Protocol Title: A Phase 1, Open-label, Multicenter Study Evaluating the Safety and Tolerability, Biologic Activity, Pharmacodynamics, and Pharmacokinetics of Single and Repeated Escalating Intravitreal Doses of ICON-1 in Patients with Uveal Melanoma Who are Planned to Undergo Enucleation or Brachytherapy

Protocol date: 05 September 2016

NCT Number: NCT02771340

CLINICAL STUDY PROTOCOL

PROTOCOL TITLE:	A Phase 1, Open-label, Multicenter Study Evaluating the Safety and Tolerability, Biologic Activity, Pharmacodynamics, and Pharmacokinetics of Single and Repeated Escalating Intravitreal Doses of ICON-1 in Patients with Uveal Melanoma Who are Planned to Undergo Enucleation or Brachytherapy
PROTOCOL NUMBER:	IT-003
PHASE OF DEVELOPMENT:	Phase 1
INVESTIGATIONAL PRODUCT:	human Immuno-conjugate 1 (ICON-1)
INDICATION:	Uveal Melanoma
IND NUMBER:	102,472
SPONSOR:	Iconic Therapeutics, Inc. 7000 Shoreline Court Suite 270 South San Francisco, CA 94080
DATE OF PROTOCOL:	Original: 17 March 2016 Amendment 1: 05 September 2016

1 SPONSOR SIGNATURE PAGE

This study will be conducted as outlined herein in accordance with current International Conference on 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] Date

Chief Medical Officer

_____ _____

[redacted] Date

Biostatistician

2 PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Title:	A Phase 1, Open-label, Multicenter Study Evaluating the Safety and Tolerability, Biologic Activity, Pharmacodynamics, and Pharmacokinetics of Single and Repeated Escalating Intravitreal Doses of ICON-1 in Patients with Uveal Melanoma Who are Planned to Undergo Enucleation or Brachytherapy
Protocol Number:	IT-003

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 Conference on 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 Phone: (650) 437-1000
Medical Monitor:	[redacted] Medical Monitor [redacted]
Sponsor's Responsible Medical Officer:	[redacted] Chief Medical Officer [redacted]

4 PROTOCOL SYNOPSIS

Protocol Title	A Phase 1, Open-label, Multicenter Study Evaluating the Safety and Tolerability, Biologic Activity, Pharmacodynamics, and Pharmacokinetics of Single and Repeated Escalating Intravitreal Doses of ICON-1 in Patients with Uveal Melanoma Who are Planned to Undergo Enucleation or Brachytherapy
Protocol Number	IT-003
Study Phase	Phase 1
Study Sites	Approximately 7-10 centers located in the United States
Study Objectives	**Primary Objective** • To evaluate the safety and tolerability of single and repeated escalating intravitreal injections of ICON-1 administered in patients with uveal melanoma who are planned to undergo enucleation or brachytherapy. **Secondary Objectives** • To assess the pharmacokinetics and pharmacodynamic effect of ICON-1 in patients with uveal melanoma. • To describe preliminary evidence of the biologic activity of ICON-1 as determined by changes in visual acuity, and tumor size **Exploratory Objective** • To explore the prognostic indicator of the genetic profile of the tumor in relation to Tissue Factor expression and response to ICON-1 therapy. • To describe preliminary evidence of the biologic activity of ICON-1 as determined by changes in tumor pathology, and proteomic analysis of vitreous humor.
Study Design	This is a phase 1, open-label, sequential-group, multicenter study to evaluate the safety and tolerability, biological activity, pharmacokinetics, and pharmacodynamic activity of single and repeated escalating intravitreal injections of ICON-1 in patients with primary uveal melanoma who are planned to undergo enucleation or brachytherapy.

	Patients diagnosed with primary uveal melanoma involving the posterior uveal tract for which the selected treatment management plan is enucleation or brachytherapy may be screened for this study. Eligible patients will be assigned to one of three cohorts that will be enrolled consecutively: Cohort 1 (enucleation or brachytherapy): Single dose of 0.3 mg (300 µg/100 µl) ICON-1, (n=2) Cohort 2 (enucleation or brachytherapy): Two doses of 0.3 mg (300 µg/100 µl) ICON-1 each administered one week apart, (n=3) Cohort 3 (enucleation or brachytherapy): Two doses of 0.6 mg (300 µg/100 µl + 300 µg/ 100 µl) ICON-1 each administered one week apart, (n=5) Each dose level will be evaluated for clinical safety before escalating to the next cohort. Clinical and safety data will be reviewed by the IT-003 Safety Review Committee (SRC) comprised of at least one participating Clinical Investigator and the Iconic Therapeutics internal Safety Management Committee. The following ocular adverse events (even if non-serious) are considered Adverse Events of Special Interest (AESIs), and will be reported by the investigator to the sponsor and SRC as appropriate: • Ocular inflammatory event of CTCAE Grade ≥ 3 • Vitreous or retinal hemorrhage event interfering with visualization of the tumor or retina of CTCAE Grade ≥ 2 • Any acute onset treatment-emergent vision-threatening condition as assessed by the investigator Patient data will be evaluated by the SRC for the occurrence of ocular Dose Limiting Toxicity (DLT) events. An ocular DLT is defined as an ocular inflammatory adverse event of 3+ or more severity or a grade 2 or higher unexpected vitreous or retinal hemorrhage interfering with the visualization of the tumor or retina. All patients at a given dose level must complete their pre-procedure safety assessment after receiving their last dose of ICON-1 to enable evaluation of the safety of that dose level. For cohorts 1 and 2, if no patients experience a DLT, escalation to the next dose level will take place. If no patients experience a DLT in cohort 3, then cohort 3 will be considered the maximum administered dose (MAD). If one patient experiences a DLT in any cohort, an additional patient will be enrolled and evaluated at that dose level. For cohorts 1 and 2, if two or more patients experience a DLT in the original cohort or the expanded cohort, then enrollment in that cohort will be suspended

	and any subsequent cohorts will not be enrolled. For cohort 3, if two or more patients experience a DLT in the original cohort or the expanded cohort, then enrollment in the cohort will be suspended and the IT-003 Safety Review Committee will examine the safety data to determine if changes are warranted. If an AESI occurs while the patient is at the study center and requires clinical management, the patient will remain at the study center according to the Investigator's judgment. The patient will be managed according to the routine treatment practices of the study center. The patient will complete all subsequent study visits. All AESIs, serious adverse events, patient discontinuations and pregnancy reports must be reported to Iconic Therapeutics within 24 hours of the investigator learning of the event. ICON-1 will be administered on Day 0 for all cohorts, and in addition on Day 7 for cohorts 2 and 3 only. Patients will return to the study center on Day 1 for a safety follow-up visit (all cohorts) and 1 day post Day 7 (cohorts 2 and 3 only). All patients will return to the clinic for safety, clinical, and imaging assessments prior to the scheduled surgical procedure. Patients will have their planned Standard of Care surgical procedure (enucleation or brachytherapy) as early as 4 days after the last ICON-1 treatment, and return to the study center 30 days post-procedure for follow-up safety assessments (and ocular assessments for brachytherapy patients) and end of study visit. Safety will be evaluated by means of occurrence of adverse events, clinical laboratory tests (serum chemistry, hematology, coagulation, and anti-drug antibody levels (ADA)), vital signs measurements, abbreviated physical examinations, 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), color fundus photography (CFP), fluorescein angiography (FA), ophthalmic ultrasound, and optionally (according to investigator judgment) indocyanine green (ICG) angiography and enhanced-depth imaging optical coherence tomography (EDI-OCT). Pharmacokinetic (PK) and Pharmacodynamic (PD) markers will be evaluated by means of measuring plasma concentrations of ICON-1, serum cytokine levels, circulating tissue factor (TF), immunophenotyping, and circulating tumor DNA (CTDNA). **For enucleation patients:** immediately following the enucleation procedure, vitreous humor will be aspirated for intraocular ICON-1 and proteomic analysis of TF and cytokine levels. Following the clinical site's standard of care pathology of the tumor, prepared slides and/or tumor block samples will be sent to a central laboratory for the

	study for additional study-related pathology evaluation of the tumor (including ICON-1 binding, TF expression, protease activating receptors 2 (PAR2) expression, immune infiltrate, and alterations of the vasculature), genetic profiling, and Exome sequencing of the tumor. Genetic profiling of the tumor previously performed with fine needle aspiration of the tumor does not require repeated testing. **For brachytherapy patients:** the plaque placement procedure and associated follow-up will be according to the standard of care at each site. 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 patient discontinues from the study prematurely.
Study Duration	Enrollment is anticipated to take approximately 9 months and patient participation will be up to approximately 7-8 weeks including up to 7 days for screening, and up to approximately 6-7 weeks for treatment and follow-up.
Number of Subjects	Up to 13 patients will be enrolled in the study
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, ≥18 years of age. 3. Clinical diagnosis of primary uveal melanoma involving the posterior uveal tract (choroid and/or ciliary body) in the study eye. Patients with metastatic disease are eligible. 4. Planned enucleation or brachytherapy for primary uveal melanoma in the study eye. 5. 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 if they have a 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. Uveal melanoma in the study eye originating in the anterior uveal tract (iris). 2. Chronic uncontrolled glaucoma or ocular hypertension in the study eye defined as an IOP >25mmHg regardless of concomitant treatment with IOP-lowering medications. 3. Previous participation in an investigational study of ICON-1. 4. Known serious allergy to fluorescein sodium or indocyanine green for injection in angiography. 5. Use of two or more concomitant anticoagulant treatments (direct thrombin inhibitor class of drugs such as Coumadin (warfarin), Pradaxa (dabigatran), and Xarelto (rivaroxaban)). Aspirin is not considered an anticoagulant in this study. For patients receiving one chronic anticoagulant treatment (e.g., patients with a history of cardiovascular/cerebrovascular diseases [events] or hospitalization due to such conditions), the patient must have 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., Eliquis (apixaban)). 6. Hereditary or chronic hemorrhagic or coagulopathy conditions (i.e., hemophilia). 7. 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. 8. History or presence of other concurrent conditions deemed by the Investigator to be likely to impact the subject's clinical safety 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 or other inflammatory intraocular conditions in the study eye. 9. 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.

	10. 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.
Investigational Product	The investigational product is human Immuno-conjugate 1 (ICON-1). ICON-1 is a recombinant fusion protein that targets and binds to the aberrantly expressed Tissue Factor in retinal disease, tumors and supporting stroma (vasculature, infiltrating mononuclear cells). 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. ICON-1 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 $CaCl_2$.
Test Article Administration	Patients will be enrolled in one of three cohorts: • 0.3 mg (300 µg/100 µl) ICON-1 administered on Day 0 • 0.3 mg (300 µg/100 µl) ICON-1 administered on Day 0 and Day 7 • 0.6 mg (300 µg/100 µl + 300 µg/100 µl) ICON-1 administered on Day 0 and Day 7 Using aseptic technique, ICON-1 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 intravitreal injection. Adequate topical anesthesia and broad-spectrum microbicide will be given prior to injection. IOP will be measured before and after each injection. For cohort 3, the second intravitreal injection will be administered the same day 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 first injection.
Study Endpoints	**Primary Endpoints** Safety • Occurrence of ocular and systemic serious adverse events and adverse events

	• Changes in standard clinical laboratory tests (serum chemistry, hematology, coagulation) and ADA levels • Changes in vital signs, and physical and ophthalmic examinations **Secondary Endpoints** Pharmacokinetics and Pharmacodynamic Markers • Plasma levels of ICON-1 following intravitreal injections of ICON-1 • Change in circulating TF levels and serum cytokine levels following intravitreal injections of ICON-1 • Characterization of immunophenotyping patterns Pharmacodynamic and Biological Activity • Change in tumor size (thickness, volume) as assessed by imaging techniques (CFP, FA, sdOCT, ultrasound, ICG angiography, EDI-OCT) from baseline **Exploratory Endpoints** • Characterization of the genetic profile of the tumor (Type 1 or Type 2), and associated changes in the tumor TF with ICON-1 treatment • Characterization of pathologic findings of the tumor (ICON-1 staining of tumor structures, TF and PAR2 expression, characterization of the immune infiltrate, and alterations of the vasculature) • ICON-1 and proteomic analysis (TF and other cytokine levels) of the vitreous humor
Statistical Analyses	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. 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 with the dose escalation rules.

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6 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	anti-drug antibody
ADL	Activities of Daily Living
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AMD	age-related macular degeneration
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BCVA	best-corrected visual acuity
BUN	blood urea nitrogen
CBC	complete blood count
CFP	color fundus photography
CFR	Code of Federal Regulations
CMC	circulating metastatic cells
CNV	choroidal neovascularization
CO2	carbon dioxide
CPK	creatine phosphokinase
CrCl	creatinine clearance
CRO	Contract Research Organization
CRP	C-reactive protein
CRT	Central Retinal Thickness
CST	central retinal subfield thickness
CTCAE	Common Terminology Criteria for Adverse Events
CTDNA	Circulating tumor DNA
DC	dendritic cell
DLT	Dose Limiting Toxicity
DMP	Data Management Plan
EC	Ethics Committee
eCRF	electronic case report form
EDC	electronic data capture
ERG	electroretinography
EDI-OCT	enhanced depth imaging optical coherence tomography
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescein angiography

FAF	fundus autofluorescence
Fc	fragment crystallizable
FDA	Food and Drug Administration
g	gram
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
GM-CSF	granulocyte-macrophage colony-stimulating factor
Hct	hematocrit
Hgb	hemoglobin
ICON-1	human Immuno-conjugate 1 (ICON-1)
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICGA	Indocyanine green angiography
ICH	International Conference on Harmonisation
IgG	immunoglobulin G
IHC	immunohistochemistry
INR	International Normalized Ratio
IOP	intraocular pressure
IRB	Institutional Review Board
IUD	intrauterine contraceptive device
IVT	intravitreal
kg	kilogram
LDH	lactic dehydrogenase
Lin	lineage markers
MAb	monoclonal antibody
MAD	maximum administered dose
M-CSF	macrophage colony-stimulating factor
MCV	mean corpuscular volume
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MDSC	myeloid derived suppressor cell
mg	milligram
mL	milliliter
MPV	mean platelet volume

MTD	maximum tolerated dose
NCI	National Cancer Institute
ng	nanogram
NK	natural killer
NOAEL	no-observed-adverse-effect-level
OM	ocular melanoma
OTC	over-the-counter
PAR2	protease activating receptors 2
PCV	polypoid choroidal vasculopathy
PD	pharmacodynamics
PI	Principal Investigator
PK	pharmacokinetics
PT	Prothrombin Time
RBC	red blood cell
RDW	red cell distribution width
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
sdOCT	spectral-domain optical coherence tomography
SEER	Surveillance, Epidemiology, and End Results
SOC	Standard-of-Care
SRC	Safety Review Committee
TAM	tumor-associated macrophage
TCR	Tissue-Cross-Reactivity
TF	tissue factor
USPC	uterine serous papillary adenocarcinoma
UM	uveal melanoma
VEGF	vascular endothelial growth factor
VA	visual acuity
WBC	white blood cell
WOCBP	women of child-bearing potential

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

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 is properly constituted and compliant with International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) requirements, and all applicable laws and local regulations.

The study will not be initiated at your 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
- 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 50, 54, 56, and 312), the ICH document "Guidance for Good Clinical Practice, E6 (R1)," 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 (R1)," 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

Ocular melanoma (OM) is the second most common primary malignant melanoma in adults and leads to significant mortality and ocular morbidity [1]. About 95% of OM tumors can be described as Uveal Melanoma (UM), which develop in the melanocytes (pigment cells) of the eye and primarily affect the choroid, iris and ciliary body of the uveal tract [2,3]. Using data from the Surveillance, Epidemiology, and End Results (SEER) program the mean age-adjusted incidence of UM in the US is estimated to be 5.1 per million. An estimated 2,000 new cases of UM are diagnosed each year (2,4). In Europe the rate of new cases ranges from over 2 per million in Spain and Italy to over 6 per million in northern European countries [5,6].

Current Therapies and Unmet Therapeutic Need

Standard-of-Care (SOC) for OM is currently radiation therapy or surgical removal of the eye (enucleation). There are no chemotherapy agents or targeted biologics approved by the FDA for treatment of OM. Small tumors (<10 mm in diameter and <2 mm in height) are often observed until growth is documented. Symptomatic patients with medium or large tumors usually receive some form of radiation, either plaque radiotherapy (brachytherapy) or proton beam radiation [2]. However, these radioactive therapies are highly invasive and lead to further complications including retinopathy, cataracts, glaucoma and significant vision loss. For large tumors enucleation is usually performed. Thus, there is a need for treatment of OM that avoids the loss of an eye or the acute and chronic complications of radiation, while still preserving sight.

Neither radiation nor enucleation affects the rate at which metastatic disease occurs [7]. While local recurrence in the eye is rare, five- and ten-year rates of distant metastasis of 25 and 34 percent have been reported [8] and nearly half of all ocular melanomas will eventually develop distant metastasis, primarily in the liver, with lung and bone marrow the other sites. Once metastases have occurred, median survival is between 6 and 12 months. In fact, approximately 50 percent of all patients will die of metastatic disease within 10 years following diagnosis, despite early diagnosis of the primary tumor, successful local treatment, and close follow-up [9]. There is an urgent need for new therapeutic strategies for OM that are not only less or non-invasive, but that also have a potential to slow the onset of metastases.

Prognostic Markers in Uveal Melanoma

Proper assessment of the extent of disease and propensity for metastasis is one of the major challenges in the current management of UM. For example, UM is not only a localized ocular disease; circulating tumor cells (CTCs) have been observed as early as initial diagnosis [10]. In uveal melanoma patients, the presence of tyrosinase RNA in the peripheral blood was found to be associated with the stage of disease and predicted disease progression in patients with early as well as advanced melanoma [11,12,13]. In fact, the presence of tyrosinase or MelanA/MART1 transcripts is an independent prognostic factor in patients with high-risk primary UM [14,15,16]. However, as with cutaneous melanoma [17], multiple markers will likely be needed to increase the sensitivity of tumor cell detection, i.e. micrometastasis, in UM.

The Molecular Pathogenesis of Uveal Melanoma

Uveal melanoma harbors early activating mutations in GNAQ or GNA11 found in 80 percent of primary uveal melanomas [18]. Mutations in BRCA1-associated protein-1 (BAP1) and splicing factor 3B subunit 1 (SF3B1) occur later in tumor progression and are mutually exclusive [19]. Ciliary body tumor location has also been associated with monosomy 3 and gains in chromosome 8, both molecular markers of poor prognosis [20].

Uveal Melanomas Classification

Type 1 Low Risk of Metastasis or Type 2 High Risk of Metastasis are based on gene expression profile. Genes that discriminate class 1 (low-risk) from class 2 (high-risk) include highly significant clusters of down-regulated genes on chromosome 3 and up-regulated genes on chromosome 8q [21]. Tumors have begun to be classified as having low (class 1) or high (class 2) metastatic potential, depending on the expression of 15 genes [22].

Why Target Tissue Factor in Uveal Melanoma

Tissue Factor is a 46kd 263 amino acid single chain transmembrane glycoprotein. Tissue Factor plays a key role in health and disease. In normal homeostasis it is involved in the initiation of coagulation via its external domain and mediation of pro-inflammatory pathways via extra and intracellular signaling. In tumor biology it has been shown to trigger angiogenesis, tumor growth and metastasis, and promote an inflammatory immune environment (via extra- and intracellular signaling). [SEP]

Two studies support the role of TF in UM. Direct evidence comes from Walker *et al* who showed TF was expressed at elevated levels in cell lines of uveal melanoma compared with normal uveal melanocytes by several techniques including Western blotting, RNAase protection and Reverse Transcription PCR [23]. In another study, Van Raamsdonk *et al* found that 83% of the 713 uveal melanomas they analyzed had somatic mutations in GNAQ or GNA11, both of which are genes coding for the alpha subunit of G proteins. They concluded that GNAQ and GNA11 are activated in a MET-PI3K-dependent manner, and are significant contributors to the development of UM [18]. Activation of the MET-P13K pathway has been shown to increase TF expression in cancer (Figure 1) [24].

Figure 1: Signaling Pathways Involved in TF Expression

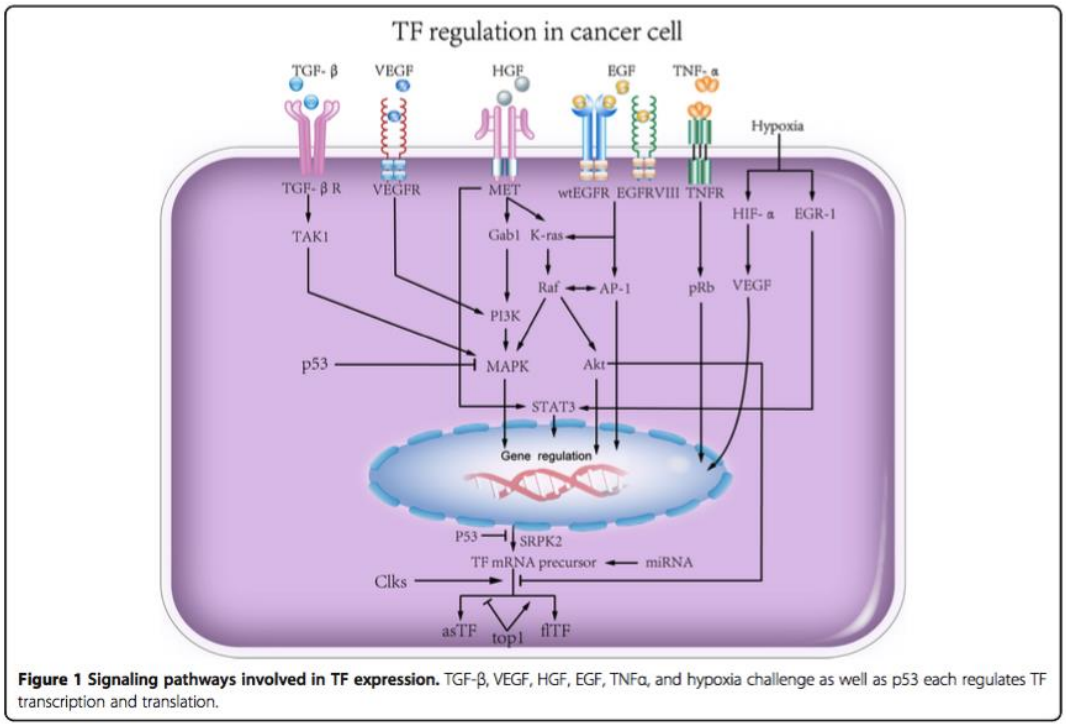


Figure 1 Signaling pathways involved in TF expression. TGF-β, VEGF, HGF, EGF, TNFα, and hypoxia challenge as well as p53 each regulates TF transcription and translation.

(Figure 1 from Han et al. Journal of Hematology & Oncology 2014,7:54)

Molecular Basis for Tissue Factor Signaling in Tumorigenesis and Metastasis

1) *TF regulates tumor cell proliferation and apoptosis.* The TF/Vll complex initiates many of its activities by activation of Protease Activated Receptors (PAR2) (Figure 2). The TF/Vll/PAR2 complex can lead to activation of enzymatic pathways (PKC, MAPK, P13K) regulating cell proliferation as well as inhibition of apoptosis by prevention of activation of caspase 3 [25].

2) *TF promotes tumor angiogenesis and metastasis*. Blood vessels in tumor tissues are essential for tumor progression and neovasculature is a prerequisite for blood-borne metastasis. TF/FVIIa/PAR2 induces the production of proangiogenic factors (VEGF) and migration promoting factors such as fibroblast growth factor 2 (FGF2), cysteine-rich 61 (Cyr61), CXCL1 and IL-8 [26]. TF exhibits its pro-metastatic characteristics in part by initiating the pro-coagulant cascade in the tumor microenvironment, including thrombin formation, fibrin generation and platelet activation. This fibrin-platelet "clot" formation is essential for generating a shield around tumor cells to facilitate the spread of tumor cells and the escape of newly formed micrometastasis from natural killer (NK) cell-mediated cytolysis [27].

Figure 2: Function of TF in Cancer Progression

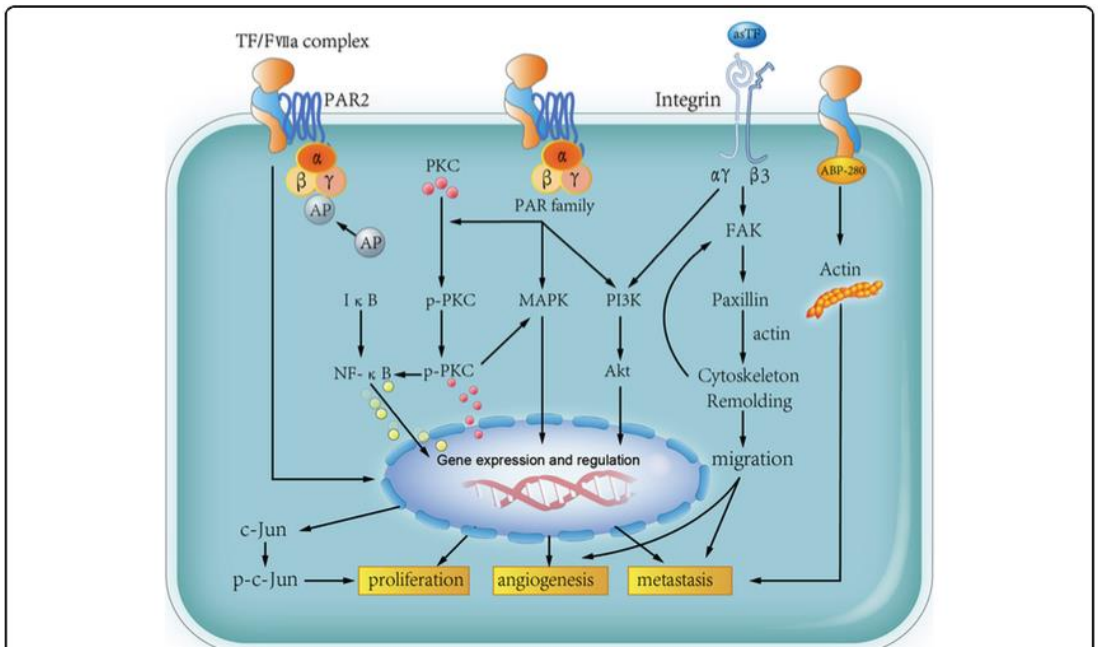


Figure 2. Function of TF in cancer progression. TF forms TF/FVIIa complex and subsequently induce PAR signaling using GPR alpha, beta, gamma (G protein coupled receptors). PKC is phosphorylated by activated PAR complex, which leads to p-PKC translocation. PAR can also induce MAPK and PI3K activation, both of which trigger pro-tumor effects, such as proliferation, angiogenesis and metastasis. Binding to activator protein (AP) can also induce c-Jun up regulation and in turn promote tumor progression. Moreover, TF binding to ABP-280 leads to actin modulation, resulting in tumor cells metastasis. As TF binds to integrin receptor and enhances the ability of migration, in turn leading to tumor cell angiogenesis and migration (From Han et al. Journal of Hematology & Oncology 2014, 7:54).

Immuno-oncology: TF can modulate immune responses within the tumor microenvironment. Once thrombin is generated, it can directly cleave complement component C5 to produce C5a and C5b. C5a has a pro-tumor effect via recruiting myeloid derived suppressor cells to the tumor microenvironment, resulting in an immunosuppressive milieu [28].

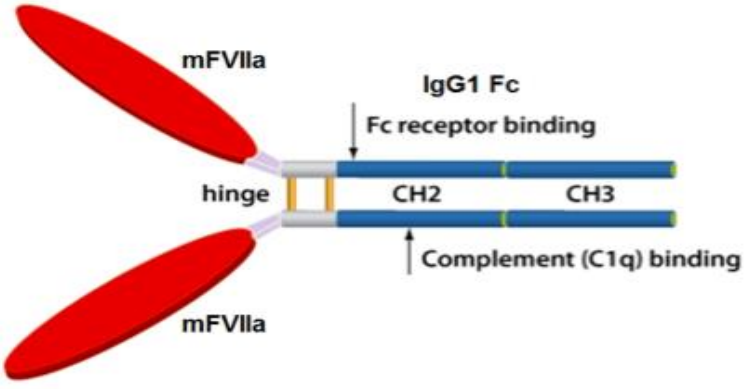
Increased TF expression by cancer cells and supporting stroma leads to the secretion of a variety of chemokines, cytokines and to the accumulation of Type 2 macrophages (TAMs) within the tumor. Tumor-associated macrophages (TAMs) actively promote tumor growth by supporting the recruitment and development of myeloid derived suppressor cells (MDSCs). Tumor associated macrophages (Type 2 macrophages) produce high levels of IL-10, TGF-beta and low levels of IL-12. Type 1 macrophages produce low levels of IL-10 and high levels of IL-12. Myeloid derived suppressor cells (MDSCs) are characterized by the ability to suppress cytotoxic functions of T cells and NK cells - a key mechanism of tumor defense. MDSCs originate from myeloid progenitor cells and are immature cells that do not differentiate into granulocytes, macrophages, or dendritic cells (DCs).

In general, human MDSCs are defined as CD11b-positive, CD33-positive, HLA-DR-negative or low, and lineage markers (Lin) (CD3, CD14, CD19, CD56) negative. Multiple tumor-derived factors secreted from the tumor and tumor stroma (tumor associated macrophages, fibroblasts and vascular endothelium) drive MDSC recruitment and differentiation. These tumor- derived factors include granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-SCF), macrophage colony-stimulating factor (M-CSF), IL-1β, IL-6, VEGF, IL-13, IL-10, prostaglandin E2. Among these factors, GM-CSF and IL-6 may be most powerful in inducing MDSCs from bone marrow progenitors. GM-CSF is required for recruitment of MDSCs to the tumor microenvironment. Tumor-derived CXCR2 ligands (IL-8, CXCL1, CXCL2, CXCL5) also attract MDSCs to the tumor microenvironment [29].

ICON-1

Iconic Therapeutics, Inc. has developed a therapeutic immunoprotein known as ICON-1 to target and bind TF. [redacted]

Figure 3: Molecular Structure of ICON-1



[redacted]

[redacted]

8.2 Nonclinical Studies

Several *in vitro* and *in vivo* studies support the characterization of the nonclinical pharmacodynamics, safety pharmacology, pharmacokinetics, and toxicology of ICON-1 in models of TF overexpression.

A summary of the toxicology and immunogenicity studies conducted with ICON-1 via intravenous, intravitreal and subcutaneous administration are listed in **Table 1**. The intravitreal administration animal studies tested both single and repeated doses of ICON-1.

Table 1: Toxicology and Immunogenicity Studies of ICON-1

Study Type	Animal Model	Number of Animals	Route	Dose	Duration
GLP; Tissue Cross Reactivity	human	≥3	*in vitro*	5, 30 µg/mL	NA
Exploratory	mini-pig	3	IV	3-24 µg/kg	12 days
Exploratory	mini-pig	3	IVT	510 µg	12 days
GLP; Single dose, PK	mini-pig	24	IV	6, 20, 60 µg/kg	8 days
GLP; Single dose	rabbit	9	IVT	150 µg	8 days
GLP; Repeat dose	mini-pig	24	IVT	60, 200, 600 µg	94 days
Potential immunogenicity	monkey and dog	6	SC	600 µg	43 days

Pharmacokinetic evaluations were conducted in the mini-pig from which a half-life and no-observed-adverse-effect-level (NOAEL) were determined. [redacted]

[redacted]

Single intravitreal (IVT) administration of ICON-1 in the rabbit eye induced a mild ocular inflammatory response. Repeated dosing in the mini-pig induced a robust immune response and resulted in ocular inflammatory reactions, most evident after the second dose. The subcutaneous administration of ICON-1 in dogs and monkeys resulted in a robust immune response in anti-drug antibodies in all animals, as early as 15 days after the drug administration.

These nonclinical results indicated that a single IVT dose of up to 600 µg of ICON-1 was tolerable and safe in mini-pigs. The mutated FVIIa present in the ICON-1 molecule has minimal thrombin generation activity. The ocular reactions observed with the repeated IVT dose in mini-pigs as well as the anti-drug antibody (ADA) response after subcutaneous administration in dogs and monkeys, suggested a species-specific immune response most likely due to the heterologous nature of the human protein in the three different species.

These results were the basis of and supported the initiation of a single IVT ascending dose study of ICON-1 in humans, patients with CNV associated with wet AMD.

Anti-cancer Activity of ICON-1

TF is overexpressed in the pathological neovasculature of solid cancerous tumors and plays a role in tumor growth, tumor angiogenesis, metastasis, and thrombosis. Previous attempts to target TF have resulted in disruption of the clotting cascade, resulting in unacceptable safety profiles. ICON-1 has demonstrated activity against tumors by binding to TF, as well as preliminary safety data showing it does not disrupt normal clotting.

Table 2 lists *in vitro* and *in vivo* nonclinical studies demonstrating the anti-cancer activity of ICON-1. The *in vivo* studies showed that ICON-1 was safe and effective when administered systemically.

The *in vitro* studies suggest that part of the mechanism of action of ICON-1 is due to cell-dependent cytotoxicity. Cocco et al [30] examined the response of chemotherapy-resistant primary uterine serous papillary adenocarcinoma (USPC) cell lines to ICON-1 treatment in chromium release assays. Using rituximab as a control, USPCs overexpressing TF were shown to be highly sensitive to ICON-1 as measured by cell-mediating killing (65.6% ± 3.7%; range 57.5 - 77.0%, P< 0.001). In contrast, virtually no cytotoxicity against USPCs was observed in controls (controls = untreated, no ICON-1; rituximab treatment).

When the molecule was tested in animal models of carcinoma, murine ICON-1 (delivered by an adenoviral vector) was shown to be effective in SCID-Hu and full murine models against

cutaneous melanoma, uterine, prostate and tongue carcinoma [31,32,33,34]. Adenoviral vector production of murine ICON-1 cause tumor regression in xenografts models.

Table 2: Summary of Preclinical Data Showing Anti-cancer Activity of ICON-1

Year	Author	Type of cancer
1999	Hu et al [31]	Tumor vasculature endothelial cells
1999	Wang et al [35]	Human melanoma cells
2000	Hu and Garen [32]	Human and mouse melanoma cells
2001	Hu and Garen [33]	Tumor vasculature endothelial cells and mouse prostate cancer cells
2010	Hu and Li [34]	Human tongue cancer cells
2010	Cocco et al [30]	Uterine serous papillary carcinoma
2010	Cocco et al [36]	Adenocarcinoma and squamous cell carcinoma of cervix

8.3 Clinical Experience with ICON-1

In clinical studies conducted by Iconic Therapeutics, more than one hundred (100) patients have been administered ICON-1 as single doses, or repeated doses either as monotherapy or in combination with other therapies. A first-in-human Phase 1 study (IT-001) initiated in October 2010 and completed in July 2012, evaluated administration of single doses of ICON-1 in 18 patients with choroidal neovascularization (CNV) due to age-related macular degeneration (wet AMD). The study population included both treatment-naïve patients and patients previously treated with chronic anti-VEGF therapy. In an ongoing Phase 2, randomized, double-masked, active-controlled study (IT-002) in patients with CNV secondary to AMD, 88 patients have been enrolled.

The Phase 1 study (IT-001) was an open-label, single intravitreal dose, dose-escalating design. There were no control groups in this study. Six patients each were enrolled in one of three different cohorts of ICON-1; 60 µg, 150 µg, and 300 µg. The three cohorts were enrolled sequentially employing a traditional 3+3 design. The planned maximum administered dose in this study was 300 µg ICON-1. The maximum tolerated dose (MTD) of ICON-1 would be identified as the maximum dose at which no more than 1 of 6 patients had a confirmed significant safety event (or 300 µg, the highest dose contemplated in the protocol). At the investigator's discretion, treatment with bevacizumab (Avastin®) or ranibizumab (Lucentis®) therapy was allowed two weeks after injection of ICON-1 as rescue therapy. Patients could receive standard of care anti-VEGF therapy at any time thereafter. Patients were followed for safety and efficacy for 6 months following administration of ICON-1. The primary objectives of the study were to establish a preliminary safety profile of ascending doses of ICON-1 and to determine the MTD that can be administered by intravitreal injection as measured by the

occurrence of ocular and systemic adverse events. Ocular and systemic events were assessed by means of vital signs measurement, ophthalmic examinations, intraocular pressure measurement, and the presence of anti-ICON-1 antibodies.

The administration of single intravitreal doses of ICON-1 was demonstrated to be safe and well tolerated in all three doses tested. There were no systemic or ocular dose-limiting toxicities and a maximum tolerated dose was not determined up to the maximum administered dose of 300 μg ICON-1. Most frequently reported adverse events were ocular (conjunctival hemorrhage [n=5], vitreous floaters [n=3], conjunctival edema [n=3], and signs of macular degeneration [n=3]) and commonly related to the injection procedure or the retinal signs of the underlying AMD. Only one adverse event, a case of vitritis in the 300 μg cohort was considered by the Investigator to be related to study drug. No retinal or choroidal abnormalities were noted on clinical examination or angiographically. There were no systemic adverse events reported. No significant systemic levels of ICON-1 or antibodies to ICON-1 were detected. Single dose administration of ICON-1 in the Phase 1 study demonstrated preliminary evidence of biologic activity and pharmacodynamic effect relevant to wet AMD; clinical improvement in BCVA, associated with a reduction in CRT (on OCT) and a decrease of CNV area of leakage (on FA) in some patients.

The ongoing Phase 2 study (IT-002) is the first study to examine administration of repeated intravitreal doses of ICON-1. Eighty eight (88) patients ≥50 years of age with CVN secondary to AMD were enrolled in this study from approximately 49 centers located in the United States. The study was designed to test the safety of repeated intravitreal injections of 0.3 mg ICON-1 administered as monotherapy or in combination with ranibizumab (Lucentis®) compared to ranibizumab monotherapy, and to test proof of concept by evaluating biologic activity and clinical outcomes of the three treatment arms. Patients will receive up to six (6) monthly intravitreal administrations of study treatment and followed for safety and efficacy through one month following administration of the last intravitreal treatment. Safety is evaluated by means of the occurrence of ocular and systemic adverse events, and changes in clinical laboratory tests, vital signs and ophthalmic evaluations. In addition, the pharmacokinetic and immunogenetic evaluation of the presence of ICON-1 in the systemic circulation is being performed. Biologic and pharmacodynamic effect is assessed by means of changes in visual acuity, qualitative and quantitative anatomic changes to the retina and CNV as measured by sdOCT, FA, fundus autofluorescence imaging (FAF) and CFP.

Eighty six (86) patients received three or more doses of ICON-1 alone, in combination with Lucentis®, or Lucentis® alone. Thirteen SAEs in nine patients have been reported to date. There are currently no ocular or non-ocular safety events that led to study unmasking. No ocular or non-ocular safety signals have emerged to date and the study continues to be conducted as planned.

8.4 Study Rationale

Uveal melanoma is a life-threatening and devastating disease characterized by poor overall survival and limited therapeutic options resulting in either the loss of an eye or complications leading to significant vision loss. Data from preclinical studies, and current and ongoing clinical studies in wet AMD (described above) supports investigating ICON-1 as a potentially less

invasive therapeutic option delaying the need for enucleation as well as possibly prolonging the onset of metastases.

Patients scheduled for enucleation or brachytherapy as treatment of uveal melanoma provide an opportunity to examine the clinical safety of intravitreal administration of ICON-1 within a tumor environment. Examining the excised tissue after enucleation will allow confirmation of the extent of TF expression and whether intravitreally administered ICON-1 binds to TF expressed on uveal melanoma tumor cells and supporting stroma (target engagement). The short term biologic response of ICON-1 binding will be examined with a comprehensive panel of in-vitro and in-vivo outcome measures. This study may shed light on the ability of ICON-1 to produce cytotoxic damage to the tumor or inhibit tumor growth as shown in earlier pre-clinical models of tumor xenografts.

The dose-escalating design and sample size for this study are based on the standard accepted clinical toxicity evaluation and are intended to establish a preliminary safety profile of ICON-1 administered for the first time in patients with uveal melanoma and to provide preliminary evidence of biologic activity in support of additional studies.

9 STUDY OBJECTIVES

9.1 Primary Objective

The primary objective of this study is:

- To evaluate the safety and tolerability of single and repeated escalating intravitreal injections of ICON-1 administered in patients with uveal melanoma who are planned to undergo enucleation or brachytherapy.

9.2 Secondary Objectives

The secondary objectives of this study are:

- To assess the pharmacokinetics and pharmacodynamic effect of ICON-1 in patients with uveal melanoma.
- To describe preliminary evidence of the biological activity of ICON-1 as determined by changes in visual acuity, and tumor size.

9.3 Exploratory Objective

- To explore the prognostic indicator of the genetic profile of the tumor in relation to Tissue Factor expression and response to ICON-1 therapy.
- To describe preliminary evidence of the biological activity of ICON-1 as determined by changes in tumor pathology, and proteomic analysis of vitreous humor.

10 INVESTIGATIONAL PLAN

10.1 Overall Study Design and Plan

This is a phase 1, open-label, sequential-group, multicenter study to evaluate the safety and tolerability, biological activity, pharmacokinetics, and pharmacodynamic activity of single and repeated escalating intravitreal injections of ICON-1 in patients with primary uveal melanoma who are planned to undergo enucleation or brachytherapy.

Patients diagnosed with primary uveal melanoma involving the posterior uveal tract for which the selected treatment management plan is enucleation or brachytherapy may be screened for this study. Eligible patients will be assigned to one of three cohorts that will be enrolled consecutively:

Cohort 1 (enucleation or brachytherapy): Single dose of 0.3 mg (300 µg/100 µl) ICON-1, (n=2)

Cohort 2 (enucleation or brachytherapy): Two doses of 0.3 mg (300 µg/100 µl) ICON-1 each administered one week apart, (n=3)

Cohort 3 (enucleation or brachytherapy): Two doses of 0.6 mg (300 µg/100 µl + 300 µg/ 100 µl) ICON-1 each administered one week apart, (n=5)

Each dose level will be evaluated for clinical safety before escalating to the next cohort. Clinical and safety data will be reviewed by the IT-003 Safety Review Committee (SRC) comprised of at least one participating Clinical Investigator and the Iconic Therapeutics internal Safety Management Committee. The following ocular adverse events (even if non-serious) are considered Adverse Events of Special Interest (AESIs), and will be reported by the investigator to the sponsor and SRC as appropriate:

- Ocular inflammatory event of CTCAE Grade ≥ 3
- Vitreous or retinal hemorrhage event interfering with visualization of the tumor or retina of CTCAE Grade ≥ 2
- Any acute onset treatment-emergent vision-threatening condition as assessed by the investigator

Patient data will be evaluated by the SRC for the occurrence of ocular Dose Limiting Toxicity (DLT) events. An ocular DLT is defined as an ocular inflammatory adverse event of 3+ or more severity or a grade 2 or higher unexpected vitreous or retinal hemorrhage interfering with the visualization of the tumor or retina.

If an AESI occurs while the patient is at the study center and requires clinical management, the patient will remain at the study center according to the Investigator's judgment. The patient will be managed according to the routine treatment practices of the study center. The patient will complete all subsequent study visits.

All AESIs, serious adverse events, patient discontinuations and pregnancy reports must be reported to Iconic Therapeutics within 24 hours of the investigator learning of the event.

ICON-1 will be administered on Day 0 for all cohorts, and in addition on Day 7 for cohorts 2 and 3 only. Patients will return to the study center on Day 1 for a safety follow-up visit (all cohorts) and 1 day post Day 7 (cohorts 2 and 3 only). All patients will return to the clinic for safety, clinical, and imaging assessments prior to the scheduled surgical procedure. Patients will have their planned surgical procedure (enucleation or brachytherapy plaque placement) as early as 4 days after the last ICON-1 treatment, and return to the study center 30 days post-procedure for follow-up safety assessments (and ocular assessments for brachytherapy patients) and end of study visit.

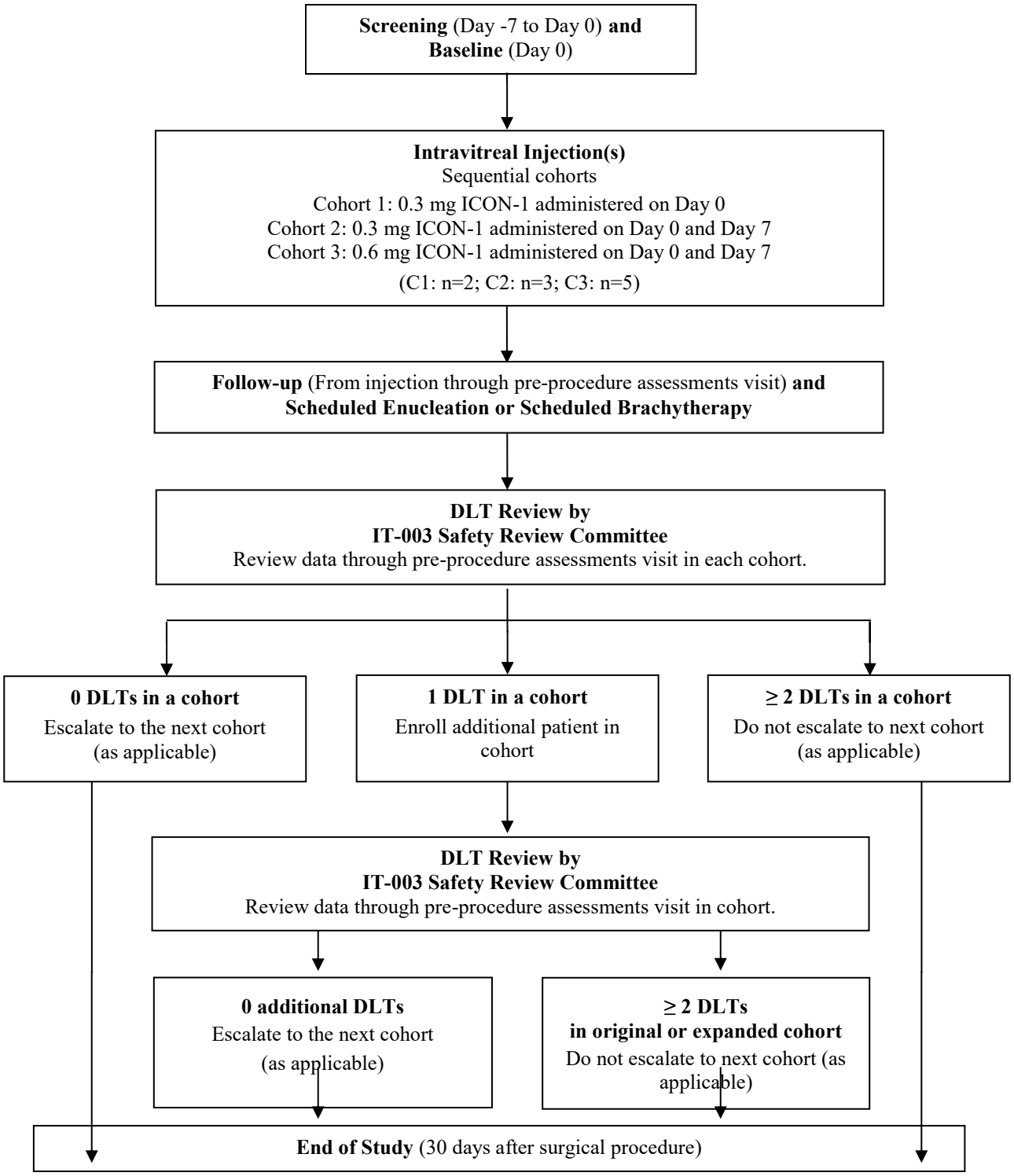
Safety will be evaluated by means of occurrence of adverse events, clinical laboratory tests (serum chemistry, hematology, coagulation, and plasma anti-drug antibody levels (ADA)), vital signs measurements, abbreviated physical examinations, slit-lamp biomicroscopy, intraocular pressure (IOP), and dilated ophthalmoscopy. Pharmacodynamic and biological activity will be measured by means of BCVA by ETDRS, spectral-domain optical coherence tomography (sdOCT), color fundus photography (CFP), fluorescein angiography (FA), ophthalmic ultrasound, and optionally (according to investigator judgment) ICG angiography, and enhanced-depth imaging optical coherence tomography (EDI-OCT). Pharmacokinetic (PK) and Pharmacodynamic (PD) markers will be evaluated by means of measuring plasma concentrations of ICON-1, serum cytokine levels, circulating tissue factor (TF), immunophenotyping and circulating tumor DNA (CTDNA).

For enucleation patients: immediately following the enucleation procedure, vitreous humor will be aspirated for intraocular ICON-1 and proteomic analysis of TF and cytokine levels. Following the clinical site's standard of care pathology of the tumor, prepared slides and/or tumor block samples will be sent to a central laboratory for additional study-related pathology evaluation of the tumor (including ICON-1 binding, TF and PAR2 expression, immune infiltrate and alterations of the vasculature), genetic profiling, and Exome sequencing of the tumor. Genetic profiling of the tumor previously performed with fine needle aspiration of the tumor does not require repeated testing.

For brachytherapy patients: the plaque placement procedure and associated follow-up will be according to the standard of care at each site.

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 patient discontinues from the study prematurely.

Figure 4: Study Design Schema



10.2 Study Sites

Approximately 7-10 centers located in the US will participate in this study.

10.3 Discussion of Study Design

In this Phase 1 study ICON-1 will be intravitreally administered for the first time in patients with uveal melanoma. The starting dose of ICON-1 (300 µg/100 µl) is the maximum dose administered in the Phase 1 single IVT administration study, and the ongoing Phase 2 repeated IVT administration study in patients with CNV secondary to AMD. As this dose has been administered to approximately sixty (60) patients and found to be well tolerated to date, a cohort of two patients which may be expanded to three patients is thought to be sufficient to make a determination to escalate to the subsequent higher dose level of two doses of 0.3 mg (300 µg/100 µl) ICON-1 administered one week apart. The cohort size is increased (cohort 2; n=3, cohort 3; n=5), as the dose and volume is escalated in subsequent cohorts. Each of these cohorts may be expanded by one patient in the event of a DLT. A toxicity rate of one third or less in a cohort is within the accepted clinically observed toxicity standards to establish a preliminary safety profile of ICON-1 administered in patients with uveal melanoma and to support additional studies. In this study, the maximum administered dose will not exceed 0.6 mg (300 µg/100 µl + 300 µg/100 µl) ICON-1.

Pharmacodynamic and biologic activity markers are utilized to explore preliminary evidence of activity with respect to target engagement (ICON-1 binding to TF in the tumor) as measured by tissue staining of the tumor and supporting stroma within the enucleated eye, assessment of immune infiltrate in the tumor, measurement of TF and PAR2 dependent cytokines/chemokines in blood, TF and cytokine levels in vitreous humor, and changes in tumor size and volume as well as changes in BCVA by ETDRS. Ophthalmic ultrasound is utilized to assess and measure changes in the size of the ocular tumor. Ophthalmic imaging including sdOCT, EDI-OCT, FA, ICGA, and CFP are utilized for measuring and evaluating changes in vasculature, in the anatomic layers of the retina, choroid, and ocular tumor and the associated pathology of the lesions (such as exudation).

The study duration, including a one to two week dosing period prior to a scheduled enucleation or plaque placement procedure is considered an adequate period to assess safety, PK and preliminary pharmacodynamic and biologic activity without delaying or interfering with standard of care treatment for uveal melanoma.

10.4 Appropriateness of Measurements

The primary aim for data analyses in this study is to assess the safety and tolerability of escalating doses of ICON-1 administered in patients with uveal melanoma. The choice of safety and biological activity parameters to be evaluated in this study reflect experience in preclinical studies, the Phase 1 study in patients with wet AMD, and the ongoing phase 2 study in patients with wet AMD. The PK and immunogenicity assessments in this study are used widely and are generally recognized as reliable, accurate, and relevant. Validated clinical bioanalytical assays will be used for this purpose.

Preliminary evidence of pharmacodynamic and biologic activity will be explored by measuring changes in BCVA via ETDRS, and tumor thickness, volume and vascularization via sdOCT and EDI-OCT, ophthalmic ultrasound, CFP, FA, and ICG angiography. Ophthalmic imaging modalities are routine assessments and are appropriate for documenting clinical findings of the retina, choroid, the ocular tumor and their vascularization at baseline and changes across the duration of the study for comparison.

11 STUDY POPULATION

11.1 Target Population

The target population for this study is men and women age 18 years and older with a diagnosis of primary uveal melanoma involving the choroidal and/or ciliary body who are scheduled to undergo a standard of care enucleation procedure or brachytherapy.

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, ≥18 years of age.
3. Clinical diagnosis of primary uveal melanoma involving the posterior uveal tract (choroid and/or ciliary body) in the study eye. Patients with metastatic disease are eligible.
4. Planned enucleation or brachytherapy for primary uveal melanoma in the study eye.
5. 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 if they have a 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. Uveal melanoma in the study eye originating in the anterior uveal tract (iris).
2. Chronic uncontrolled glaucoma or ocular hypertension in the study eye defined as an IOP >25mmHg regardless of concomitant treatment with IOP-lowering medications.
3. Previous participation in an investigational study of ICON-1.
4. Known serious allergy to fluorescein sodium indocyanine green for injection in angiography.

5. Use of two or more concomitant anticoagulant treatments (direct thrombin inhibitor class of drugs such as Coumadin (warfarin), Pradaxa (dabigatran), and Xarelto (rivaroxaban)). Aspirin is not considered an anticoagulant in this study. For patients receiving one chronic anticoagulant treatment (e.g., patients with a history of cardiovascular/cerebrovascular diseases [events] or hospitalization due to such conditions), the patient must have 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., Eliquis (apixaban)).
6. Hereditary or chronic hemorrhagic or coagulopathy conditions (i.e., hemophilia).
7. 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.
8. History or presence of other concurrent conditions deemed by the Investigator to be likely to impact the subject's clinical safety 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 or other inflammatory intraocular conditions in the study eye.
9. 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.
10. Woman who is pregnant or lactating.

11.4 Study Eye Determination

The study eye is defined as the eye that meets all of the inclusion criteria and none of the exclusion criteria.

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 the aberrantly expressed Tissue Factor (TF). It is a dimeric antibody-like protein; each monomer has two functional domains joined by a linker. The molecular weight is 157 kDa. 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 Test Article Administration

Patients will be enrolled in one of three cohorts:

- 0.3 mg (300 µg/100 µl) ICON-1 administered on Day 0
- 0.3 mg (300 µg/100 µl) ICON-1 administered on Day 0 and Day 7
- 0.6 mg (300 µg/100 µl + 300 µg/100 µl) ICON-1 administered on Day 0 and Day 7

Using aseptic technique, ICON-1 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.

IOP will be measured before and after each intravitreal injection.

For Cohort 3, the second intravitreal injection will be administered the same day 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 first 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 $CaCl_2$.

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 for up to 60 days. ICON-1 vials should be thawed by 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.

12.3 Selection of Doses and Timing of Doses

The starting dose of ICON-1 was selected based on the results of preclinical efficacy and toxicology studies, a phase 1 study of single IVT administration and an ongoing phase 2 study of repeated IVT administration in patients with CNV secondary to AMD. The highest dose tested was 0.3 mg ICON-1 administered by intravitreal injection, and repeated doses up to 6 monthly doses per patient were found to be well tolerated in all patients to date. A maximum tolerated dose was not determined in the phase 1 study. In the phase 2 clinical study 300 µg/100 µl ICON-1 is being administered intravitreally followed by 0.5 mg/50 µl ranibizumab after 30 minutes, a total injection volume of 150 µl. A total injection volume of 200 µl for cohort 3 is supported by a preclinical study in mini-pigs where three cycles of 600 µg ICON-1 were administered as two doses of 300 µg/100 µl each, two days apart (see Section 8.1 for information regarding the preclinical, Phase 1 and Phase 2 studies).

12.4 Criteria for Dose-Escalation and Stopping Rules

Eligible patients will be assigned to one of three cohorts that will be enrolled consecutively:

Cohort 1(enucleation or brachytherapy): Single dose of 0.3 mg (300 µg/100 µl) ICON-1, (n=2)

Cohort 2 (enucleation or brachytherapy): Two doses of 0.3 mg (300 µg/100 µl) ICON-1 each administered one week apart, (n=3)

Cohort 3 (enucleation or brachytherapy): Two doses of 0.6 mg (300 µg/100 µl + 300 µg/ 100 µl) ICON-1 each administered one week apart, (n=5)

Each dose level will be evaluated for clinical safety before escalating to the next cohort. Clinical and safety data will be reviewed by the IT-003 Safety Review Committee comprised of at least one participating Clinical Investigator and the Iconic Therapeutics internal Safety Management Committee. Patients will be evaluated for the occurrence of ocular Dose Limiting Toxicity (DLT) events. An ocular DLT is defined as an ocular inflammatory adverse event of 3+ or more severity or a grade 2 or higher unexpected vitreous or retinal hemorrhage interfering with the visualization of the tumor or retina.

All patients at a given dose level must complete their pre-procedure safety assessment after receiving their last dose of ICON-1, to enable evaluation of the safety of that dose level. For cohorts 1 and 2, if no patients experience a DLT, escalation to the next dose level will take place. If no patients experience a DLT in cohort 3, then cohort 3 will be considered the maximum administered dose (MAD).

If one patient experiences a DLT in any cohort, an additional patient will be enrolled and evaluated at that dose level.

For cohorts 1 and 2, if two or more patients experience a DLT in the original cohort or the expanded cohort, then enrollment in that cohort will be suspended, any subsequent cohorts will not be enrolled. For cohort 3, if two or more patients experience a DLT in the original cohort or the expanded cohort, then enrollment in the cohort will be suspended and the IT-003 Safety Review Committee will examine the safety data to determine if changes are warranted.

A maximum of three patients may be enrolled in cohort 1, a maximum of four patients may be enrolled in cohort 2, and a maximum of six patients may be enrolled in cohort 3.

12.5 Measurement of Study Drug Compliance

All study treatment will be administered by the Investigator 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 study 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 the 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.

Use of two or more concomitant anticoagulant treatments (direct thrombin inhibitor class of drugs such as Coumadin (warfarin), Pradaxa (dabigatran), and Xarelto (rivaroxaban)) is prohibited. Aspirin is not considered an anticoagulant treatment in this study. Concomitant treatment with one chronic anticoagulant (e.g., patients with a history of cardiovascular/cerebrovascular diseases [events] or hospitalization due to such conditions) is not prohibited.

Use of treatment for concomitant metastatic disease is allowed during the study.

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.

The Medical Monitor should be notified before prohibited medication or therapy is administered unless the safety of the patient requires immediate action. 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 study treatment intravitreal injections will include 1-cc tuberculin syringes, 5-micron 19-gauge x 1-1/2 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 TREATMENT ASSIGNMENT

13.1 Subject Identification Numbers

Patients will be enrolled in one of three cohorts following confirmation from the study Medical Monitor. Each patient will be assigned a unique Screening Number after informed consent is obtained. The Screening Number will be used as the Subject Number throughout the study.

13.2 Enrollment and Method of Assigning Patients to Treatment Arms

This is an open-label, sequential-group, multicenter study. The Investigator will evaluate the inclusion and exclusion criteria to determine patient eligibility for entry into the study. When a potential patient is identified, the investigator must contact the Medical Monitor at Iconic Therapeutics to confirm availability in the cohort.

The Sponsor, Investigator, research staff and participants will know the treatment that is being administered as well as the cohort assignment. Cohort 1 (single dose of 0.3 mg ICON-1) will be enrolled first, followed by cohort 2 (two doses of 0.3 mg ICON-1 administered one week apart), and then cohort 3 (two doses of 0.6 mg ICON-1 administered one week apart). Clinical and safety data will be reviewed by the IT-003 Safety Review Committee after all patients in a cohort have completed their pre-procedure safety assessment visit before enrolling patients into subsequent cohorts.

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. An ICF must be signed and dated by the patient or the patient'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 Screening Number should be assigned to the patient after informed consent is obtained.

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

14.1 Visit 1 (All cohorts): Screening (Day -7 through 0)

Screening must take place within 7 days prior to the intravitreal injection on Day 0 (Baseline Visit). Patients will undergo Screening assessments to determine if they are eligible to enroll in the study. If there is study drug available at the clinical site, Screening assessments to confirm eligibility may be performed on Day 0, prior to any intravitreal injection and any additional baseline specific assessments.

The following procedures will be performed at Screening:

- Obtain written informed consent
- Obtain demographic data
- Obtain medical and ocular history including surgical and medication history. Prior and concomitant medications taken within the last 30 days will be recorded.
- Vital signs
- Blood samples for clinical laboratory tests (serum chemistry, hematology and coagulation), prior to injection of Fluorescein and ICG dye (as applicable)
- Blood sample for anti-drug antibody levels, prior to injection of Fluorescein and ICG dye (as applicable)
- Blood sample for serum pregnancy test (women of child bearing potential only), prior to injection of Fluorescein and ICG dye (as applicable)
- Abbreviated physical examination including height and weight
- 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 (both eyes)
- sdOCT (study eye only)
- EDI-OCT optional according to investigator judgment (study eye only)
- Ophthalmic ultrasound (study eye only)
- Fluorescein angiography (both eyes)
- ICG angiography optional according to investigator judgment (both eyes)

14.2 Visit 2 (All cohorts): Baseline (Treatment Day 0)

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

- Vital signs
- Perform the following ophthalmic procedures:
  - Best-corrected visual acuity by ETDRS (both eyes)
  - Slit lamp biomicroscopy (both eyes)
  - IOP; cohorts 1 and 2: pre-injection (both eyes) and post injection (study eye only), cohort 3: pre-injection (both eyes) and post each injection (study eye only)
  - Dilated ophthalmoscopy (study eye only)
- Blood sample (pre-injection and 4 hours ±1 hour after dose administration. For cohort 3, after the second injection) for pharmacodynamic assessment
- Blood samples (pre-injection and 4 hours ±1 hour after dose administration. For cohort 3, after the second injection) for pharmacokinetic assessment
- Administration of intravitreal injection(s)
- Assessment of adverse events
- Record concomitant medications

- Instruct patients to contact site study personnel immediately if their treated eye becomes red, sensitive to light, painful, or develops a change in vision.

14.3 Visit 3 (All cohorts): Day 1

The following procedures will be performed at Day 1:

- Vital signs
- Perform the following ophthalmic procedures:
    - Best-corrected visual acuity by ETDRS (study eye only)
    - Slit lamp biomicroscopy (study eye only)
    - IOP (study eye only)
- Blood sample for pharmacodynamic assessment
- Blood sample for pharmacokinetic assessment
- Assessment of adverse events
- Record concomitant medication

14.4 Visit 4 (Cohorts 2 and 3 only): Treatment Day 7 (±2 days)

The following procedures will be performed at Day 7:

- Vital signs
- Perform the following ophthalmic procedures, prior to dose administration:
    - Best-corrected visual acuity by ETDRS (both eyes)
    - Slit lamp biomicroscopy (both eyes)
    - IOP; cohort 2: pre-injection (both eyes) and post injection (study eye only), cohort 3: pre-injection (both eyes) and post each injection (study eye only)
    - Dilated ophthalmoscopy (study eye only)
    - sdOCT (study eye only)
    - EDI-OCT optional according to investigator judgment (study eye only)
    - Ophthalmic ultrasound (study eye only)

- Blood samples for clinical laboratory tests (serum chemistry, hematology and coagulation)
- Blood samples (pre-injection and 4 hours ±1 hour after dose administration. For cohort 3, after the second injection) for pharmacodynamic assessment
- Blood samples (pre-injection and 4 hours ±1 hour after dose administration. For cohort 3, after the second injection) for pharmacokinetic assessment
- Administration of intravitreal injection(s)
- Assessment of adverse events
- Record concomitant medication
- Instruct patients to contact site study personnel immediately if their treated eye becomes red, sensitive to light, painful, or develops a change in vision.

14.5 Visit 5 (Cohorts 2 and 3 only): 1 day post Day 7 treatment

The following procedures will be performed on the day after Day 7 treatment:

- Vital signs
- Perform the following ophthalmic procedures:
    - Best-corrected visual acuity by ETDRS (study eye)
    - Slit lamp biomicroscopy (study eye)
    - IOP (study eye)
- Blood sample for pharmacodynamic assessment
- Blood sample for pharmacokinetic assessment
- Assessment of adverse events
- Record concomitant medication

14.6 Visit 6 (All Cohorts): Procedure Assessments (On or 1 day prior to Surgical Procedure day)

The following procedures will be performed on or 1 day prior to the Surgical Procedure day:

- Vital signs

- Perform the following ophthalmic procedures, (prior to Surgical Procedure):
    - Best-corrected visual acuity by ETDRS (both eyes)
    - Slit lamp biomicroscopy (both eyes)
    - IOP (both eyes)
    - Dilated ophthalmoscopy (both eyes)
    - Color fundus photography (both eyes)
    - sdOCT (study eye only)
    - EDI-OCT optional according to investigator judgment (study eye only)
    - Ophthalmic ultrasound (study eye only)
    - Fluorescein angiography (both eyes)
    - ICG angiography optional according to investigator judgment (both eyes)
- Blood samples for clinical laboratory tests (serum chemistry, hematology, and coagulation)
- Blood sample for pharmacodynamic assessment
- Assessment of adverse events
- Record concomitant medication

Surgical Procedure will be performed ≥4 days after the last injection:

The surgical procedure (enucleation or plaque placement) is scheduled independent of this study according to standard of care clinical management of uveal melanoma per patient's treating physician and is not a study procedure.

For Patients Undergoing Enucleation Only: After enucleation, the following samples will be obtained:

- Vitreous humor aspirate for ICON-1 and proteomic analysis
- A subset of pathology mounted slides and/or tumor block samples from the globe and tumor will be provided by the local pathology laboratory to the central laboratory for genetic tumor profiling and Exome sequencing

14.7 Visit 7 (All Cohorts): End of Study: 30 days ±5 days post Surgical Procedure

The following procedures will be performed 30 ±5 days after the Surgical Procedure:

- Vital signs
- Perform the following ophthalmic procedures (brachytherapy patients only):
    - Best-corrected visual acuity by ETDRS (both eyes)
    - Slit lamp biomicroscopy (both eyes)
    - IOP (both eyes)
    - Dilated ophthalmoscopy (both eyes)
    - Color fundus photography (both eyes)
    - sdOCT (study eye only)
    - Ophthalmic ultrasound (study eye only)
- Abbreviated physical examination
- Blood samples for clinical laboratory tests (serum chemistry, hematology, and coagulation)
- Blood sample for anti-drug antibody levels
- Blood sample for serum pregnancy test (women of child bearing potential only)
- Assessment of adverse events
- Record concomitant medication

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 15.22.10

14.8 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:

- Vital signs
- Blood samples for clinical laboratory tests (serum chemistry, hematology, and coagulation), prior to injection of Fluorescein and ICG dye (as applicable)

- Blood sample for anti-drug antibody levels, prior to injection of Fluorescein and ICG dye (as applicable)
- Blood sample for serum pregnancy test (women of child bearing potential only), prior to injection of Fluorescein and ICG dye (as applicable)
- Blood sample for pharmacodynamic assessment (collect only if Day 1 or 1 day post Day 7 treatment PD samples were not collected following injection on Day 0 or Day 7), prior to injection of Fluorescein and ICG dye (as applicable)
- Blood sample for pharmacokinetic assessment (collect only if Day 1 or 1 day post Day 7 treatment PK samples were not collected following injection on Day 0 or Day 7), prior to injection of Fluorescein and ICG dye (as applicable)
- Abbreviated physical examination
- Perform the following ophthalmic procedures (note: ocular assessments are performed only if early termination occurs prior to Surgical Procedure):
    - Best-corrected visual acuity by ETDRS (both eyes)
    - Slit lamp biomicroscopy (both eyes)
    - IOP (both eyes)
    - Dilated ophthalmoscopy (both eyes)
    - Color fundus photography (both eyes)
    - sdOCT (study eye only)
    - EDI-OCT optional according to investigator judgment (study eye only)
    - Ophthalmic ultrasound (study eye only)
    - Fluorescein angiography (both eyes)
    - ICG angiography optional according to investigator judgment (both eyes)
- Assessment of adverse events
- Record concomitant medication

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 15.22.10.

14.9 Unscheduled Visits

Unscheduled visits may be necessary due to AEs or other reasons. The Investigator may examine a patient as often as is medically necessary while the patient is enrolled in the study. Any follow-up that is performed to monitor patient safety should be recorded as an Unscheduled Visit.

14.10 Patient Withdrawal from Treatment or Study

14.10.1 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 patient discontinues from the study prematurely. If a patient withdraws from the study, he or she may not reenter the study.

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

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

At the time of withdrawal, the Principal Investigator should advise the patient of the other available options. When a patient is withdrawn from the study for any reason, the reason(s) for withdrawal will be recorded in the eCRF. For any patient 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 patient fails to return for a scheduled visit, it is the responsibility of the Principal Investigator or designee to document all efforts to contact the patient and to determine the reason the patient did not return. If a patient cannot be contacted with 3 documented telephone call attempts,

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 patient 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 patient 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 patient 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.

14.10.2 Replacements

Patients who discontinue from the study prior to the pre-procedure safety evaluation following their last injection may be replaced.

14.10.3 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 with 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

The Investigator must contact the study Medical Monitor when a potential patient is identified for the study to ensure there is space in the cohort. Screening assessments will be used to determine eligibility before enrolling a patient in the study cohort.

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 patient. 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 patient's source record should include start and stop dates, dose, route, frequency, and indication.

15.6 Vital Signs

Vital signs should be taken when the patient is adequately rested (after the patient 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).

15.7 Abbreviated Physical Examination

Abbreviated physical examination should include at a minimum assessments of general appearance, cardiovascular, respiratory, neck/HEENT (head, eyes, ears, nose and throat), and dermatologic. Height and weight will be measured at Screening only. Additional assessments should be completed at the judgment of the Investigator.

15.8 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)-like retro-illuminated charts. BCVA will be recorded as the total letter score in each eye.

Visual acuity testing will be performed by qualified 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 patient throughout the study.

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

15.9 Slit-lamp Biomicroscopy

Slit-lamp biomicroscopy will be performed for each eye by qualified site personnel. Slit-lamp biomicroscopy, including magnification, will be performed without dilation of the pupil and consistent with standard clinical practice. The patient 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.

15.10 Intraocular Pressure

At each study visit IOP will be measured according to routine clinical practice using contact tonometry (e.g. Goldmann Applanation, Tono-Pen). It is recommended that the same instrument be used throughout the duration of the study for each patient. At injection visits, IOP will be measured in both eyes before the injection by qualified site personnel, and in the study eye only after intravitreal injection (in Cohort 3, IOP will be measured in the study eye following each of the two injections). Measurements will be recorded in mmHg (e.g., 19 mmHg). At the 1 day post-treatment visits, a single IOP measurement will be performed in the study eye only. At other study visits IOP will be measured in both eyes by qualified site personnel. Elevated IOP should be clinically managed in accordance with routine clinical care of the practice and in accordance with investigator judgment.

The tonometer must be calibrated for accuracy before the first patient in the study at a given site undergoes the first examination, and continue to be performed in accordance with the manufacturer's specifications until the last patient at the site has exited the study.

15.11 Dilated Ophthalmoscopy

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

- Vitreous body
- Peripheral 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.

15.12 Color Fundus Photography

Color fundus photography (CFP) for each eye will be performed to assess the retina and characteristics of the ocular tumor in the study eye. Color fundus photographs will be obtained using a digital fundus camera and will be performed by designated qualified site personnel.

For detailed instructions regarding performance of CFP, please refer to the BCVA testing and imaging procedures manual provided separately.

15.13 Ophthalmic Ultrasound

Ophthalmic ultrasound of the study eye will be performed to assess and measure (depth, width, and height) the ocular tumor from the external surface of the sclera. Ophthalmic ultrasound will be performed by designated qualified site personnel.

For detailed instructions regarding collection of ultrasound measurements, please refer to the BCVA testing and imaging procedures manual provided separately.

15.14 Spectral-Domain Optical Coherence Tomography

Spectral-domain optical coherence tomography (sdOCT) imaging of the study eye will be performed to measure and assess cross-sectional images of the anatomic layers of the retina, the ocular tumor and associated pathological changes. sdOCT will be performed pre-treatment during visits in which ICON-1 is administered. sdOCT imaging will be obtained using a Spectral-Domain (High Definition) OCT device by designated qualified site personnel. Preferably the same machine will be used for initial and follow-up assessments of each patient.

For detailed instructions regarding collection of sdOCT imaging, please refer to the BCVA testing and imaging procedures manual provided separately.

15.15 Enhanced Depth Imaging Optical Coherence Tomography

Enhanced depth optical coherence tomography (EDI-OCT) imaging of the study eye will be performed optionally, according to investigator judgment, to evaluate the structural changes of the choroid in the area of the tumor.

EDI-OCT will be performed pre-treatment during visits in which ICON-1 is administered. EDI-OCT imaging will be obtained using an EDI-OCT device by designated qualified site personnel. Preferably the same machine will be used for initial and follow-up assessments of each patient.

For detailed instructions regarding collection of EDI-OCT imaging, please refer to the BCVA testing and imaging procedures manual provided separately.

15.16 Fluorescein Angiography

Fluorescein angiography (FA) imaging (after intravenous administration of Fluorescein dye) for each eye will be performed to examine the circulation of the retina and characteristics of the ocular tumor in study eye according to standard FA image capture protocol. FA images will be obtained using a digital camera by designated qualified site personnel.

For detailed instructions regarding collection of FA images, please refer to the BCVA testing and imaging procedures manual provided separately.

15.17 ICG Angiography

Indocyanine green angiography (ICGA) imaging (after intravenous administration of Indocyanine Green dye) for each eye will be performed optionally, according to investigator judgment, to examine the blood vessels and connective tissue of the choroid and the ocular tumor in the study eye. ICGA images will be obtained using an infra-red sensitive camera by designated qualified site personnel.

For detailed instructions regarding collection ICG imaging, please refer to the BCVA testing and imaging procedures manual provided separately.

15.18 Clinical Laboratory Evaluations and Immunogenicity

Blood samples for routine clinical laboratory tests and immunogenicity tests will be collected. 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, mean platelet volume [MPV], and C-reactive protein [CRP])
- Serum chemistry profile (albumin, alkaline phosphatase, alanine aminotransferase [ALT], aspartate aminotransferase [AST], blood urea nitrogen [BUN], calcium, serum chloride, carbon dioxide [CO2], 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, uric acid)
- Serum pregnancy test for women of child bearing potential
- Coagulation (PT, INR, fibrinogen, and activated partial thromboplastin time [aPTT])
- Immunogenicity (plasma anti-drug antibody [ADA])

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.

Blood samples will be obtained to measure systemic levels of anti-drug antibodies. Blood samples for measurement of anti-drug antibodies will be drawn before the first intravitreal injection at Screening/Baseline before the intravitreal injection and at Week 2, Week 8 and the Early Termination visit (as applicable).

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.

It is the investigator's responsibility to perform clinical laboratory assessments more frequently if clinically indicated.

Hematology, serum chemistry, coagulation, and serum pregnancy tests will be performed by a central laboratory. ADA samples will be batch analyzed by a central bioanalytical laboratory. For detailed instructions regarding collection, storage and handling of clinical laboratory and immunogenicity samples, please refer to the Laboratory Manual provided separately.

15.19 Pharmacokinetic and Pharmacodynamic Markers

Blood samples for PK (plasma ICON-1 concentrations) and PD markers (including serum cytokine levels, circulating TF, immunophenotype patterns and CTDNA) analyses will be drawn from all study patients at pre-specified time points prior to and after administration of ICON-1.

For all cohorts, blood samples for PK and PD analysis will be collected on Day 0 pre-injection and 4 hours ±1 hour post injection (for cohort 3 prior to the first injection and after the second injection), and on Day 1. For cohorts 2 and 3, blood samples for PK and PD analysis will also be collected on Day 7 prior to the first injection and 4 hours ±1 hour post injection (for cohort 3, prior to the first injection and after the second injection), and 1 day post Day 7 treatment. In addition, for all cohorts, a blood sample for PD markers will be collected prior to enucleation or plaque placement, as applicable.

Blood samples for CTDNA will be collected along with the other PD marker samples on Day 0 (all cohorts, pre-injection), Day 7 (cohorts 2 and 3 only, pre-injection), and prior to enucleation or plaque placement (all cohorts).

A PK and PD sample will also be obtained at the Early Termination visit if Day 1 or 1 day post Day 7 treatment PK/PD samples were not collected following injection on Day 0 or Day 7, as applicable.

For detailed instructions regarding collection, storage and handling of PK and PD samples, please refer to the Laboratory Instruction Manual provided separately.

15.20 Proteomic Analysis of Vitreous

For Patients Undergoing Enucleation Only: Immediately following the enucleation procedure, vitreous humor aspirate will be collected for assessment of ICON-1 levels and proteomic analysis of TF and other cytokines, and will be sent to the central study laboratory.

For detailed instructions regarding collection, storage, and handling of vitreous humor samples, please refer to the Laboratory Instruction Manual provided separately.

15.21 Tumor Pathology, Genetic Profiling and Exome Sequencing

For Patients Undergoing Enucleation: Following the enucleation procedure, the eye globe will be sent to the local site laboratory for pathology according to the clinical site's standard of care practice. A subset of pathology slides and/or tumor block samples will be prepared by the local laboratory and sent to the study central laboratory for study-related assessments, including ICON-1 binding to TF within the tumor, TF and PAR2 expression, characterization of the immune infiltrate, and alterations of the vasculature, genetic profiling (Type 1 or Type 2), and Exome sequencing. Genetic profiling previously performed with fine needle aspiration of the tumor does not require repeated testing.

A central laboratory designated for the study will perform the above testing for the provided slides and/or tumor block samples. For detailed instructions regarding specimens preparation, handling and shipping, please refer to the Laboratory Instruction Manual provided separately.

For Patients Undergoing Plaque Placement: If standard of care fine needle aspiration of the tumor is performed prior to plaque placement for genetic profile testing, the results of that testing will be recorded.

15.22 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

15.22.1 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 (including the planned enucleation surgery or brachytherapy, and associated inpatient hospitalization, as applicable) 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 15.22.8.

- For cohort 3, if the IOP in the study eye following the first intravitreal injection does not stabilize sufficiently to the pre-injection level (i.e., within 5 mmHg of the pre-injection IOP) to perform the second intravitreal injection, the change in IOP should be reported as an AE.

- For cohort 3, elevated IOP in the study eye following the first intravitreal injection should be considered an AE if: (1) two or more follow-up IOP measurements 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 second 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 patient 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.

15.22.2 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.

15.22.3 AE Severity

The severity of an AE should be determined by the intensity of the AE and will be assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (June 14, 2010) Eye Disorders section.

Table 3: CTCAE Grading

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

15.22.4 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.

15.22.5 Adverse Events of Special Interest (AESIs)

AESIs are events of medical and scientific concern specific to the investigational product, for which ongoing monitoring and rapid communications by the investigator to the sponsor and Safety Review Committee is appropriate. Ocular adverse events that qualify as an AESI (even if non-serious) include the following:

- Ocular inflammatory event of CTCAE Grade ≥ 3
- Vitreous or retinal hemorrhage event interfering with visualization of the tumor or retina of CTCAE Grade ≥ 2
- Any acute onset treatment-emergent vision-threatening condition as assessed by the investigator

15.22.6 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 and AESIs, whether or not related to study drug, must be reported immediately to the Sponsor or designee by entering the SAE/AESI 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:

Safety Notification

Email: drugsafety@iconictherapeutics.com
Fax: 650-246-9011
(or email or fax number provided on Safety Notification Cover Sheet)

15.22.7 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 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.

15.22.8 Pregnancy

Pregnancy alone is not an AE. However, any report of pregnancy that occurs in a female 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 15.22.5.

15.22.9 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 15.22.5.

15.22.10 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 patient withdraws consent, or the patient is lost to follow-up. This may imply that follow-up will continue after the patient 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, a follow-up SAE report should be sent 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.

15.22.11 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

Safety as measured by:

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

16.2 Secondary Endpoints

Pharmacokinetics and Pharmacodynamic Markers

- Plasma levels of ICON-1 following intravitreal injections of ICON-1
- Change in circulating TF and serum cytokine levels following intravitreal injections of ICON-1
- Characterization of immunophenotyping patterns

Pharmacodynamic and Biological Activity

- Change in tumor size (thickness, volume) as assessed by imaging techniques (CFP, FA, sdOCT, ultrasound, ICG angiography, EDI-OCT) from baseline

16.3 Exploratory Endpoints

- Characterization of the genetic profile of the tumor (Type 1 or Type 2), and associated changes in the tumor with ICON-1 treatment
- Characterization of pathologic findings of the tumor (ICON-1 target engagement within the tumor, TF and PAR2 expression, characterization of immune infiltrate, and alterations of the vasculature)
- ICON-1 and proteomic analysis (TF and other cytokine levels) of the vitreous humor

17 STATISTICAL ANALYSIS AND METHODS PLANNED

17.1 Statistical Analysis Plans

This phase 1 study is exploratory and its sample size is not determined by statistical power considerations. Hence, no inferential testing will be performed. Data analysis for this study will be geared toward descriptive and graphical summaries.

As descriptors of the three cohorts, univariate data summaries will be provided. For 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.

All patients who receive ICON-1 will be considered evaluable and will be included in the analysis. 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 will be provided in the Statistical Analysis Plan (SAP).

17.2 Analysis of the Conduct of the Study

The number of patients enrolled will be tabulated by study site and cohort. Patient disposition (the number of subjects enrolled, treated, and completing the study) will be tabulated by cohort. Subject discontinuations and reasons for discontinuation will be summarized.

17.3 Handling of Dropouts or Missing Data

Patients who discontinue from the study prior to completing the one week safety evaluation following their last injection may be replaced.

17.4 Analysis of Treatment Arm Comparability

Summary statistics of patient demographics, such as age, sex, and race will be provided by cohort to assess comparability. Other baseline characteristics such as genetic profile of the tumor may be summarized.

17.5 Treatment Exposure

The total dose received will be summarized by cohort. The dose level, and number of doses received will also be summarized by cohort. Study drug administration data will be listed for each patient.

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 physical and ophthalmic examinations. Adverse events will be mapped using MedDRA. 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 cohort will also be provided.

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

Changes in laboratory data will be summarized by cohort.

17.7 Biological Activity Analyses

Mean changes in tumor size and characteristics of pathologic tumor findings over time will be summarized for each patient. Mean changes in BCVA, retina and tumor thickness and volume, and areas of vascular leakage/ exudation over time will be summarized for each patient. Graphical displays of changes over time in ophthalmic ultrasound measures and ocular function may be constructed for each patient. Patient profiles, aggregating patient level data across many biological activity domains, may be used to explore joint biological effects in each patient. Vitreous humor (ICON-1, TF, and other cytokine levels) results over time will be summarized, if obtained.

17.8 Pharmacokinetic and Pharmacodynamic Markers Analyses

Pharmacokinetic analyses will be conducted on data from patients who have received at least 1 dose of ICON-1 and have at least one post-dose sample collected to allow estimation of the PK parameters.

Individual (patient) plasma ICON-1 concentrations at each sampling time will be listed; corresponding summary statistics at each sampling time will be calculated for the ICON-1. Plasma ICON-1 versus time profiles (with concentrations on both a log and linear scale) will be plotted for each patient; corresponding summary time plots will likewise be constructed for cohort.

When applicable, pharmacokinetic parameters will be calculated using non-compartmental techniques from plasma ICON-1 concentrations and will include the following parameters: $t_{1/2}$, C_{max}, T_{max}, and $AUC_{0-\infty}$. Individual ICON-1 PK parameters will be listed for each patient, and summary statistics will be calculated for each cohort.

17.9 Interim Analysis

No formal interim analysis is planned for this study. However, all individual patient data including safety data will be examined on an ongoing basis to ensure patient safety and to comply with the dose level escalation rules.

17.10 Sample Size Determination

Up to 13 patients with uveal melanoma involving the posterior uveal tract will be enrolled from approximately seven to ten centers in the United States. Patients who discontinue before the one week safety evaluation following their last injection may be replaced. This study is exploratory and its sample size is not determined by statistical power considerations and no sample size calculations were performed.

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 Principal Investigator 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 and concomitant medications, preferred terms will be assigned to the original terms entered on the eCRFs using MedDRA and WHO Drug dictionaries, respectively.

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 subjects' 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 study must provide new 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 – Cohort 1 (Patients Undergoing Enucleation or Brachytherapy)

Study Day	**Screening[1]** **Day -7 to 0**	**Baseline Treatment Day 0**	**Day 1**	**NA for Cohort 1**	**Procedure Assessments (On or 1 day prior to Surgical Procedure[7] day)**	**End of Study 30 days ±5 days post Surgical Procedure**	**Early Termin-ation**
Visit	**1**	**2**	**3**	**4[2] & 5[2]**	**6**	**7**	**ET**
Demographic Data	X						
Medical/Ocular/Surgical/ Medication History	X						
Vital Signs	X	X	X		X	X	X
Serum Chemistry, Hematology and Coagulation Blood Samples	X				X	X	X
Anti-drug Antibody levels (ADA)	X					X	X
Serum Pregnancy Test (WOCBP only)	X					X	X
Abbreviated Physical Exam	X[3]					X	X
Best-corrected Visual Acuity by ETDRS	OU	OU	SE		OU	OU[9]	OU[10]
Slit Lamp Biomicroscopy	OU	OU	SE		OU	OU[9]	OU[10]
Intraocular Pressure[4] **Pre-injection** **Post-injection(s)**	OU	 OU SE	SE		OU	OU[9]	OU[10]
Dilated Ophthalmoscopy	OU	SE			OU	OU[9]	OU[10]
Color Fundus Photography	OU				OU	OU[9]	OU[10]
Spectral-domain Optical Coherence Tomography	SE				SE	SE[9]	SE[10]

Study Day	**Screening[1]** **Day -7 to 0**	**Baseline Treatment Day 0**	**Day 1**	**NA for Cohort 1**	**Procedure Assessments (On or 1 day prior to Surgical Procedure[7] day)**	**End of Study 30 days ±5 days post Surgical Procedure**	**Early Termin-ation**
Visit	**1**	**2**	**3**	**4[2] & 5[2]**	**6**	**7**	**ET**
Enhanced Depth Imaging Optical Coherence Tomography (optional according to investigator judgment)	SE				SE		SE[10]
Ophthalmic Ultrasound	SE				SE	SE[9]	SE[10]
Fluorescein Angiography	OU				OU		OU[10]
ICG Angiography (optional according to investigator judgment)	OU				OU		OU[10]
Pharmacodynamic Assessments (blood sample pre and post treatment)		X[5]	X		X		X[6]
Pharmacokinetic Assessment (blood sample pre and post treatment)		X[5]	X				X[6]
Intravitreal Injection: COHORT 1		X					
Scheduled Enucleation or Plaque Placement Procedure[7] (≥4 days after injection according to standard of care)					X		
Mandatory Vitreous and Tumor Sample for Enucleation Patients[8]					X		
Adverse Events		X	X		X	X	X
Concomitant Medications	X	X	X		X	X	X

SE=Study Eye, OU=Both Eyes

[1] If there is study drug available at the clinical site, Screening assessments may be conducted on same day as Baseline visit (Day 0), prior to enrollment and intravitreal injection. Informed consent must be obtained before any study related screening activity or treatment is undertaken that is not part of routine care.

[2] Cohort 1 does not have Visit 4 or 5; the next visit after Visit 3 is Visit 6.

[3] Height and weight measured at Screening only.

[4] IOP measured using routine practice with a calibrated contact tonometer. For study eyes, IOP will be measured pre and post injection(s).

[5] Blood samples for PK and PD assessments will be drawn before and 4 hours ±1 hour post injection.

[6] At Early Termination, blood samples for PK and PD assessments will be drawn if Day 1 PK/PD blood samples were not collected following injection on Day 0.

[7] The surgical procedure is scheduled independent of this study according to standard of care clinical management of uveal melanoma per patient's treating physician and is not a study procedure.

[8] Following enucleation, vitreous humor will be collected for ICON-1 and proteomic analysis of TF and other cytokine levels. In addition to the pathology standard procedures of the clinical site, the study-related pathology slides and/or tumor block sample will be prepared and shipped to a central study laboratory for additional evaluations of the tumor (TF expression, ICON-1 binding, immune infiltrate, genetic profiling, and Exome sequencing). Genetic profiling of the tumor previously performed with fine needle aspiration of the tumor does not require repeated testing.

[9] Ocular assessments for brachytherapy patients only.

[10] Ocular assessments at early termination visit only if early termination occurs prior to surgical procedure.

21.2 Appendix B: Study Flowchart and Assessments – Cohorts 2 and 3 (Patients Undergoing Enucleation or Brachytherapy)

Study Day	Screening[1] Day -7 to 0	Baseline Treatment Day 0	Day 1	Treatment Day 7 ±2 days	1 day post Day 7 Treatment	Procedure Assessments (On or 1 day prior to Surgical Procedure[7] day)	End of Study 30 days ±5 days post Surgical Procedure	Early Termin-ation
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**ET**
Demographic Data	X							
Medical/Ocular/Surgical/ Medication History	X							
Vital Signs	X	X	X	X	X	X	X	X
Serum Chemistry, Hematology and Coagulation Blood Samples	X			X		X	X	X
Anti-drug Antibody levels (ADA)	X						X	X
Serum Pregnancy Test (WOCBP only)	X						X	X
Abbreviated Physical Exam	X[2]						X	X
Best-corrected Visual Acuity by ETDRS	OU	OU	SE	OU	SE	OU	OU[9]	OU[10]
Slit Lamp Biomicroscopy	OU	OU	SE	OU	SE	OU	OU[9]	OU[10]
Intraocular Pressure[3]	OU		SE		SE	OU	OU[9]	OU[10]
Pre-injection		OU		OU				
Post-injection(s)		SE[6]		SE[6]				
Dilated Ophthalmoscopy	OU	SE		SE		OU	OU[9]	OU[10]
Color Fundus Photography	OU					OU	OU[9]	OU[10]
Spectral-domain Optical Coherence Tomography	SE			SE		SE	SE[9]	SE[10]

Study Day	**Screening[1]** **Day -7 to 0**	**Baseline Treatment Day 0**	**Day 1**	**Treatment Day 7 ±2 days**	**1 day post Day 7 Treatment**	**Procedure Assessments (On or 1 day prior to Surgical Procedure[7] day)**	**End of Study 30 days ±5 days post Surgical Procedure**	**Early Termin-ation**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**ET**
Enhanced Depth Imaging Optical Coherence Tomography (optional according to investigator judgment)	SE			SE		SE		SE[10]
Ophthalmic Ultrasound	SE			SE		SE	SE[9]	SE[10]
Fluorescein Angiography	OU					OU		OU[10]
ICG Angiography (optional according to investigator judgment)	OU					OU		OU[10]
Pharmacodynamic Assessments (blood sample pre and post treatment)		X[4]	X	X[4]	X	X		X[5]
Pharmacokinetic Assessment (blood sample pre and post treatment)		X[4]	X	X[4]	X			X[5]
Intravitreal Injection: COHORT 2		X		X				
Intravitreal Injection: COHORT 3		XX[6]		XX[6]				
Scheduled Enucleation or Plaque Placement Procedure[7] (≥4 days after last injection according to standard of care)						*X*		

Study Day	Screening[1] Day -7 to 0	Baseline Treatment Day 0	Day 1	Treatment Day 7 ±2 days	1 day post Day 7 Treatment	Procedure Assessments (On or 1 day prior to Surgical Procedure[7] day)	End of Study 30 days ±5 days post Surgical Procedure	Early Termin-ation
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**ET**
Mandatory Vitreous and Tumor Sample for Enucleation Patients[8]						*X*		
Adverse Events		X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X

SE=Study Eye, OU=Both Eyes, XX=two injections

[1] If there is study drug available at the clinical site, Screening assessments may be conducted on same day as Baseline visit (Day 0), prior to enrollment and intravitreal injection. Informed consent must be obtained before any study related screening activity or treatment is undertaken that is not part of routine care.

[2] Height and weight measured at Screening only.

[3] IOP measured using routine practice with a calibrated contact tonometer. For study eyes, IOP will be measured pre and post injection(s).

[4] Blood samples for PK and PD assessments will be drawn before and 4 hours ±1 hour post injection (for cohort 3, after the second injection).

[5] At Early Termination, blood samples for PK and PD assessments will be drawn if Day 1 or 1 day post Day 7 treatment PK/PD blood samples were not collected following injection on Day 0 or Day 7.

[6] For Cohort 3, the study eye receives two study drug injections. The second study drug injection will occur following stabilization of IOP to within 5 mmHg of the pre injection measurement and ≥30 minutes after the first injection at the visit.

[7] The surgical procedure is scheduled independent of this study according to standard of care clinical management of uveal melanoma per patient's treating physician and is not a study procedure.

[8] Following enucleation, vitreous humor will be collected for ICON-1 and proteomic analysis of TF and other cytokine levels. In addition to the pathology standard procedures of the clinical site, the study-related pathology slides and/or tumor block sample will be prepared and shipped to a central study laboratory for additional evaluations of the tumor (TF expression, ICON-1 binding, immune infiltrate, genetic profiling, and Exome sequencing). Genetic profiling of the tumor previously performed with fine needle aspiration of the tumor does not require repeated testing.

[9] Ocular assessments for brachytherapy patients only.

[10] Ocular assessments at early termination visit only if early termination occurs prior to surgical procedure.