Graybug Vision Inc.

CLINICAL STUDY PROTOCOL

Official Title: A Phase 2a Multicenter Study Evaluating the Safety, Tolerability, and Pharmacodynamics of a Single Injection of a Long-acting Intravitreal Sunitinib Malate Depot Formulation (GB-102) in Subjects with Diabetic Macular Edema (DME) and Retinal Vein Occlusion (RVO)

Protocol Number: GBV-102-003

NCT Number: 04085341

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Sponsor:	Graybug Vision, Inc. 275 Shoreline Drive, Suite 450 Redwood City, CA 94065
IND Number:	128451
Indication:	Macular edema secondary to diabetic retinopathy and retinal vein occlusion
Protocol Number (Phase):	GBV-102-003 (Phase 2a)
Clinical Medical Officer:	[redacted]
Medical Monitor:	[redacted]
Protocol Version/Date:	Version 2.0 / 13 November 2019 (Amendment 1) Version 1.0 / 18 July 2019 (Original)

CONFIDENTIALITY STATEMENT

The information in this document is confidential and will not be disclosed to others without written authorization from Graybug Vision, Inc., except to the extent necessary to obtain informed consent from persons who are potential participants in the study or their legal guardians, persons participating in the conduct of the study, appropriate institutional review boards or independent ethics committees, or duly authorized representatives of the United States Food and Drug Administration or national regulatory authority.

STUDY ACKNOWLEDGEMENT

This protocol has been approved by Graybug Vision, Inc. and will be conducted as outlined herein in accordance with International Council for Harmonisation (ICH) guidelines, Good Clinical Practice (GCP), the Declaration of Helsinki, and will comply with the obligations and requirements of the Sponsor as listed in Title 21 of the United States Code of Federal Regulations. The following signature documents approval of the protocol.

[redacted]

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Graybug Vision, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)	Signature
Date	Study Center Number

PROTOCOL SYNOPSIS

Study GBV-102-003
Graybug Vision, Inc.
275 Shoreline Drive, Suite 450
Redwood City, CA 94065

Study Title:	A Phase 2a Multicenter Study Evaluating the Safety, Tolerability, and Pharmacodynamics of a Single Injection of a Long-acting Intravitreal Sunitinib Malate Depot Formulation (GB-102) in Subjects with Diabetic Macular Edema (DME) and Retinal Vein Occlusion (RVO)
Study Centers Planned:	Approximately 4 to 6 study centers in the United States
Objectives:	**Primary Objective** To evaluate the safety and tolerability of a single intravitreal injection of two different dose strengths of GB-102 (1 mg, 2 mg) in subjects with macular edema secondary to diabetic retinopathy or retinal vein occlusion who have received prior treatment with anti-vascular endothelial growth factor (VEGF) **Secondary Objectives** To evaluate the pharmacodynamic response as measured by best corrected visual acuity (BCVA) and central subfield thickness (CST) and time to first rescue injection.
Study Design:	Multicenter, open-label, single injection, parallel arms, non-controlled safety, tolerability and pharmacodynamics study. Eligible subjects will be consecutively enrolled to 1 of 2 concurrently initiated open-label GB-102 treatment arms: **Group 1**: 1 mg (50-µL) (N=10) **Group 2**: 2 mg (50-µL) (N=10) GB-102 will be administered on Day 1 in both Groups (Table 3-1). Subjects will return to the study center on Days 14, 30, 60, 90, 120, 150, and 180 for safety and clinical assessments. Subjects will exit the study following all study assessments on Day 180. The safety parameters to be collected include adverse events (AEs) and serious adverse events (SAEs), physical examination, vital signs, BCVA using the Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol, slit-lamp biomicroscopy findings, intraocular

	pressure (IOP) measurements, dilated ophthalmoscopy results, and date of administration of rescue treatment. Pharmacodynamic activity will be assessed by means of BCVA (using the ETDRS Protocol), retinal central subfield thickness (CST) using spectral-domain optical coherence tomography (SD-OCT), and color fundus photography (CFP) (including wide field fundus photography, if available). *Safety Monitoring* The medical monitor will evaluate the on-going open-label safety data. *Masking* This is an open-label study and the injecting investigator/physician may be the assessing investigator. The SD-OCT and CFP technicians and other site personnel, the Sponsor, and CRO are unmasked to treatment assignment. *Rescue Treatment* Rescue treatment (any anti-VEGF agent; aflibercept, bevacizumab, or ranibizumab) will be permitted in the study eye in ***any*** of the study arms if the qualifying criteria are met for rescue treatment.
Study Eye Determination:	The **study eye** is defined as the eye that meets all the inclusion criteria and none of the exclusion criteria. If both eyes meet the inclusion and none of the exclusion criteria, the eye with the worst visual acuity at baseline will be selected. If both eyes have the same baseline visual acuity, the right eye will be selected as the **study eye**.
Rescue Treatment Criteria:	Rescue treatment (any anti-VEGF agent; aflibercept, bevacizumab, or ranibizumab) for all subjects enrolled is allowed at any visit following the Day 30 study assessments in subjects who meet any of the following criteria regarding decrease in BCVA and/or increase in CST: Decrease in BCVA: o ≥ 10 ETDRS letter decrease compared with best on-study (i.e., post-treatment) BCVA ETDRS letter score Increase in CST (any of the following criteria): o ≥ 75 µm compared with the average of the last 2 on-study (i.e., post-treatment) visit CST measurements (µm), and/or,

- ≥ 100 μm compared with the lowest on-study (i.e., post-treatment) CST measurement (μm)

The investigator may elect to withhold rescue treatment if, in the opinion of the investigator, further clinical monitoring is warranted (e.g., subject has difficulty reading eye chart due to seasonal allergies and experiences a decline in BCVA but the OCT imaging shows no evidence of fluid).

Rescued subjects will remain in the study for continued scheduled follow-up observation.

Number of Subjects Planned:	Approximately 20 subjects are planned: 10 subjects treated with 1 mg GB-102 and 10 subjects treated with 2 mg GB-102. There is no pre-set limitation on the proportion of DME or RVO subjects per dose group.
Target Population:	Subjects eligible for screening must have a history of macular edema in the **study eye** secondary to DME or RVO that was diagnosed in the 6 weeks to 24 months prior to screening, treated with at least 3 prior intravitreal (IVT) injections of anti-VEGF (aflibercept, bevacizumab, or ranibizumab), and demonstrated a response anti-VEGF treatment. The most recent anti-VEGF treatment must be administered within 42 days of screening. The investigator will interpret SD-OCT used to determine subject eligibility; there is no third-party independent reading center confirmation of any images during screening or treatment/observation.
Duration of Study Participation:	Approximately 210 days (up to 30 days for screening and 180 days of treatment/observation)
Inclusion Criteria:	**All Subjects (DME or RVO)** 1. Verbal and written informed consent obtained from the subject 2. Males or females ≥ 21 years of age 3. Willing and able to give informed consent, comply with all study procedures, and be likely to complete the study 4. Subjects with known diagnosis of diabetic macular edema or macular edema due to retinal vein occlusion (central or branch) in the 6 weeks to 24 months prior to screening who have received at least 3 prior IVT injections of any anti-VEGF agent in the **study eye** and demonstrated a pharmacodynamic response in the **study eye** to IVT anti-VEGF treatment (aflibercept, bevacizumab, or ranibizumab) within 16 weeks of the first anti-VEGF treatment as

determined by the investigator and documented by **at least 1** of the following:

4a. Reduction of intraretinal/subretinal fluid by ≥ 10% from the initial diagnosis as determined using SD-OCT

4b. Reduction of excess CST by ≥ 10% from the initial diagnosis as determined using SD-OCT (assuming nominal thickness is 300 microns)

5. Demonstrate a maintained anti-VEGF response (as determined by the investigator) compared with the initial diagnosis (prior to any anti-VEGF treatment) as assessed by SD-OCT following the most recent anti-VEGF injection (defined as reduction in central subfield thickness, intraretinal/subretinal fluid, or maintenance of a dry retina)
6. Subjects must have the most recent anti-VEGF agent administered within 42 days (6 weeks) of screening in the **study eye**.
7. Screening and baseline BCVA letter score (by ETDRS protocol) of 31 to 88 (20/240 to 20/20 Snellen equivalent)
8. If the screening and baseline BCVA letter score (by ETDRS protocol) in the **nonstudy eye** is worse than the **study eye**, the BCVA score in the **nonstudy eye** must be at least 53 letters (20/100 Snellen equivalent) or better
9. Clear ocular media and adequate pupil dilation in both eyes to permit good quality photographic imaging
10. Women of childbearing potential (ie, not postmenopausal for at least 12 months or not surgically sterile [bilateral tubal ligation, hysterectomy, or bilateral oophorectomy]) must have a negative urine pregnancy test at screening and baseline, and must use adequate birth control throughout the study if she has a nonsurgically sterile male sexual partner; adequate methods of birth control include hormonal contraceptives, intrauterine comtraceptive devices, condom with spermicide, diaphragm with spermicide, and cervical cap with spermicide.

Exclusion Criteria:

1. History, within 6 months prior to screening, of any of the following: myocardial infarction, any cardiac event requiring hospitalization, treatment for acute congestive heart failure, transient ischemic attack, or stroke
2. Uncontrolled hypertension with systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 95 mmHg at the Screening Visit

3. Uncontrolled diabetes mellitus, defined as hemoglobin A1c >12.0% at the Screening Visit
4. Chronic renal disease requiring chronic hemodialysis or renal transplantation
5. Participation in any investigational study within 30 days prior to screening, or planned use of an investigational product or device during the study; any exposure to a prior investigational drug product must be fully washed out (at least 5 half-lives)
6. Previous participation in an investigational study of GB-102
7. Spherical equivalent of the refractive error in the **study eye** demonstrating more than −6 diopters of myopia (prior to cataract or refractive surgery) at the Screening Visit
8. Uncontrolled IOP, defined as an IOP > 25 mmHg, despite antiglaucoma medications in the **study eye** at the time of screening or controlled glaucoma that requires management with > 2 topical hypotensive medications
9. Presence of any clinically significant epiretinal membrane or vitreomacular traction in the **study eye**
10. History or evidence of any of the following in the **study eye**:
    a. Macular surgery or other surgical intervention for AMD
    b. Prior retinal detachment
    c. Vitrectomy
    d. Retinal laser treatment with the exception of prior laser photocoagulation for treatment of diabetic retinopathy
    e. Glaucoma filtering surgery (eg, trabeculectomy) or glaucoma drainage device (eg, Ahmed valve or Baerveldt valve) including minimally invasive glaucoma shunts (eg, minimally invasive glaucoma surgery) prior to the Screening Visit. Selective laser trabeculoplasty (SLT) $\geq$3 months prior to Screening Visit is allowed.
    f. Cataract surgery within the 3 months prior to the Screening Visit
    g. Neodymium:yttrium-aluminum-garnet (Nd:YAG) laser capsulotomy within the 30 days prior to the Screening Visit. Note: prior Nd:YAG laser posterior capsulotomy in association with a posterior intraocular lens implantation is allowed.

h. Corneal refractive procedures (laser-assisted *in situ* keratomileusis [LASIK] or photorefractive keratectomy) within the 6 months prior to the Screening Visit or planned during the study

i. Corneal transplantation surgery

j. History of advanced glaucoma with visual field loss encroaching on central fixation

k. Intravitreal steroid injection (eg, triamcinolone suspension) within the past 3 months, bioabsorbable steroid implant (eg, Ozurdex®) within the past 12 months, and/or presence of any steroid implant in the study eye (eg, Iluvien® or Ozurdex®) at the time of the Screening Visit

l. Active retinal or iris neovascularization in the study eye

11. Anterior chamber intraocular lens, aphakia, or violation of the posterior capsule in the **study eye**

12. History or clinical evidence of other concurrent conditions deemed by the investigator to likely impact the subject's clinical safety or to interfere with the interpretation of the study results including, but not limited to:

    a. Proliferative diabetic retinopathy in the study eye

    b. Choroidal neovascular lesion secondary to wet AMD in the study eye

    c. Any retinal or choroidal vasculopathy, other than due to diabetes or retinal vein occlusion in the study eye

    d. Inflammatory conditions of the anterior or posterior segment (eg, chronic keratoconjunctivitis, uveitis, retinal vasculitis, neuritis, iritis, scleritis, or blepharitis) in the study eye

    e. Subfoveal involvement by any of the following: fibrosis, serous pigmented epithelial detachment, retinal pigmented epithelial tear, or geographic atrophy in the study eye

    f. Subfoveal hemorrhage that is ≥ 1 disc areas in size in the study eye

    g. Any media opacity that prevents proper visualization of the fundus and/or adversely alters visual acuity, in the opinion of the investigator in the study eye

    h. Prior radiation therapy in the region of the eyes

i. History of demyelinating disease (eg, multiple sclerosis, neuromyelitis optica), optic neuropathy, and/or optic neuritis.

13. Any bacterial, viral, fungal, or parasitic infection in either eye within the 30 days prior to the Screening Visit
14. Known allergy to constituents of the study drug formulation, ocular antimicrobicide solutions, or clinically relevant hypersensitivity to fluorescein
15. Women who are pregnant or lactating
16. Men who are unwilling to practice 2 measures of adequate contraception (if having sexual intercourse with a woman of child-bearing potential) or who desire to donate sperm during the time from first dose of study drug until exiting the study. If a male exits the study early and wants to donate sperm, a minimum wait period of 12 weeks following the last dose of study drug is required.
17. Presence of any other concurrent medical or social condition deemed by the investigator to likely interfere with a subject's ability to provide informed consent, comply with the study visits and assessments, or interfere with the interpretation of study results
18. Prior exposure to oral sunitinib malate in the past 6 weeks

Test Product, Dose, and Mode of Administration:

GB-102 is a depot formulation of sunitinib malate (sunitinib) intended for IVT injection. Sunitinib is a small molecule receptor tyrosine kinase that inhibits multiple pathways associated with pathologic angiogenesis including VEGF receptors (VEGFR) -1, -2, and -3 known to be associated with macular edema. The formulation consists of microparticles made from poly(lactic-co-glycolic) acid (PLGA) and methoxy-polyethylene glycol (mPEG)-PLGA. The mPEG component provides a hydrophilic, biocompatible property. During production, the microparticles are surface-treated to facilitate their aggregation upon IVT injection to form a depot in the vitreous. After IVT injection, the microparticles degrade into lactic acid, glycolic acid, and mPEG.

GB-102 is lyophilized and reconstituted with hyaluronic acid prior to intravitreal administration to produce an administered IVT dose of 1 mg or 2 mg sunitinib in a 50 µL injection using a 27-gauge needle.

Subjects will receive their assigned dose (1 mg or 2 mg GB-102) on Day 1 as a single IVT injection.

Reference Therapy, Dose, and Mode of Administration:	No reference therapy is provided in this study (ie, there is no active control arm)
Study Endpoints:	Primary Safety Endpoint • Occurrence of ocular and non-ocular adverse events and serious adverse events at all study visits Secondary Pharmacodynamic Endpoints • BCVA (ETDRS protocol) at all study visits • CST (SD-OCT) at all study visits • Observed subjects rescue-free at each study visit
Statistical Methods:	**Analysis Population** • **Safety analysis set (SS):** Includes all subjects who receive a dose of study treatment. Subjects who receive rescue treatment during the study will be included in the SS. Subjects will be analyzed according to actual treatment received. • **Full analysis set (FAS):** Includes all subjects who receive a dose of study treatment, and complete the baseline and at least one post-baseline visit. All data collected from subjects who receive rescue treatment during the study will be included in the FAS. Subjects will be analyzed according to their assigned treatment regardless of actual treatment received. • **Per protocol analysis set (PP):** Consists of a subset of the FAS and includes subjects with no major protocol violations that would affect the assessment of the pharmacodynamics and rescue data. Data collected after the receipt of rescue therapy during the study will not be included in PP analyses. *Safety Endpoint Analyses* All reported adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) will be summarized by system organ class (SOC) and preferred term (PT). Frequencies and percentages will be provided by treatment group for subjects with TEAEs, treatment related TEAEs, serious TEAEs, serious treatment related TEAEs, TEAEs leading to premature study discontinuation and TEAEs by maximum severity. Separate analyses will be performed for ocular AEs in the study eye, ocular AEs in the non-study eye, and nonocular AEs.

The SS will be the primary population used for analysis of the primary safety endpoint.

Pharmacodynamic Endpoint Analyses

Observed values at each visit and change from baseline values at each follow up visit for BCVA, CST will be summarized using descriptive statistics (eg, means, median, range). The FAS and PP will be used to analyze the pharmacodynamic endpoints.

Sample Size Considerations

The sample size of this study was not selected to support specific statistical hypothesis testing. A sample size of approximately 20 evaluable subjects in the SS analysis set allows for detection of adverse events rates that exceed 15% overall and exceed 30% for each dose with approximately 95% confidence.

Missing Data and Sensitivity Analyses

A minimal amount of missing data is expected since most subjects will undergo the proposed study assessments as part of their standard of care. There will be no imputation for missing data.

Sensitivity analyses will be conducted using the per protocol population.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

GLOSSARY OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADL	activities of daily living
AE	adverse event
AMD	age-related macular degeneration
BCVA	best corrected visual acuity
BRVO	branch retinal vein occlusion
CDM	clinical data manager
CFP	color fundus photography
CFR	code of federal regulations
CI	confidence interval
CNV	choroidal neovascularization
CRA	clinical research associate
CRF	case report form
CRO	clinical research organization
CRVO	central retinal vein occlusion
CST	central subfield thickness
DLT	dose limiting toxicity
DME	diabetic macular edema
DR	diabetic retinopathy
ET	early termination
ETDRS	early treatment diabetic retinopathy study
EU	endotoxin units
FA	fluorescein angiography
FAS	full analysis set
FDA	food and drug administration
FITC	fluorescein isothiocynate
FOV	field of view
GCP	good clinical practice
GLP	good laboratory practice
HD	high dose
HIPAA	health insurance portability and accountability act
HSC	human stem cell
I0	inferior pole
IAG	image acquisition guidelines
IB	investigator's brochure
ICH	international council for harmonisation (of technical requirements for pharmaceuticals for human use)
IgG	immunoglobulin
IOP	intraocular pressure
IRB	institutional review board

IRT	interactive response technology
IVT	intravitreal
LASIK	laser-assisted *in situ* keratomileusis
LD	low dose
LLQ	lower limit of quantitation
LOCF	last observation carried forward
MCMC	monte carlo markov chain
MedDRA	medical dictionary for regulatory activities
MP	microparticles
mPEG	methoxy-polyethylene glycol
NCI-CTCAE	national cancer institute – common terminology criteria for adverse events
Nd:YAG	neodymium:yttrium-aluminum-garnet
NDA	new drug application
NOAEL	no observed adverse effect level
ON	optic nerve
ONL	outer nuclear layer
OU	both eyes
PBS	phosphate buffered solution
PDGF	platelet-derived growth factor
PK	pharmacokinetic
PLGA	poly(lactic-co-glycolic) acid
PP	per protocol
PT	preferred term
RET	re-arranged during transcription tyrosine kinase receptor
RGC	retinal ganglion cell
RPE	retinal pigment epithelium
RVO	retinal vein occlusion
S0	superior pole
SAE	serious adverse event
SAP	statistical analysis plan
SD-OCT	spectral domain – optical coherence tomography
SOC	system organ class
SS	safety set
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
TKI	tyrosine kinase inhibitor
T_{max}	peak exposure
µg	microgram
µl	microliter
US	united states
VEGF	vascular endothelial growth factor

VEGFR	vascular endothelial growth factor receptor

1 INTRODUCTION

1.1 Diabetic Macular Edema (DME)

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes and is a leading cause of vision loss and blindness in working aged adults in the United States and the industrialized world. Diabetic macular edema (DME) is swelling of the central retina that causes vision loss and is an advanced complication of DR. The prevalence of DME increases from < 5% in subjects with recent diagnoses to approximately 30% in those with diabetes for two decades or more. Because the population of people with diabetes is nearly 300 million worldwide and growing rapidly, vision loss from DR is a significant public health issue (Nguyen 2010).

Currently approved treatments for DME/DR include intravitreal (IVT) administration of anti-vascular endothelial growth factor (anti-VEGF) agents, such as aflibercept (EYLEA®) and ranibizumab (LUCENTIS®), or off-label use of bevacizumab (AVASTIN®). Monthly or every other month administration of these agents have demonstrated stabilization or improvements in visual acuity and corresponding reductions in VEGF-mediated retinal edema as observed on optical coherence tomography.

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

Retinal vein occlusions (RVO) is a blockage of veins that drain the retina and are a common type of retinal vascular disease, second only to diabetic retinopathy. The retinal vascular bed is highly organized with little or no overlap in vascular distribution. RVO occurs most commonly due to atherosclerosis of the high-pressure retinal arteries that can compress and occlude the low-pressure draining veins. When retinal vessels are obstructed, there are few collaterals to compensate, and the retina becomes swollen and ischemic leading to the expression of VEGF which, in turn, leads to further vascular permeability and/or hemorrhage, and subsequent vision loss. RVO includes branch vein occlusions (BRVO) and central retinal vein occlusion (CRVO). The incidence of RVO is estimated at 180,000 eyes per year in the United States of which BRVOs account for nearly 80% (Campochiaro 2010).

Currently approved treatments for RVO (BRVO and CRVO) include IVT administration of anti-vascular endothelial growth factor (anti-VEGF) agents of aflibercept and ranibizumab, or off-label use of bevacizumab. Monthly or every other month administration of these agents have demonstrated stabilization or improvements in visual acuity and corresponding reductions in VEGF-mediated retinal edema as observed on optical coherence tomography.

1.3 Unmet Need in DME and RVO: Less Frequent Injections

Despite the effectiveness of IVT anti-VEGF agents to reduce the edema associated with DME/RVO, treatment requires frequent IVT injections to manage these often-chronic conditions – approximately every 4 to 8 weeks. An international survey of retinal specialists reported that the most significant unmet need in managing retinal disease are long-acting sustained drug delivery to reduce the treatment burden for both patients and physicians (ASRS 2016).

To address the unmet medical need in patients with DME and RVO, Graybug Vision has developed a proprietary drug product (GB-102) intended to reduce the frequency of IVT injections (once every 6 to 12 months) and provide a mechanism of action involving blockade of multiple VEGF receptor targets associated with angiogenesis, vascular permeability, and cellular proliferation, which are key biologic processes associated with the progression of macular edema seen in DME and RVO.

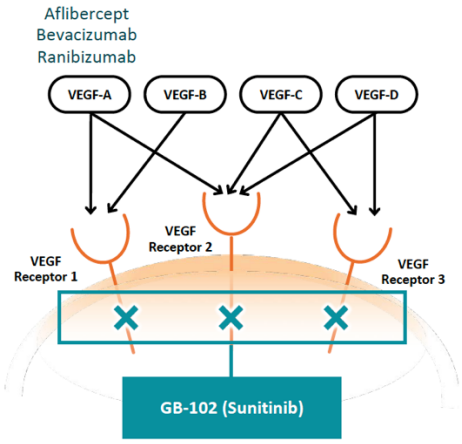
1.4 Investigational Product

GB-102 is a depot formulation of sunitinib malate intended for IVT injection. The formulation consists of microparticles made from poly(lactic-co-glycolic) acid (PLGA) and methoxy-polyethylene glycol (mPEG)-PLGA. The mPEG component provides a hydrophilic, biocompatible property. During production, the microparticles are surface treated to facilitate their aggregation upon IVT injection to form an implant-like depot in the vitreous. After IVT injection, the microparticles degrade into lactic acid, glycolic acid, and mPEG. GB-102 has been engineered to deliver therapeutic doses of sunitinib for at least 6 months with a single 50-µL IVT injection based upon clinical data, theoretically enabling dosing twice yearly as described in Section 1.5.

SUTENT® (sunitinib malate) was approved by the Food and Drug Administration (FDA) and the European Medicines Agency in 2006 in oral capsule form for the treatment of gastrointestinal stromal tumor and renal cell carcinoma, and in 2011 for the treatment of pancreatic neuroendocrine tumor and represents a class of small molecules referred to as receptor tyrosine kinase inhibitors (TKIs).

Sunitinib malate is a small molecule (532.6 g/mol) and is a multiple receptor TKI that prevents receptor phosphorylation and “turns off” the downstream effects of selected receptors, particularly all the vascular endothelial growth factor receptors (VEGFR-1, -2, and -3) (Figure 1-1) which are known to influence macular edema. GB-102 offers the potential for more complete blockade of VEGF-mediated angiogenesis compared to blockade of VEGF-A ligand alone (eg, aflibercept, bevacizumab, or ranibizumab). A full description of sunitinib is provided in the Investigator’s Brochure.

Figure 1-1. Sunitinib Mechanism of Action



1.5 General Information

1.5.1 Nonclinical Studies

Sunitinib malate has been evaluated in nonclinical safety studies in compliance with International Council for Harmonisation (ICH) guidelines to support its approval for cancer indications (SUTENT®). Nonclinical IND-enabling studies describing SUTENT's primary and secondary pharmacodynamics, safety pharmacology, pharmacokinetics (PK), toxicology/toxicokinetics (single and repeat dose), genotoxicity, reproductive toxicity, phototoxicity, and local tolerance (dermal and ocular) have been published in the literature and can be referenced in the Investigator's Brochure for GB-102 (IB).

A summary of the ocular pharmacology, tissue PK, and toxicology for GB-102 and sunitinib follows.

1.5.1.1 Primary Pharmacology - Ocular

Sunitinib has demonstrated evidence of inhibiting angiogenesis, vascular permeability, proliferation, and fibrosis – key findings associated with DME, RVO, and choroidal neovascular lesions in neovascular age-related macular degeneration (nAMD).

Sunitinib has also demonstrated evidence in neuroprotection.

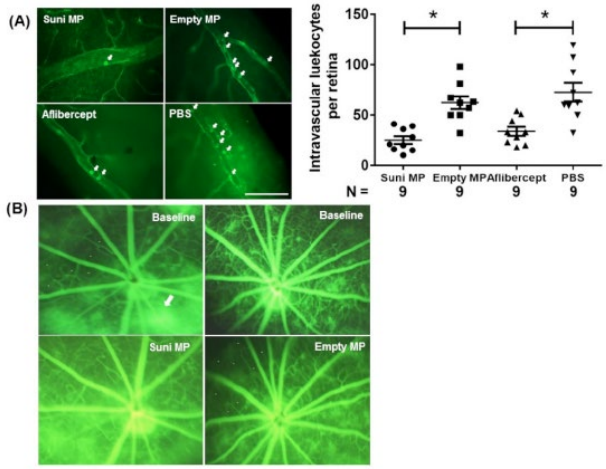
Single Intravitreal Administration of GB-102 Reduces VEGF-induced Leukostasis and Retinal Nonperfusion

VEGF plays a critical role in the pathogenesis of diabetic retinopathy as well as nAMD. Increased levels of VEGF in the retina cause leukocytic plugging and closure of retinal vessel exacerbating retinal hypoxia, the main driver of progression of DR. Adult rho/VEGF mice were given an intravitreous injection of 10 µg sunitinib (GB-102) or 40 µg of aflibercept in one eye and an equivalent mass of empty microparticles (MPs) or phosphate buffered saline (PBS) in the

fellow eye. After one week, mice were perfused with PBS through the left ventricle to remove all non-adherent erythrocytes and leukocytes, and then perfused with FITC-concanavalin A to stain remaining adherent leukocytes. Compared with eyes injected with empty MPs, those injected with sunitinib MPs had a significant reduction in the mean number of adherent intravascular leukocytes (Figure 1-2A). Similarly, aflibercept-injected eyes had a significant reduction in the mean number of adherent intravascular leukocytes compared with PBS-injected eyes.

Rho/VEGF mice also had fluorescein angiography at baseline and then were given an intravitreous injection of 10 µg of sunitinib (GB-102) in one eye and 10 µg of empty MP in the other eye. Some areas of retinal nonperfusion at baseline showed improved perfusion 1 week after injection of GB-102, but this was not seen in empty MP-injected eyes (Figure 1-2B) **(Data on file, 2019)**

Figure 1-2. Intravitreal Injection of GB-102 in rho/VEGF Mice Reduces Leukocytes and Improves Retinal Perfusion

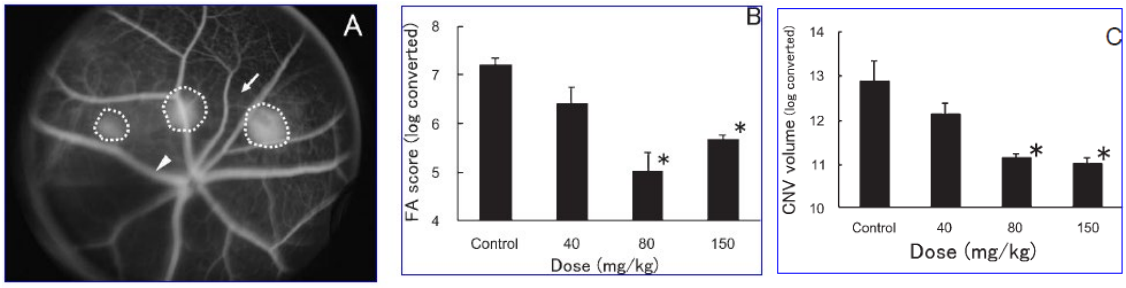


*p< 0.001 by Mann Whitney for difference from corresponding fellow eye control.

Oral Sunitinib Malate Inhibits Choroidal Neovascularization (CNV) in a Murine Laser Injury Model

The initial evidence to demonstrate the ability of sunitinib malate to inhibit choroidal neovascular permeability was in a laser-induced CNV mouse model (Takahashi 2006). Three groups of mice (N = 5 per group) were orally administered 40, 80, 150 mg/kg sunitinib malate or vehicle for 5 days following laser endophotocoagulation of the retina and Bruch's membrane. Permeability leakage of the CNV lesions was assessed by fluorescein angiography (FA) *in vivo.* Volume of the CNV lesions was quantified histologically in ocular cross-sections. The authors reported a dose-response in both the FA scores and histologic CNV lesion volume compared with vehicle control (Figure 1-3).

Figure 1-3. Oral Dosing of Sunitinib Reduces Laser-Induced Choroidal Neovascularization in a Murine Model

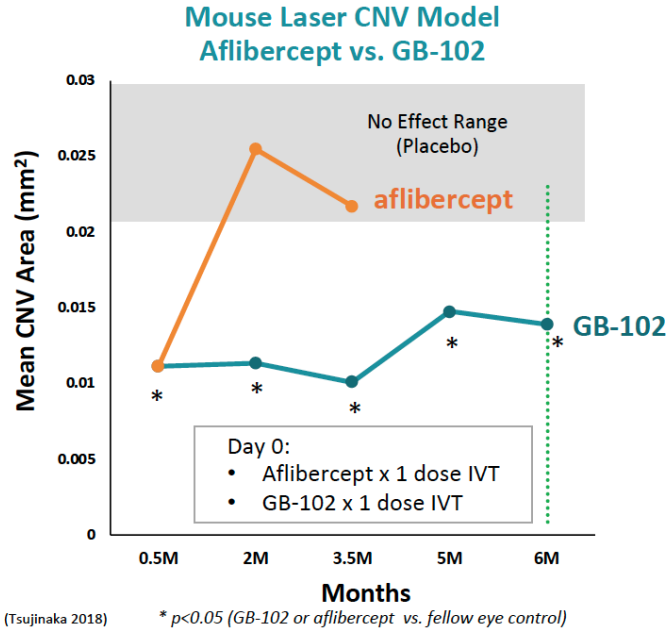


CNV = choroidal neovascularization; FA = fluorescein angiogram
(A) FA
(B) FA scores
(C) CNV histology scores
Source: Takahashi, 2006

Single Intravitreal Administration of GB-102 Demonstrates Sustained Inhibition of CNV in a Murine Laser Injury Model for Up to 6 Months

The murine model of laser-induced rupture of Bruch's membrane results in CNV that is similar to type 2 CNV in patients with nAMD, because the new vessels originate from the choroid and penetrate through Bruch's membrane and the retinal pigmented epithelium (RPE) into the subretinal space (**Data on file, 2019**). Studies in this model helped to implicate VEGF as a critical stimulus for nAMD and predicted the clinical benefits seen with aflibercept, a recombinant VEGF-neutralizing protein commonly used to treat patients subjects with nAMD. In order to assess the efficacy of GB-102 microparticles (MPs) over time, C57BL/6 mice were given an IVT injection of microparticles (MPs) containing 10 µg sunitinib in one eye and empty MPs in the fellow eye and then had laser-induced rupture of Bruch's membrane at 3 locations in each eye at time points ranging from 1 to 24 weeks after injection. Compared with empty MP fellow eye controls, the mean area of CNV at Bruch's membrane rupture sites was significantly less in eyes injected with MPs containing 10 µg sunitinib at each time point through week 24 (Figure 1-4). There was significant suppression of CNV 0.5 months after injection of 40 µg of aflibercept, but not 2 months or 3.5 months after injection.

Figure 1-4. Sustained Reduction in Laser-Induced CNV Following Single Injection of IVT GB-102 Compared to IVT Aflibercept



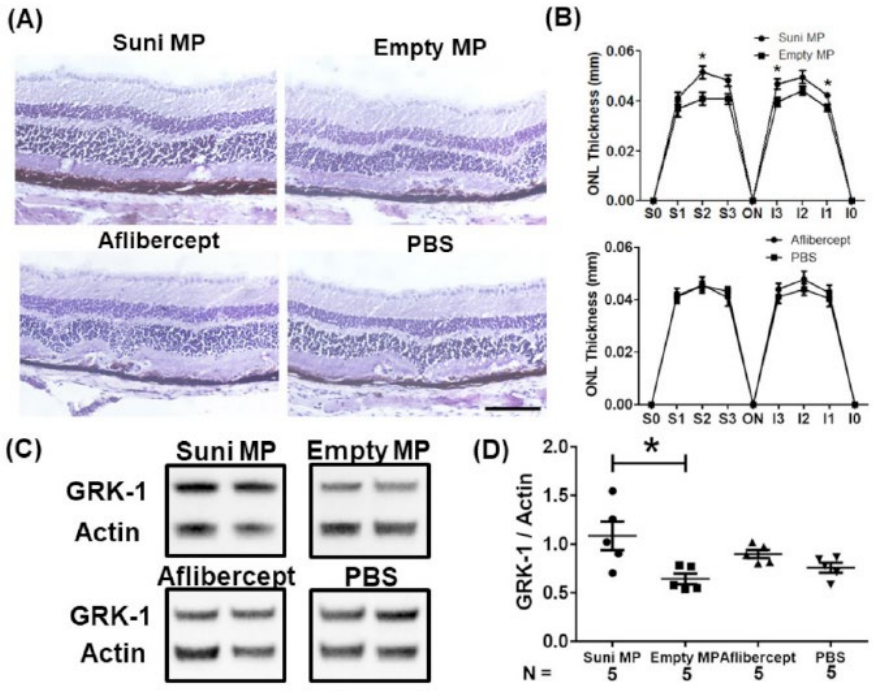
Sunitinib Exhibits In Vitro and In Vivo Neuroprotective Effects in Photoreceptors and Retinal Ganglion Cells

Sunitinib malate was identified as one of the most potent small molecules in promoting retinal ganglion cell (RGC) survival and neurite outgrowth following high through-put screening of various small molecule libraries (Zack 2011). The neuroprotective effects of sunitinib appear to reduce stress-induced apoptosis of RGCs in models of ischemia and optic nerve crush injury (Sharma 2011). Sunitinib also promotes photoreceptor survival and function as demonstrated in a murine light damage model of retinal degeneration (Kim 2015).

Intravitreal GB-102 has been shown to reduce photoreceptor death in preclinical murine models of Type 3 CNV (Figure 1-5) (**Data on file, 2019**) Rho/VEGF mice were given an intravitreous injection of 10 µg of sunitinib microparticles (GB-102) in one eye and 10 µg of empty MP in the other eye or 40 µg of aflibercept in one eye and PBS in the fellow eye. At P42, mice (n=7 for each group) were euthanized and serial frozen ocular sections were cut from the superior pole of the eye (S0) to the inferior pole (I0) and sections 25% (S1 and I1), 50% (S2 and I2), and 75% (S3 and I3) of the distance between each pole and the optic nerve (ON) were stained with hematoxylin and outer nuclear layer (ONL) thickness was measured by image analysis by a masked investigator. The ONL of sections from the S2 location of GB-102-injected eyes appeared thicker than those from empty MP-injected eyes, but those from aflibercept-injected eyes appeared similar to those from PBS-injected eyes (Figure 1-5A). The mean (±SEM) ONL thickness was significantly greater at 3 of 6 locations in GB-102-injected eyes compared with

empty MP-injected eyes, but there was no difference between aflibercept- and PBS-injected eyes (Figure 1-5B). At P49, mice (n=5 for each group) were euthanized and immunoblots of retinal homogenates from GB-102-injected eyes showed prominent bands for rhodopsin kinase (GRK-1) (Figure 1-5C). Densitometry showed that the mean (±SEM) GRK-1/Actin ratio was significantly greater in retinas from GB-102-injected eyes compared with empty MP-injected fellow eyes, but not aflibercept-injected eyes versus PBS-injected fellow eyes (Figure 1-5D).

Figure 1-5. Single Injection of Intravitreal GB-102 Reduces Photoreceptor Death in Rho/VEGF Mice with Type 3 CNV



**p< 0.01 by Mann Whitney for difference from fellow eye empty MP control.

1.5.1.2 Pharmacokinetics of Intravitreal Administration of GB-102 – Preclinical Studies

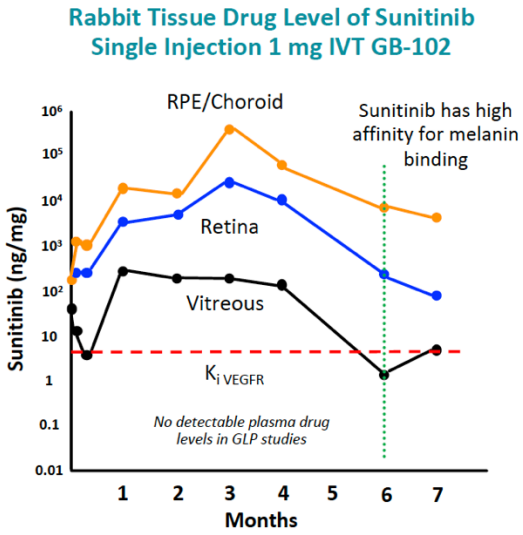
Single Intravitreal Injection of GB-102 Sustains Inhibitory Levels of Drug in the Retinal Pigment Epithelium-Choroid up to 6 Months in Pigmented Rabbits up to 6 Months

Ocular tissue PK was conducted in male pigmented New Zealand rabbits receiving a single IVT administration of sunitinib malate GB-102 (1.0 mg/eye). Tissue levels of drug were determined in the posterior segment (retina, RPE-choroid, vitreous humor) and anterior segment (cornea, iris-ciliary body, and lens) as determined by liquid chromatography/tandem mass spectrometry at various time points (Peterson 2016).

Following injection, sunitinib drug levels are highest in tissues containing melanin pigment (Figure 1-6). Tissue drug levels, in descending order, are as follows: RPE-choroid > iris-ciliary body > retina/lens > cornea > vitreous. There were no toxicological concerns related to pigment-binding discovered during preclinical testing. Drug concentrations of sunitinib are present in RPE-choroid and retina at 2- to 3-log orders higher than the kinetic inhibition constant to suppress VEGFR through 6 months. The depot is fully resorbed by 12- to 14-weeks on ophthalmic examination. The sustained drug levels in the posterior segment tissue following resorption of the depot is attributed to the secondary reservoir effect of the RPE-choroid (melanin binding).

Sunitinib was cleared from posterior segment ocular tissues with an average half-life of approximately 19 days with a range of 2-3.5 weeks. Peak exposure (T_{max}) was typically within 3 to 4 months for retina and RPE-choroid, whereas vitreous T_{max} occurred at 1 month. Given a T_{max} at 3 to 4 months and a half-life of 0.64 months, sunitinib would be cleared from the posterior segment ocular tissues within 6 to 8 months.

Figure 1-6. Ocular Tissue Drug Levels of Sunitinib Following a Single Intravitreal Injection of 1.0 mg GB-102 in Pigmented New Zealand Rabbits



No Systemic Levels of Sunitinib Are Detected Following a Single Intravitreal Injection of 2 mg Dose/Eye of GB-102 in Pigmented Rabbits

A Good Laboratory Practice (GLP) plasma toxicokinetics study was conducted in Dutch belted rabbits receiving a single IVT administration of a 2.0 mg/eye dose of GB-102 (50 µL) (CRL Report 5700643). Plasma samples were assayed for sunitinib (lower limit of quantitation [LLQ] > 0.3 ng/mL) predose and on Days 1, 2, 7, 16, 37, and 99 postdose. No measurable levels of sunitinib were detected systemically at any time point.

1.5.1.3 Toxicology

Sunitinib malate was originally developed as an orally administered agent for the treatment of advanced malignancies at a daily dose of 37 to 50 mg (SUTENT® capsules) The steady state plasma levels of sunitinib at the oral recommended daily dose is approximately 60 to 100 ng/mL. Based on allometric scaling from nonclinical ocular PK studies (rabbits, rats) to humans, it is estimated that a single orally administered approved dose of 50 mg sunitinib in man results in uveal tissue concentration of drug that are 1-log to 2-log orders higher than a single IVT injection of GB-102 containing 1 mg sunitinib (Peterson 2016, Speed 2012).

Three GLP ocular toxicology studies were conducted with GB-102: a single dose study in rabbits, a repeat dose study in rabbits, and a repeat dose study in minipigs.

The ocular toxicity following a single IVT injection (50 µL) of GB-102 at doses of 0, 0.25, 0.5, 1.0, and 2.0 mg/eye in pigmented rabbits was evaluated in a GLP study with up to 19 weeks observation. Assessments were conducted with *in vivo* ophthalmic examination, including ERGs, and postmortem histopathology of the enucleated eyes. The main findings included 1) time- and dose-dependent lens opacities, which were due to the high injection volume (50 µL), and 2) mild anterior and vitreous inflammation, which was due to endotoxin contamination of the test materials.

In the repeat-dose rabbit study, animals received IVT injections of 0.125, 0.25 and 0.5 mg/eye GB-102 (in volumes up to 12 µL). Animals were injected on Day 1 and Day 141 over the course of 40 weeks. GB-102 was well tolerated compared to the GLP single dose ocular toxicology study in rabbits. The main findings in the repeat dose rabbit study included transient ocular inflammation at all dose levels regardless of dose volume, which was not test article related. Focal, peripheral and inferior lens opacities occurred in 3 out of 4 groups, which were test article related.

In the repeat dose minipig study, animals received IVT injections of 0.25, 0.5, and 1 mg/eye GB-102 (in volumes up to 24 µL). Animals were injected on Day 1 and Day 141 over the course of 40 weeks. GB-102 was well tolerated based on all endpoint assessments including no findings on histology. There were no clinical observations of adverse events and no test article-related effects on hematology, coagulation or clinical chemistry parameters, which is consistent with a lack of detectable systemic exposure. The clinical ocular examination observations were limited to a transient, yellow discoloration of the vitreous humor and lens in some animals and there were no test article-related microscopic findings. Therefore, the no-observed-adverse-effect-level (NOAEL) is above the highest dose (1 mg/eye) tested in this study.

Overall, toxicology results indicate that IVT injections of GB-102 twice with a 5-month interval and up to a 10-month observation period in rabbits or minipigs at a corresponding injection volume in the clinic, was well tolerated in the eyes and supports IVT administration of up to 2 mg GB-102 every 6 months in the clinic.

1.6 Clinical Studies

There have been no prior studies of GB-102 in subjects with DME or RVO.

A single IVT injection Phase 1/2a clinical study with GB-102 in subjects with nAMD has been completed and results are provided in the Investigator's Brochure.

1.7 Study Rationale for Protocol GBV-102-003

The purpose of this study is to assess the safety and pharmacodynamics of a single injection of 2 dose levels of GB-102 (1 mg, 2 mg) in subjects with a known diagnosis of macular edema secondary to DME or RVO who have been treated with at least three prior injections of any anti-VEGF agent (aflibercept, bevacizumab, or ranibizumab) and shown evidence of a prior response to anti-VEGF treatment.

1.8 Compliance

This study will be conducted in compliance with this protocol, and in accordance with ICH guidelines, Good Clinical Practice (GCP), the Declaration of Helsinki, and will comply with the obligations and requirements of the Sponsor as listed in Title 21 of the US Code of Federal Regulations (CFR).

2 OBJECTIVES

2.1 Primary Objective

To evaluate the safety and tolerability of a single intravitreal injection of two different dose strengths of GB-102 (1 mg, 2 mg) in subjects with macular edema secondary to diabetic retinopathy or retinal vein occlusion who have received prior treatment with anti-vascular endothelial growth factor (VEGF)

2.2 Secondary Objectives

To evaluate the pharmacodynamic response as measured by best corrected visual acuity (BCVA) and central subfield thickness (CST) and time to first rescue injection.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design Summary

This is a Phase 2a, multicenter, open-label, single injection, parallel arm, non-controlled safety, tolerability and pharmacodynamics study.

Eligible subjects will be consecutively enrolled to 1 of 2 concurrently initiated open-label GB-102 treatment arms (Appendix 18.1):

Group 1: 1 mg (50 µL) (N=10)

Group 2: 2 mg (50 µL) (N=10)

GB-102 will be administered on Day 1 in both Cohorts (Table 3-1). Subjects will return to the study center on Days 14, 30, 60, 90, 120, 150, and 180 for safety and clinical assessments. Subjects will exit the study following all study assessments on Day 180.

The safety parameters to be collected include adverse events (AEs) and serious adverse events (SAEs), physical examination, vital signs, BCVA using the Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol, slit-lamp biomicroscopy findings, intraocular pressure (IOP) measurements, dilated ophthalmoscopy results, and date of administration of rescue treatment.

Pharmacodynamic activity will be assessed by means of BCVA (using the ETDRS Protocol), retinal central subfield thickness (CST) using spectral-domain optical coherence tomography (SD-OCT), and color fundus photography (CFP) (including wide field fundus photography, if available).

Safety Monitoring

The medical monitor will evaluate the on-going safety data in this open-label study.

Masking

This is an open-label study and the injecting investigator/physician may be the assessing investigator. The SD-OCT and CFP technicians and other site personnel, the Sponsor, and CRO are unmasked to treatment assignment.

Rescue Treatment

Rescue treatment (any anti-VEGF agent; aflibercept, bevacizumab, or ranibizumab) will be permitted in the study eye in ***any*** of the study arms if the qualifying criteria are met for rescue treatment.

3.2 Study Design Rationale

The proposed study is designed to assess the safety and pharmacodynamics of a single injection of 2 dose levels of GB-102 (1 mg, or 2 mg) administered in subjects with DME/macular edema

due to RVO who have demonstrated a prior response to at least 3 prior injections of any IVT anti-VEGF agent.

The medical monitor will evaluate masked safety data on an on-going basis.

The planned study assessments (eg, AEs, abbreviated physical examinations, clinical laboratory tests, vital sign measurements, BCVA assessments, IOP, slit-lamp biomicroscopy examinations, SD-OCT, CFP (including wide field of view imaging, if available), dilated ophthalmoscopy evaluations) are conventional parameters used to evaluate the safety and pharmacodynamic activity of pharmacologic agents in retinal disease.

The sample size of this study was not selected to support specific statistical hypothesis testing. A sample size of approximately 20 evaluable subjects in the SS analysis set allows for detection of adverse events rates that exceed 15% overall and exceed 30% for each dose with approximately 95% confidence.

Rescue treatment (any anti-VEGF agent; aflibercept, bevacizumab, or ranibizumab) for the study eye is within the standard-of-care for subjects with DME/macular edema due to RVO for the maintenance of visual acuity and/or the prevention of vision loss.

3.3 Appropriateness of Measurements

The primary aim of the data analyses in this study is to assess the safety, tolerability and pharmacodynamics of a single IVT injections of GB-102 in subjects with DME/macular edema due to RVO who have shown prior response to IVT anti-VEGF agents.

The safety, tolerability and pharmacodynamic parameters to be evaluated in this study are consistent with landmark, randomized, multicenter, registrational drug studies of IVT agents used to treat DME and RVO (Nguyen 2010, Campochiaro 2010).

Table 3-1. Study Plan and Schedule of Assessments

Activity/Assessment	S[a]	B	W 2	M 1	M 2	M 3	M 4	M 5	M 6 (ET)
Visit Day ± Window[b]	**−30 to −3**	**1**	**14±2**	**30±4**	**60±7**	**90±7**	**120±7**	**150±7**	**180±7**
Informed Consent/HIPAA	X								
Inclusion/Exclusion Criteria	X								
Demographics Data	X								
Medical/Medication History	X								
Physical Examination	X								X
Pregnancy Testing[c]	X	X				X			X
Clinical Laboratory Tests[d]	X								
Adverse Events	X	X[e]	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Vital Signs[f]	X	X							X
BCVA (ETDRS)[g]	OU	OU	OU	OU	OU	OU	OU	OU	OU
Slit-lamp Biomicroscopy	OU	OU	OU	OU	OU	OU	OU	OU	OU
IOP[h]	OU	OU	OU	OU	OU	OU	OU	OU	OU
Dilated Ophthalmoscopy	OU	OU	OU	OU	OU	OU	OU	OU	OU
SD-OCT[i]	OU	OU	OU	OU	OU	OU	OU	OU	OU
Intravitreal Depot Photography[j]		SE	SE	SE	SE	SE	SE	SE	SE
GB-102 Injection[k]		SE							
Postinjection Assessment[l]		SE							
Follow-Up Call[e]		+1 day							

B = Baseline Visit; BCVA = best corrected visual acuity; ET = Early Termination; ETDRS = Early Treatment Diabetic Retinopathy Study; HIPAA = Health Insurance Portability and Accountability Act; IOP = intraocular pressure; M = month; OU = both eyes; S = Screening Visit; SD-OCT = spectral domain-optical coherence tomography; SE = study eye; V = visit; W = week

a Screening Visit to occur 3 to 30 days before study baseline (Day 1) to ensure that laboratory results are obtained. Imaging eligibility based on SD-OCT will be investigator determined; there is no reading center confirmation.

b 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 examinations, and ophthalmic imaging must be performed on the same day and cannot be split across 2 or more days. Evaluations should be performed by the same evaluator for the same subject throughout the study whenever possible. If it is not possible to use the same evaluator to follow the subject, then evaluations should overlap (examine the subjects together and discuss findings) for at least 1 visit.

c Urine pregnancy test in women of childbearing potential only; additional pregnancy tests may be performed at any time/day during the study.

d **Chemistry** (non-fasting blood): hemoglobin A1c.

e All subjects will receive a telephone call for the day after the intravitreal injection to assess for any significant complaints or adverse events.

f Heart rate, blood pressure; additional collection of height (without shoes) will be measured at Screening and body weight will be measured at Screening and Month 6/exit.

g Visual acuity assessment using ETDRS protocol at 4 m with manifest refraction will be performed at all visits; 1 m may be performed if needed.

h Goldmann applanation tonometry or Tono-Pen acceptable; however, technique used at baseline must be used at all subsequent visits. Intraocular pressure will be checked before dilation and the IVT injection of study drug at the dosing visit (Baseline [Day 1]).

i Measurements for CST determined by the investigator (no central reading center confirmation)

j Wide field color fundus photography (eg, Optos Ultra-widefield or Zeiss Clarus 500 or other ultra-widefield equipment) of the intravitreal GB-102 depot will be obtained following the dilated ophthalmic examination at all visits – if available at the study site. The initial images of the depot should be obtained at baseline (Day 1) ***after*** the IVT injection of GB-102 and conducted through (and include) the final study visit and any unscheduled visits. The photographs may be used to document the general appearance and rate of bioabsorbability of the depot. If no wide-FOV camera available, standard 30-degree field of view (FOV) imaging documenting the visual axis will be sufficient. For detailed instructions regarding collection of the intravitreal depot CFP imaging, refer to the separately provided guideline.

k Following intravitreal injection of GB-102, the subject should remain seated for approximately 15 minutes post-injection with minimal to no movement of the head (e.g., bending over, shaking head, laying down) and avoid significant eye movement.

l Postinjection assessment to consist of checking for count fingers or hand motion vision within 15 minutes after injection; if needed, subject can be examined (eg, additional IOP assessment or ophthalmoscopy, per discretion of the investigator) prior to going home.

4 SUBJECT POPULATION

4.1 Number of Subjects and Subject Selection

Subjects eligible for screening must have the diagnosis of macular edema secondary to DME or RVO in the **study eye** that was diagnosed in the 6 weeks to 24 months prior to screening and treated with at least 3 prior IVT injections of an anti-VEGF agent (aflibercept, bevacizumab, or ranibizumab) and demonstrated a response to prior treatment within 16 weeks of initial diagnosis and treatment. Subjects must have the most recent anti-VEGF agent administered within 42 days of screening. Eligibility will be determined by the investigating physician based upon his/her interpretation of SD-OCT evaluation of the disease. There is no third-party reading center confirmation of any imaging parameters in this study.

The complete inclusion and exclusion criteria are presented, respectively, in Sections 4.3 and 4.4.

The study is planned to be conducted at approximately 4 to 6 study centers in the US.

4.2 Study Eye Determination

The **study eye** is defined as the eye that meets all the inclusion criteria and none of the exclusion criteria. If both eyes meet the inclusion and exclusion criteria, the eye with the worst visual acuity at Baseline will be selected. If both eyes have the same baseline visual acuity, the right eye will be selected.

4.3 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study.

1. Verbal and written informed consent obtained from the subject
2. Males or females ≥ 21 years of age
3. Willing and able to give informed consent, comply with all study procedures, and be likely to complete the study
4. Subjects with known diagnosis of diabetic macular edema or macular edema due to retinal vein occlusion (central or branch) in the 6 weeks to 24 months prior to screening who have received at least 3 prior IVT injections of any anti-VEGF agent in the **study eye** and demonstrated a pharmacodynamic response in the **study eye** to IVT anti-VEGF treatment (aflibercept, bevacizumab, or ranibizumab) within 16 weeks of the first anti-VEGF treatment as determined by the investigator and documented by **at least 1** of the following:

    4a. Reduction of intraretinal/subretinal fluid by ≥ 10% from the initial diagnosis as determined using SD-OCT

    4b. Reduction of excess CST by ≥ 10% from the initial diagnosis as determined using SD-OCT (assuming nominal thickness is 300 microns)

5. Demonstrate a maintained anti-VEGF response (as determined by the investigator) compared with the initial diagnosis (prior to any anti-VEGF treatment) as assessed by SD-OCT following the most recent anti-VEGF injection (defined as reduction in central subfield thickness, intraretinal/subretinal fluid, or maintenance of a dry retina)
6. Subjects must have the most recent anti-VEGF agent administered within 42 days (6 weeks) of screening in the **study eye**.
7. Screening and baseline BCVA letter score (by ETDRS protocol) of 31 to 88 (20/240 to 20/20 Snellen equivalent)
8. If the screening and baseline BCVA letter score (by ETDRS protocol) in the **nonstudy eye** is worse than the **study eye**, the BCVA score in the **nonstudy eye** must be at least 53 letters (20/100 Snellen equivalent) or better
9. Clear ocular media and adequate pupil dilation in both eyes to permit good quality photographic imaging
10. Women of childbearing potential (ie, not postmenopausal for at least 12 months or not surgically sterile [bilateral tubal ligation, hysterectomy, or bilateral oophorectomy]) must have a negative urine pregnancy test at screening and baseline, and must use adequate birth control throughout the study if she has a nonsurgically sterile male sexual partner; adequate methods of birth control include hormonal contraceptives, intrauterine comtraceptive devices, condom with spermicide, diaphragm with spermicide, and cervical cap with spermicide.

4.4 Exclusion Criteria

1. History, within 6 months prior to screening, of any of the following: myocardial infarction, any cardiac event requiring hospitalization, treatment for acute congestive heart failure, transient ischemic attack, or stroke
2. Uncontrolled hypertension with systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 95 mmHg at the Screening Visit
3. Uncontrolled diabetes mellitus, defined as hemoglobin A1c >12.0% at the Screening Visit
4. Chronic renal disease requiring chronic hemodialysis or renal transplantation
5. Participation in any investigational study within 30 days prior to screening, or planned use of an investigational product or device during the study; any exposure to a prior investigational drug product must be fully washed out (at least 5 half-lives)
6. Previous participation in an investigational study of GB-102
7. Spherical equivalent of the refractive error in the **study eye** demonstrating more than −6 diopters of myopia (prior to cataract or refractive surgery) at the Screening Visit
8. Uncontrolled IOP, defined as an IOP > 25 mmHg, despite antiglaucoma medications in the **study eye** at the time of screening or controlled glaucoma that requires management with > 2 topical hypotensive medications

9. Presence of any clinically significant epiretinal membrane or vitreomacular traction in the **study eye**
10. History or evidence of any of the following in the **study eye**:
    a. Macular surgery or other surgical intervention for AMD
    b. Prior retinal detachment
    c. Vitrectomy
    d. Retinal laser treatment with the exception of prior laser photocoagulation for treatment of diabetic retinopathy
    e. Glaucoma filtering surgery (eg, trabeculectomy) or glaucoma drainage device (eg, Ahmed valve or Baerveldt valve) including minimally invasive glaucoma shunts (eg, minimally invasive glaucoma surgery) prior to the Screening Visit. Selective laser trabeculoplasty (SLT) ≥3 months prior to Screening Visit is allowed.
    f. Cataract surgery within the 3 months prior to the Screening Visit
    g. Neodymium:yttrium-aluminum-garnet (Nd:YAG) laser capsulotomy within the 30 days prior to the Screening Visit. Note: prior Nd:YAG laser posterior capsulotomy in association with a posterior intraocular lens implantation is allowed.
    h. Corneal refractive procedures (laser-assisted *in situ* keratomileusis [LASIK] or photorefractive keratectomy) within the 6 months prior to the Screening Visit or planned during the study
    i. Corneal transplantation surgery
    j. History of advanced glaucoma with visual field loss encroaching on central fixation
    k. Intravitreal steroid injection (eg, triamcinolone suspension) within the past 3 months, bioabsorbable steroid implant (eg, Ozurdex®) within the past 12 months, and/or presence of any steroid implant in the study eye (eg, Iluvien® or Ozurdex®) at the time of the Screening Visit
    l. Active retinal or iris neovascularization in the study eye
11. Anterior chamber intraocular lens, aphakia, or violation of the posterior capsule in the **study eye**
12. History or clinical evidence of other concurrent conditions deemed by the investigator to likely impact the subject's clinical safety or to interfere with the interpretation of the study results including, but not limited to:
    a. Proliferative diabetic retinopathy in the study eye
    b. Choroidal neovascular lesion secondary to wet AMD in the study eye
    c. Any retinal or choroidal vasculopathy, other than due to diabetes or retinal vein occlusion in the study eye

d. Inflammatory conditions of the anterior or posterior segment (eg, chronic keratoconjunctivitis, uveitis, retinal vasculitis, neuritis, iritis, scleritis, or blepharitis) in the study eye

e. Subfoveal involvement by any of the following: fibrosis, serous pigmented epithelial detachment, retinal pigmented epithelial tear, or geographic atrophy in the study eye

f. Subfoveal hemorrhage that is ≥ 1 disc areas in size in the study eye

g. Any media opacity that prevents proper visualization of the fundus and/or adversely alters visual acuity, in the opinion of the investigator in the study eye

h. Prior radiation therapy in the region of the eyes

i. History of demyelinating disease (eg, multiple sclerosis, neuromyelitis optica), optic neuropathy, and/or optic neuritis.

13. Any bacterial, viral, fungal, or parasitic infection in either eye within the 30 days prior to the Screening Visit
14. Known allergy to constituents of the study drug formulation, ocular antimicrobicide solutions, or clinically relevant hypersensitivity to fluorescein
15. Women who are pregnant or lactating
16. Men who are unwilling to practice 2 measures of adequate contraception (if having sexual intercourse with a woman of child-bearing potential) or who desire to donate sperm during the time from first dose of study drug until exiting the study. If a male exits the study early and wants to donate sperm, a minimum wait period of 12 weeks following the last dose of study drug is required.
17. Presence of any other concurrent medical or social condition deemed by the investigator to likely interfere with a subject's ability to provide informed consent, comply with the study visits and assessments, or interfere with the interpretation of study results
18. Prior exposure to oral sunitinib malate in the past 6 weeks

5 INVESTIGATIONAL PRODUCTS

5.1 Study Drug and Administration

5.1.1 Investigational Product (GB-102)

GB-102 is a depot formulation of sunitinib malate intended for IVT injection.

The formulation consists of microparticles made from PLGA and mPEG-PLGA. The mPEG component provides a hydrophilic, biocompatible property. During production, the microparticles are surface treated to facilitate their aggregation upon IVT injection to form an implant-like depot in the vitreous. After IVT injection, the microparticles degrade into lactic acid, glycolic acid, and mPEG. GB-102 microparticles are approximately 25 μm in diameter, which allows IVT delivery in a 50-μL injection using a 27 G thin-walled needle in the inferior *pars plana* (6 o'clock region). The mPEG surface treatment of the microparticles facilitates aggregation into a single bioabsorbable, implant-like depot following IVT injection. This delivery method allows the microparticles to assume residence in the inferior portion of the posterior segment, away from the visual axis. The depot slowly biodegrades over 4 to 6 months. Because the released sunitinib avidly binds to ocular melanin, the RPE serves as a secondary drug reservoir to maintain therapeutic levels of sunitinib even though the depot is fully resorbed.

5.1.2 Study Drug Administration

Each study center will have a trained, technician who will prepare the study drug syringes for IVT injection. The Sponsor will provide the necessary training and all supplies required for the reconstitution of study drug, including vials containing lyophilized GB-102 dry powder, pre-filled syringe with hyaluronic acid, needles, and syringes.

Rescue medication allowed is any anti-VEGF (aflibercept, bevacizumab, or ranibizumab) and should be used in accordance with the sites standard practice in administering these agents for the treatment of DME or RVO. The Sponsor will not supply rescue medication.

Adequate anesthesia and eye preparation materials (eg, povidone iodine solution) will be given prior to the IVT injection per the injecting investigator's standard-of-care. IOP measurement will be obtained before the injection at Baseline (Day 1). The investigational product, regardless of concentration, should be prepared and administered as follows in the study:

GB-102: Reconstituted drug will be administered via IVT injection using a 1-cc tuberculin Luer Lock syringe with a 27 G thin-walled needle.

5.2 Treatment Assignment

5.2.1 Subject Identification Numbers

After signing the informed consent form, each subject will be assigned a unique screening number by the site staff. All screening numbers will be assigned in strict numerical sequence at a study center and no numbers will be skipped or omitted. Subjects who meet all entry criteria (ie, all the inclusion and none of the exclusion criteria) will be confirmed for enrollment. The screening numbers will be used to identify all enrolled subjects throughout the study.

5.2.2 Enrollment and Method of Assigning Subjects to Treatment Groups

This study is open-label with consecutive enrollment. When a potential subject is identified, the investigator must contact Graybug Vision's designated project manager or assigned team member managing enrollment to confirm availability for enrollment/dosing group in the study.

5.3 Study Drug Packaging, Labeling, and Storage

The study drug will be packaged, labeled, and supplied by Graybug Vision's designated supplier. GB-102 will be supplied in sterile, single use, glass vials. One single dose vial, one pre-filled syringe with hyaluronic acid and required materials for reconstitution and syringe preparation for IVT injection will be included in the kits. The designated medication kits should be stored at 2-8°C (36-46°F) and prevented from freezing. A second kit will be provided to include ancillary supplies such as needles, syringes, a drape cloth, alcohol spray, etc. to use during the reconstitution process. The ancillary supplies kits may be stored at room temperature. Additional details are provided in the pharmacy manual.

Rescue medication allowed is any anti-VEGF (aflibercept, bevacizumab, or ranibizumab). The Sponsor will not supply rescue medication nor ancillary supplies used to administer these agents. These anti-VEGF agents should be stored in accordance to the standard practices of the site.

All medication and ancillary supplies kits will be labeled with numbers. The label will also specify the storage conditions and state that the study medication is limited to investigational use.

The study drug must be stored in a secure area and administered only to subjects who entered the clinical study, at no cost to the subject, in accordance with the conditions specified on the study medication kit label and the pharmacy manual.

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

5.4 Study Drug Compliance

All notifications for assignment of medication kits are to be maintained with the study source documents. Additionally, the date, time of study treatment, and the name of the injecting investigator must be documented for each subject in the source record.

5.5 Study Drug Accountability

The investigator must keep accurate accounting of the number of medication kits received from Graybug Vision's designated vendor, the number dispensed to the subjects, and the number returned to the vendor during and at the completion of the study. A detailed dispensing record must also be completed. Only an appropriately qualified person must dispense the study medication to subjects in the study. The medication is to be used in accordance with the protocol by subjects who are under the direct supervision of an investigator.

All clinical study medications/treatments and/or supplies should be stored, inventoried, reconciled and destroyed (on site) per site destruction standard operating procedure according to applicable state and federal regulations or returned to Graybug Vision's designee for destruction.

5.6 Prior and Concomitant Therapy

All past and current use of therapies (eg, aflibercept, bevacizumab, ranibizumab, pegaptanib, and/or verteporfin) to treat CNV prior to screening will be recorded. The subject's source record should include start and stop dates or dates of administration, doses, routes, frequencies, and indications for all therapies.

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

5.6.1 Rescue Treatment

Rescue treatment (any anti-VEGF agent; aflibercept, bevacizumab, or ranibizumab) for all subjects enrolled is allowed at any visit following the Day 30 study assessments in subjects who meet any of the following criteria regarding decrease in BCVA and/or increase in CST:

- Decrease in BCVA:
    - ≥ 10 ETDRS letter decrease compared with best on-study (i.e., post-treatment) BCVA ETDRS letter score
- Increase in CST (any of the following criteria):
    - ≥ 75 µm compared with the average of the last 2 visit on-study (i.e., post-treatment) CST measurements (µm), and/or,
    - ≥ 100 µm compared with the lowest on-study (i.e., post-treatment) CST measurement (µm)

Before rescue treatment is administered, the assessing investigator should confirm, if possible, with the medical monitor.

Use of rescue treatment will be recorded on the case report forms (CRFs) and source documents.

5.6.2 Other Permitted Medications

Medications that are permitted during the study include the following:

- Direct thrombin inhibitor class of drugs such as warfarin, dabigatran, or rivaroxaban
- Aspirin (acetylsalicylic acid)
- Any intravitreally administered anti-VEGF therapy in the **nonstudy eye** for the treatment of wet AMD, DME, and/or RVO (aflibercept, bevacizumab, or ranibizumab)
- Any exposure to a prior investigational drug product that is fully washed out (at least 5 half-lives) and/or or does not meet any of the exclusion criteria

5.6.3 Prohibited Medications

Medications that are not permitted during the study include the following:

- Use of more than 2 topical hypotensive medications for the treatment of glaucoma in the **study eye**
- Intravitreal steroid injection (eg, triamcinolone suspension)
- Any steroid implant in the study eye (eg, Iluvien® or Ozurdex®)
- Oral sunitinib malate
- Any intravitreally administered anti-VEGF therapy in the **study eye** for the treatment of wet AMD, DME, and/or RVO (aflibercept, bevacizumab, or ranibizumab) unless the subject qualifies for rescue treatment per the rescue treatment criteria

5.7 Other Study Supplies

Graybug Vision or its designee will make provisions (directly or indirectly) to supply the study centers with supplies for study drug preparation (syringes, needles, vortex mixers, vial adapters, drape towels, alcohol spray, alcohol prep pads and vial stand), and blood sampling and shipment kits for sunitinib exposure assessment.

Study centers will be allowed to use their own ETDRS supplies, once verified through the BCVA certification process. Study centers will use their own medications/supplies (anti-infective ophthalmic solution, local anesthetic eye drop, dilating eye drop, povidone iodine, cotton tip swabs, sterile fields, and cellulose sponges) to prep the eye for ocular assessments and/or study drug administrations. CLIA-approved urine pregnancy test kits and lab kits for collection of Hemoglobin A1c assessment should be supplied by the site's local laboratory.

6 STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Table 3-1. The procedures to be conducted are summarized by visit within Section 6.2. The investigator must document any deviation from the prespecified protocol procedures and notify the Sponsor or contract research organization if/when deviations occur.

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 examinations, and ophthalmic imaging must be performed on the same day and cannot be split across 2 or more days.

6.1 Subject Entry Procedures

Prospective subjects who meet the entry criteria (inclusion/exclusion criteria) defined in Sections 4.3 and 4.4 will be considered for inclusion in this study.

The study will be discussed with each subject and a subject wishing to participate must give informed consent prior to the study center performing any study related procedures or changes in concomitant treatment. All subjects must also give authorization and other written documentation in accordance with relevant country and local privacy requirements (where applicable) prior to the study center performing any study related procedures or changes in concomitant treatment.

Each subject who provides informed consent will be assigned a screening number that will be used on all source documentation throughout the study. A subject is considered to enrolled into the study at the time of administration of the first dose on Day 1.

Subject eligibility based on lesion characteristics must be determined by the investigating prior to subject treatment; there is no third-party confirmation of images obtained at screening or during the conduct of the study. In addition, screening laboratory test (i.e., hemoglobin A1c) must be performed, and the results must be evaluated and determined to be acceptable to the investigator prior to subject enrollment into the study.

A urine pregnancy test administered to women of childbearing potential at the Screening and Baseline visit must be negative for the subject to receive study drug at the Baseline visit.

6.2 Study Visit Procedures

6.2.1 Screening (Day −30 through Day −3)

The Screening Visit should occur 3 to 30 days before study Baseline (Day 1) to ensure that laboratory results are obtained and the investigator has confirmed eligibility. The following procedures are to be performed at this visit:

- Obtain informed consent and authorization
- Collect demographic information and medical and ophthalmic history
- Collect information about concomitant medications and procedures
- Conduct a physical examination
- Draw blood samples for hemoglobin A1c
- Conduct a urine pregnancy test on women of childbearing potential (note that additional pregnancy tests may be performed at any time/day during the study)
- Obtain vital signs (blood pressure, heart rate, height [without shoes] and weight)
- Assess BCVA (using the ETDRS protocol with manifest refraction) in both eyes
- Perform the slit-lamp biomicroscopy of both eyes
- Measure IOP (via Goldmann applanation tonometry or Tono-Pen) in both eyes (the same measurement method should be used throughout the study)
- Perform dilated ophthalmoscopy of both eyes
- Obtain SD-OCT imaging of both eyes
- Assess the subject regarding the inclusion/exclusion criteria
- Query for AEs
- If the subject meets the entry criteria, schedule the subject to return for the Baseline visit, otherwise, exit the subject from the study as a screen failure

6.2.2 Baseline (Day 1)

The following procedures are to be performed:

- Review concomitant medications and procedures
- Query for AEs
- Conduct a urine pregnancy test on women of childbearing potential (note that additional pregnancy tests may be performed at any time/day during the study)
- Obtain vital signs (blood pressure and heart rate)

- Assess BCVA (using the ETDRS protocol with manifest refraction) in both eyes
- Perform the slit-lamp biomicroscopy of both eyes
- Measure IOP (via Goldmann applanation tonometry or Tono-Pen) in both eyes (must be performed prior to the IVT injection of study drug)
- Perform dilated ophthalmoscopy of both eyes
- Obtain SD-OCT imaging of both eyes

After completion of these procedures, if the subject still meets entry criteria, and the investigator has confirmed subject eligibility based on ocular inclusion/exclusion criteria, the results from the screening blood chemistry (i.e., hemoglobin A1c) and urine pregnancy tests, as well as BCVA assessments, and obtained sponsor confirmation to enroll, the subject can be prepared for treatment.

- When medically appropriate, dispense pre-injection and postinjection anti-infectives according to standard clinic procedure at the study center
- Perform the IVT injection of the allocated dose of study drug into the study eye
- Perform the postinjection assessment of the study eye checking for count fingers or hand motion vision within 15 minutes after injection while ensuring that the subject has minimal to no movement of the head and avoids significant eye movement during the 15 minutes after injection. If needed, the subject can be examined (eg, additional IOP or ophthalmoscopy) per the discretion of the injecting investigator prior to going home.
- Perform CFP in the study eye to document the position of the depot and the status of the visual axis
- Schedule the subject to return for the Week 2 visit
- All subjects will receive a telephone call from qualified study center personnel as a safety follow-up the day after the IVT injection procedure

6.2.3 Week 2 and Months 1, 2, 3, 4, and 5

The visits windows are as follows: Week 2 (Day 14 ± 2) and Months 1, 2, 3, 4, and 5 (Day 30 ± 4, Day 60 ± 7, Day 90 ± 7, Day 120 ± 7, Day 150 ± 7).

The following procedures are to be performed at each of the visits unless otherwise specified:

- Review concomitant medications and procedures
- Query for AEs

- Conduct a urine pregnancy test on women of childbearing potential at Month 3 only (note that additional pregnancy tests may be performed at any time/day during the study)
- Assess BCVA (using the ETDRS protocol with manifest refraction) in both eyes
- Perform the slit-lamp biomicroscopy of both eyes
- Measure IOP (via Goldmann applanation tonometry or Tono-Pen) in both eyes
- Perform dilated ophthalmoscopy of both eyes
- Obtain SD-OCT imaging of both eyes
- Perform CFP in the study eye to document the position of the depot and the status of the visual axis
- Schedule the subject to return for the next study visit

6.2.4 Month 6 (Day 180 ± 7) / Early Termination

The following procedures are to be performed:

- Review concomitant medications and procedures
- Query for AEs
- Conduct a physical examination
- Conduct a urine pregnancy test on women of childbearing potential
- Obtain vital signs (blood pressure, heart rate and weight)
- Assess BCVA (using the ETDRS protocol with manifest refraction) in both eyes
- Perform the slit-lamp biomicroscopy of both eyes
- Measure IOP (via Goldmann applanation tonometry or Tono-Pen) in both eyes
- Perform dilated ophthalmoscopy of both eyes
- Obtain SD-OCT imaging of both eyes
- Perform CFP in the study eye to document the position of the depot and the status of the visual axis
- Exit the subject from the study

If follow-up is needed after the early termination visit, it should occur as a poststudy, unscheduled visit at the discretion of the investigator.

Subjects with an ongoing SAE at this visit should be followed until the event resolves or stabilizes as described in Section 8.8.

6.3 Screen Failures

Subjects who miss a scheduled visit prior to the baseline (Day 1) visit or do not qualify for enrollment in the study will be considered screen failures.

6.4 Unscheduled Study Visits

Unscheduled visits may be necessary due to AEs or other reasons. The investigator may examine a subject as often as is medically necessary while the subject is enrolled in the study. Any follow-up that is performed to monitor subject safety should be recorded as an unscheduled visit. The following procedures may also be conducted at an unscheduled visit as well as any procedures deemed necessary by the investigator to assess safety:

- Monitor and query AEs
- Record changes in concomitant medications

6.5 Subject Discontinuation

Subjects should not be withdrawn due to an AE (unless related to subject death), pregnancy, lack of efficacy, protocol deviations, or other reason except for the subject withdrawing consent, or being lost to follow-up. If a subject is enrolled in the study and discontinues from treatment, he/she should be encouraged to remain in the study through study completion to allow continued safety assessment and monitoring, unless the subject withdraws consent.

In the event of subject withdrawal prior to the end of the study, study assessments for the early termination visit should be conducted whenever possible. If a subject withdraws from the study, he or she may not re-enter the study. At the time of withdrawal, the investigator should advise the subject of other available treatment options. When a subject withdraws from the study, the reason(s) for withdrawal will be recorded on the CRF.

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

If a subject fails to return for a scheduled visit, it is the responsibility of the investigator or designee to document all efforts made to contact the subject and to determine the reason the subject did not return. If a subject cannot be contacted with 3 documented telephone call attempts, followed by a certified letter, and does not have a known reason for discontinuation (eg, withdrawal of consent), 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.

6.6 Subject Replacement

One rescreening of a nontreated screen failure subject may be allowed.

If an enrolled (i.e., treated) subject withdraws prior to Month 3, for any reason, the subject may be replaced following discussion with the medical monitor.

6.7 Study Termination Criteria

The Sponsor may terminate this study at any time for any reason. The Sponsor also may discontinue participation by an individual investigator or study center for poor enrollment or noncompliance. At the time of study termination, any active subjects should complete the early termination visit. All ongoing AEs should be followed as appropriate and all ongoing SAEs should be followed until the resolution or stabilization.

7 STUDY ASSESSMENTS

This section describes the study assessment procedures. Refer to Appendix 18.1 and Table 3-1 for information regarding the timing of each assessment.

7.1 Demographic Data

Demographic data will be recorded including date of birth, sex, eye color, race, and ethnicity.

7.2 Medical and Medication History/ Concomitant Medications

Medical history will be recorded and should elicit all major illnesses, diagnoses, and surgeries for the subject within the past two years prior to screening. All ocular history will also be recorded and should be specific to eye involvement, as appropriate.

All past and current use of therapies (eg, aflibercept, bevacizumab, and ranibizumab) to treat DME/RVO prior to screening will be recorded. The subject's source record and CRF should include start and stop dates, dose, route, frequency, and indication.

Other prior and concomitant medications taken from 30 days prior to screening through the last study visit will be recorded and will include any prescription and over-the-counter medications, as well as herbal or nutritional supplements; the subject's source record should include start and stop dates, dose, route, frequency, and indication.

Prior SD-OCT assessments and visual acuity values must also be recorded for the past 24 months if available.

7.3 Physical Examination

The physical examination will consist of, at a minimum, a routine evaluation of the organ systems including general appearance, neck, head, ears, nose, throat, cardiovascular, respiratory, abdomen, and skin/extremities. At the final study visit, the physical examination will include a query of the subject to determine if changes in his/her physical condition have occurred since the screening examination.

7.4 Pregnancy Testing

Urine pregnancy testing will be conducted on women of childbearing potential as appropriate. Women of childbearing potential (ie, not postmenopausal for at least 12 months or not surgically sterile [bilateral tubal ligation, hysterectomy, or bilateral oophorectomy]) must have a negative urine pregnancy test at Screening and Baseline, and must use adequate birth control throughout the study if she has a nonsurgically sterile male sexual partner. Adequate methods of birth control include hormonal contraceptives, intrauterine contraceptive device, condom with spermicide, diaphragm with spermicide, and cervical cap with spermicide.

7.5 Blood Chemistry

Blood samples for Hemoglobin A1c will be collected using the site's local laboratory. Samples and results should be obtained prior to administration of study drug. The minimum tests to be performed include the following:

- Nonfasting chemistry (blood): Hemoglobin A1c

7.6 Vital Signs

Vitals signs will consist of blood pressure and heart rate measurements. Systolic and diastolic pressure and heart rate (bpm) will be measured after subjects have been at rest (seated) for at least 5 minutes. The same arm and method of obtaining blood pressure and heart rate should be used throughout the study. Measurements may be repeated once at the discretion of the investigator. Along with the vital signs, height (without shoes) will be measured at Screening and body weight will be measured at Screening and Month 6.

7.7 Best Corrected Visual Acuity

Manifest refraction will be conducted prior to BCVA. The BCVA assessment will be conducted for each eye, prior to dilating pupils, using the standard ETDRS protocol with back-illuminated eye charts. A study-specific manifest refraction and BCVA testing protocol is described in a separately provided BCVA Manual.

Visual acuity testing will be performed by a certified visual acuity examiner and should occur before any examination requiring contact with the eye. The same BCVA examiner should be utilized for each subject throughout the study when possible.

7.8 Slit-lamp Biomicroscopy

Slit-lamp biomicroscopy will be performed for each eye by a qualified assessing investigator at each study visit. Slit-lamp biomicroscopy, including magnification, will be performed without dilation of the pupil and consistent with standard practice. The subject will be seated during the examination. This procedure should be conducted in the same manner for all subjects and will include an assessment of each of the following as normal or abnormal:

- Eyelids
- Conjunctiva
- Cornea
- Anterior chamber
- Iris

- Pupil
- Lens

If any findings are abnormal, exact findings should be specified and noted as either clinically or not clinically significant.

7.9 Intraocular Pressure

IOP will be measured according to routine clinical practice using Goldmann applanation tonometry or Tono-Pen in both eyes at all study visits. At the Baseline (Day 1) dosing visit, IOP must be performed prior to dilation and the IVT injection of study drug. A single measurement will be made to obtain a determination of the IOP at each study visit. Whether Goldmann applanation tonometry or Tono-Pen is used during the study, the Investigator's standard technique will be used throughout the study. In addition, all reasonable efforts will be made to have the same examiner obtain all IOP measurements for a given subject using the same instrument for screening and the subject follow-up assessments for each subject.

The Goldmann applanation tonometer or Tono-Pen instrument must be calibrated for accuracy before the first subject in the study at a given study center undergoes the first examination, and continue to be performed in accordance with the manufacturer's specifications until the last subject at the study center has exited the study. For detailed instructions regarding instrument calibration, refer to the calibration instructions supplied with the instrument.

7.10 Dilated Ophthalmoscopy

Dilated fundus examination of both eyes will be performed in all subjects by designated qualified study center personnel (i.e., an ophthalmologist). The following will be observed for the presence of abnormalities:

- Vitreous body
- Macula
- Peripheral retina
- Choroid
- Optic nerve

If any findings are abnormal, exact description of the findings should be specified and noted as either clinically or not clinically significant. All abnormal findings that are clinically significant and were not present at baseline, will be described and reported as AEs.

7.11 Spectral Domain – Optical Coherence Tomography

The SD-OCT imaging will be performed for both eyes to measure and assess cross-sectional images of the anatomic layers of the retina and to detect the presence of retinal fluid. Images will be obtained using a SD-OCT device by designated certified study center personnel. Preferably the same device will be used for screening and the subsequent follow-up assessments for each subject. For detailed instructions regarding collection of SD-OCT imaging, refer to the separately provided Image Acquisition Guidelines (IAG).

7.12 Intravitreal Depot Color Fundus Photography

CFP images will be taken on each subject's study eye to help identify the IVT GB-102 depot and the status of the visual axis. The initial images of the depot in the study eye, as well as the status of the visual axis should be obtained at baseline (Day 1) ***after*** the IVT injection and conducted through study completion at each visit for all subjects. Where available, Zeiss Clarus 500, Optos California Ultra-widefield or other specified Fundus Imaging systems should be used to collect these images.

The photographs may be used to document the general appearance and rate of bioabsorbability of the depot and to confirm that the depot is not interfering with the visual axis. For detailed instructions regarding collection of the IVT depot CFP imaging, refer to the separately provided guideline.

7.13 Postinjection Assessments

Following intravitreal injection of GB-102 at the Baseline (Day 1) visit, the subject should remain seated for approximately 15 minutes post-injection with minimal to no movement of the head (e.g., bending over, shaking head, laying down) and avoid significant eye movement.

During this 15 minute-time period, the injecting investigator/physician will assess postinjection safety using count fingers or hand motion vision. The injecting investigator/physician can conduct additional safety assessments (eg, additional IOP measurement and/or ophthalmoscopy), if needed, prior to the subject leaving the clinic. All subjects will receive a telephone call from the study center the following day to ensure there are no significant complaints or AEs.

8 ADVERSE EVENTS

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

- Event description (diagnosis preferred, if unknown, record the signs/symptoms)
- Onset and resolution dates
- Severity (intensity)
- Relationship to study drug or study procedure (causality) as determined by the assessing investigator
- Seriousness
- Expectedness
- Action taken with study drug
- Action taken with nondrug therapy
- Outcome

8.1 Definition of an Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

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
- Vital sign or ophthalmic assessment that is assessed as clinically significant and different from baseline (eg, 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 (eg, "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 (eg, "cough, rhinitis, and sneezing" might be grouped together as "upper respiratory tract infection").

- Progression of neovascular AMD, including worsening of anticipated clinical signs or symptoms, which are collected as clinical efficacy variable and assessed as unequivocally associated with the disease progression and/or lack of efficacy, should NOT be reported as AEs unless disease progression is greater than anticipated in the natural course of the disease.

- A pre-existing condition is not considered an AE unless the condition worsens (increases in frequency, severity, or specificity) during or following study drug administration. Fluctuations in a pre-existing condition should be assessed by the investigator, and those that fall within the limits of expected fluctuations for the disease state (and are not assessed as worsening of the disease) should not be considered AEs. Any change assessed as clinically significant worsening of the disease from baseline must be documented as an AE.

- Elective surgery or routine diagnostic procedures are not considered AEs. However, an untoward medical event occurring during the prescheduled 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.

A treatment emergent adverse event (TEAE) is an AE with an onset anytime from when the subject has received study drug through 30 days after the study ends whether or not it is considered causally related to the study drug.

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

8.1.1 Severity

Refer to Appendix 18.2 and Appendix 18.3 for definitions and assessment scales for ocular and nonocular/systemic AEs.

8.1.2 Expectedness

The expectedness of an AE should be determined based upon existing safety information about the investigational product using these explanations:

- *Unexpected*: an AE that is not listed in the IB or is not listed at the specificity or severity that has been observed.

- *Expected*: an AE that is listed in the IB at the specificity and severity that has been observed.

- *Not applicable:* an AE unrelated to the investigational product.

Adverse events that are mentioned in the IB as occurring with a class of products or as anticipated from the pharmacological/ mechanical (or other) properties of the product, but are not specifically mentioned as occurring with the particular product under investigation are to be considered unexpected.

The investigator should initially classify the expectedness of an AE, but the final classification is subject to the Medical Monitor's and Sponsor's determination.

8.2 Serious Adverse Event

All AEs will be assessed as either serious or nonserious. An SAE is any event that involves or results in any of the following outcomes:

- Death

- Life-threatening occurrence (ie, 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 in-patient 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)

An 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 jeopardizes the subject or requires 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 in-patient hospitalization, or the development of drug dependency or drug abuse.

8.3 Study Drug Causality

The assessing investigator will assess the relationship of the AE to the study drug or study procedure as either related or not related. The following should be taken into consideration when assessing AE 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

8.4 Adverse Event Reporting Procedures

The occurrence of AEs should be sought by nonleading 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?" An AE may also be detected when volunteered by the subject during and between visits, or through physical examination or other assessments. All AEs (serious and nonserious) 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 CRF.

All SAEs, whether or not related to study drug, must be reported to the Sponsor or Sponsor's designated Pharmacovigilance contact immediately and must be submitted on an SAE report form within 24 hours after the investigator becomes aware of the event.

If an SAE occurs, the study center should immediately notify Graybug Vision email notification: GB102@oraclinical.com. The project manager will notify the medical monitor and/or the Sponsor immediately (within 24 hours).

Alternatively, the investigator may contact the medical monitor directly:

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 Sponsor's designated project manager 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 Sponsor's designated project manager. If only limited information is initially available, follow-up reports are required. Additional relevant information

such as hospital records, laboratory test results, or autopsy reports should be provided as soon as these are available.

8.5 Reporting Serious Adverse Events to Regulatory Agencies

An AE, whether serious or nonserious, is considered "unexpected" if the event is not reported in the clinical safety section of the reference document (eg, an IB or package insert) or if the event is of greater severity or frequency than is reported in the reference document.

Expedited reporting of SAEs is required for serious events that are both unexpected based on the reference document and considered related to the study drug (ie, 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 (eg, 21 CFR 312.32).

Expedited reports will also be distributed to investigators. Upon receiving such notices, the investigator must immediately submit a copy of this information to the governing institutional review board (IRB) in accordance with the board's guidelines and any applicable local regulations.

8.6 Pregnancy

Pregnancy alone is not an AE. However, any report of pregnancy in a female subject at any time during the study and that becomes known to the investigator, must be reported to the Sponsor even if the subject is withdrawn from the study. The pregnancy should be followed to term, reporting the outcome after delivery.

8.7 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 CRF. Overdoses leading to an SAE will be handled in accordance with SAE reporting procedures.

8.8 Follow-up of Adverse Events

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

All nonserious AEs will be followed through the last study visit. If a nonserious AE is first identified at the last scheduled study visit, the event will be recorded on the AE CRF with the current status noted, but no further follow-up is required.

9 STATISTICAL CONSIDERATIONS

9.1 General Methods of Analysis

No formal hypothesis testing will be conducted

General descriptive statistics will be used to evaluate the data (eg, means, median, ranges, standard deviations). All summaries will be presented by treatment group and, where appropriate, by visit.

9.2 Study Endpoints

9.2.1 Primary Endpoint

- Occurrence of ocular and nonocular AEs and SAEs

9.2.2 Secondary Pharmacodynamic Endpoints

- BCVA at all study visits
- CST at all study visits
- Observed subjects who are rescue-free at each study visit

9.3 Analysis Populations

Three analysis sets will be defined as follows:

- **Safety analysis set (SS)**: Includes all subjects who receive a dose of study treatment. Subjects who receive rescue treatment during the study will be included in the SS. Analyses will group subjects according to the treatment actually received.
- **Full analysis set (FAS):** Includes all subjects who receive a dose of study treatment, and complete the baseline and at least one post-baseline visit. All data collected from subjects who receive rescue treatment during the study will be included in the FAS. Subjects will be analyzed according to their assigned treatment regardless of actual treatment received. The analyses conducted on the FAS will be considered primary for all efficacy analyses.
- **Per protocol analysis set (PP):** Consists of a subset of the FAS and includes subjects with no major protocol violations that would affect the assessment of the pharmacodynamics and rescue data. Data collected after the receipt of rescue therapy during the study will not be included in PP analyses. The PP analyses will be considered secondary for all efficacy analyses.

9.4 Sample Size Considerations

The sample size of this study was not selected to support specific statistical hypothesis testing. A sample size of approximately 20 evaluable subjects in the SS analysis set allows for detection of adverse events rates that exceed 15% overall and exceed 30% for each dose with approximately 95% confidence.

9.5 Analyses

9.5.1 Safety Analyses

All reported adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) will be summarized by system organ class (SOC) and preferred term (PT). Frequencies and percentages will be provided by treatment group for subjects with TEAEs, treatment related TEAEs, serious TEAEs, serious treatment related TEAEs, TEAEs leading to premature study discontinuation, and TEAEs by maximum severity. Separate analyses will be performed for ocular AEs in the study eye, ocular AEs in the non-study eye, and nonocular AEs.

The SS will be the primary population used for analysis of the primary safety endpoint.

9.5.2 Pharmacodynamic Analyses

Observed values at each visit and change from baseline values at each follow up visit for BCVA, CST will be summarized using descriptive statistics (eg, means, median, range). The FAS and PP will be used to analyze the pharmacodynamic endpoints.

9.6 Changes in the Conduct of the Study

Only Graybug Vision may modify the protocol. Any change in study conduct considered necessary by the investigator will be made only after consultation with Graybug Vision, who will then issue a formal protocol amendment to implement the change. The only exception is when an investigator considers that a subject's safety could be compromised without immediate action. In these circumstances, immediate approval of the chairman of the IRB must be sought, and the investigator should inform Graybug Vision and the full IRB within 2 working days after the emergency occurs.

With the exception of minor administrative or typographical changes, the IRB must review and approve all protocol amendments. Protocol amendments that have an impact on subject risk or the study objectives, or require revision of the informed consent document, must receive approval from the IRB prior to their implementation.

When a protocol amendment substantially alters the study design or the potential risks or burden to subjects, the informed consent document will be amended and approved by Graybug Vision and approved by the IRB; all active subjects must provide written informed consent using the revised consent form once available.

10 DATA QUALITY ASSURANCE

Graybug Vision personnel (or designee) will visit the study center prior to initiation of the study to review with the study center personnel information about the study drug, protocol and other regulatory document requirements, any applicable enrollment procedures, source document requirements, CRF completion, monitoring requirements, and procedures for reporting AEs, including SAEs.

At visits during and after the study, the Sponsor and/or designee will monitor the study center for compliance with regulatory documentation, with a focus on accurate and complete recording of data on CRFs from source documents, adherence to protocol, randomization (if applicable), SAE reporting, and drug accountability records.

A Sponsor-designated clinical data management group will design and program a study database and corresponding CRFs, and will provide training for study centers and clinical research associates (CRA) on data entry and cleaning procedures. The data quality control and analysis will be performed by Graybug Vision (or designee), including study monitoring and clinical data management, based on a predefined data management plan and a SAP.

11 ELECTRONIC CASE REPORT FORMS AND SOURCE DOCUMENTS

Electronic data capture will be used. Therefore, subject data from source documents will be entered directly into the clinical database at the study centers using electronic CRFs. Designated study center personnel must complete the applicable CRFs as soon as possible after a subject visit, and the CRFs must be available for review at the next scheduled monitoring visit. Prior to locking the clinical database, the investigator must review and approve the completed CRFs to verify their accuracy.

Electronic CRF completion guidelines that are approved by Graybug Vision, or designee, will designate how to appropriately enter data into CRFs from the source documents. Typically, blank fields are not acceptable. If a field is blank because the item was not done, the field will be marked "ND." If the item is unknown, the field will be marked "UNK." If the item is not applicable, the field will be marked "NA."

Discrepancies (ie, queries) will be generated for suspect data (eg, vital signs that are out of expected range, potential protocol compliance concerns, and date discrepancies) and missing data in the clinical database. Some discrepancies will be automatically generated during data entry into the CRFs as potential data quality issues arise. Other discrepancies will be automatically generated after batch validation is executed on the clinical database during which more advanced, cross-panel edit checks are executed. Finally, manual discrepancies may be generated by investigators, CRAs, the clinical data manager (CDM), or clinical data analysts as the study data is further analyzed during monitoring visits or data listing reviews. All discrepancies will be routed within the clinical database system to the appropriate clinical study staff, typically beginning with the study center coordinator and ending with either the CRA or the CDM for resolution. When these discrepancies are opened within the system on CRF pages that have already been verified by the CRA or approved by the investigator, the database system will automatically require the CRA to reverify and the investigator to reapprove the applicable pages.

Graybug Vision policy is that CRF study data must be verifiable to the source data, which necessitates access to all original recordings, laboratory reports, and subject records. In addition, all source data should be attributable (signed and dated). The investigator must therefore agree to allow direct access to all source data. Subjects must also allow access to their medical records (ie, records at the study center that have previous medical history/information), and subjects will be informed of this and will confirm their agreement when giving written informed consent. If an investigator or institution refuses to allow access to subject records because of confidentiality, arrangements must be made to allow an "interview" style of data verification.

A CRA designated by Graybug Vision will compare the CRFs with the original source documents at the study center and evaluate the CRFs for completeness and accuracy. If necessary, the study center's personnel will be contacted for corrections and/or clarifications. Data that are modified in the clinical database to resolve related discrepancies must be supported in the source documents.

After the clinical database is locked, compact disks with copies of all applicable subjects' CRFs will be provided to each study center to be maintained on file by the investigator.

12 STUDY MONITORING AND AUDITING

Qualified individuals designated by Graybug Vision will monitor all aspects of the study according to ICH and GCP and standard operating procedures for compliance with applicable government regulations. The investigator agrees to allow these monitors direct access to the clinical supplies, dispensing, and storage areas and to the clinical files, including original medical records, of the study subjects, and, if requested, agrees to assist the monitors. The investigator and staff are responsible for being present or available for consultation during routinely scheduled study center visits conducted by Graybug Vision, the contract research organization, or its designees. A review of the subjects' 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 monitoring plan.

Members of Graybug Vision GCP Compliance Department or designees may conduct an audit of a study center at any time during or after completion of the study. The investigator will be informed if an audit is to take place and advised as to the scope of the audit. Representatives of the FDA or other regulatory agencies may also conduct an audit of the study. If informed of such an inspection, the investigator should notify Graybug Vision immediately. The investigator will ensure that the auditors have access to the clinical supplies, study center facilities, original source documentation, and all study files. All inspections and audits will be carried out giving consideration to data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

13 RETENTION OF RECORDS

The investigator must retain all study records required by Graybug Vision and by the applicable regulations in a secure and safe facility. The investigator must consult a Graybug Vision representative before disposal of any study records, and must notify Graybug Vision of any change in the location, disposition, or custody of the study files. The investigator/institution must take measures to prevent accidental or premature destruction of essential documents, that is, documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (eg, subject charts), as well as any original source documents that are electronic as required by applicable regulatory requirements.

All study records must be retained for at least 2 years after the last approval of a marketing application in the US or an ICH region and until (1) there are no pending or contemplated marketing applications in the US or an ICH region or (2) at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. The investigator/institution should retain subject identifiers for at least 15 years after the completion or discontinuation of the study. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution, or private practice, but not less than 15 years. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by a Graybug Vision agreement. Graybug Vision must be notified and will assist with retention should the investigator/institution be unable to continue maintenance of subject files for the full 15 years. It is the responsibility of Graybug Vision to inform the investigator/institution as to when these documents no longer need to be retained.

14 USE OF INFORMATION AND PUBLICATION

Graybug Vision 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 Study Agreement between Graybug Vision, the contract research organization, and the investigator.

Due to the confidential nature of this development program, the results of the study may not be published or publicly presented without the prior approval of Graybug Vision. Any investigator wishing to publish or present any study finding must present a manuscript or abstract to Graybug Vision 120 days prior to submission for publication or presentation to provide Graybug Vision an opportunity for review and comment.

15 ETHICS

15.1 Institutional Review Board

The protocol, IB, informed consent form, advertisements to be used for subject recruitment, and any other written information provided to subjects for this study, including all consent forms translated to a language other than the native language of the study center must be approved by the investigator's IRB before the study is initiated at the study center. Documentation of this approval must be maintained by the study center and provided to the Sponsor (or designee) and must be made available during an inspection by the US 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 ICH and GCP requirements, and all applicable laws and local regulations.

The study will not be initiated at the study center until documentation confirming approval of the protocol, informed consent form, and any written materials supplied to the subject are received by the Sponsor or its designee. Approval documentation from the IRB should be signed by the IRB chairperson or designee, identify the IRB 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 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. The investigator must provide written documentation of the following to the Sponsor (or designee):

- IRB periodic (eg, semi-annually, annually) re-approval of the protocol as required by the study center's IRB
- IRB approvals of any amendments to the protocol or revisions to the informed consent form
- IRB receipt of safety and SAE reports, as appropriate
- Any additional submissions (including an end of study report) required by the study center's IRB

15.2 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.

15.3 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 subject prior to entering the study or performing any study related procedure. An informed consent template will be provided by the Sponsor (or designee) to the study centers. The informed consent will be submitted by the investigator or IRB for review and approval prior to the start of the study. If any modifications to the content are proposed or made by the study center, the informed consent should be reviewed by the Sponsor (or designee) prior to IRB submission.

The investigator is responsible for obtaining written informed consent from each subject participating in the study. If there are any revisions to the informed consent during the course of the study, all active participating subjects must be reconsented using the revised informed consent in a timely fashion.

Written informed consent must be obtained from the subject 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 subject before signing the informed consent. The subject will be informed that participation is voluntary and he/she can withdraw from the study at any time. The subject will be allowed to read the IRB approved informed consent. If a subject is unable to read the consent, an impartial witness should be present during the entire informed consent discussion. Once the investigator or designee is assured the subject agrees to participate in the study, the subject will be asked to give consent by signing the informed consent. The informed consent must be signed and dated by the subject, and by the person who conducted the informed consent discussion, and impartial witness (if required). The investigator shall provide a copy of the signed and dated informed consent to the subject. The original shall be maintained in the subject's medical records at the study center. This document should not be displayed or made accessible to any third party except the Sponsor, its designee or regulatory agency representatives.

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

16 INVESTIGATOR RESPONSIBILITIES

Conduct of Study and Protection of Human Subjects

In accordance with FDA Form 1572, the investigator will ensure that:

- He or she will conduct the study in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the Sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

- He or she will personally conduct or supervise the study.

- He or she will inform any potential subjects, or any persons used as controls, that the drugs are being used for investigational purposes and he or she will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and IRB review and approval in 21 CFR Part 56 are met.

- He or she will report to the Sponsor adverse experiences that occur in the course of the investigation in accordance with 21 CFR 312.64.

- He or she has read and understands the information in the IB, including potential risks and side effects of the drug.

- His or her staff and all persons who assist in the conduct of the study are informed about their obligations in meeting the above commitments.

- He or she will ensure that adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

- He or she will ensure that the IRB complies with the requirements of 21 CFR Part 56, and other applicable regulations, and conducts initial and ongoing reviews and approvals of the study. He or she will also ensure that any change in research activity and all problems involving risks to human subjects or others are reported to the IRB. Additionally, he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

- He or she agrees to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

17 REFERENCES

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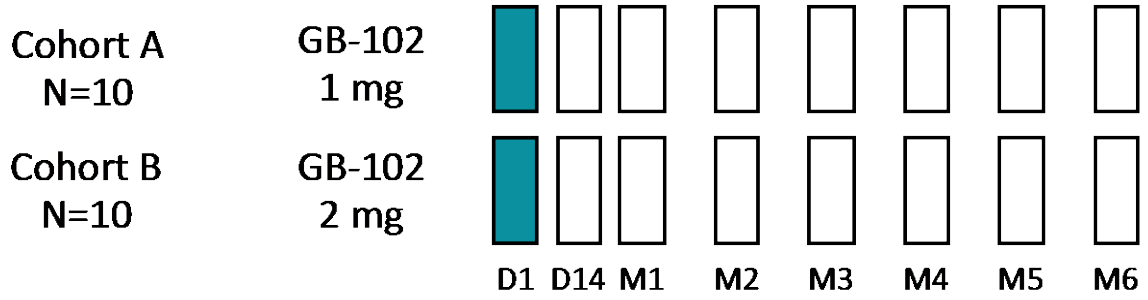
18 APPENDICES

18.1 Study Schema Protocol GBV-102-003

(Green box = administration of GB-102)



18.2 Nonocular and Systemic Adverse Event Severity Assessment

The NCI-CTCAE (version 4.03) is a descriptive terminology that will be used to grade the severity of nonocular and systemic AEs reported in this study.

The NCI-CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observation only; intervention not indicated

Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limited self-care ADL**

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to an AE

A semicolon indicates “or” within the above descriptions. A single dash (-) can be used to indicate that a grade is not available. Not all grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than 5 options for grade selection.

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

** Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden.

18.3 Ocular Adverse Event Severity Assessment

The severity of an ocular AE will be defined as a qualitative assessment of the degree of intensity of an ocular AE as determined by the investigator or reported to him/her by the subject. The assessment of severity will be made irrespective of relationship to investigational product or seriousness of the event and should be evaluated according to the following scale:

- *Mild:* Event is noticeable to the subject, but is easily tolerated and does not interfere with the subject's daily activities
- *Moderate:* Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities
- *Severe:* Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities

18.4 Ocular Grading Scales

Ocular inflammation, fundus hemorrhage, and vitreous haze will be assessed during slit-lamp biomicroscopy and indirect ophthalmoscopy. The standard practice for the slit-lamp biomicroscopy and indirect ophthalmoscopy assessments should be used.

18.4.1 Grading Scale for Ocular Inflammation

Anterior Chamber Cells	
Grade	**Cells in Field (1 mm × 1 mm slit beam)**
0	None
+0.5	1 - 5
+1	6 - 15
+2	16 - 25
+3	26 - 50
+4	> 50

Source: (Jabs 2005)

Anterior Chamber Flare	
Grade	**Description**
0	None
+1	Trace
+2	Moderate (iris and lens detail clear)
+3	Marked (iris and lens detail hazy)
+4	Intense (fibrin or plastic aqueous)

Source: (Jabs 2005)

18.4.2 Grading Scale of Retinal or Vitreous Hemorrhage

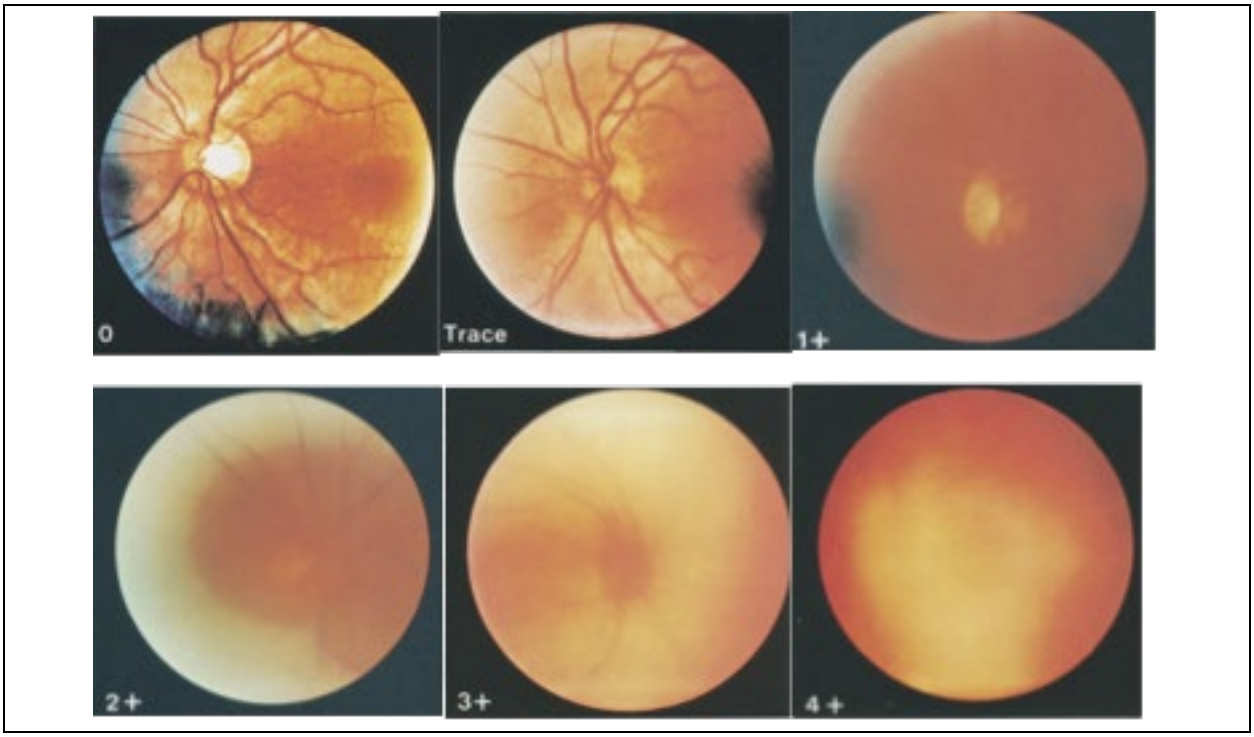
Grade	**Hemorrhage Size (Disc Areas)**
0	None present
+1	< 3
+2	3 to 6 (inclusive)
+3	> 6

Source: (Krzystolik 2002)

18.4.3 Grading of Vitreous Haze

Grade	Amount of Vitreal Haze
0	None
+0.5	Trace
+1	Clear optic disc and vessels; hazy nerve fiber layer
+2	Hazy optic disc and vessels
+3	Optic disc visible
+4	Optic disc not visible

Source: (Nussenblatt 1985)



Source: (Nussenblatt 1985)

18.5 Age-Related Eye Disease Study Lens Scale

Presence and severity of nuclear sclerosis, cortical opacities, and posterior subcapsular opacities will be evaluated according to the Age-Related Eye Disease Study (AREDS) Clinical Lens Grading Protocol (Chew 2010). Biomicroscopic findings will be compared with standard photographs. The Sponsor or its delegate will supply the investigational centers with a copy of the standard photographs.

18.5.1 Nuclear Sclerosis

Grade	Description
+1	Opacity is absent
+2	Opacity is present, but less than Nuclear Standard Photograph #2
+3	Opacity is present, and as severe or worse than Nuclear Standard Photograph #2

Source: (Chew 2010)

18.5.2 Cortical Opacities

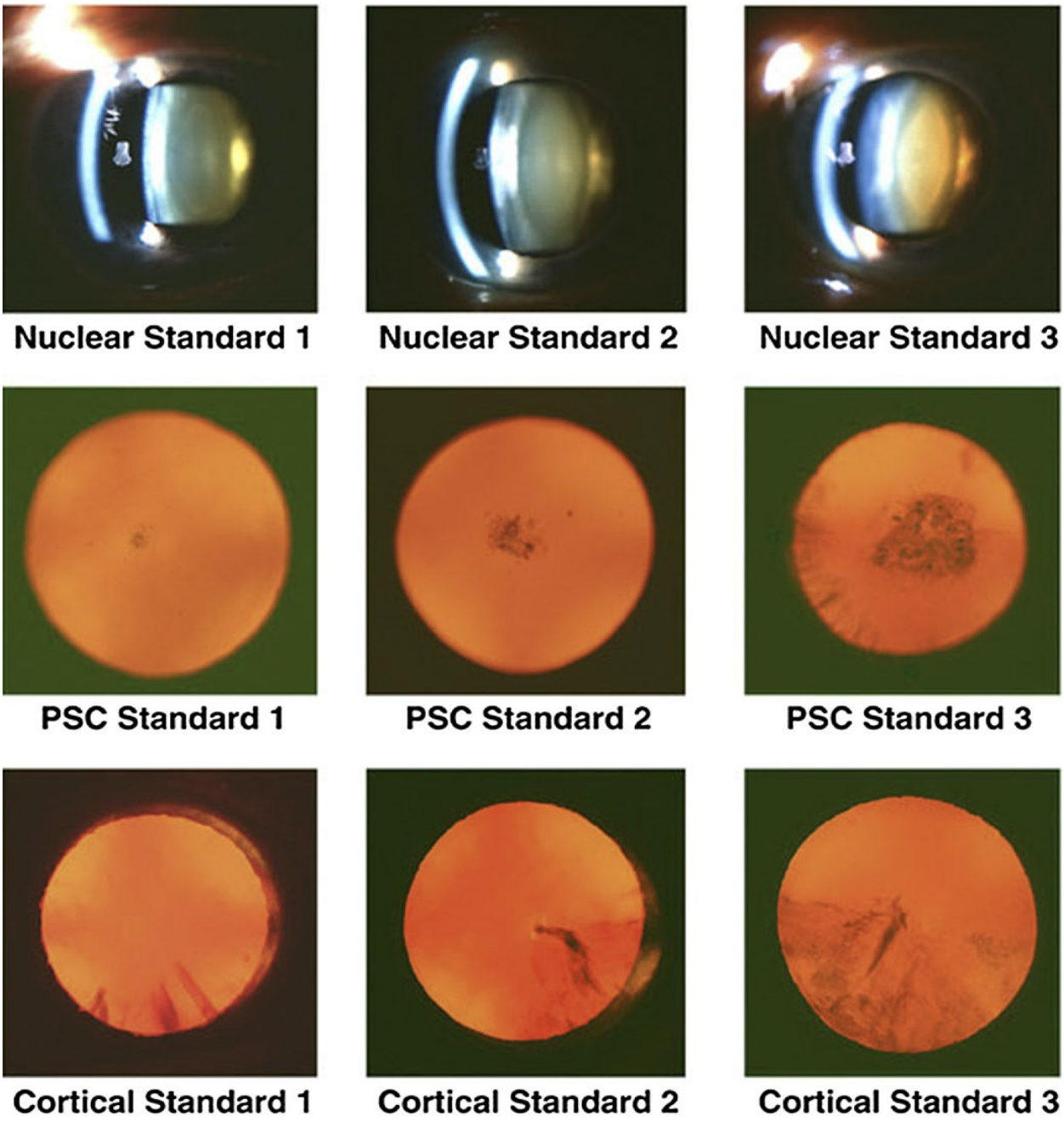
Grade	Description
+1	Opacity is absent
+2	Opacity is present, but less than Cortical Standard Photograph #2
+3	Opacity is present, and as severe or worse than Cortical Standard Photograph #2

Source: (Chew 2010)

18.5.3 Posterior Subcapsular Opacities

Grade	Description
+1	Opacity is absent
+2	Opacity is present, but less than PSC Standard Photograph #2
+3	Opacity is present, and as severe or worse than PSC Standard Photograph #2

PSC = posterior subcapsular opacity
Source: (Chew 2010)



Source: (Chew 2010)

18.6 Protocol Amendment Summary

This summary includes changes made to Protocol Amendment 1 GBV-102-003 (Version 2.0) dated 13 November 2019.

Graybug Vision, Inc. has added Appendix 18.5, Age-Related Eye Disease Study Lens Scale as a reference for sites to utilize to document biomicroscopic findings.