Protocol Number:	SF0166-C-001
Protocol Title:	A Phase I/II Randomized, Double-Masked, Multicenter Clinical Trial Designed to Evaluate the Safety and Exploratory Efficacy of SF0166 Topical Ophthalmic Solution in the Treatment of Diabetic Macular Edema (DME)
Study Phase:	I/II
Sponsor Name and Address:	SciFluor Life Sciences, Inc. 300 Technology Square, Suite 201 Cambridge, MA 02139
Medical Monitor:	Pharmacovigilance: Gary Foulks, MD 3103 Joy Place Wilmington, NC 28409 Retina Expert: Quan Dong Nguyen, MD, MSc 1421 North 143rd Street Omaha, NE 68154
Investigational Product (IP):	SF0166 Topical Ophthalmic Solution
Indication Studied:	Diabetic Macular Edema

Investigator Agreement:

I have read the clinical study described herein, recognize its confidentiality, and agree to conduct the described study in compliance with Good Clinical Practices (GCP), the ethical principles contained within the Declaration of Helsinki, this protocol, and all applicable regulatory requirements; including United States (US) Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) 312.

Principal Investigator:	
Site Name/Address:	
Signature:	Date:

1.0 SYNOPSIS

Sponsor:	SciFluor Life Sciences, LLC 300 Technology Square, Suite 201 Cambridge, MA 02139
Protocol Number:	SF0166-C-001
Protocol Title:	A Phase I/II Randomized, Double-Masked, Multicenter Clinical Trial Designed to Evaluate the Safety and Exploratory Efficacy of SF0166 Topical Ophthalmic Solution in the Treatment of Diabetic Macular Edema
Investigational Product:	SF0166 Topical Ophthalmic Solution (SF0166)
Active Ingredient:	SF0166 ($\alpha_v\beta_3$ antagonists)
Number of Investigative Sites:	Approximately 10
Investigative Site Locations:	US
Number of Subjects:	Approximately 40 (20 in each arm)
Duration of Treatment:	28 days
Study Population:	Male and female subjects, aged 18 or older, with diabetic macular edema (i.e., retinal thickening secondary to type 1 or type 2 diabetes mellitus with DME with central subfield thickness ≥325 microns (µm) on spectral domain optical coherence tomography [OCT]) and no treatment with anti-vascular endothelial growth factor (VEGF) therapy within up to 60 days of study entry in the study eye
Objective(s):	To evaluate the safety and exploratory efficacy of SF0166 topical ophthalmic solution in patients with DME
Study Design & Methodology:	This is a prospective, randomized, double-masked multicenter, Phase I/II clinical study in which approximately 40 eligible subjects with active DME will be randomized to 1 of 2 treatment arms in a 1:1 ratio as follows: • SF0166 2.5% low dose twice daily (BID) • SF0166 5.0% high dose BID Randomization will be stratified by best-corrected visual acuity (BCVA) using Early Treatment Diabetic Retinopathy Study (ETDRS) testing (<40 letters versus ≥40 letters at Visit 1 – Screening/Randomization). Eligibility and all site-related treatment decisions will be made based on Investigator assessment of OCT. All OCT images will also be reviewed by a central reading facility; however, eligibility is based on the Investigator's assessment at the time the

	potential study subject is examined. The primary efficacy outcome is determined by the OCT assessments from the reading center. Study subjects will administer the randomly assigned treatment for 28 days. There is an additional 28-day post-treatment follow-up period. All study subjects will return for examination every 2 weeks for 8 weeks (2 months). Clinical assessments will include slit-lamp examination, intraocular pressure (IOP) measurement, BCVA, OCT, fluorescein angiography (FA), and fundus photography. Adverse events (AEs) will be recorded at all study visits. Rescue therapy with a VEGF inhibitor can be administered to any study subject who experiences a significant decrease in BCVA, defined as BCVA loss of >7 letters from baseline (Visit 1 – Screening/Randomization), accompanied by an increase in OCT central subfield thickness of >75μm as compared to the previous study visit, as assessed by the Investigator. Potential study participants will be asked to sign an informed consent document prior to screening. Once it is determined that all eligibility criteria have been met, subjects will be randomized to 1 of the 2 treatment arms. All study subjects and site staff will be masked to the treatment assignment. The safety and exploratory efficacy of SF0166 will be evaluated over the course of the study. Since this is Phase I/II clinical study, no formal hypotheses testing is planned; descriptive statistics will be used to summarize the study outcomes.	
Treatments:	• SF0166 2.5% low dose BID • SF0166 5.0% high dose BID	
Subject Selection:	Inclusion Criteria:	1. Male or female, 18 years of age or older. 2. Retinal thickening secondary to type 1 or type 2 diabetes mellitus with DME defined as central subfield thickness ≥325 μm on spectral domain OCT in the study eye. 3. BCVA between 78 and 25 letters, inclusive, in the study eye at the screening/randomization visit using ETDRS testing, with BCVA decrement primarily attributable to DME. 4. Treatment naïve (i.e., no previous anti-VEGF treatment in the study eye) or previously treated study eye with adequate washout defined below: a. Lucentis (ranibizumab): 30-day washout

		b. Avastin (bevacizumab): 30-day washout c. Eylea (aflibercept): 60-day washout d. Macugen (pegaptanib): 45-day washout 5. Willing and able to return for all study visits. 6. Able to adhere to the study dosing requirements. 7. Understands and signs the written informed consent form.
	Exclusion Criteria:	1. Active proliferative diabetic retinopathy (PDR) in the study eye, such as neovascularization of the optic disc (NVD), neovascularization elsewhere (NVE), vitreous hemorrhage, or neovascular glaucoma. 2. Uncontrolled glaucoma or ocular hypertension in the study eye defined as an IOP >25 millimeter of mercury (mmHg) regardless of concomitant treatment with IOP-lowering medications. 3. Uncontrolled hypertension defined as systolic >180 mmHg or >160 mmHg on 2 consecutive measurements (during the same visit) or diastolic >100 mmHg on optimal medical regimen. 4. Screening glycated hemoglobin (HbA1c) blood test >12.0%. 5. Previous panretinal photocoagulation (PRP) in the study eye within 4 months of study enrollment, or the need for PRP during the study based on the Investigator's opinion. 6. Previous focal laser photocoagulation in the study eye, within the foveal avascular zone. 7. Intravitreal/periocular/topical ocular steroids of any type in the study eye within 90 days (3 months) prior to study enrollment. 8. Placement of Iluvien® or Retisert® (fluocinolone acetonide intravitreal implant) in the study eye within 36 months (3 years) prior to study enrollment. 9. Use of Ozurdex® (dexamethasone intravitreal implant) in the study eye within 180 days (6 months) prior to study enrollment. 10. Significant epiretinal membrane, posterior hyaloidal traction, and/or vitreomacular traction in the study eye as determined by the OCT results. 11. Previous pars plana vitrectomy in the study eye. 12. Any intraocular surgery in the study eye within 90 days (3 months) prior to study enrollment. 13. Yttrium aluminium garnet (YAG) laser treatment

		in the study eye within 30 days (1 month) prior to study enrollment. 14. Concomitant use of any topical ophthalmic medications in the study eye, including dry eye or glaucoma medications, unless on a stable dose for at least 90 days (3 months) prior to study enrollment and expected to stay on stable dose throughout study participation. Artificial tears are allowed. 15. High myopia in the study eye, with a spherical equivalent of >8.00 Diopters (D) at screening. 16. Chronic or recurrent uveitis in the study eye. 17. Ongoing ocular infection or inflammation in either eye. 18. A history of cataract surgery complicated by vitreous loss in the study eye. 19. Congenital eye malformations in the study eye. 20. A history of penetrating ocular trauma in the study eye. 21. Mentally handicapped. 22. Females of childbearing potential (i.e., who are not postmenopausal for at least 1 year or surgically sterile for at least 6 weeks prior to Visit 1 – Screening/Randomization) who are lactating, or who are pregnant as determined by a positive urine pregnancy test (UPT) at Visit 1 – Screening/Randomization. Women of childbearing potential must agree to use acceptable methods of birth control throughout the study. Acceptable methods of birth control include tubal ligation, transdermal patch, intrauterine devices/systems, oral/implantable/injectable or contraceptives, sexual abstinence, double barrier method, or vasectomized partner. 23. Participation in any other investigational device or drug clinical research study within 30 days of Visit 1 – Screening/Randomization. 24. Contraindication to the study medications or fluorescein dye. 25. Other ocular pathologies that in the Investigator's opinion would interfere with the subject's vision in the study eye.
Assessments:	• Spectral Domain OCT	

	• Best Corrected Visual Acuity (ETDRS) • Slit-Lamp Biomicroscopy • IOP by Tonopen or Applanation • Indirect Ophthalmoscopy/Dilated Fundus Examination • Fundus Photography • Fluorescein Angiography • AEs	
Outcomes:	Efficacy:	The primary efficacy outcome is the mean change in anatomic center subfield thickness and macular volume, measured by OCT. All OCT images will be read by the Investigator and a central reading facility. The primary efficacy outcome is determined by the OCT assessments from the reading center. The secondary efficacy outcome is the mean change from baseline in BCVA.
	Safety:	Safety parameters to be evaluated include BCVA, slit-lamp and fundus findings, IOP, and AEs.
Statistical Methods:	Descriptive statistics will be used to tabulate and summarize study outcomes. Background and demographic characteristics will be presented. Continuous variables will be summarized by descriptive statistics (sample size, mean and standard deviation, median, minimum and maximum). Discrete variables will be summarized by frequencies and percentages. Adverse events will be summarized by presenting the number and percentage of patients having any adverse event. Any other information collected (such as severity or relationship to investigational product) will be listed, as appropriate. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.	
Sample Size Justification:	Twenty subjects in each study arm are expected to provide an adequate sample size to distinguish any efficacy and safety differences between the dose groups.	

1.1 Comprehensive Cumulative History

Protocol Version 3 dated 16Nov2016 supersedes Version 2 dated 12Oct2016. Below is a summary of changes:

- Section 9.2: Usage information was clarified to indicate that a subject may be treated bilaterally if a subject qualifies in both eyes, at the discretion of the Investigator.
- Sections 1.0 and 9.3.2: Anti-VEGF washout periods were updated to:
  - Lucentis (ranibizumab): 30-day washout
  - Avastin (bevacizumab): 30-day washout
  - Eylea (aflibercept): 60-day washout
  - Macugen (pegaptanib): 45-day washout
- Section 1.0: Updated exclusion criterion #5 from:
  Previous PRP in the study eye or the need for PRP within 2 months from the time of study enrollment, based on the Investigator's opinion;
  to
  Previous PRP in the study eye within 4 months of study enrollment, or the need for PRP during the study based on the Investigator's opinion.
- Section 15.6: FA information was updated to clarify that fluorescein sodium dye is injected into the peripheral vein of the arm of the subject.

Protocol Version 2 dated 12Oct2016 supersedes Version 1 dated 09Jun2016. Below is a summary of the changes:

- General: Minor editorial and formatting changes occurred throughout the document for consistency and clarity purposes.
- Section 1.0: BCVA inclusion criterion was changed from:
  BCVA of 0.3 to 1.2 ETDRS (logarithmic minimum angle of resolution; logMAR) in the study eye (85 to 40 letters equivalent),
  to:
  BCVA between 78 and 25 letters, inclusive, in the study eye at the screening/randomization visit using ETDRS testing (see Inclusion #3).
- Section 1.0: The following exclusion criterion was added: Uncontrolled glaucoma or ocular hypertension in the study eye defined as an IOP >25 millimeter of mercury (mmHg) regardless of concomitant treatment with IOP-lowering medications (see Exclusion #2).
- Section 1.0: Exclusion criterion for Triessence (triamcinolone acetonide) within 90 days of study enrollment was removed, as this treatment is already excluded under the criterion covering intravitreal/periocular steroids in the study eye (see Exclusion #7).
- Section 1.0: Retisert, another fluocinolone acetonide intravitreal implant, was added as another exclusion since it is similar to Illuvien (see Exclusion #8).
- Section 1.0: Exclusions related to pregnant or nursing females were combined into one criterion and acceptable contraception language was added (see Exclusion #22).
- Section 1.0: The concurrent enrollment in another clinical study exclusion was further defined to include studies evaluating investigational devices or drugs (see Exclusion #23).
- Sections 1.0, 8.0, 10.7, and 15.0: BCVA scores were revised to include required

letters by ETDRS testing rather than logMAR equivalents.

- Section 2.0: Overview of Study Plan was updated to clarify that the Visit 5 procedures should be completed in the event of early termination visits. A footnote was also added to clarify that all ocular assessments are to be completed for both eyes.
- Section 9.3: Permitted treatments were updated to clarify that Anti-VEGF treatments are allowed in the non-study eye during study participation. Prohibited treatments were updated to include Retisert (fluocinolone acetonide intravitreal implant).
- Section 10.5: It was clarified that the Visit 5 procedures should be completed in the event of early termination.
- Section 15.0: The BCVA with ETDRS testing procedure was updated to note that standardized ETDRS procedures should be utilized and the scores should be reported in letters.

2.0 OVERVIEW OF STUDY PLAN

Visit Number	1	2	3	4	5	Unscheduled
Visit Window	0 days	14 ± 2 days (2 weeks)	28 ± 2 days (4 weeks)	42 ± 2 days (6 weeks)	56 ± 2 days (8 weeks) or Early Termination	N/A
			Procedure/Assessment			
Informed Consent	X					
Demographics	X					
Medical/Ocular History	X					
Concomitant Medications	X	X	X	X	X	X
Urine Pregnancy Test (UPT)[1]	X				X	(X)
HbA1c Test	X					
BCVA (ETDRS)[2]	X	X	X	X	X	(X)
Slit Lamp Biomicroscopy[2]	X	X	X	X	X	(X)
IOP by Tonopen or Applanation[2]	X	X	X	X	X	(X)
Spectral Domain OCT[2]	X	X	X	X	X	(X)
Indirect Ophthalmoscopy/Dilated Fundus Examination[2]	X	X	X	X	X	(X)
Fundus Photography[2]	X	X	X	X	X	(X)
Fluorescein Angiography[2]	X		X			(X)
Inclusion/Exclusion	X					
Adverse events	X[3]	X	X	X	X	X
Dispense IP	X	X				(X)
Dispense instructions/diary	X	X				(X)
Collect IP and dosing diary		X	X			(X)

(x) = as needed
[1] = Required for females of childbearing potential (i.e., who are not postmenopausal for at least 1 year or surgically sterile for at least 6 weeks from Visit 1 – Screening/Randomization)
[2] = Performed on both eyes
[3] = collected from the time of informed consent

3.0 ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AR	Adverse Reaction
BCVA	Best corrected visual acuity
BID	Twice daily
CFR	Code of Federal Regulations
CRA	Clinical Research Associate
CRO	Contract Research Organization
D	Diopters
DME	Diabetic Macular Edema
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Glycated hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HCL	Hydrochloric Acid
HPBCD	Hydroxypropyl-beta-cyclodextrin
IB	Investigator Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IOP	Intraocular pressure
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-treat
IWRS	Interactive Web Response System
logMAR	Logarithmic minimum angle of resolution
m	Meters
mg	Milligrams
mL	Milliliters
mm	Millimeter
mmHg	Millimeter of mercury
NaEDTA	Disodium ethylene diamine tetra acetate
NVD	Neovascularization of the optic disc
NVE	Neovascularization elsewhere
OCT	Optical coherence tomography
OD	Right eye
OS	Left eye
PDR	Proliferative Diabetic Retinopathy
pH	Power of hydrogen

Abbreviation	Definition
PI	Principal Investigator
PP	Per Protocol
PRP	Panretinal photocoagulation
SAE	Serious Adverse Event
SAR	Suspected Adverse Reaction
UPT	Urine Pregnancy Test
US	United States
VA	Visual acuity
VEGF	Vascular endothelial growth factor
YAG	Yttrium aluminium garnet
µm	Microns

4.0 TABLE OF CONTENTS

5.0 INTRODUCTION

Diabetic macular edema is the result of breakdown of the blood-retinal barrier and/or insufficient activity of the retinal pigment epithelium to pump out fluid from the retina, and is a sight-threatening condition common in diabetic retinopathy. There is extensive evidence that angiogenic cytokines (e.g., VEGF) and inflammatory cytokines are involved in the development of DME. It is widely thought that these cytokines are responsible for the accumulation of fluid within and below the retina (Feng 2013, Funatsu 2009, Funk 2009, Kaneda 2011, Noma 2006, and Noma 2011).

Currently available treatments for DME include macular grid laser photocoagulation, anti-VEGF agents, and corticosteroids; though, none of these treatments is fully satisfactory (Ozkaya 2013). Laser photocoagulation is generally palliative, and may take many months to develop a therapeutic effect. Anti-VEGF therapies can require monthly intravitreal injections, and some patients do not respond to these treatments. Intravitreal corticosteroid therapy can cause cataract and increased IOP with long-term treatment, and also is not effective in all patients (Sarao 2014 and Shamsi 2013).

SF0166 is intended to address the current limitations in the treatment of DME, which requires intravitreal injection every 4 to 12 weeks under topical anesthesia. The frequent visits to a retina specialist required for intravitreal injection represent a significant burden to patients, particularly for DME patients, many of whom are of working age. An alternative mode of drug administration, particularly topical eye drops, represents a very attractive treatment option.

The objective of this study is to determine an efficacy and safety profile of SF0166 in humans. Preclinical studies with SF0166 have demonstrated notable anti-angiogenic activity, and shown that the fluorination in the compound does have a positive impact on the ability for the treatment to get to the back of the eye. Activity of SF0166 in VEGF-driven models appears similar to anti-VEGF biologics. Moreover, SF0166 also blocks angiogenic signaling driven by other growth factors (platelet-derived and fibroblast growth factor), so clinical efficacy could exceed that of marketed drugs that only target VEGF.

Based on the pre-clinical information, it is expected that the benefits of SF0166 outweigh the risks of its use.

6.0 ETHICS

This clinical study will be conducted in accordance with the principles of the Declaration of Helsinki, in compliance with the International Conference on Harmonization (ICH) E6 GCP Consolidated Guideline, and other applicable regulations. The Investigator and personnel will conduct the clinical study in compliance with the protocol. The Investigator will ensure that all personnel involved in the conduct of the study are qualified to perform their assigned responsibilities through relevant education, training, and experience.

Prior to study initiation, this protocol, the informed consent form, and any other written information given to subjects must be approved by an Independent Ethics Committee/Institutional Review Board (IEC/IRB). The Investigator must provide documentation of the IEC/IRB approval to the Sponsor. The approval must be dated and must identify the applicable protocol, amendments (if any), informed consent form, applicable recruiting materials, written information for the subject, and subject compensation. The IEC/IRB must be provided with a copy of the Investigator's Brochure (IB), any periodic safety updates, and all other information as required by local regulation and/or the IEC/IRB. At the end of the study, the Investigator will notify the IEC/IRB about the study's completion. The IEC/IRB must also be notified if the study is terminated prematurely. Finally, the Investigator will report to the IEC/IRB on the progress of the study at intervals stipulated by the IEC/IRB.

Voluntary informed consent will be obtained from every subject (and/or legal representative, as applicable) prior to the initiation of any screening or other study-related procedures. The Investigator should have a defined process for obtaining consent. Specifically, the Investigator, or designee, will explain the clinical study to each potential subject and the subject must indicate voluntary consent by signing and dating the approved informed consent form. The subject must be provided an opportunity to ask questions of the Investigator, and if required by local regulation, other qualified personnel. The Investigator must provide the subject with a copy of the consent form written in a language the subject understands.

The consent document must meet all applicable local laws and will provide subjects with information regarding the purpose, procedures, requirements, and restrictions of the study, along with any known risks and potential benefits associated with the IP, the available compensation, and the established provisions for maintaining confidentiality of personal protected health information. Subjects will be told about the voluntary nature of participation in the study. Subjects will be provided with contact information for the appropriate individuals should questions or concerns arise during the study. The subject also will be told that their records may be accessed by appropriate authorities and Sponsor-designated personnel. The Investigator must keep the original, signed copy of the consent and must provide a duplicate copy to each subject.

7.0 PROTOCOL AMENDMENTS

Modification of the protocol is prohibited without prior written agreement in the form of a protocol amendment. All amendments will be created by the Sponsor and must be approved by the IEC/IRB prior to implementation; except when required to mitigate immediate safety risks or when the changes involve only logistical or administrative revisions. Amendments may necessitate that the informed consent and other study-related material be revised. If the consent form is revised, all subjects currently enrolled in the study may be required by the IRB/IEC to sign the approved, revised informed consent form.

This is Version 3 (Amendment 2) of this protocol.

8.0 SUBJECT POPULATION

The study population includes approximately 40 subjects, 18 years of age or older, randomized at approximately 10 sites. The goal is to enroll 40 subjects, 20 in each study arm, allowing for a minimum of 30 subjects to complete the study. To participate in the study, the subject must have center-involved diabetic macular edema (i.e., retinal thickening secondary to type 1 or type 2 diabetes mellitus with DME and central subfield thickness ≥325 µm on spectral domain OCT) in the study eye, either be treatment naïve or have been previously treated in the study eye with an adequate washout period (see Sections 1.0 and 9.3), achieve BCVA between 78 and 25 letters, inclusive, in the study eye using ETDRS testing, with BCVA decrement primarily attributable to DME, be willing able to attend all study visits and adhere to study regimen, and be willing to give written informed consent.

The duration of study participation is 8 weeks (± 2 days); including an on-treatment period of 28 days, and a post-treatment follow-up period of 28 days.

The complete inclusion and exclusion criteria are presented in Section 1.0.

9.0 TREATMENTS ADMINISTERED

Upon signing the informed consent form, the subject will be screened for eligibility. Once it is determined that all eligibility criteria have been met, subjects will be randomized to 1 of the 2 treatment arms according to the Interactive Web Response System (IWRS) system.

9.1 Identity of Investigational Products (IP)

The formulation of SF0166 Ophthalmic Solution consists of SF0166, hydroxypropyl-beta-cyclodextrin (HPBCD) (50 milligrams [mg]/milliliter [mL]), boric acid (10 mg/mL), disodium ethylene diamine tetra acetate (NaEDTA) (0.1%), benzalkonium chloride (0.02%) in water at power of hydrogen (pH) of 8. Two doses will be used in this study; a low dose (SF0166 2.5%) administered BID and a high dose (SF0166 5.0%) administered BID. The chemical composition of the IP is presented in Table 9-1.

TABLE 9-1: SF0166 COMPOSITION

Ingredient	Function	Concentration (w/v)
SF0166	Active pharmaceutical ingredient	5.0% (high dose) or 2.5% (low dose)
Hydroxypropyl β- Cyclodextrin	Permeation enhancer and precipitation prevention	5.0%
Boric Acid	Buffering agent	1%
Na-EDTA	Metal chelator	0.1%
1N Hydrochloric Acid (HCl)	pH adjustment	As needed
Benzalkonium chloride	Preservative	0.02%
Sterile Water for Injection	Diluent	88.88% (high dose) or 91.38% (low dose)

9.1.1 *Test Product 1*
SF0166 2.5% (low dose) BID

9.1.2 *Test Product 2*
SF0166 5.0% (high dose) BID

9.1.3 *Packaging*
SF0166 will be packaged in multi-use, pre-sterilized, low-density polyethylene dropper bottles with a tamper-evident cap.

Both doses of the test product will be provided with investigational labels; including kit number, site number, subject number, instructions for use, and investigational use statement. The randomization kit boxes will include 2 cartons with the kit number, each containing 3 bottles of SF0166 and bearing the same kit number.

9.2 Usage
If a subject meets inclusion/exclusion criteria at Visit 1, the site will enter the required data into the IWRS in order to randomize the subject to a treatment arm. After subjects are randomized, they are dispensed SF0166 in 1 of 2 dose groups. The subject will use SF0166 BID for 28 days (1 drop in the study eye). If a subject qualifies in both eyes, SF0166 may be administered to both eyes (study eye and non-study eye) at the discretion of the Investigator. The study eye is defined as the eye with the worse BCVA at baseline (Visit 1 - Screening/Randomization).

At Visit 1, the site staff will dispense 1 carton (3 bottles) from the subject kit. At Visit 2, the site staff will collect the used IP bottles, and dispense an additional carton (3 bottles) from the kit. It is expected that subjects will use 2 bottles between each visit. The additional 3rd bottle in each carton is a back-up supply. If a subject requires a re-supply for any reason, an unscheduled re-supply can be completed through the IWRS.

SF0166 should be stored at 2–8ºC and protected from light.

Throughout the study, the Investigator or designee will be responsible for the accounting of all IP. The Investigator must ensure that the IP are not used in an unauthorized manner.

9.3 Concomitant Treatments

9.3.1 *Permitted Treatments*

Medications not specifically excluded in Section 9.3.2 may be taken as necessary. For clarity, the following are permitted:

- Anti-VEGF injections for treatment of the non-study eye, including:
  - Eylea (aflibercept)
  - Lucentis (ranibizumab)
  - Avastin (bevacizumab)
  - Macugen (pegaptanib)
- Concomitant treatment with antibiotics at the discretion of the Investigator
- Artificial tears

9.3.2 *Prohibited Treatments*

Use of the following treatments is not allowed during the study and for the timeframes specified:

- Within 36 months (3 years) prior to study enrollment
  - Illuvien (fluocinolone acetonide intravitreal implant)
  - Retisert (fluocinolone acetonide intravitreal implant)
- Within 180 days (6 months) prior to study enrollment
  - Ozurdex (dexamethasone intravitreal implant)
- Within 90 days (3 months) prior to study enrollment
  - Focal laser photocoagulation or intravitreal/periocular/topical ocular steroids of any type in the study eye
  - Any intraocular surgery in the study eye
  - Any change in dose to a concomitant topical ophthalmic medication in the study eye
- Within 60 days (2 months) prior to study enrollment
  - Eylea (aflibercept) in the study eye
- Within 45 days prior to enrollment
  - Macugen (pegaptanib) in the study eye
- Within 30 days (1 month) prior to enrollment

- Lucentis (ranibizumab) in the study eye
- Avastin (bevacizumab) in the study eye
- YAG laser treatment in study eye

Subjects taking a stable dose of topical ophthalmic medications at study enrollment should be instructed not to dose study medication within 1 hour of investigational product dosing.

9.4 Accountability

Upon receipt of the IP, site personnel designated to handle the IP will conduct an inventory of the shipment(s). The site personnel designated to handle the IP must maintain sufficient accountability records for the duration of the study. Study treatment dispensation and collection for each subject should be included in the IP accountability records. The records must be made available to the Clinical Research Associate (CRA) for the purposes of verifying and accounting the clinical IP. Any discrepancies between the observed disposition and the written account must be recorded along with an explanation. The Investigator is ultimately responsible, although he/she may delegate this responsibility, to return all used/unused IP at the conclusion of the study.

9.5 Compliance

Compliance will be assessed by comparing study drug accountability records with the dosing information recorded daily by the subject. The site will document this comparison along with verification of the numbers of used and unused study product bottles. The numbers of missed doses as assessed at each clinic visit should be documented in the electronic Case Report Form (eCRF).

9.6 Investigational Product (IP) Shipment and Assignment

The site will confirm all IP shipments received from the sponsor within the IWRS. Details of this process are outlined in a separate manual. Upon confirmation, the shipment will show as part of the site's IP stock.

9.7 Subject Confidentiality and Methods Used to Minimize Bias

The Investigator must ensure that the subject's anonymity is maintained throughout the course of the study. In particular, the Investigator must keep an enrollment log with confidential identifying information that corresponds to the subject numbers and initials of each study participant. At the end of the study, the Sponsor will collect a copy of the enrollment log without any identifying subject information. All documents submitted to the Sponsor will identify the subjects exclusively by number and demographic information. No other personally identifying information should be transmitted to the Sponsor, including subject initials.

The intent of masking is to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of the clinical study. Bias could arise from the influence that the knowledge of a specific treatment assignment may have on the recruitment of subjects, their subsequent care, the assessment of endpoints, the handling of

withdrawals, etc. Therefore, the essential aim of masking is to prevent identification of the treatments by the Investigator, subject, and others associated with the conduct of the study.

Subjects will be assigned to a study arm according to the next available randomization schedule as assigned by the IWRS. The randomization schedule will be blocked to ensure a balance of study arms at the study level. The randomization scheme will be generated and maintained by the Sponsor. Individual subject randomization schemes will be unmasked after all study data has been verified, validated, and the database is locked.

Using a masked study team is a required activity designed to protect the masking of the study personnel at the site and at the Sponsor. The Sponsor involved in reporting, obtaining, and/or reviewing the clinical data will not be aware of the specific dose being administered.

For purposes of this study, the subject, Principal Investigator (PI), and site staff will be masked to the IP dose. Investigators, site staff members, and sponsor personnel directly involved with the study will not be aware of the randomized dose group for each randomized subject. In the event of a medical emergency where the knowledge of dose group is required, the Investigator will have the ability to learn the dose group in order to properly treat the medical emergency, but should only exercise this ability when absolutely necessary.

The masked site personnel must coordinate all study activities as necessary to protect masking and minimize bias during the study. This level of masking will be maintained throughout the conduct of the study.

10.0 STUDY PROCEDURES

10.1 Visit 1 – Screening/Randomization

After obtaining written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization, site staff will perform/assess the following in the order suggested below.

1. Each screened subject should be assigned a subject identifying number, based on the next available number in the eCRF.
2. Collect subject demographic information.
3. Collect ocular and non-ocular medical history.
4. Collect concomitant medications taken during the previous 12 months. Ask specifically about the use of Iluvien during the previous 36 months.
5. Administer UPT for female subjects of child-bearing potential.
6. Conduct in-office HbA1c test following test manufacturer guidelines.
7. Conduct the following ocular assessments on both eyes (refer to Section 15.0 for further details):

a. BCVA by ETDRS
b. Slit-lamp Biomicroscopy
c. IOP by Tonopen or Applanation
d. Spectral Domain OCT
e. Indirect Ophthalmoscopy/Dilated Fundus Examination
f. Fundus Photography
g. Fluorescein Angiography

8. Assess inclusion/exclusion criteria.
9. If subject is eligible, randomize the subject by entering information into the IWRS.
10. Dispense kit number provided by IWRS and provide dosing instructions/diary to the subject.
11. The first dose of study medication should be administered within the clinic under site staff supervision, and subsequent doses will be self-administered following the subject's visit.
12. Assess for any AEs occurring from the time of informed consent.
13. Provide instruction for the subject to:
    a. Dose IP as instructed
    b. Complete dosing information in subject diary.
    c. Return for Visit 2 (Day 14) in 2 weeks (± 2 days).
14. Prepare and upload OCT images to the central reading center, and upload fundus photography to ShareFile.

Note: Subjects can be re-screened at the discretion of the Investigator if there is reasonable clinical evidence to suggest the subject may qualify after initial screen failure. The Investigator should contact the Sponsor to discuss re-screenings prior to conducting the visits.

10.2 Visit 2 (Day 14)

This visit will occur on Day 14 ± 2 days as calculated from Visit 1 (Day 0), and the following evaluations will be performed:

1. Collect and record any AEs occurring since the last visit.
2. Collect and record any new or changed concomitant medications since the last visit.
3. Conduct the following ocular assessments on both eyes (refer to Section 15.0 for further details):
    a. BCVA by ETDRS
    b. Slit-lamp Biomicroscopy
    c. IOP by Tonopen or Applanation
    d. Spectral Domain OCT
    e. Indirect Ophthalmoscopy/Dilated Fundus Examination

f. Fundus Photography

4. Collect used IP kit/dosing diary and conduct drug accountability. Ensure that any dosing noncompliance is addressed with the subject.
5. Dispense kit number provided by IWRS and provide dosing instructions/diary to the subject.
6. Provide instruction for the subject to:
    a. Dose IP as instructed.
    b. Complete dosing information in subject diary.
    c. Return for Visit 3 (Day 28) in 2 weeks (± 2 days).
7. Prepare and upload OCT images to the central reading center, and upload fundus photography to ShareFile.

10.3 Visit 3 (Day 28)

This visit will occur on Day 28 ± 2 days as calculated from Visit 1 (Day 0), and the following evaluations will be performed:

1. Collect and record any AEs occurring since the last visit.
2. Collect and record any new or changed concomitant medications since the last visit.
3. Conduct the following ocular assessments on both eyes (refer to Section 15.0 for further details):
    a. BCVA by ETDRS
    b. Slit-lamp Biomicroscopy
    c. IOP by Tonopen or Applanation
    d. Spectral Domain OCT
    e. Indirect Ophthalmoscopy/Dilated Fundus Examination
    f. Fundus Photography
    g. Fluorescein Angiography
4. Collect used IP kit/dosing diary and conduct drug accountability.
5. Provide instruction for the subject to:
    a. Return for Visit 4 (Day 42) in 2 weeks (± 2 days).
6. Prepare and upload OCT images to the central reading center, and upload fundus photography to ShareFile.

10.4 Visit 4 (Day 42)

This visit will occur on Day 42 ± 2 days as calculated from Visit 1 (Day 0), and the following evaluations will be performed:

1. Collect and record any AEs occurring since the last visit.

2. Collect and record any new or changed concomitant medications since the last visit.
3. Conduct the following ocular assessments on both eyes (refer to Section 15.0 for further details):
    a. BCVA by ETDRS
    b. Slit-lamp Biomicroscopy
    c. IOP by Tonopen or Applanation
    d. Spectral Domain OCT
    e. Indirect Ophthalmoscopy/Dilated Fundus Examination
    f. Fundus Photography
4. Provide instruction for the subject to:
    a. Return for Visit 5 (Day 56) in 2 weeks (± 2 days).
5. Prepare and upload OCT images to the central reading center, and upload fundus photography to ShareFile.

10.5 Visit 5 (Day 56) or Early Termination Visit

This visit will occur on Day 56 ± 2 days as calculated from Visit 1 (Day 0), or on the date of early termination, if applicable. The following evaluations will be performed:

1. Collect and record any AEs occurring since the last visit.
2. Collect and record any new or changed concomitant medications since the last visit.
3. Administer UPT to females of child-bearing potential.
4. Conduct the following ocular assessments on both eyes (refer to Section 15.0 for further details):
    a. BCVA by ETDRS
    b. Slit-lamp Biomicroscopy
    c. IOP by Tonopen or Applanation
    d. Spectral Domain OCT
    e. Indirect Ophthalmoscopy/Dilated Fundus Examination
    f. Fundus Photography
5. Prepare and upload OCT images to the central reading center, and upload fundus photography to ShareFile.

10.6 Unscheduled Visit(s)

Unscheduled visits may occur at any time for any reason. The following evaluations should be performed during these visits:

1. Collect and record any AEs occurring since the last visit.

2. Collect and record any new or changed concomitant medications since the last visit.

The following evaluations *may* be performed during these visits:

3. Administer UPT to females of child-bearing potential.
4. Conduct the following ocular assessments on both eyes (refer to Section 15.0 for further details):
    a. BCVA by ETDRS
    b. Slit-lamp Biomicroscopy
    c. IOP by Tonopen or Applanation
    d. Spectral Domain OCT
    e. Indirect Ophthalmoscopy/Dilated Fundus Examination
    f. Fundus Photography
    g. Fluorescein Angiography
5. Dispense kit number provided by IWRS and provide dosing instructions/diary to the subject.
6. Collect used IP kit/dosing diary and conduct drug accountability.
7. Provide instruction for the subject to:
    a. Dose IP as instructed, if applicable
    b. Complete dosing information in subject diary, if applicable
    c. Return for next regularly scheduled visit, or follow-up unscheduled visit.
8. Prepare and upload OCT images to the central reading center, and upload fundus photography to ShareFile.

10.7 Rescue Therapy

Rescue therapy with a VEGF inhibitor can be administered to any study subject who experiences a significant decrease in BCVA, defined as BCVA loss of >7 letters from baseline (Visit 1 – Screening/Randomization), accompanied by an increase in OCT center subfield thickness of >75μm as compared to the previous study visit, as assessed by the Investigator. The OCT images completed during the assessment for rescue therapy initiation should also be uploaded to the central reading center.

Therapies can include:

- Avastin (bevacizumab), or
- Lucentis (ranibizumab), or
- Eylea (aflibercept), or
- Macugen (pegaptanib)

Note: Steroid and focal laser photocoagulation rescue is not permitted during the study.

Subjects who discontinue IP and are started on rescue therapy should continue with the visit schedule and assessments through the end of the study.

11.0 ANALYSIS PLAN

11.1 Analysis Data Sets

The primary analysis population will be the Per Protocol (PP) population, defined as all subjects who were randomized, completed the study as planned (i.e., after 28-day on-treatment period and 28-day follow-up period), and did not have significant protocol deviations. Protocol deviations will be reviewed by the study team and assessed for importance (i.e., the potential exclusion of a subject) prior to database lock.

The modified intent-to-treat (ITT) population will include subjects who were randomized and completed at least 1 on-IP study visit. The safety analysis set will include all randomized subjects.

11.2 Demographic and Baseline Characteristics

Descriptive statistics will be used to tabulate and summarize study outcomes. Background and demographic characteristics will be presented.

11.3 Efficacy Analyses

11.3.1 *Primary Efficacy*

The primary efficacy outcome is the mean change in anatomic center subfield thickness and macular volume, measured by OCT. All OCT images will be read by the Investigator and a central reading facility. The primary efficacy outcome is determined by the OCT assessments from the reading center. The Investigator assessed OCT values will be analyzed for informational purposes.

11.3.1.1 Statistical Hypotheses

Not applicable, as no formal hypothesis testing is planned.

11.3.1.2 Analysis Methods

Both the Investigator assessed OCT values and the centrally read OCT values will be collected and analyzed. Descriptive statistics will be used to summarize the study outcomes. Continuous variables will be summarized by descriptive statistics (sample size, mean and standard deviation, median, minimum and maximum). Discrete variables will be summarized by frequencies and percentages. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

11.3.2 *Secondary Efficacy*

The secondary efficacy outcome is the mean change from baseline in BCVA.

11.3.2.1 Statistical Hypotheses

Not applicable, as no formal hypothesis testing is planned.

11.3.2.2 Analysis Methods

Descriptive statistics will be used to summarize the study outcomes. Continuous variables will be summarized by descriptive statistics (sample size, mean and standard deviation, median, minimum and maximum). Discrete variables will be summarized by frequencies and percentages. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

11.3.3 *Supportive Efficacy*

Not applicable.

11.3.4 *Safety Analysis*

Safety parameters to be evaluated include BCVA, slit-lamp and fundus findings, IOP and AEs. Adverse events will be summarized by presenting the number and percentage of subjects having any adverse event. Any other information collected (such as severity or relationship to investigational product) will be listed as appropriate.

11.4 Discontinued Subjects

Discontinued subjects will not be replaced. If a subject requires discontinuation of IP and placement on rescue therapy, that subject should be continued in the study and followed through the end of the study.

12.0 SAFETY

12.1 Safety Outcomes

The safety parameters for the study include:

- BCVA
- Slit-lamp findings
- Fundus findings
- IOP
- AEs

The Investigator may choose to discontinue a subject at any time, if in his/her opinion, it is in the best interest of the subject's safety.

12.2 Safety Definitions

- AE: Any untoward medical occurrence associated with the use of an IP in humans, whether or not considered drug related.
- Adverse Reaction (AR): any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.
- Suspected Adverse Reaction (SAR): Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. A SAR implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.
- Unexpected: An AE or SAR is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator's Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.
- Life-threatening: An AE or SAR is considered "life-threatening" if, in the view of either the Investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- Serious Adverse Event (SAE): Any AE or suspected adverse reaction occurring at any dose that:
    - Results in death.
    - Is life-threatening.
    - Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
    - Requires inpatient hospitalization.
    - Prolongs inpatient hospitalization.
    - Is a congenital anomaly/birth defect.
    - Is a significant medical event (i.e., one that may jeopardize the subject or may require intervention to prevent one or more of the other outcomes listed above).
- Non-serious AE: Any AE that does not meet the definitions for SAEs as described above.

12.3 Classification, Relationship, and Intensity

Each AE will be classified as serious or non-serious using the definitions provided above.

The severity of each ae will be classified as mild, moderate, or severe using the following definitions:

- Mild: An AE is mild if the subject is aware of but can easily tolerate the sign or symptom.
- Moderate: An AE is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities.
- Severe: An AE is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activities.

The Investigator will review each event and assess its relationship to use of IP (unrelated, unlikely, possibly, probably, definitely). The AE will be assessed using the following definitions:

- Unrelated
  - Event occurring before dosing.
  - Event or intercurrent illness due wholly to factors other than IP use.
- Unlikely
  - Poor temporal relationship with IP use.
  - Event easily explained by subject's clinical state or other factors.
- Possible
  - Reasonable temporal relationship with IP use.
  - Event could be explained by subject's clinical state or other factors.
- Probable
  - Reasonable temporal relationship with IP use.
  - Likely to be known reaction to agent or chemical group, or predicted by known pharmacology.
  - Event cannot easily be explained by subject's clinical state or other factors.
- Definite
  - Distinct temporal relationship with IP use.
  - Known reaction to agent or chemical group, or predicted by known pharmacology.
  - Event cannot be explained by subject's clinical state or other factors.

12.4 Pregnancy

Pregnancy occurring during study conduct should be reported immediately to the sponsor on an SAE form, following the reporting requirements listed in Section 12.5. The reason for reporting should be noted as "significant medical event."

12.5 Procedures for Recording and Reporting

All AEs must be documented on the AE eCRF by the site and are monitored on a routine basis by the Sponsor. AEs are collected from the time of informed consent. Any pre-existing medical conditions or symptoms present in a subject are not considered AEs in the study unless there is a clinically significant worsening.

The Investigator must also promptly (i.e., within 24 hours of awareness) document all SAEs with details including the date of occurrence, severity, treatment (if applicable), outcome, and assessments of the seriousness and causality. The site must submit all available information on SAEs to the study Sponsor immediately as follows:

- All available information should be reported into the eCRF and on paper SAE form within 24 hours of becoming aware of the event.
- Document all relevant information from discharge summary, autopsy report, certificate of death, etc. (as applicable), in narrative section of SAE eCRF. Copies of this relevant source documentation should also be redacted and submitted to the Contract Research Organization (CRO), Lexitas Pharma Services, via fax.
- Additional relevant information after initial reporting is to be entered into the eCRF and on paper SAE form as soon as the data become available.
- Document any changes to concomitant medications on the appropriate eCRFs.

The Investigator must also report all SAEs to the IRB/IEC, according to the institution's requirements.

12.6 Unmasking of the Study Information

Masked information on the identity of the randomized treatment should not be disclosed during the study. If the treatment code needs to be broken in the interest of subject safety, the Investigator is encouraged to contact an appropriate study Sponsor representative prior to unmasking the information. Dependent upon the individual circumstances (i.e., medical emergency), the code may be broken prior to contact with the study Sponsor. However, the Sponsor does not anticipate the need for this as all subjects will be on active treatment at varying dose levels. If unmasking does occur without Sponsor consultation, the study Sponsor must be informed of all cases in which the code was broken and of the circumstances involved. Additionally, the study Sponsor may be required to unmask the information in order to fulfill expedited regulatory reporting requirements.

12.7 Follow-Up of Safety Information

The Investigator is responsible for adequate and safe medical care of subjects during the study and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the study. The Investigator should provide the study Sponsor with any new safety information (which includes new AEs and changes to previously reported AEs) that may affect the safety evaluation of the IP. Any

additional data from these follow-up procedures must be documented and available upon the study Sponsor's request.

13.0 DATA HANDLING AND ADMINISTRATIVE REQUIREMENTS

13.1 Completion of Source Documents and Electronic Case Report Forms

The nature and location of all source documents will be identified to ensure that original data required to complete the eCRFs exist and are accessible for verification by the site monitor. If electronic records are maintained, the method of verification must be determined in advance of starting the study. At a minimum, source documents should include the following information for each subject:

- Subject identification (name, sex, race/ethnicity). Documentation of subject eligibility
- Date of informed consent
- Dates of visits
- Documentation that protocol specific procedures were performed
- Results of study parameters, as required by the protocol
- IP accountability records
- Documentation of AEs and other safety parameters (if applicable)
- Records regarding medical histories and the use of concomitant therapies prior to and during the study
- Date of study completion and reason for early discontinuation, if applicable

It is required that the author of an entry in the source documents be identifiable. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the eCRF are consistent with the original source data.

eCRFs will be provided to the sites via a web-based program, and only designated individuals may complete the eCRFs. The eCRFs will be submitted at regular intervals based upon the clinical study visit schedule. It is expected that all data reported will have corresponding entries in the source documents and that the Principal Investigator will review the reported data and certify that the eCRFs are accurate and complete. No subject identifiers should be recorded on the eCRFs beyond subject number, and demographic information.

13.2 Data Review and Clarifications

The eCRF data will be reviewed against the subject's source data by the study monitors to ensure completeness and accuracy. After monitoring has occurred at the clinical sites and the eCRFs have been submitted, additional data clarifications and/or additions may be needed. Data clarifications and/or additions are documented and are part of each subject's eCRFs.

13.3 Regulatory Documentation and Records Retention

The Investigator is required to maintain up-to-date, complete regulatory documentation as indicated by the Sponsor and the Investigator's files will be reviewed as part of the ongoing study monitoring. Financial information is not subject to regulatory inspection and should be kept separately.

Additionally, the Investigator must keep study records and source documents until the Sponsor provides written approval for their destruction. If the Investigator retires, relocates, or for any other reason withdraws from responsibility of keeping the study records, the Sponsor must be notified and suitable arrangements made for retention of study records and source documents needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the latest marketing approval).

13.4 Quality Assurance and Quality Control

The Sponsor will be responsible for implementing and maintaining quality assurance and quality control systems to ensure the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and applicable regulatory requirements. The Sponsor will secure agreement from all involved parties to ensure direct access to all study related sites, source data and documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by domestic and foreign regulatory authorities. Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. Agreements made by the Sponsor with the Investigator/Institution and any other parties involved in the clinical study will be provided in writing as part of the protocol or as a separate agreement.

14.0 REFERENCES

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15.0 APPENDICES

15.1 BCVA (ETDRS)

The site staff should follow their standard procedures for conducting BCVA using ETDRS testing. The general procedure is as follows:

Overview

1. BCVA at a single site should be done consistently throughout the study using the same equipment, lighting conditions etc.
2. BCVA should be performed prior to instillation of any drops to dilate or anesthetize the eye and prior to any examination that requires contact with the eye, including the measurement of IOP.
3. Subjective refraction, using standard ETDRS methods, should be performed prior to measurement of BCVA and the appropriate correction worn in a trial frame.
4. The subject may be seated or may stand and the chart should be at eye level.
5. All eyes are first tested at 4 meters (m) including those that could not be refracted at 4m. Note: for eyes refracted at 1 meter, the additional +0.75 D sphere should be subtracted from the spherical correction before testing vision at 4m.
6. The right eye (OD) should be is tested first using Chart 1 then the left eye (OS) is tested using Chart 2.
7. Each chart should remain hidden from view until the eye in question is to be examined.
8. If less than 20 letters are read with either eye at 4m the eye(s) with the reduced acuity is tested at 1m.

ETDRS Scoring

1. At the end of the test count up the number of letters read correctly by each eye.
2. If 1-meter testing was not required, then add 30 to get the ETDRS letters score.
3. If 1-meter testing was required, the ETDRS letters score is the sum of the letters read at 4 meters and at 1 meter.

To qualify for SF0166-C-001, the subject must have BCVA between 78 and 25 letters, inclusive, in the study eye at the screening/randomization visit using ETDRS testing. There is no visual acuity requirement for the non-study eye.

15.2 Slit-Lamp Biomicroscopy

The biomicroscopy exam will be performed using the Investigator's standard procedure. Areas to be assessed include conjunctiva, cornea, anterior chamber, and lens. Grading scales for these are below.

Conjunctiva	
Bulbar Injection	
0	Absent
1	Mild
2	Moderate
3	Severe
Erythema	
0	Absent
1	Mild
2	Moderate
3	Severe

Cornea	
Edema	
0	Absent
1	Mild
2	Moderate
3	Severe

Anterior Chamber	
Cells	
0	No cells seen
1	1 - 5 cells
2	6 - 15 cells
3	16 - 30 cells
4	Greater than 30 cells
Flare	
0	None
1	Mild (trace to clearly noticeable, visible)
2	Moderate (without plastic aqueous humor)
3	Marked (with plastic aqueous humor)
4	Severe (with fibrin deposits and/or clots)
Hyphema	
0	Absent
1	Mild
2	Moderate
3	Severe

Lens	
Opacity	
0	No opacity in the lens
1	Any opacity in the lens

15.3 IOP

IOP will be measured using a Tonopen or Goldmann applanation. The same method of measurement should be used throughout the study. However, if Tonopen is primarily used and IOP measures ≥25 mmHg during a visit, the measurement should be repeated for confirmation using Goldmann applanation according to the Investigator's standard procedure. All pressures will be recorded in mmHg.

15.4 Spectral Domain OCT

SD-OCT will be performed using either Spectralis Ophthalmic Imaging System SD-OCT (Heidelberg Engineering Inc., Carlsbad, CA 92008) or Cirrus HD-OCT (Carl Zeiss Meditec, Inc., Dublin, CA 94568). The subject's pupil should be dilated and the fast macular thickness map protocol should be utilized. This method obtains data from 6 radial line scans over a diameter of 6 millimeter (mm). Both the average center subfield thickness and the macular volume are of interest in the study. The OCT results will be read by the Investigator and a central reading facility.

15.5 Indirect Ophthalmoscopy/Dilated Fundus Examination

Indirect ophthalmoscopy/dilated fundus examination will be performed according to the Investigator's standard protocol. Areas to be assessed include vitreous, fundus, optic nerve (including cup to disc ratio), macula and choroid, vessels and peripheral retina. An assessment of normal or abnormal will be made for each area. The specific finding for areas that are abnormal will be recorded.

15.6 Fluorescein Angiography

Fluorescein angiography (FA) will be performed according to the Investigator's standard procedure, by injecting fluorescein sodium dye into a peripheral vein of the arm of the subject.

15.7 Fundus Photography

Fundus photographs with a Zeiss FF450 (or comparable) camera will be taken before and after FA, for visits with FA completed. For all other visits, photographs will be taken once during indirect ophthalmoscopy/dilated fundus examination. Images will be uploaded to ShareFile and printed for filing in the subject source documents.

15.8 Dosing Diary

Subjects will be asked to record the following information related to administration of IP each day:

- Date
- Time of Administration

This will be in the format of an IRB-approved dosing diary. The subjects will be requested to bring the diary to the clinic for Visit 2 and Visit 3.

SIGNATURES:	DATE:
 NAME: BEN ASKEW, PHD TITLE: VICE PRESIDENT, RESEARCH FUNCTION: RESEARCH AND DEVELOPMENT	22 NOV 2016
 NAME: HEATHER COULTAS, MSHS TITLE: CLINICAL PROJECT MANAGER FUNCTION: CLINICAL RESEARCH MANAGER	22 NOV 2016