initiated at a site. Documentation of this approval must be maintained by the clinical site and provided to the Sponsor (or designee) and must be made available during an inspection by the US Food and Drug Administration (FDA) or other regulatory agency inspectors. Prior to initiating the study, the Investigator will obtain written confirmation that the IRB/EC is properly constituted and compliant with International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) requirements, and all applicable laws and local regulations.

The study will not be initiated at a given clinical site until documentation confirming approval of the protocol, ICF, and any written materials supplied to the patient are received by the Sponsor or its designee. Approval documentation from the IRB/EC should be signed by the IRB/EC chairperson or designee, identify the IRB/EC by name and address, refer to the study protocol by title and/or protocol number and version or date, identify documents reviewed, and include the date of the review and approval or favorable opinion was granted.

Appropriate reports on the progress of the study will be made to the IRB/EC and to the Sponsor (or designee) by the Investigator in accordance with applicable governmental regulations and local regulations, and in agreement with policies of the IRB/EC. The Investigator must provide written documentation of the following to the Sponsor (or designee):

- IRB/EC periodic (e.g., semi-annually, annually) re-approval of the protocol as required by the site's IRB/EC
- IRB/EC approvals of any amendments to the protocol or revisions to the ICF
- IRB/EC receipt of safety and SAE reports, as appropriate
- Any additional submissions (including an end of study report) required by the site's IRB/EC

7.2 Ethical Conduct of the Study

This study will be conducted in compliance with GCP as described in FDA regulations (21 CFR parts 11, 50, 54, 56, and 312), the ICH document "Guidance for Good Clinical Practice, E6 (R2)," and the principles of the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, including all amendments and Notes of Clarification. The Investigator is expected to comply with the requirements of the protocol, and will conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

7.3 Subject Information and Consent

Written informed consent in compliance with FDA regulations (21 CFR 50.25), the ICH document "Guideline for Good Clinical Practice, E6 (R2)," and other applicable local regulations shall be obtained from each patient prior to entering the study or performing any study related procedure. An ICF template will be provided by the Sponsor (or designee) to clinical sites. The ICF will be submitted by the Investigator to his or her IRB/EC for review and approval prior to the start of the study. If any modifications to the content are proposed or made by the site, the ICF should be reviewed by the Sponsor (or designee) prior to IRB/EC submission.

The investigator is responsible for obtaining written informed consent from each patient participating in the study. If there are any revisions to the ICF during the course of the study, all active participating patients must be re-consented using the revised ICF in a timely fashion.

Informed consent must be obtained from the patient before any study related screening activity or treatment is undertaken that is not part of routine care. This includes, but is not limited to, the performance of diagnostic or therapeutic procedures and the administration of the first dose of the study treatment. All pertinent aspects of the study must be explained to the prospective patient and/or the patient's legally authorized representative before signing the ICF. The patient and/or patient's legally authorized representative will be informed that participation is voluntary and he/she can withdraw from the study at any time. The patient and/or patient's legally authorized representative will be allowed to read the IRB/EC approved ICF. Once the Investigator or designee is assured the patient/patient's legally authorized representative agrees to participate in the study, the patient/legally authorized representative will be asked to give consent by signing the ICF. The ICF must be signed and dated by the patient or by the patient's legally authorized representative, and by the person who conducted the informed consent discussion, and witness (if required). The Investigator shall provide a copy of the signed and dated ICF to the patient/patient's legally authorized representative. The original shall be maintained in the patient's medical records at the site. This document should not be displayed or made accessible to any third party except the Sponsor, its designee or regulatory agency representatives.

If a patient permanently revokes informed consent and declines further observation and/or contact, then this must be clearly documented in the patient's chart and recording of further data will be discontinued.

8 INTRODUCTION

8.1 Background

Age-related macular degeneration (AMD) refers to the chronic, progressive degenerative pathology of the macula that results in loss of central vision. According to the Macula Vision Research Foundation and the National Eye Institute, as many as fifteen million people in the United States suffer from some form of AMD, with similar numbers in Europe and other continents. Neovascular AMD (also referred to as exudative or "wet" AMD) is the leading cause of severe vision loss and blindness in elderly patients over the age of fifty in the industrialized world. In the United States alone, more than 1.5 million people suffer from neovascular AMD [1]. It is expected that the AMD incidence and prevalence will further increase with the ageing population, thus leading to a significant increase in the number of patients with wet AMD in the United States and worldwide.

AMD has been at the forefront of research in ophthalmology in recent years and significant advances were made in the understanding, diagnosis and treatment of the disease. Vascular endothelial growth factor (VEGF) has been shown to be a potent stimulator of angiogenesis and vascular permeability in the etiology of choroidal neovascularization (CNV) due to AMD [2]. The role of the VEGF has been also clinically demonstrated through the recently developed anti-VEGF therapies which have been successful in substantially improving central visual function in approximately one third of the treated patients and stopping severe vision loss in the majority of patients [3,4]. The biological anti-VEGF therapies have thus become the currently approved standard of clinical care for neovascular AMD.

However, due to the multifaceted aspects of the AMD pathogenesis [5], targeting VEGF alone is likely insufficient to modify or halt the progression of the disease towards the advanced CNV-associated degenerative processes. Supporting evidence of immune dysfunction is increasingly growing and potent pro-angiogenic signaling via macrophages that exacerbate CNV pathogenesis have been reported [6,7]. Therefore, beyond blocking neovascular growth and leakage, an improved therapy should aim to target additional aspects and mechanisms involved in the CNV biology.

Angiogenesis research first suggested that Tissue Factor (TF) may be implicated in the pathophysiology of neovascular AMD. TF was shown to be expressed in retinal pigment epithelial (RPE) cells and macrophages of both post-mortem and surgically excised CNV specimens, with increased staining in "inflammatory-active" versus "inflammatory-inactive" lesions [8]. The potential role of TF in CNV formation was further indicated in human diabetic retinas in which TF was associated with pathological neovessels but not with normal capillaries [9]. In addition to being the key initiator of coagulation, TF was shown to have other major biological functions: TF signaling induces angiogenesis by upregulating VEGF and is involved in the inflammatory cascade of cytokine release, both key processes that underlie CNV pathogenesis [10]. Increased expression of intraocular TF was demonstrated in AMD eyes versus non-AMD eyes and further supports the association with CNV pathogenesis [11]. This collective evidence provides the scientific rationale that TF is potentially an important therapeutic target for CNV, the pathophysiologic hallmark of wet AMD.

Therapeutic proteins are molecules that bind selectively to disease-causing or disease-related targets and remove them or their related effect in the affected tissue. They are designed to preferentially target pathological cells on which these targets are present at considerably higher levels than on normal cells. A well-known example of such a therapeutic protein that targets pathological cells through this mechanism is Herceptin® (Genentech/ Roche), a monoclonal antibody (MAb) treatment for breast cancer. Herceptin binds to a receptor that is over-expressed only on the surface of certain breast cancer cells.

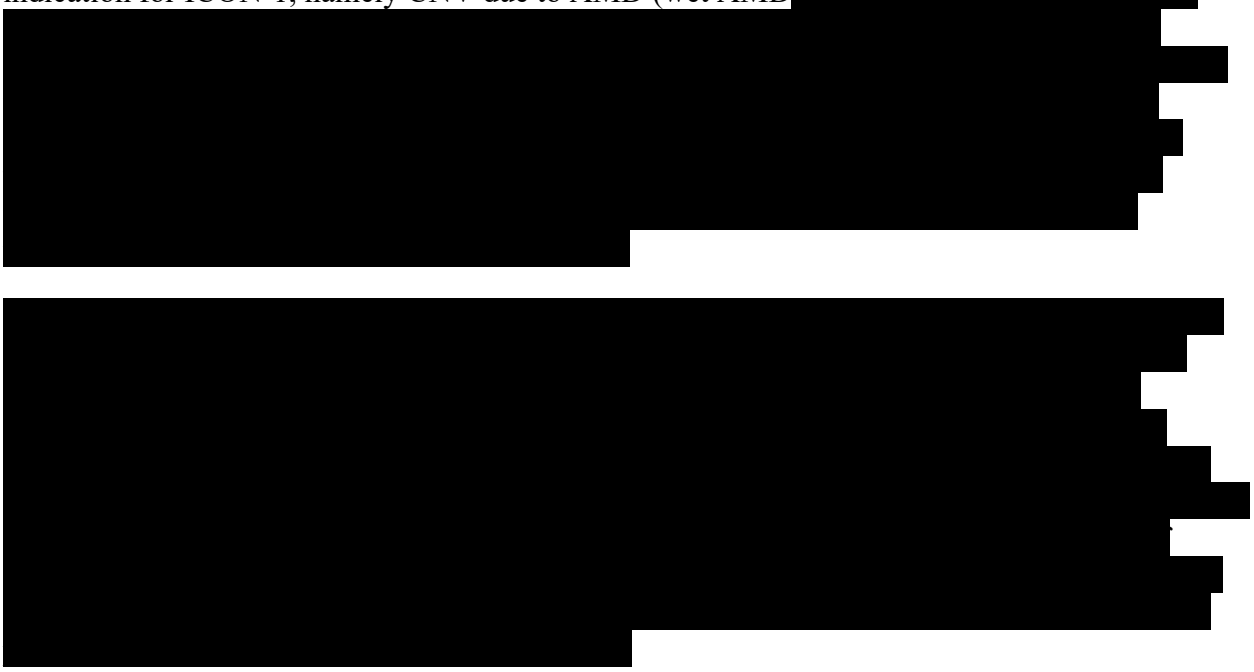
Iconic Therapeutics, Inc. has developed one such therapeutic protein known as ICON-1 to target TF. [redacted]

The toxicity, safety and tolerability, as well as the efficacy of Icon molecules have been evaluated to date in 12 preclinical studies, including wet AMD animal models and four Good Laboratory Practice (GLP) toxicology studies; a Phase 1 single ascending dose (SAD) study in patients with wet AMD; a Phase 2 repeated dose study in patients with wet AMD; and a Phase 1 single or repeated dose study in patients with uveal melanoma. A summary of these studies and their results is detailed below.

Preclinical and Toxicity Studies

The preclinical studies were designed to generate evidence in support of the initial therapeutic

indication for ICON-1, namely CNV due to AMD (wet AMD



The preclinical efficacy, safety and toxicity models results were the basis for conducting a first-in-human single ascending dose Phase 1 study in patients with wet AMD. A single IVT dose of up to 300 μg of ICON-1 was considered to be reasonably safe for a period of 2 to 4 weeks.

Clinical Studies

In clinical studies conducted by Iconic Therapeutics, a total of 88 patients have received treatment with ICON-1. Seventy-eight (78) patients with wet AMD have been administered 0.3 mg ICON-1 as single or repeated doses, as monotherapy or in combination with other therapies (studies IT-001 and IT-002); and ten (10) patients with uveal melanoma have been administered up to 0.6 mg ICON-1 as single or repeated doses one week apart (study IT-003)

The Phase 1 study (IT-001), was an open-label, single intravitreal (IVT) dose, dose-escalating study in 18 patients with CNV due to AMD, including both treatment-naïve patients and patients previously treated with chronic anti-VEGF therapy. The safety results showed that ICON-1 was safe at all doses tested (0.06 mg, 0.15 mg, and 0.3 mg), and there were no systemic or ocular dose limiting toxicities. The serum PK results determined that the systemic absorption of ICON-1 after a single IVT injection was below the limit of quantification in the majority of patients. None of the patients developed detectable anti-drug antibodies up to 12 weeks after receiving an IVT injection of up to 0.3 mg of ICON-1. In conclusion, the safety, tolerability and biologic activity outcomes established in the completed Phase 1 study were shown to be consistent with the preclinical evaluations and supported the further evaluation of the ICON-1 molecule in a Phase 2 study.

The Phase 2 study (IT-002) was a signal-seeking, randomized, double-masked, active-controlled study to evaluate the safety and biological activity of repeated IVT injections of ICON-1 0.3 mg

in 88 patients with CNV secondary to AMD who were naïve to treatment for CNV in the study eye. Patients were randomly assigned to one of three treatment arms (ICON-1 + ranibizumab combination therapy, ICON-1 monotherapy + sham injection, or ranibizumab monotherapy + sham injection), and received up to 6 monthly administrations of study treatment over a 5-month dosing period, with one month of follow up.

The safety results showed that there were no unexpected ocular and non-ocular safety signals with IVT ICON-1 injection administered in monotherapy or in combination with ranibizumab, in repeated doses of 0.3 mg up to 6 months. The ICON-1 + ranibizumab combination therapy arm had a greater decrease in the CNV lesion size than ranibizumab alone or ICON-1 alone. In addition, the mean time from treatment end until the first re-treatment needed was longer in patients in the ICON-1 + ranibizumab combination therapy arm than in the ranibizumab monotherapy and ICON-1 monotherapy arms. The study met its endpoint to explore the safety of ICON-1 0.3 mg as a Tissue Factor antagonist leading to CNV lesion modification and supports further study of ICON-1 in higher doses.

A Phase 1 study in uveal melanoma (IT-003) was an open-label, sequential-group study to evaluate the safety, tolerability, biological activity, pharmacokinetics, and pharmacodynamic activity of single and repeated escalating intravitreal injections of ICON-1 in 10 patients with primary uveal melanoma scheduled to undergo enucleation or brachytherapy. Patients were enrolled and administered ICON-1 in one of three dosing cohorts (single dose of 0.3 mg, repeated doses of 0.3 mg one week apart, or repeated doses of 0.6 mg one week apart). The safety results showed that intravitreal ICON-1 administered as single or repeated doses of up to 0.6 mg over one week was well tolerated with no notable safety signals observed.

8.2 Study Rationale

The initial Phase 1 study has shown that a single IVT dose of ICON-1 up to 0.3 mg was well tolerated and safe in both naïve and previously treated wet AMD patients. The follow-up Phase 2 study has shown that repeated IVT doses of ICON-1 0.3 mg were well-tolerated and safe in treatment naïve wet AMD patients. Additionally, a Phase 1 study in ocular melanoma patients has shown that single or repeated IVT doses of ICON-1 up to 0.6 mg were well tolerated. These outcomes provide support to further explore a higher dose in both a maintenance and combination dosing regimen of 0.6 mg IVT ICON-1 in this Phase 2 study. The safety assessments and endpoints are based on both ocular (adverse events, description and follow up of the ocular events, such as inflammation) and systemic (adverse events, follow up and description of systemic events) clinical safety outcomes. In addition, the immunogenicity evaluation of the presence of anti-ICON-1 antibodies in the systemic circulation will be performed.

[redacted]. To evaluate how the different mechanism may translate into

different biological activity and clinical outcomes, in this Phase 2 study, ICON-1 will be dosed as either maintenance or combination therapy with an anti-VEGF agent.

The biological activity and the pharmacodynamic effect will be measured using both functional and anatomical assessments. [redacted] The anatomical markers will be collected via standard practice imaging techniques (color fundus photography [CFP], fundus fluorescein angiography [FA], spectral-domain optical coherence tomography [sdOCT], optical coherence tomography angiography [OCT-A]).

Based on historical evidence in treating CNV due to AMD with Eylea, after 3-monthly doses the clinical response to treatment can be assessed [20-22], therefore both treatment arms will initiate treatment in this study with 3 monthly aflibercept (Eylea®) IVT doses. After Month 3, patients remain in their treatment arm and continue to be treated and evaluated until Month 8. Starting at Month 4, aflibercept (Eylea®) may be administered based on the individual patient response to treatment. As has been observed in previous studies with anti-VEGF treatment administered as needed (*pro re nata*, PRN), after 3 initial injections, there are patients that have an optimal BCVA and CST response to treatment and do not require additional dosing for some period of time.

The 9-month duration of the study is considered appropriate in naïve patients with wet AMD to demonstrate clinical proof of concept of clinical safety and biological activity. The second and final comparative evaluation of both safety and biological activity endpoints will be performed at the Month 9, end of study time point.

To minimize the risk of severe wet AMD progression despite availability of efficacious standard of clinical care therapy, in cases in which clinical signs of AMD progression are observed, patients will have access to retreatment with standard of care aflibercept (Eylea®) therapy, as labeled, during the as needed observation period.

9 STUDY OBJECTIVES

The objectives of this study are to evaluate the safety and pharmacodynamics effects of repeated intravitreal injections of ICON-1 0.6 mg administered as maintenance therapy or in combination with aflibercept (Eylea®) in patients with neovascular (wet) age-related macular degeneration (AMD).

10 INVESTIGATIONAL PLAN

10.1 Overall Study Design and Plan

This is a signal-seeking, Phase 2, randomized, open-label, multicenter study to evaluate the safety and pharmacodynamics effects of repeated intravitreal injections of ICON-1 0.6 mg in patients with wet AMD who are naive to treatment for wet AMD in the selected study eye.

Eligible patients will be randomly assigned to one of the following two treatment arms in the selected study eye in a 1:1 ratio:

- **ICON-1 Maintenance Therapy:** Aflibercept (Eylea®) monthly during Months 0-2 and ICON-1 0.6 mg monthly during Months 2-4, then aflibercept retreatment up to every 8 weeks as needed during Months 4-8, based on the retreatment criteria.

- **ICON-1 + AFL Combination Therapy:** Aflibercept (Eylea®) monthly and ICON-1 0.6 mg monthly (administered 0-7 days after aflibercept) during Months 0-2, then aflibercept retreatment up to every 8 weeks as needed during Months 4-8, based on the retreatment criteria.

During Months 0-4, patients will receive up to three intravitreal injections in the study eye at each injection visit according to the patient's assigned treatment arm.

At treatment visits with two injections, both intravitreal injections will be administered on the same day. At treatment visits with three injections, the three intravitreal injections (first injection: aflibercept 2 mg, second injection: ICON-1 0.3 mg, and third injection: ICON-1 0.3 mg) may be administered on the same day OR the three injections may be administered across two separate days up to 7 days apart. If the three injections will be split across two days, the entire 0.6 mg dose of ICON-1 (two injections of 0.3 mg) must be administered on the same day.

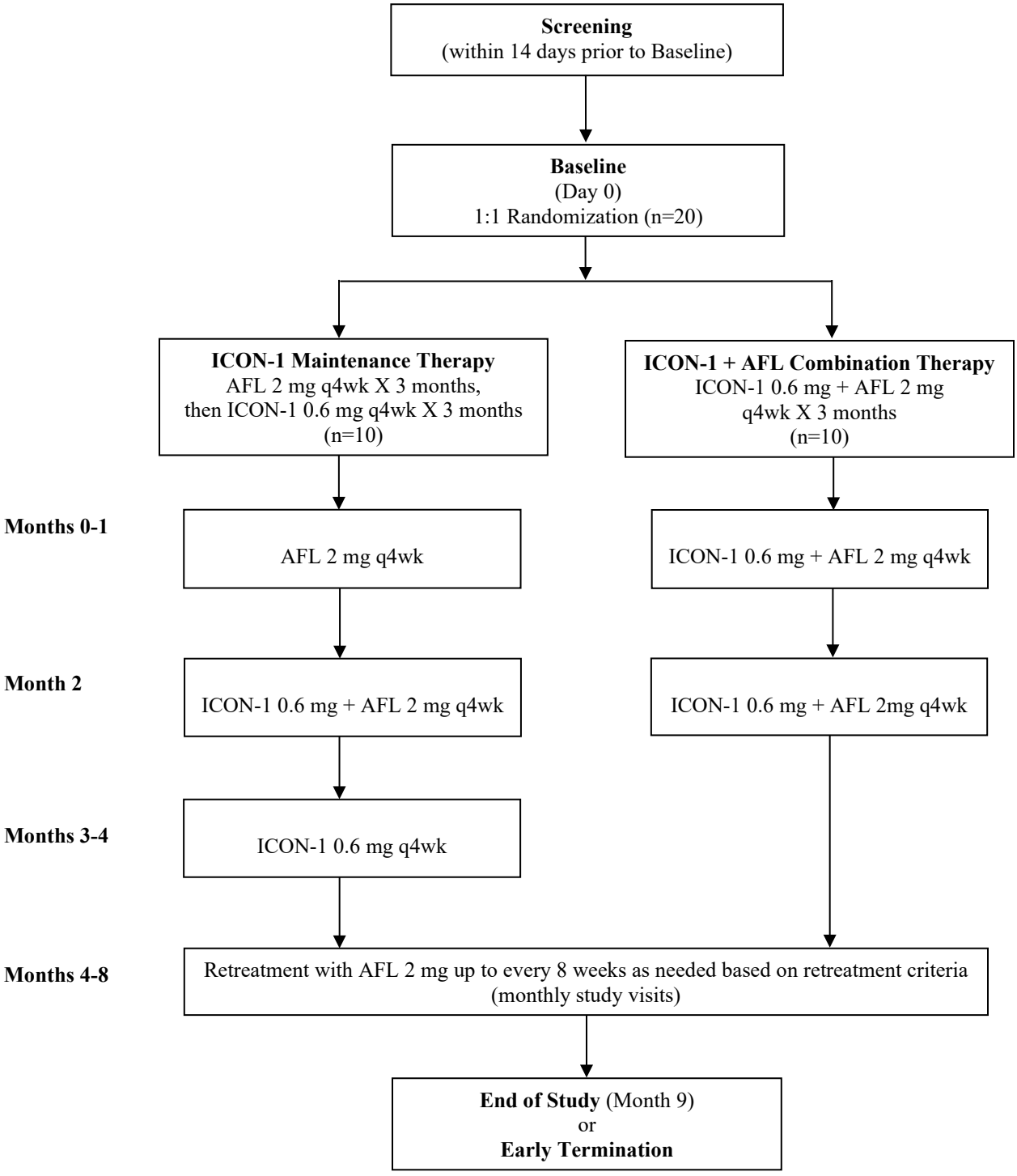
During Months 4-8, as needed aflibercept retreatment will be administered based on the following pre-specified criteria:

- Clinically significant anatomical evidence of increased or persistent CNV activity (e.g. new or persistent fluid on OCT, leakage or hemorrhage on FA) compared to the previous scheduled visit, as determined by the Investigator

Safety will be evaluated by means of occurrence of adverse events, clinical laboratory tests (serum chemistry, hematology, and coagulation), vital signs measurements, slit-lamp biomicroscopy, intraocular pressure (IOP), and dilated ophthalmoscopy. Pharmacodynamic and biological activity will be measured by means of BCVA by ETDRS, color fundus photography (CFP), spectral-domain optical coherence tomography (sdOCT), optical coherence tomography angiography (OCT-A), and fundus fluorescein angiography (FA). Immunogenicity will be evaluated by means of measuring plasma anti-drug antibodies.

Patients (or their legally authorized representative) may choose to withdraw from the study for any reason at any time without prejudice. Study assessments for an Early Termination Visit should be conducted in the event a subject discontinues from the study prematurely.

Figure 1: Study Design Schema



10.2 Study Sites

Up to 10 centers located in the US will participate in this study.

10.3 Discussion of Study Design, Including the Choice of Control Groups

In this Phase 2 Proof of Concept study, the safety and pharmacodynamics effects of ICON-1 maintenance or combined with an anti-VEGF (aflibercept) will be evaluated. Anti-VEGF therapy is the current treatment of choice for CNV secondary to AMD. Aflibercept binds VEGF reducing vascular leakage and new blood vessel formation. In contrast to anti-angiogenic agents, ICON-1 binds directly to specific receptors that are over expressed on the endothelial cells of pathologic vasculature and thus may change the biological characteristics of the choroidal neovascular complex. This capability to interfere directly with the growth and possibly lead to the destruction of the existing pathologic vessels differentiates ICON-1 from the anti-angiogenic agents and offers a novel therapeutic approach for the treatment of neovascular, wet AMD.

Randomization will be used in the study to minimize bias in patient selection and treatment assignments but treatment assignments will not be masked. The study duration of 9 months is considered to be an adequate treatment and follow up period to assess safety and biologic activity of the treatments in patients with treatment-naïve CNV secondary to AMD.

10.4 Appropriateness of Measurements

The choice of safety and biological activity parameters of pharmacodynamics effect to be evaluated in this study reflect experience in the non-clinical studies and the completed human Phase 1 and Phase 2 clinical trials, including two previous studies in CNV secondary to AMD. The immunogenicity assessment in this study is used widely and is generally recognized as reliable, accurate, and relevant.

The primary aim for data analyses in this trial is to characterize the anatomical outcomes after ICON-1 administration as assessed by fundus fluorescein angiography (FA) and optical coherence tomography angiography (OCT-A) over time. Secondary aims include evaluation of the functional and anatomical outcomes after ICON-1 administration as measured by BCVA and imaging markers of the retina and subretinal space (via sdOCT and CFP) to longitudinally assess changes in the features of the CNV complex, exudative changes, fibrotic and atrophic, and other morphology changes over time compared to baseline.

11 STUDY POPULATION

11.1 Target Population

The target population for this study is treatment-naïve men and women age 50 years and older with a diagnosis of active primary CNV secondary to AMD. The defined population is further characterized by parameters of disease characteristics and clinical status that are within the severity range that is thought to be reversible and will enable the evaluation of a biological response to ICON-1.

11.2 Inclusion Criteria

Patients must meet all of the following criteria to be included in the study:

1. Verbal and written informed consent obtained from the subject or the subject's legal representative (as applicable).
2. Males or females of any race, ≥50 years of age.
3. Clinical diagnosis of treatment-naïve, active primary CNV secondary to AMD in the study eye as determined by the Investigator.
4. BCVA of 83 to 24 ETDRS letters (20/25 to 20/320 Snellen equivalent) in the study eye at Screening.
5. Study eye meets all of the following lesion characteristics at Screening as determined by the Investigator:
    a) Total lesion size <4 disc areas based on fundus fluorescein angiography (FA) and <10 mm^2 on OCT-A
    b) CNV area is >50% of total lesion size based on FA
6. Adequate clarity of ocular media and adequate pupillary dilation to permit good quality imaging of fundus in the study eye as determined by the Investigator.
7. If a woman of childbearing potential (WOCBP) (i.e., not postmenopausal for at least 2 years or not surgically sterile), must have a negative serum pregnancy test at Screening, and must use adequate birth control with their non-surgically sterile male sexual partner throughout the study. Adequate methods of birth control include hormonal contraceptives, intrauterine contraceptive device (IUD), condom with spermicide, contraceptive sponge with spermicide, diaphragm with spermicide and cervical cap with spermicide.

11.3 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Monocular patient or patient with BCVA of ≤35 letters (20/200 or worse Snellen equivalent) in the better seeing eye.

2. CNV secondary to other causes in the study eye as determined by the Investigator.
3. Any prior treatment of CNV or advanced AMD in the study eye (e.g., laser, pharmacological [e.g., anti-VEGF agents] or surgical treatment, or any investigational therapy), except for dietary supplements or vitamins.
4. Presence in the study eye of suspected polypoid choroidal vasculopathy (PCV) and retinal angiomatous proliferation (RAP) lesion components, hemorrhagic pigment epithelial detachment (PED), retinal tears or rips, or vitelliform macular dystrophy as determined by the Investigator.
5. History of recurrent CNV in the study eye as determined by the Investigator
6. Presence of any of the following lesion characteristics in the study eye as determined by the Investigator:
    a) Retinal hemorrhage area >50% of total lesion area based on FA
    b) Fibrosis area >50% of total lesion area based on FA
    c) Subfoveal scar, fibrosis or atrophy visible on sdOCT
7. Chronic, uncontrolled glaucoma or ocular hypertension in the study eye defined as an IOP >25mmHg regardless of concomitant treatment with IOP-lowering medications.
8. Previous participation in an investigational study of ICON-1
9. Known serious allergy to fluorescein sodium for injection in fluorescein angiography.
10. Known hypersensitivity to aflibercept (Eylea®) or any of the excipients in Eylea®.
11. History of intraocular or ocular surface surgery (including cataract surgery and YAG laser procedures) in the study eye within 3 months prior to Screening.
12. History of vitrectomy in the study eye.
13. For a patient receiving chronic anticoagulant treatment (e.g., patients with a history of cardiovascular/cerebrovascular diseases [events] or hospitalization due to such conditions), the patient is without confirmation of stable clotting time using the appropriate test (Prothrombin Time (PT), International Normalized Ratio (INR) (e.g., Coumadin), or activated partial thromboplastin time (aPTT) (e.g., Pradaxa)) over the last 6 months from the patient's treating physician. Some agents do not require PT/INR/aPTT monitoring (e.g., aspirin, Eliquis (apixaban)).
14. Hereditary or chronic hemorrhagic or coagulopathy conditions (i.e., hemophilia).
15. Use of any investigational product or device within 30 days prior to Screening, or planned use of an investigational product or device during the study. Age-related Eye Disease Study (AREDS)-formulated vitamins (which have been under investigation) are allowed during the study.
16. History or presence of other concurrent conditions deemed by the Investigator to be likely to impact the subject's visual acuity in the study eye or to interfere with the interpretation of the study results, such as optic neuritis or atrophy (related to multiple sclerosis or other neurological disease), uveitis, or retinal vasculitis

17. Presence of any other concurrent medical condition, including mental illness or substance abuse, deemed by the Investigator to be likely to interfere with a subject's ability to provide informed consent, comply with monthly study visits and assessments, or interfere with the interpretation of the study results.
18. Woman who is pregnant or lactating.

11.4 Study Eye Determination

The study eye will be determined as the eye that meets all of the inclusion criteria and none of the exclusion criteria. If both eyes meet the criteria for entry, the eye with the worst BCVA will be selected as the study eye.

12 STUDY TREATMENTS

12.1 Study Drug Dosage and Administration

12.1.1 Investigational Product (ICON-1)

The investigational product is human Immuno-conjugate 1 (ICON-1). ICON-1 is a recombinant fusion protein that targets and binds to Tissue Factor (TF) overexpressing cells and suppresses the aberrant TF signaling that lies at the root of overly vascularized disease states like wet AMD. It is a dimeric antibody-like protein with a molecular weight of 157 kDa; each monomer has two functional domains joined by a linker. The targeting domain of ICON-1 is a mutated FVIIa protein conjugated to an Fc effector moiety of a human IgG1 immunoglobulin.

12.1.2 Comparator Product

There will be no active comparator in this study.

12.1.3 Test Article Administration

Patients will be randomly assigned to one of two treatment arms in a 1:1 ratio:

- **ICON-1 Maintenance Therapy:** Aflibercept (2 mg/50 µL) monthly during Months 0-2 and ICON-1 0.6 mg (two injections of 0.3 mg [300 µg/100 µL]) monthly during Months 2-4, then aflibercept up to every 8 weeks as needed during Months 4-8, based on retreatment criteria.
- **ICON-1 + AFL Combination Therapy:** Aflibercept (2 mg/50 µL) monthly and ICON-1 0.6 mg (two injections of 0.3 mg [300 µg/100 µL]) monthly during Months 0-2, then aflibercept up to every 8 weeks as needed during Months 4-8, based on retreatment criteria.

Using aseptic technique, ICON-1 or aflibercept will be administered by first withdrawing vial contents through a 5-micron 19-gauge filter needle attached to a 1-cc tuberculin or Luer Lock syringe and then replacing the filter needle with a 30-gauge x ½ inch needle for the intravitreal injection. Adequate topical anesthesia and broad-spectrum microbicide will be given prior to injection.

At treatment visits with two injections of study drug, both intravitreal injections will be administered on the same day.

At treatment visits with three injections of study drug, the three intravitreal injections (first injection: aflibercept 2 mg, second injection: ICON-1 0.3 mg, and third injection: ICON-1 0.3 mg) may be administered on the same day OR the three injections may be administered across two separate days up to 7 days apart. If the three injections will be split across two days, the entire 0.6 mg dose of ICON-1 (two injections of 0.3 mg) must be administered on the same day.

IOP will be measured before and after each intravitreal injection. When multiple study drug injections are administered on the same day, the second injection and the third injection (if applicable) will be administered following stabilization of IOP to the pre-injection level (i.e., within 5 mmHg of the pre-injection IOP) AND a minimum of 30 minutes after the prior injection.

12.2 Study Drug Packaging, Labeling and Storage

ICON-1 will be provided by the Sponsor, and is supplied in single-use glass vials containing 0.28 mL of a sterile solution of ICON-1 at a concentration of 3 mg/mL in 15 mM HEPES, 150 mM NaCl, 25 mM Arginine, pH 7.4 with 0.01% of Polysorbate-80 and 5 mM $CaCl_2$. Each vial will be provided in an individual kit box with a foam insert, and kits will be labeled with a unique kit number.

Vials of ICON-1 will be shipped frozen on dry ice and should be stored frozen at ≤ -60ºC until just before use. Temporary storage is permitted at -20ºC ± 5ºC for up to 90 days. ICON-1 vials should be thawed by removing the vial from the box and foam insert, and leaving at room temperature for approximately 10-15 minutes prior to administration. Verify that the study drug is completely thawed by taking the vial and gently swirling it. ICON-1 may NOT be refrozen once it has been thawed. Time between thawing and administration should be as minimal as possible and should not exceed 4 hours. Vials of ICON-1 are for single-use only.

Commercial aflibercept (Eylea®) will be supplied by the clinical site. Eylea® is provided in cartons containing one single-use, sterile, 3-cc glass vial designed to deliver 0.05 mL of 40 mg/mL of aflibercept. Each carton also contains one 5-micron, 19-gauge x 1-½-inch filter needle for withdrawal of vial contents, one 30-gauge x ½-inch injection needle for the intravitreal injection, one 1-mL syringe for administration, and one package insert. Eylea® should be refrigerated at 2ºC - 8˚C (36ºF - 46ºF). DO NOT FREEZE. Do not use beyond the date stamped on the carton and container label. Eylea® should be protected from light, and stored in its original carton until time of use.

12.3 Selection of Doses and Timing of Doses

Doses of ICON-1 selected for this study are based on the results of non-clinical efficacy and toxicology studies, clinical Phase 1 and 2 studies in patients with wet AMD, and a Phase 1 study in patients with uveal melanoma. Results of the Phase 1 and 2 studies in wet AMD showed ICON-1 was well tolerated at all doses tested up to 0.3 mg for up to 6 monthly doses, and results of the Phase 1 study in uveal melanoma showed ICON-1 was well-tolerated in doses up to 0.6 mg for up to two weekly doses. These data support further evaluation of repeated doses of 0.6 mg in this Phase 2 study. ICON-1 administered at monthly intervals for loading doses is thought to be an optimal dosing regimen with respect to safety and effectiveness (see Section 8.1 for information regarding the non-clinical, Phase 1 and Phase 2 studies).

12.4 Criteria for Retreatment with Aflibercept

Patients will be administered aflibercept intravitreal injections in the study eye once every four weeks at Months 0, 1 and 2. As of Month 4 (at Months 4, 5, 6, 7 and 8), patients may be retreated

with aflibercept up to every 8 weeks as needed, based on their individual observed treatment response. The Investigator will use the following retreatment criteria to determine if treatment is required at each retreatment visit:

- Clinically significant anatomical evidence of increased or persistent CNV activity (e.g., new or persistent fluid on OCT, leakage, hemorrhage on FA) compared to the previous scheduled visit, as determined by the Investigator

At a given month when retreatment is required, the injection procedure(s) and timing will remain the same. See Section 21.2 (Appendix B) for the Study Treatment Flowchart and Section 21.4 (Appendix D) for the Retreatment Decision Tree.

12.5 Measurement of Study Drug Compliance

All study treatment will be administered by the Investigator or designated physician at each clinical site. The date and time of study treatment must be documented for each subject in the source record. Treatment assignment and dose must be documented in records with access restricted to authorized study personnel only.

12.6 Study Drug Accountability

The Investigator or designee is responsible for maintaining accurate records of study drug supplies. Reasons for any departure from the expected dispensing regimen must be recorded. Study drug may not be used for any other purpose other than that described in the protocol. All study drug supplies and accountability records must be stored in a secure location with limited access restricted to authorized personnel only.

All vials of study drug will be recorded on a Drug Accountability Log accounting for all vials received, administered, not used, and destroyed. Drug Accountability will be performed by a Study Monitor during site visits. Once reconciled, study drug will be returned to the Sponsor or destroyed at the site, as directed by the Sponsor. If study drug is to be destroyed at the site, it is the Investigator's responsibility to ensure arrangements have been made for appropriate destruction according to applicable regulations, guidelines and procedures. Appropriate records of the destruction must be maintained.

12.7 Prior and Concomitant Therapy

All medications (prescription, over-the-counter (OTC) and herbal) and nutritional supplements taken by a subject from 30 days prior to Screening through the completion of the study will be recorded. Changes in the dosing and/or frequency of concomitant medication must be captured with new start and stop dates indicating the previous and current doses/frequencies.

Any prior or concomitant treatment of CNV or advanced AMD in the *study eye* (e.g. laser, pharmacological [e.g., anti-VEGF agents] or surgical treatment, or any investigational therapy) is prohibited, except for dietary supplements or vitamins.

Treatment of the *fellow eye* is allowed during the course of the study, and may be performed by any qualified physician in accordance with the site's standard of care.

Use of topical ocular anti-glaucoma medications is allowed during the study.

Use of any investigational product or device within 30 days before Screening through the completion of the study is prohibited. Age-related Eye Disease Study (AREDS)-formulated vitamins (which have been under investigation) are allowed during the study.

In the event of an emergency, any needed medications or therapies may be prescribed without prior approval, but the Medical Monitor must be notified of the use immediately thereafter. The decision to administer a prohibited medication or therapy should be done with the safety of the patient as the primary consideration. If permissibility of a specific medication or therapy is in question, the Investigator should contact the Medical Monitor.

12.8 Other Study Supplies

Additional supplies for administering ICON-1 intravitreal injections will include 1-cc tuberculin syringes, 5-micron 19-gauge x 1-½ inch filter needles for withdrawal of the study drug vial contents, and 30-gauge x ½ inch needles for intravitreal injections of ICON-1.

13 RANDOMIZATION AND MASKING

13.1 Enrollment and Subject Identification Numbers

Each subject will be assigned a unique screening number after informed consent is obtained. The screening number will be used as the subject ID number throughout the study. Patients will be randomized to one of two treatment arms using a central randomization list generated by the Sponsor. The screening number and the randomization number will both serve as unique subject identifiers throughout the study.

13.2 Method of Assigning Patients to Treatment Arms

The Investigator will evaluate the inclusion and exclusion criteria to determine patient eligibility for entry into the study. After the patient is determined to be eligible by the Investigator, study site personnel will contact the Sponsor (or designee) for assignment of a subject randomization number and treatment arm assignment.

Patients will be randomized in a 1:1 ratio to receive intravitreal aflibercept (2 mg) and ICON-1 (0.6 mg) maintenance therapy or ICON-1 (0.6 mg) + aflibercept (2 mg) combination therapy (see Section 12.1 for description of ICON-1 or aflibercept injection). Patients will be randomized on or before the day treatment is to be initiated (Day 0) based on the Screening visit assessments.

13.3 Masking

This is an open-label study in which treatment assignments will be known to the study patients, study site personnel, and the Sponsor and its agents.

14 STUDY PROCEDURES

The Study Flowchart and Assessments is presented in Section 21.1 (Appendix A). A detailed accounting of the assessments performed at each study visit is presented below.

The protocol-specified procedures for a given study visit may be split across 2 days as long as all procedures are completed within the visit-specific window; however, for each visit all BCVA testing, ophthalmic exams and imaging must be performed on the same day and cannot be split across 2 or more days.

14.1 Visit 1: Screening (Day -14 to -1)

Screening must take place within 14 days prior to Baseline (Month 0/Day 0). Patients will undergo Screening assessments to determine if they are eligible to enroll in the study.

An ICF must be signed and dated by the subject or the subject's legally authorized representative, the person who conducted the informed consent discussion, and witness (if required) before any Screening assessments or treatment is undertaken that is not part of routine care.

The following procedures will be performed at Visit 1:

- Obtain written informed consent and then assign a unique Screening Number to the subject
- Obtain demographic data
- Obtain medical history including surgical history
- Obtain ocular history
- Record prior (within the last 30 days) and concomitant medications
- Perform the following ophthalmic procedures:
    - Best-corrected visual acuity by ETDRS-like charts (both eyes)
    - Slit lamp biomicroscopy (both eyes)
    - IOP (both eyes)
    - Dilated ophthalmoscopy (both eyes)
    - Color fundus photography (study eye only)
    - sdOCT (study eye only)

  - OCT-A (study eye only)
  - Fundus fluorescein angiography
- Vital signs
- Blood samples for clinical laboratory tests (serum chemistry, hematology and coagulation), prior to injection of fluorescein for FA
- Blood sample for serum pregnancy test (women of child-bearing potential only), prior to injection of fluorescein for FA
- Assessment of adverse events
- Assessment of eligibility (Note: If an eligible subject is not assigned and dosed within the 14-day screening period the Investigator must confer with the Medical Monitor regarding repeating screening procedures.)
- Schedule subject to return for Visit 2 (Baseline, Month 0/Day 0) within the specified window

14.2 Visit 2: Baseline (Month 0/Day 0)

Baseline assessments will be completed on Day 0. The following procedures will be performed at Visit 2:

- Assessment of adverse events
- Record concomitant medications
- Perform the following ophthalmic procedures:
  - Best-corrected visual acuity by ETDRS (both eyes)
  - Slit lamp biomicroscopy (both eyes)
  - IOP (pre-injection, both eyes)
  - Dilated ophthalmoscopy (both eyes)
  - sdOCT (study eye only)
  - OCT-A (study eye only)
- Vital signs
- Assessment of eligibility

- Obtain randomization number and treatment assignment from Sponsor (or designee) (Note: The subject's randomization assignment may be requested prior to the Baseline visit once the Investigator has determined that the subject is eligible for the study based on the Screening visit assessments.)
- Blood samples for clinical laboratory tests (serum chemistry, hematology, and coagulation)
- Pre-dose blood sample for plasma anti-drug antibodies
- Administration of intravitreal injection(s) (designated physician only)
- Post-injection IOP after each intravitreal injection, as applicable (designated physician or designated site staff member only, study eye only)
- Assessment of adverse events
- Instruct patients to contact site study personnel immediately if their treated eye becomes red, sensitive to light, painful, or develops a change in vision
- Schedule subject return for Visit 3 (Month 1) within the specified window

14.3 Visit 3: Month 1 (Day 28 ±3 days)

The following procedures will be performed at Visit 3:

- Assessment of adverse events
- Record concomitant medications
- Perform the following ophthalmic procedures:
    - Best-corrected visual acuity by ETDRS (both eyes)
    - Slit lamp biomicroscopy (both eyes)
    - IOP (pre-injection, both eyes)
    - Dilated ophthalmoscopy (both eyes)
    - sdOCT (study eye only)
    - OCT-A (study eye only)
- Vital signs

- Only if patient is in ICON-1 + AFL Combination Therapy arm, pre-dose blood sample for plasma anti-drug antibodies, prior to injection of fluorescein for FA
- Administration of intravitreal injection(s) (designated physician only)
- Post-injection IOP after each intravitreal injection, as applicable (designated physician or designated site staff member only, study eye only)
- Assessment of adverse events
- Instruct patients to contact site study personnel immediately if their treated eye becomes red, sensitive to light, painful, or develops a change in vision
- Schedule subject to return for Visit 4 (Month 2) within the specified window

14.4 Visit 4: Month 2 (Day 56 ±3 days)

The following procedures will be performed at Visit 4:

- Assessment of adverse events
- Record concomitant medications
- Perform the following ophthalmic procedures:
    - Best-corrected visual acuity by ETDRS (both eyes)
    - Slit lamp biomicroscopy (both eyes)
    - IOP (pre-injection, both eyes)
    - Dilated ophthalmoscopy (both eyes)
    - sdOCT (study eye only)
    - OCT-A (study eye only)
- Vital signs
- Only if patient is in ICON-1 + AFL Combination Therapy arm, pre-dose blood sample for plasma anti-drug antibodies
- Administration of intravitreal injection(s) (designated physician only)
- Post-injection IOP after each intravitreal injection, as applicable (designated physician or designated site staff member only, study eye only)

- Assessment of adverse events
- Instruct patients to contact site study personnel immediately if their treated eye becomes red, sensitive to light, painful, or develops a change in vision.
- Schedule subject to return for Visit 7 (Month 3) within the specified window

14.5 Visit 5: Month 3 (Day 84 ±3 days)

The following procedures will be performed at Visit 5:

- Assessment of adverse events
- Record concomitant medication
- Perform the following ophthalmic procedures:
    - Best-corrected visual acuity by ETDRS (both eyes)
    - Slit lamp biomicroscopy (both eyes)
    - IOP (pre-injection, both eyes)
    - Dilated ophthalmoscopy (both eyes)
    - Color fundus photography (study eye only)
    - sdOCT (study eye only)
    - OCT-A (study eye only)
    - Fundus fluorescein angiography
- Vital signs
- Blood samples for clinical laboratory tests (serum chemistry, hematology, and coagulation), prior to injection of fluorescein
- Pre-dose blood sample for plasma anti-drug antibodies, prior to injection of fluorescein for FA
- If the patient is to be treated, administration of intravitreal injection(s) (designated physician only)
- If a patient is treated, perform a post-injection IOP after each intravitreal injection, as applicable (designated physician or designated site staff member only, study eye only)
- Assessment of adverse events

- If a patient is treated, instruct patients to contact site study personnel immediately if their treated eye becomes red, sensitive to light, painful, or develops a change in vision.
- Schedule subject to return for Visit 6 (Month 4) within the specified window

14.6 Visit 6: Month 4 (Day 112 ±3 days)

The following procedures will be performed at Visit 6:

- Assessment of adverse events
- Record concomitant medications
- Perform the following ophthalmic procedures:
    - Best-corrected visual acuity by ETDRS (both eyes)
    - Slit lamp biomicroscopy (both eyes)
    - IOP (pre-injection, both eyes)
    - Dilated ophthalmoscopy (both eyes)
    - sdOCT (study eye only)
    - OCT-A (study eye only)
- Vital signs
- Only if patient is in ICON-1 Maintenance Therapy arm, pre-dose blood sample for plasma anti-drug antibodies
- Determine if patient meets retreatment criteria
- If a patient is to be treated with ICON-1 and/or retreated with aflibercept, administration of intravitreal injection(s) (designated physician only)
- If a patient is treated/retreated, perform a post-injection IOP after each intravitreal injection, as applicable (designated physician or designated site staff member only, study eye only)
- Assessment of adverse events
- If a patient is treated/retreated, instruct patients to contact site study personnel immediately if their treated eye becomes red, sensitive to light, painful, or develops a change in vision.

- Schedule subject to return for Visit 7 (Month 5) within the specified window

14.7 Visits 7-10: Months 5, 6, 7, 8 (Days 140, 168, 196, 224 ±3 days)

The following procedures will be performed at Visits 7-10:

- Assessment of adverse events
- Record concomitant medications
- Perform the following ophthalmic procedures:
    - Best-corrected visual acuity by ETDRS (both eyes)
    - Slit lamp biomicroscopy (both eyes)
    - IOP (pre-injection, both eyes)
    - Dilated ophthalmoscopy (both eyes)
    - sdOCT (study eye only)
    - OCT-A (study eye only)
    - Only at Month 6, color fundus photography (study eye only)
    - Only at Month 6, fundus fluorescein angiography
- Vital signs
- Only at Month 5 and if patient is in ICON-1 Maintenance Therapy arm, pre-dose blood sample for plasma anti-drug antibodies
- Determine if patient meets retreatment criteria
- If a patient is to be retreated with aflibercept, administration of the intravitreal injection (designated physician only)
- If a patient is retreated, perform a post-injection IOP after the intravitreal injection (designated physician or designated site staff member only, study eye only)
- Assessment of adverse events
- If a patient is retreated, instruct patients to contact site study personnel immediately if their treated eye becomes red, sensitive to light, painful, or develops a change in vision.
- Schedule subject to return for the next scheduled visit within the specified window

14.8 Visit 11: End of Study, Month 9 (Day 252 ±3 days)

The following procedures will be performed at Visit 11:

- Assessment of adverse events
- Record concomitant medications
- Perform the following ophthalmic procedures:
    - Best-corrected visual acuity by ETDRS (both eyes)
    - Slit lamp biomicroscopy (both eyes)
    - IOP (both eyes)
    - Dilated ophthalmoscopy (both eyes)
    - Color fundus photography (study eye only)
    - sdOCT (study eye only)
    - OCT-A (study eye only)
    - Fundus fluorescein angiography
- Vital signs
- Blood samples for clinical laboratory tests (serum chemistry, hematology, and coagulation), prior to injection of fluorescein for FA
- Blood sample for serum pregnancy test (women of child-bearing potential only), prior to injection of fluorescein for FA
- Blood sample for plasma anti-drug antibodies, prior to injection of fluorescein for FA
- Assessment of adverse events
- Exit subject from study

If follow-up is needed after the End of Study visit, it should occur as a post-study unscheduled visit at the discretion of the Investigator. Patients with an ongoing SAE at this visit will be followed until the event is resolved or stabilized as described in Section 15.17.9.

14.9 Early Termination Visit

Patients who discontinue study drug or withdraw from the study prematurely will undergo an Early Termination (ET) visit. At this visit, the following will be performed:

- Assessment of adverse events
- Record concomitant medication
- Perform the following ophthalmic procedures:
    - Best-corrected visual acuity by ETDRS (both eyes)
    - Slit lamp biomicroscopy (both eyes)
    - IOP (both eyes)
    - Dilated ophthalmoscopy (both eyes)
    - Color fundus photography (study eye only)
    - sdOCT (study eye only)
    - OCT-A (study eye only)
    - Fundus fluorescein angiography
- Vital signs
- Blood samples for clinical laboratory tests (serum chemistry, hematology, and coagulation), prior to injection of fluorescein for FA
- Blood sample for serum pregnancy test (women of child-bearing potential only), prior to injection of fluorescein for FA
- Blood sample for plasma anti-drug antibodies, prior to injection of fluorescein for FA
- Assessment of adverse events

If follow up is needed after the Early Termination visit, it should occur as a post-study unscheduled visit at the discretion of the Investigator. Patients with an ongoing SAE at this visit will be followed until the event is resolved or stabilized as described in Section 15.17.9.

14.10 Unscheduled Visits

Unscheduled visits may be necessary due to AEs or other reasons. The Investigator may examine a subject as often as is medically necessary while the subject is enrolled in the study. Any follow-up that is performed to monitor patient safety should be recorded as an Unscheduled Visit. The Investigator is responsible for monitoring patient AEs, and additional assessments performed at an unscheduled visit are at the discretion of the Investigator. Additional clinical laboratory assessments should be performed by the central laboratory as needed and when possible.

14.11 Subject Withdrawal from Treatment or Study

14.11.1 Handling of Withdrawals

Patients (or their legally authorized representative) may choose to withdraw from the study for any reason at any time without prejudice. The study assessments for the Early Termination Visit should be conducted in the event a subject discontinues from the study prematurely. If a subject withdraws from the study, he or she may not re-enter the study.

The Principal Investigator or the Sponsor may withdraw a subject from the study for any of the following reasons:

- Adverse event
- Prohibited therapy (subject requires concomitant medication or a medical procedure prohibited by the protocol)
- Subject noncompliance (subject does not adhere to the requirements specified by the protocol)
- Subject improper entry (subject was enrolled in the study but did not meet the eligibility criteria)
- Subject withdrawal of consent
- Pregnancy (subject becomes pregnant)
- Lost to follow-up
- Death

At the time of withdrawal, the Principal Investigator should advise the subject of the other available options. When a subject is withdrawn from the study for any reason, the reason(s) for withdrawal will be recorded in the eCRF. For any subject who withdraws due to an AE, the reason for withdrawal must be recorded as an AE and not any other reason. Whenever possible, all patients who withdraw from the study prematurely will undergo assessments listed for the Early Termination visit.

If a subject fails to return for a scheduled visit, it is the responsibility of the Principal Investigator or designee to document all efforts to contact the subject and to determine the reason the subject did not return. After randomization, if a subject cannot be contacted with 3 documented telephone call attempts over a period of 2 weeks, followed by a certified letter, and does not have a known reason for discontinuation (e.g., withdrawal of consent or an AE), the reason for discontinuation will be recorded as “lost to follow-up”. The date that the certified letter was mailed will be considered the date of study withdrawal.

In the event of a subject death during the study, the date of death (as listed on the death certificate) will be used as the date of study withdrawal.

It is vital to obtain follow-up data on any subject who is withdrawn due to an AE. In such cases, every effort must be made to undertake protocol-specified safety follow-up procedures.

The Medical Monitor should be notified promptly when a subject is withdrawn.

The Sponsor may terminate the study at any time for clinical or administrative reasons and may discontinue participation by an individual Investigator or site for poor enrollment or noncompliance.

14.11.2 Replacements

Patients who are withdrawn from the study may be replaced at the sponsor's discretion.

14.11.3 Sponsor or Regulatory Agency Termination of the Study

Although the Sponsor intends to complete the study, the right is reserved to discontinue the study at any time for clinical or administrative reasons, or if required by the local regulatory authority.

15 STUDY ASSESSMENTS

This section describes the study assessment procedures. See Study Flowchart and Assessments (Section 21.1 - Appendix A) for timing of each assessment.

15.1 Informed Consent

Each site will be required to obtain IRB/EC approval of the ICF. Before any study specific procedures are performed, the investigator or designee will provide the subject or the subject's legally authorized representative with a copy of the current IRB/EC approved ICF and allow adequate time for review and the opportunity to ask any questions regarding the study and/or ICF. The Investigator should answer all questions to the best of his ability and to the satisfaction of the subject or the subject's legally authorized representative before performing any study visit assessments. The ICF should be signed and dated by the subject or subject's legally authorized representative, the Investigator or his designee, and witness (where applicable) before any study specific procedures are performed.

The consenting process must be conducted in accordance to the ICH GCP and local regulatory and/or IRB/EC requirements. A copy of the signed and dated ICF should be given to the subject or the subject's legally authorized representative and a copy should be maintained in the subject's medical records. The consenting process should be documented in the subject's source record including the names of persons participating in the discussions and a brief summary of what was discussed including questions and responses.

If the protocol is amended or new safety information becomes available, and revisions are required to the ICF, the subject or subject's legally authorized representative will be required to sign the updated IRB/EC approved ICF.

If a subject or subject's legally authorized representative withdraws consent at any time the date and time and details of the discussion should be recorded in the subject's source record along with the names of the persons participating in the discussion.

15.2 Eligibility Assessment

Screening assessments will be used to determine eligibility before randomizing a subject for entry in the study. The Investigator is responsible for assessing patient eligibility. Patients who meet the eligibility criteria will be randomized to one of the two treatment arms.

15.3 Demographic Data

Demographic data will be recorded including date of birth, gender, race and ethnicity.

15.4 Medical, Surgical, and Ocular History

Medical history will be recorded and should elicit all major illnesses, diagnoses, and surgeries for the subject. Ocular history will also be recorded and should be specific to which eye as appropriate.

15.5 Prior and Concomitant Therapy

Prior and Concomitant Therapy taken from 30 days prior to Screening through the last study visit will be recorded. The subject's source record should include start and stop dates, dose, route, frequency, and indication.

15.6 Best-corrected Visual Acuity

Best-corrected visual acuity (BCVA) will be measured for each eye, pre-treatment prior to dilating eyes, using standard Early Treatment Diabetic Retinopathy Study (ETDRS) retro-illuminated charts. BCVA will be recorded as the total letter score in each eye.

Visual acuity testing will be performed by designated site personnel, and should occur before any examination requiring contact with the eye. In order to provide standardization and well-controlled measurements of BCVA during the study, all measurements at a single site must be consistently done using the same lighting conditions, correction, chart type, and measurement procedure for an individual subject throughout the study.

A study specific refraction and BCVA testing protocol will be provided in a separate BCVA manual.

15.7 Slit-lamp Biomicroscopy

Slit-lamp biomicroscopy will be performed for each eye by designated site personnel. Slit-lamp biomicroscopy, including magnification, will be performed without dilation of the pupil and consistent with standard clinical practice. The subject will be seated during the examination. This procedure should be conducted in the same manner for all patients and will include an assessment of each of the following as normal or abnormal:

- Eyelids
- Conjunctiva
- Cornea
- Anterior chamber
- Iris
- Lens

All abnormal findings that are clinically significant will be described. A change from normal to abnormal for any biomicroscopic variable will be considered clinically significant.

15.8 Intraocular Pressure

At each study visit, IOP will be measured with a Goldmann applanation tonometer or Tono-Pen tonometer, consistent with standard clinical practice and consistent over the study visits. At injection visits, IOP will be measured by designated site personnel in each eye before the first injection, and in the study eye only at least 30 minutes after each intravitreal injection. Measurements will be recorded in mmHg (e.g., 19 mmHg). At other study visits, a single IOP measurement will be performed in both eyes by designated site personnel.

The tonometer must be calibrated for accuracy before the first subject in the study at a given site undergoes the first examination, and at least once every 30 days thereafter, until the last subject at the site has exited the study. Tonometer calibration may be completed by any qualified site personnel, and should be performed in accordance with the manufacturer's specifications. Only adequately calibrated instrument should be used for IOP measurement.

15.9 Dilated Ophthalmoscopy

A dilated fundus examination will be performed pre-treatment for each eye in all patients by designated site personnel. The following will be observed for the presence of abnormalities:

- Vitreous body
- Retina
- Macula
- Choroid
- Optic nerve

All abnormal findings that are clinically significant will be described. A change from normal to abnormal for any ophthalmoscopic variable will be considered clinically significant.

15.10 Color Fundus Photography

Color fundus photography (CFP) will be performed to assess CNV lesion characteristics in the study eye at the Screening Visit and at the Month 3, Month 6, and Month 9 or Early Termination visits. CFP will be performed pre-treatment during visits in which study treatment is administered.

Color fundus photographs will be obtained using a digital fundus camera, and will be performed by designated site personnel.

15.11 Spectral-Domain Optical Coherence Tomography

Spectral-domain optical coherence tomography (sdOCT) imaging will be performed to assess CNV lesion characteristics in the study eye at all scheduled study visits and at the Early Termination visit (if applicable). sdOCT will be performed pre-treatment during visits in which study treatment is administered.

sdOCT imaging will be obtained using a Spectral-Domain (High Definition) OCT device, and will be performed by designated site personnel.

15.12 Optical Coherence Tomography Angiography

Optical coherence tomography angiography (OCT-A) imaging will be performed to assess CNV lesion characteristics and *en face* chorioretinal space morphology in the study eye at all scheduled study visits and at the Early Termination visit (if applicable). OCT-A will be performed pre-treatment during visits in which study treatment is administered.

OCT-A imaging will be obtained using an FDA-approved OCT-A device, and will be performed by designated site personnel.

15.13 Fundus Fluorescein Angiography

Fundus fluorescein angiography (FA) imaging (after intravenous administration of fluorescein dye) will be performed to examine the circulation of the retina and the CNV lesion characteristics in the study eye according to standard FA image capture protocol. Intravenous FA must be performed pre-treatment, but after all other scheduled imaging has been completed. FA will be performed at the Screening Visit and at the Month 3, Month 6, and Month 9 or Early Termination visits.

Fundus fluorescein angiographic images will be obtained using a digital camera, and will be performed by designated site personnel.

15.14 Vital Signs

Vital signs should be taken when the subject is adequately rested (after the subject has been resting in a seated position for at least 5 minutes). Vital signs measurements include blood pressure (systolic and diastolic in millimeter of mercury (mmHg)), heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (°C).

15.15 Clinical Laboratory Evaluations

Blood samples for routine clinical laboratory tests will be collected at the Screening and Baseline visits and at the Month 3 and Month 9 or Early Termination visits. Samples will be collected pre-treatment during visits in which study treatment is administered. The minimum tests to be performed include:

- Hematology (complete blood count including white blood cell [WBC] count, WBC differential, red blood cell [RBC] count, hematocrit [Hct], hemoglobin [Hgb], mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], red cell distribution width [RDW], platelet count, and mean platelet volume [MPV])
- Serum chemistry profile (albumin, alkaline phosphatase, alanine aminotransferase [ALT], aspartate aminotransferase [AST], blood urea nitrogen [BUN], calcium, serum chloride, carbon dioxide [CO_2], creatinine, BUN/creatinine ratio, creatinine clearance [CrCl] using Cockcroft-Gault formula, creatine phosphokinase [CPK], direct and total bilirubin, triglycerides, gamma-glutamyl transferase [GGT], globulin, glucose, lactic dehydrogenase [LDH], phosphorus, potassium, sodium, total cholesterol, total protein, and uric acid)
- Serum pregnancy test for women of child-bearing potential
- Coagulation (prothrombin time [PT], international normalized ratio [INR], fibrinogen, and activated partial thromboplastin time [aPTT])

Any abnormal test results determined to be clinically significant by the Investigator should be repeated at the discretion of the Investigator until the cause of the abnormality is determined, the value returns to baseline or to within normal limits, or the Investigator determines that the abnormal value is no longer clinically significant. Clinical laboratory results should be initialed and dated by the Investigator and any abnormal results should be marked as clinically significant or not clinically significant. Clinically significant laboratory results should be recorded as an AE, preferably as a diagnosis where possible.

Female patients with a positive pregnancy test at Screening do not meet the eligibility criteria and may not enroll in the study. Women must have been in menopause for at least 2 years, or had a tubal ligation at least 1 year prior to Screening, or have had a total hysterectomy to be considered **not** of child-bearing potential.

Laboratory tests will be performed by a central laboratory. For detailed instructions regarding collection, storage and handling of laboratory samples, please refer to the Laboratory Manual provided separately.

15.16 Measurement of Plasma Anti-drug Antibodies

Blood samples will be obtained to measure systemic (plasma) levels of anti-drug antibodies (ADA). Blood samples for measurement of ADA will be drawn before the first intravitreal injection at the Baseline visit and at the Month 1, Month 2, Month 3, and Month 9 or Early Termination visits. Samples will be collected pre-treatment during visits in which study treatment is administered.

ADA samples will be analyzed by a central bioanalytical laboratory. For detailed instructions regarding collection, storage and handling of ADA samples, please refer to the Laboratory Manual provided separately.

15.17 Evaluation of Adverse Events

Adverse events (AEs) will be monitored continuously during the study from the time that the subject has provided written informed consent through the subject's last day of study participation. AEs may be reported spontaneously by the subject, discovered by Investigator or study staff through questioning, or observed through physical examination or other means. It is the responsibility of the Investigator to assess and document all AEs that occur during the course of the study, regardless of the causal relationship with the study drug.

The following information will be collected for all AEs and recorded on the subject's source document and AE eCRF:

- Event description (diagnosis preferred, if unknown, record the signs/symptoms)
- Onset and resolution dates
- Severity (intensity)
- Frequency (intermittency)
- Relationship to study drug (causality) as determined by the Investigator

- Seriousness
- Action taken with study drug
- Corrective action taken
- Outcome

15.17.1 Definition of an Adverse Event

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

An AE can therefore be:

- Any unfavorable and unintended medical diagnosis, sign or symptom
- Any new undesirable medical occurrence or unfavorable or unintended change in a pre-existing condition that occurs during or after study treatment
- Laboratory abnormality, vital sign or ophthalmic assessment that is assessed as clinically significant and different from baseline (e.g., requiring discontinuation of study treatment, specific treatment, or a change in subject management). If possible, changes in laboratory results or changes in vital signs that meet the definition of an AE should be reported as a medical diagnosis rather than as the abnormal value (e.g., “hypertension” rather than “blood pressure increased”).

The following are special considerations when determining and reporting AEs:

- Whenever possible, the Investigator should group signs or symptoms that constitute a single diagnosis under a single AE term (e.g., “cough, rhinitis, and sneezing” might be grouped together as “upper respiratory tract infection”).
- Pre-existing conditions are not considered AEs unless the condition worsens (increase in frequency, severity or specificity) during or following study drug administration. Fluctuations in a pre-existing condition should be assessed by the Investigator, and those that fall within the limits of expected fluctuations for the disease state, and are not assessed as worsening of the disease, should not be considered AEs. Any change assessed as clinically significant worsening of the disease from baseline must be documented as an AE.
- Elective surgery or routine diagnostic procedures are not considered AEs. However, an untoward medical event occurring during the pre-scheduled elective surgery or diagnostic procedure should be recorded as an AE.
- Death itself is not considered an AE; it is instead the outcome of an AE.
- Pregnancy is not considered an AE, but it is an important medical event that must be followed up as described in Section 15.17.7.

- Elevated IOP in the study eye following an intravitreal injection should be considered an AE if, at least 30 minutes after the injection: (1) two or more follow-up IOP measurements (taken at least 15 minutes apart) are required to demonstrate stabilization to the pre-injection level (i.e., within 5 mmHg of the pre-injection value), thereby delaying the time of the planned subsequent intravitreal injection; or (2) interventional therapy is required to return IOP to within 5 mm Hg of the pre-injection value.

A treatment-emergent AE (TEAE) is any AE with an onset from any time after the subject has received study drug through 30 days after the last dose of study drug, whether or not it is considered causally related to the study drug.

15.17.2 Serious Adverse Event

All AEs will be assessed as either serious or non-serious. A serious adverse event (SAE) is any event that results in any of the following outcomes:

- Death
- Life-threatening (i.e., if in the view of the Investigator or Sponsor, the event's occurrence placed the subject at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization. (Hospitalization for elective surgery for a pre-existing condition or for surgery planned before study entry is not considered an SAE.)
- A persistent or significant disability/incapacity (permanent or substantial disruption of the subject's ability to perform normal life functions). This definition is not intended to include experiences of relatively minor or temporary medical significance.
- Congenital anomaly/birth defect (an AE that occurs in the child or fetus of a subject exposed to study drug prior to conception or during pregnancy).

Important medical event or serious medical condition that does not meet any of the above criteria may be considered an SAE if, based upon appropriate medical judgment, it may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

15.17.3 AE Severity

The severity of an AE should be determined by the intensity of the AE and will be assessed using the following 3-point scale:

Table 1: Categories of Severity for Adverse Events

1-Mild	Discomfort noticed but no limitation in normal daily activities; no medical intervention/therapy required
2-Moderate	Discomfort sufficient to reduce or affect normal daily activities; some assistance may be needed; no or minimal medical intervention/therapy required
3-Severe	Inability to perform normal daily activities; some assistance usually required; medical intervention/therapy required; hospitalization or prolongation of current hospitalization possible; may be incapacitating or life-threatening

The term "severe" is a measure of intensity. A severe AE is not necessarily a serious AE.

15.17.4 Study Drug Causality

The Investigator will assess the relationship of the AE to the study drug as either "Related" or "Not Related". The following should be taken into consideration when assessing SAE causality:

- Positive temporal relationship to study drug, such as if the study drug was withdrawn and the AE resolved or the event recurred after re-introduction.
- If there is a reasonable possibility that the AE is associated with an underlying or concomitant illness.
- Possible association with previous or concomitant therapy.
- No temporal relationship to the study drug and/or a more likely alternative etiology exists.
- If the AE is directly related to study procedures or lack of efficacy.

15.17.5 Adverse Event Reporting Procedures

The occurrence of AEs should be sought by non-direct questioning of the subject at each scheduled or unscheduled study visit. At each visit, study personnel should ask the following question: "Have you had any problems since your last visit?" AEs may also be detected when they are volunteered by the subject during and between visits or through physical examination, or other assessments. All AEs (serious and non-serious) reported by the subject will be reviewed by a qualified physician participating in the study and must be recorded on the subject's source documents and AE eCRF.

An AE that is classified as "serious" requires expeditious handling and reporting to the Sponsor (or designee) within 24 hours of site notification to comply with regulatory requirements.

All SAEs, whether or not related to study drug, must be reported immediately to the Sponsor (or designee) by entering the SAE information directly into the electronic data capture (EDC) system (AE eCRF) within 24 hours after the Investigator becomes aware of the event.

Note that any SAEs that occur after the subject has provided written informed consent but before administration of study drug and are considered related to a protocol procedure must also be reported to the Sponsor (or designee) within 24 hours after the Investigator's awareness of the event.

Investigators should not wait to receive additional information to fully document an SAE before reporting the event to the Sponsor (or designee). If only limited information is initially available, follow-up information regarding the SAE is required. Additional relevant information such as hospital records, laboratory test results, discharge summaries and/or autopsy reports should be provided as soon as these are available. These SAE follow-up documents should be uploaded into the EDC system for informational purposes; however, if a document cannot be uploaded, it should be submitted to Iconic Therapeutics Drug Safety:

SAE Notification

Email: [redacted]

Fax [redacted]

(or to the email or fax number provided on the SAE Notification Cover Sheet)

15.17.6 Reporting Serious Adverse Events to Regulatory Agencies

An AE, whether serious or non-serious, is considered "unexpected" if the event is not reported in the clinical safety section of the reference document (e.g., Investigator Brochure or Package Insert) or if the event is of greater severity or frequency than is reported in the reference document.

Expedited SAE reports are those SAEs that are both unexpected based on the reference document and considered related to the study drug (i.e., the relationship cannot be ruled out). The Sponsor will determine which SAEs qualify for expedited reporting.

Reports of those SAEs that qualify for expedited reporting will be submitted to regulatory agencies in accordance with applicable local regulation (e.g., 21 Code of Federal Regulations [CFR] 312.32 and, as applicable, European Union Directive 2001/83/EC and 2001/20/EC).

Expedited reports will be also distributed to Investigators. Upon receiving such notices, the Investigator must review and retain the notice with the Investigator Brochure and immediately submit a copy of this information to the governing IRB/IEC in accordance with institutional guidelines and local regulations.

15.17.7 Pregnancy

Pregnancy alone is not an AE. However, any report of pregnancy that occurs in a female study subject within 30 days after the subject's last administration of study drug, and that becomes known to the Investigator, must be reported to the Sponsor even if the subject is withdrawn from study.

If a subject or Investigator suspects that a subject may be pregnant prior to study drug administration, the study drug administration must be withheld until the results of blood serum pregnancy tests are available. If pregnancy is confirmed, the subject must not receive the study drug and must not be enrolled in the study. If pregnancy is suspected while the subject is receiving study treatment, the study drug must be withheld immediately until the result of a pregnancy testing is known. If pregnancy is confirmed, the study drug will be permanently discontinued and the subject withdrawn from the study. The Investigator must follow the pregnancy to conclusion, and collect data on both maternal and fetal outcome including follow-up information regarding the course of the pregnancy and perinatal and neonatal outcomes.

A Pregnancy Report form will be submitted to the Sponsor, at a minimum, initially and at the end of the pregnancy. The Investigator is also encouraged to submit to the Sponsor trimester follow up reports during the pregnancy. The outcome of the pregnancy and any complications occurring during the pregnancy or the delivery must be reported to the Sponsor.

A miscarriage or spontaneous abortion will be considered an SAE, and will be reported to the Sponsor according to the procedure described in Section 15.17.5.

15.17.8 Overdose

Overdose is defined as any dose higher than the protocol prescribed dose of study drug. Occurrences of overdose leading to an AE will be reported on the AE eCRF. An overdose leading to an SAE will be reported to the Sponsor according to the procedure described in Section 15.17.5.

15.17.9 Follow-up of Adverse Events

Patients with an ongoing SAE will be followed until the event is resolved, the significant changes return to baseline, the condition stabilizes, the event is no longer considered clinically significant by the Investigator, the subject withdraws consent, or the subject is lost to follow-up. This may imply that follow-up will continue after the subject has left the study and that additional investigation may be requested by the Sponsor. If the severity or relationship to study drug worsens for an ongoing SAE, follow-up SAE information should be reported to the Sponsor within 24 hours after the Investigator becomes aware of the change in status.

All non-serious adverse events will be followed through the study exit visit. If a non-serious AE is first identified at the last scheduled study contact, the event will be recorded on the AE eCRF with the current status noted, but no further follow-up is required.

15.17.10 Follow-up of Post-study Serious Adverse Events

Should the Investigator become aware of a new SAE that occurs within 30 days after the last scheduled study contact and the event is determined by the Investigator to be related to the study drug, the SAE should be reported to the Sponsor and followed in accordance with the procedures described in this protocol.

16 STUDY ENDPOINTS

16.1 Primary Endpoints

Change in choroidal neovascularization (CNV) by fluorescein angiography (FA) and optical coherence tomography angiography (OCT-A) over time

16.2 Secondary Endpoints

[redacted]

- Change in Best Corrected Visual Acuity over time
- Change in CST by sdOCT over time

[redacted]

- Time to retreatment during PRN aflibercept retreatment period
- Percent of patients receiving PRN aflibercept retreatment over time

16.3 Safety Endpoints:

- Occurrence of ocular and systemic serious adverse events and adverse events
- Changes in standard clinical laboratory tests (serum chemistry, hematology, coagulation)
- Changes in vital signs and ophthalmic examinations
- Systemic levels of ADA over time

17 STATISTICAL ANALYSIS AND METHODS PLANNED

17.1 Statistical Analysis Plans

This Phase 2 trial is a signal-seeking trial to assess the safety and pharmacodynamic effects of ICON-1. As such, the primary aim for data analyses in this trial is to delineate the functional and anatomical outcomes after ICON-1 treatment in either maintenance or combination with anti-VEGF. Thus, the data analyses in this study is geared towards descriptive multifactorial summaries and displays of the functional and anatomical parameters.

As descriptors of the two treatment arms, univariate data summaries will be provided. For ordinal and continuous endpoints, summary statistics will include number of patients, mean, median, standard deviation, minimum, and maximum. For categorical endpoints, summary statistics will include number of patients, frequency, and percentages.

Safety analyses will include all randomized patients who received at least one dose of ICON-1, with patients allocated to the treatment arm associated with the dosing regimen actually received. The analyses of pharmacodynamic effects and biological activity will include all randomized patients who received at least one dose of ICON-1 and who had at least one post baseline disease evaluation, with patients allocated to the treatment arm associated with the regimen actually received.

Exploratory analyses of the data not described in the following subsections may be conducted as deemed appropriate.

The baseline evaluation will be defined as the last evaluation prior to the first study treatment.

More details of the data analyses will be provided in the Statistical Analysis Plan (SAP).

17.2 Analysis of the Conduct of the Study

The number of patients randomized will be tabulated by study site and treatment arm. Subject disposition (the number of patients randomized, treated, and completing the study) will be tabulated by treatment arm. The number of patients who complete each scheduled visit and treatment will be tabulated by treatment arm and by visit. Subject discontinuations and reasons for discontinuation will be summarized. Eligibility criteria exceptions and other major protocol deviations will be summarized by treatment arm.

Treatment compliance (ratio of total dose received to total dose intended) will likewise be summarized by treatment arm.

17.3 Handling of Dropouts or Missing Data

All analyses of safety results will be performed on an available-case basis. Available data for all treated patients will be summarized by assigned treatment. No imputation for missing data will be performed, and no attempt to correct for deviations from assigned treatment will be made.

Patients who are withdrawn from the study may be replaced at the Sponsor's discretion.

17.4 Analysis of Treatment Arm Comparability

Summary statistics of the following patient characteristics will be provided by treatment arm to assess comparability:

- Patient demographics, such as age, sex, and race;
- Baseline disease characteristics, such as BCVA, CST, extent of CNV area;
- Prior disease-related therapies; and
- Concomitant medications.

Other patient baseline characteristics will be summarized as deemed appropriate.

17.5 Treatment Exposure

The total dose received of both study treatments (ICON-1, aflibercept) will be summarized by treatment arm. The duration of dosing and number of doses received will also be summarized by treatment arm.

17.6 Safety Analyses

Safety will be assessed through summaries of adverse events, changes in laboratory test results (serum chemistry, hematology, coagulation), and changes in vital signs and ophthalmic examinations. Adverse events will be mapped using MedDRA.

All collected adverse event data will be listed by treatment, study site and patient number. All adverse events occurring on or after treatment on Day 0 (treatment emergent adverse events, TEAEs) will be summarized by treatment arm. In addition, all serious adverse events, including deaths (if any), will be listed separately and summarized. Finally, all ocular TEAEs will be listed and tabulated with events for the study and fellow eye summarized separately.

Changes in laboratory data will be summarized by treatment arm with shift tables.

17.7 Analyses of pharmacodynamics effects

This Phase 2 trial is a signal-seeking trial to assess the effects of ICON-1 on the biology of the CNV complex. As such, the primary aim for the assessment of biological activity in this trial is

to delineate the functional and anatomical outcomes of ICON-1 maintenance or combined with an anti-VEGF (aflibercept), in terms of:

- Function, as tracked through visual acuity and attendant treatment implications:
  - temporal changes in BCVA, as measured by actual mean changes in BCVA; percent of patients with a BCVA gain post baseline; percent of patients with BCVA >20/40 and <20/200 post baseline; percent of patients who remain within BCVA severity level post baseline;
  - Signs of CNV activity, as measured by time to retreatment with aflibercept and percent of patients receiving aflibercept re-treatment
- Anatomic, as tracked through physical (qualitative and quantitative) longitudinal changes in the eye that can be imaged through sdOCT, FA, CFP, and OCT-A:
  - CNV complex changes;
  - Changes in CST;

Thus, the data analyses for assessing biological activity in this trial are geared towards descriptive multifactorial summaries. The CNV complex anatomical outcomes will be assessed by qualitative and quantitative measures, including but not limited to: CNV dimensions (area, volume), CNV leakage, fluid presence

Initially, descriptive univariate data summaries by treatment arm will be provided for each of the biological activity parameters listed above. For ordinal and continuous endpoints (such as changes in BCVA and in CST), summary statistics will include number of patients, mean, median, standard deviation, minimum, and maximum. For categorical endpoints (such as percent of patients receiving retreatment), summary statistics will include number of patients, frequency, and percentages.

To describe the multifactorial functional and anatomical impact of ICON-1, treatment arm profiles (ICON-1 maintenance therapy, ICON-1 + aflibercept combination therapy) with multiple parameters will be concurrently presented and comprehensively examined.

- An example of one such profile is as follows: A treatment arm CNV complex anatomy profile may be constructed with the following anatomical variables: changes in CST, CNV changes, , with benchmark summary descriptors for the corresponding baseline values.

More patient and treatment arm profiles will be constructed as appropriate, and will be detailed in the SAP.

17.8 Immunogenicity Analyses

Systemic levels of anti-drug antibodies (ADA) during the study will be collected for each patient. If there are sufficient numbers of patients exhibiting systemic levels of ADA, summary statistics by treatment arm will also be provided.

17.9 Interim Analysis

No formal interim analysis is planned for this study.

17.10 Sample Size Determination

This study is exploratory and its sample size is not determined by statistical power considerations.

18 DATA HANDLING AND RECORD KEEPING

18.1 Case Report Forms and Source Documents

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain detailed and accurate case histories of all study patients. Original data will be recorded in the subject's source documents (which may include medical records, hospital charts, clinic charts/notes, diagnostics tests such as x-rays, laboratory tests and ECGs, and electronic recordings), and transcribed onto electronic case report forms (eCRFs) provided by the Sponsor.

The Investigator agrees to maintain accurate source documentation as part of the case history for each subject. Recorded data should be updated/corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (e.g., by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected an entry should make clear who made the correction and when, by adding his/her initials and the date of the correction.

Designated site staff must complete the applicable eCRFs as soon as possible after each subject visit, and the eCRFs must be available for review at the next scheduled monitoring visit. Electronic case report form completion guidelines that describe how to appropriately enter data into eCRFs from the source documents will be provided to the study sites. If an item is not available or is not applicable, this should be indicated. Blank data fields should not be present unless otherwise directed.

Prior to locking the clinical database, the Investigator must review and approve all completed eCRFs to verify their accuracy.

18.2 Monitoring of the Study

Qualified individuals (CRAs or Study Monitors) designated by the Sponsor will follow the study closely, and monitor all aspects of the study according to ICH/GCP and standard operating procedures for compliance with applicable government regulations. The Principal Investigator (PI) agrees to allow the CRAs direct access to study drug accountability records and drug supplies, dispensing and storage areas, clinical files of the study patients (including original medical records) and the regulatory files. The PI also agrees to assist the CRAs if requested. The PI and appropriate site staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by the CRAs.

The CRA will maintain necessary email, telephone, fax, and/or mail contact with the Investigators and study site personnel, and will visit the study sites at periodic intervals. The CRA will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigators and study site staff. During those visits, the CRA will compare the subject data entered in the eCRFs against original source documents at the clinical site, and evaluate the eCRFs for completeness and accuracy. Data that are modified on the eCRFs to resolve any discrepancies must be supported by the source documents. The review of subject medical records

will be performed in a manner to ensure that subject confidentiality is adequately maintained. Further details of the study monitoring will be outlined in a separate Monitoring Plan.

18.3 Data Management

Data management for this study will be contracted to a Contract Research Organization (CRO) designated by the Sponsor. All data management procedures will be detailed in separate, specifically identified documents that collectively will be referenced as the Data Management Plan (DMP).

The designated site personnel will transcribe the information required by the protocol onto the eCRFs that will be provided using a fully validated Electronic Data Capture (EDC) system conforming to FDA requirements for the capture of electronic data. The data will be checked for missing data or suspect errors upon entry against validation programs, and appropriate flags will be displayed on the eCRFs. The Investigator or designee will make the necessary corrections or verify the correctness of the data based on these flags. The database will be backed up regularly throughout the study by the CRO or EDC vendor.

Study Monitors representing the Sponsor will review the eCRFs against the source documentation at the site for completeness and accuracy, and will discuss the need for further corrections with the Investigator or designee. In addition, computerized edit checks and manual review processes will also be performed by the CRO on an ongoing basis as outlined in the DMP until all data clarifications are resolved.

In order to classify adverse events, medical and ocular history, and concomitant medications, preferred terms will be assigned to the original terms entered on the eCRFs using MedDRA or WHO Drug dictionaries.

After all data are entered and all data queries resolved, the Investigator must certify that the subject data are complete and accurate by applying an electronic signature to the eCRF study completion page. Once all eCRFs for the study are signed and the analysis populations are determined and documented, the clinical database will be locked.

After the clinical database is locked, disks containing electronic copies of all applicable patients' eCRFs will be provided to each Investigator to be maintained on file by the Investigator.

18.4 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to all study records. The Investigator or study site may be audited by the Sponsor or its representatives and/or regulatory agencies at any time. In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, the FDA, or other regulatory agency access to all study records.

The Sponsor will review case report form data and perform electronic edit checks on the data.

The Investigator should promptly notify the Sponsor of any audits scheduled by any regulatory authorities and promptly forward copies of any received audit reports to the Sponsor.

18.5 Study Record Retention

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical study must be retained by the Investigator. Original source documents for each subject should be included in this documentation. Study documentation should be retained by the Investigator until notified by the Sponsor in writing that retention is no longer necessary. In addition, the Investigator must notify the Sponsor of any change in the location, disposition or custody of the study documentation. Study documentation includes study records, subject charts/notes, subject medical records, laboratory tests, and paper or electronic recordings. It is the responsibility of the Sponsor to inform the Investigator/institution as to when this documentation no longer needs to be retained.

Records containing subject medical information must be handled in accordance with the requirements of the applicable privacy rules and consistent with the terms of the subject authorization contained in the ICF for the study. Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the ICF. Furthermore, eCRFs and other documents to be transferred to the Sponsor should be completed in strict accordance with the instructions provided by the Sponsor, including the instructions regarding the coding of subject identities.

Essential study 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 study drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. Should the Investigator retire, relocate, or for other reasons withdraw from the responsibility of keeping the study records, custody must be transferred by the Investigator to another party who will accept the responsibility. The Sponsor must be notified in writing by the Investigator of the name and address of the new custodian and receive documented acceptance from the new custodian. If requested, the Investigator will provide the Sponsor, applicable regulatory agencies, and applicable IRB/IEC with direct access to original source documents.

19 ADMINISTRATIVE CONSIDERATIONS

19.1 Confidentiality

All records identifying the patient will be kept confidential and to the extent permitted by the applicable laws and/or regulations will not be made publicly available. Patient names and other identifying information will not be supplied by the Sponsor. Only subject number and/or subject initials will be reported in the eCRF. If the patient name or other identifying information appears on any other document or study materials, the information must be deleted before a copy of the document is supplied to the Sponsor.

The Investigator (or designee) is responsible to obtain from the patient or patient's legally authorized representative, written permission to use protected health information per country-specific regulations, such as the HIPAA in the United States. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to document this in the patient's record.

If the results of the study are published, the subject's identity will remain confidential. The Investigator is responsible for maintaining a list enabling subject's records to be identified.

19.2 Amendments to the Protocol

Any changes or deviations in the protocol will be made as an amendment to the protocol and approved by the Sponsor and the IRB/EC before they are implemented. The Investigator or designee must notify the Sponsor or designee of any inadvertent protocol deviations upon their discovery, and document the deviations appropriately in the study files.

When a protocol amendment substantially alters the study design or the potential risks or burden to patients, the ICF will be amended and approved by the IRB/EC, and all patients on treatment must provide informed consent.

19.3 Protocol Deviations

The Investigator will not deviate from any tests, procedures, eligibility criteria, or the schedule of assessments described in the protocol except in the event of a medical emergency. The Investigator should contact the Medical Monitor with any questions concerning a subject who may not meet the entry criterion. Waivers for protocol eligibility will not be allowed for this study.

All protocol deviations must be documented and explained in the subject's source documentation, and should be reported to the Study Monitor. Protocol deviations should also be reported to the site IRB/EC in a timely manner and in accordance with the policies of the IRB/EC.

19.4 Study Reporting Requirements

The Investigator is responsible for submitting progress reports annually, or more frequently if required, to their IRB/EC and any applicable institutional committees in accordance with the policies of their IRB/EC and institutional committees respectively. The Investigator is responsible for maintaining copies of these reports and any acknowledgments from the IRB/EC or institutional committees. These reports must be available for review by the Study Monitor and any regulatory agency upon request. Any changes significantly affecting the conduct of the study and/or risk to the patients should be promptly reported to the Sponsor its designee, the IRB/EC and any applicable institutional committees.

19.5 Financial Disclosure

Financial Disclosure Forms must be completed by the Principal Investigator and all Sub-Investigators listed on the Form FDA 1572 who will directly be involved in the treatment or evaluation of patients in this study.

19.6 Investigator Responsibilities

The Investigator should ensure that all persons involved in the conduct of the study are informed about the protocol, protocol amendments, study procedures, and any study-related duties. The investigator is responsible for assuring that study site staff are properly trained and credentialed to perform any delegated tasks.

The Investigator is responsible for monitoring the safety of patients who have entered this study and for providing appropriate medical care. In addition, the Investigator is responsible for managing AEs that are serious or that cause the patient to withdraw before completing the study. Frequency of follow-up beyond that mandated in the protocol is left to the discretion of the Investigator.

19.7 Clinical Trial Agreement

A fully executed (signed and dated by all applicable parties) Clinical Trial Agreement describing the responsibilities and terms of collaboration between Iconic Therapeutics and the study site is required prior to initiating the study.

19.8 Policy for Publication and Presentation of Data

Iconic Therapeutics recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and at seminars or conferences. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be described in the Clinical Trial Agreement between Iconic Therapeutics and the institution of the Investigator.

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21 APPENDICES

21.1 Appendix A: Study Flowchart and Assessments

Study Month/Day	Screening Day -14 to -1	Baseline Month 0/ Day 0	Month 1 Day 28 ±3 days	Month 2 Day 56 ±3 days	Month 3 Day 84 ±3 days	Month 4 Day 112 ±3 days	Months 5, 6, 7, 8 Day 140, 168, 196, 224 ±3 days	End of Study Month 9 Day 252 ±3 days	Early Termi-nation
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7, 8, 9, 10**	**11**	**ET**
Informed Consent	X								
Demographic Data	X								
Medical/Ocular/Surgical/Medication History	X								
Best-corrected Visual Acuity by ETDRS	OU	OU	OU	OU	OU	OU	OU	OU	OU
Slit Lamp Biomicroscopy	OU	OU	OU	OU	OU	OU	OU	OU	OU
Intraocular Pressure[1]	OU							OU	OU
Pre-injection		OU	OU	OU	OU	OU	OU		
Post-injection 1		SE	SE	SE	SE[2]	SE[2,4]	SE[4]		
Post-injection 2		SE[3]	SE[3]	SE	SE[2]	SE[2]			
Post-injection 3		SE[3]	SE[3]	SE		SE[2]			
Dilated Ophthalmoscopy	OU	OU	OU	OU	OU	OU	OU	OU	OU
Color Fundus Photography	SE				SE		SE[5]	SE	SE
Spectral-domain Optical Coherence Tomography	SE	SE	SE	SE	SE	SE	SE	SE	SE
Optical Coherence Tomography Angiography	SE	SE	SE	SE	SE	SE	SE	SE	SE
Fundus Fluorescein Angiography	OU				OU		OU[5]	OU	OU
Vital Signs	X	X	X	X	X	X	X	X	X
Serum Chemistry, Hematology and Coagulation Blood Samples	X	X			X			X	X
Serum Pregnancy Test (WOCBP only)	X							X	X

Study Month/Day		Screening Day -14 to -1	Baseline Month 0/ Day 0	Month 1 Day 28 ±3 days	Month 2 Day 56 ±3 days	Month 3 Day 84 ±3 days	Month 4 Day 112 ±3 days	Months 5, 6, 7, 8 Day 140, 168, 196, 224 ±3 days	End of Study Month 9 Day 252 ±3 days	Early Termi-nation
Visit		**1**	**2**	**3**	**4**	**5**	**6**	**7, 8, 9, 10**	**11**	**ET**
Anti-drug Antibodies Plasma Sample	**ICON-1 Maintenance Therapy**		X			X	X	X[6]	X	X
	ICON-1 + AFL Combination Therapy		X	X	X	X			X	X
Assessment of Eligibility		X	X							
Randomization			X[7]							
Study Drug Intravitreal Injection(s)[8]	**ICON-1 Maintenance Therapy**		A	A	A + I	I	A[4] + I	A[4]		
	ICON-1 + AFL Combination Therapy		A + I	A + I	A + I		A[4]	A[4]		
Adverse Events		X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X

SE=Study Eye, OU=Both Eyes, A=aflibercept 2 mg, I=ICON-1 0.6 mg (2 injections of 0.3 mg)

[1] IOP measured using Goldmann applanation tonometry or Tono-Pen tonometer. For study eyes that receive study drug injections, the post-injection IOP will be measured after each study drug injection.

[2] Performed only for patients in ICON-1 Maintenance Therapy arm.

[3] Performed only for patients in ICON-1 + AFL Combination Therapy arm.

[4] Performed for patients requiring aflibercept retreatment at Months 4-8, per the retreatment criteria.

[5] Month 6 only.

[6] Month 5 only.

[7] Subject's randomization assignment may be requested prior to the Baseline visit once the Investigator has determined that the subject is eligible for the study based on the Screening visit assessments.

[8] Study Eye receives up to three injections at each injection visit. When multiple study drug injections are administered on the same day, the second injection and the third injection (if applicable) will be administered following stabilization of IOP to the pre-injection level (i.e., within 5 mmHg of the pre-injection IOP) AND a minimum of 30 minutes after the prior injection.

21.2 Appendix B: Study Treatment Flowchart

Treatment Arm	Visit 2 Month 0/ Day 0	Visit 3 Month 1	Visit 4 Month 2	Visit 5 Month 3	Visit 6 Month 4	Visit 7-10 Months 5-8	Visit 11 Month 9
ICON-1 Maintenance Therapy	▲ ■ ■	▲ 	▲ ■ ■	 ■ ■	▲* ■ ■	▲* 	
ICON-1 + AFL Combination Therapy	▲ ■ ■	▲ ■ ■	▲ ■ ■		▲*	▲*	

▲ AFL (aflibercept 2 mg/50 μL) injection

■ ICON-1 (ICON-1 0.3 mg/100 μL) injection

* Retreatment with aflibercept up to every 8 weeks as needed during Months 4-8, based on protocol-specified retreatment criteria.

Note: The Study Eye receives up to three injections at each injection visit. When multiple study drug injections are administered on the same day, the second injection and the third injection (if applicable) will be administered following stabilization of IOP to the pre-injection level (i.e., within 5 mmHg of the pre-injection IOP) AND a minimum of 30 minutes after the prior injection.

21.3 Appendix C: Retreatment Criteria

Retreatment Criteria
ICON-1 Maintenance Therapy arm: Patients will be administered aflibercept intravitreal injections in the study eye once every four weeks at Months 0, 1 and 2, and ICON-1 intravitreal injections once every four weeks at Months 2, 3,and 4. As of Month 4 (at Months 4-8) patients may be retreated with aflibercept up to every 8 weeks as needed, based on their individual observed treatment response. **Combination Therapy arm:** Patients will be administered aflibercept and ICON-1 intravitreal injections in the study eye once every four weeks at Months 0, 1 and 2. As of Month 4 (at Months 4-8) patients may be retreated with aflibercept up to every 8 weeks as needed, based on their individual observed treatment response. **Retreatment Criteria:** The investigator will use the following retreatment criteria to determine if treatment is required at each retreatment visit: • Clinically significant anatomical evidence of increased or persistent CNV activity (e.g., new or persistent fluid on OCT, leakage, hemorrhage on FA) compared to the previous scheduled visit, as determined by the Investigator

21.4 Appendix D: Retreatment Decision Tree