Graybug Vision Inc.

Clinical Study Protocol

Official Title: A Phase 2b Multicenter Dose-Ranging Study Evaluating the Safety and Efficacy of a Long-acting Intravitreal Sunitinib Malate Depot Formulation (GB-102) Compared to Intravitreal Aflibercept in Subjects with Neovascular (Wet) Age-related Macular Degeneration (ALTISSIMO Study)

Protocol Number: GBV-102-002

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CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2b Multicenter Dose-Ranging Study Evaluating the Safety and Efficacy of a Long-acting Intravitreal Sunitinib Malate Depot Formulation (GB-102) Compared to Intravitreal Aflibercept in Subjects with Neovascular (Wet) Age-related Macular Degeneration (ALTISSIMO Study)
Sponsor:	Graybug Vision, Inc. 275 Shoreline Drive, Suite 450 Redwood City, CA 94065
IND Number:	128451
Indication:	Neovascular age-related macular degeneration
Protocol Number (Phase):	GBV-102-002 (Phase 2b)
Clinical Medical Officer:	Name: [redacted] Office: [redacted] Email: [redacted]
Medical Monitor:	Name: [redacted] Office: [redacted] Email: [redacted]
Protocol Version/Date:	Version 4.0 / 08 September 2020 (Amendment 3) Version 3.0 / 05 March 2020 (Amendment 2) Version 2.0 / 17 September 2019 (Amendment 1) Version 1.0 / 20 March 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-102-002
Graybug Vision, Inc.
275 Shoreline Drive, Suite 450
Redwood City, CA 94065

Study Title:	A Phase 2b Multicenter Dose-Ranging Study Evaluating the Safety and Efficacy of a Long-acting Intravitreal Sunitinib Malate Depot Formulation (GB-102) Compared to Intravitreal Aflibercept in Subjects with Neovascular (Wet) Age-related Macular Degeneration (ALTISSIMO Study)
Study Centers Planned:	Approximately 35 study centers in the United States
Objectives:	With this amendment, the ALTISSIMO Study is divided into the ALTISSIMO (Core Study) and the Extension Study. Unless otherwise specified, all segments of the protocol refer to ALTISSIMO (Core Study). **Primary Objective** To evaluate the safety and duration of the effect of GB-102, as measured by time to first rescue treatment across two different dosing schemes of GB-102 administered every 6 months (1 mg followed by 1 mg or 2 mg followed by 1 mg) as compared to intravitreal (IVT) aflibercept administered every 2 months in subjects with neovascular (wet) age-related macular degeneration who have received prior induction with anti-vascular endothelial growth factor (VEGF) **Secondary Objectives** • To evaluate the efficacy of two different dosing schemes of IVT GB-102 administered every 6 months in maintenance of best-correct visual acuity (BCVA, ETDRS letter score) compared to subjects receiving IVT aflibercept every 2 months • To evaluate the efficacy of two different dosing schemes of IVT GB-102 administered every 6 months in maintenance of central subfield thickness (CST, μm) compared to subjects receiving IVT aflibercept every 2 months

	EXTENSION STUDY **Objective** To monitor the safety and duration of effect of IVT GB-102 administered every 6 months compared to IVT aflibercept administered every 2 months in subjects in ALTISSIMO (Core Study) who complete all study visits through Month 12 (Day 360) and who do not require/receive rescue treatment at the Month 12 (Day 360) final study visit
Study Design:	Multicenter, visual examiner-masked, randomized, active controlled, parallel-arm design. Eligible subjects will be randomly assigned (3:3:2) to receive 50-µL IVT injections of 1 of 2 doses of study drug or aflibercept, respectively, in the study eye using a stratified, blocked randomization scheme. Stratification will include baseline BCVA (< 60 letters vs ≥ 60 letters). Approximately 15 to 20 subjects per group, 56 subjects total, will be randomized to one of the following treatment arms: **Group 1:** 1 mg GB-102 at baseline and Month 6 and sham at Months 2, 4, 8, and 10 (N=21) **Group 2:** 2 mg GB-102 at baseline and 1 mg GB-102 at Month 6 and sham at Months 2, 4, 8, and 10 (N=22) **Group 3:** 2 mg aflibercept q 2 months at baseline, Months 2, 4, 6, 8 and 10 (N=13) Assigned study drug will be administered on Day 1 (Appendix 18.1). Subjects will return to the study center on Days 14, 30, 60, 90, 120, 150, 180, 210, 240, 300, 330, and 360 for safety, clinical, and imaging assessments (Table 3-1). Subjects will exit the study following all study assessments on Day 360. An interim safety analysis was conducted when approximately 50% of subjects had 3-months of accrued data to determine if any changes to the protocol were needed prior to the Month 6 re-dosing schedule. Unmasking of the interim safety data was made available only to the Sponsor's Chief Medical Officer and the Vice President of Global Clinical Operations. The interim analysis showed no serious ocular adverse events. Four subjects experienced medication in the anterior chamber (AC) in the GB-102, 2 mg dose arm as compared to 1 subject in the GB-102, 1 mg dose arm. Based on this safety analysis, the sponsor decided to terminate the development of the GB-102 2 mg dose, and amended the protocol to use GB-102 1 mg for re-dosing of all subjects on GB-102 at the Month 6 visit, regardless of their original dose assignment. The enrollment was capped at 56 subjects

and the primary endpoint was shifted from Month 10 to Month 12 based on suggested feedback from the Food and Drug Administration (FDA).

An unmasked primary analysis for safety and efficacy is planned when all subjects complete the Day 360 visit.

The safety parameters to be collected include adverse events (AEs), serious adverse events (SAEs), physical examination findings, clinical laboratory test results, vital sign measurements, best corrected visual acuity (BCVA) assessments using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol, slit-lamp biomicroscopy findings, Age-related Eye Disease Study (AREDS) lens assessments, intraocular pressure (IOP) measurements, dilated ophthalmoscopy results, and date of administration of rescue treatment.

Efficacy parameters will be measured by means of rescue treatment, BCVA (using the ETDRS protocol), retinal central subfield thickness (CST) using spectral domain-optical coherence tomography (SD-OCT), fluorescein angiography (FA), and color fundus photography (CFP).

The systemic exposure will be based on subjects assigned to each sunitinib treatment group. An analysis of approximately 20% of the subjects assigned to each sunitinib group will be performed.

Safety Monitoring

A medical monitor (ophthalmologist) and the Sponsor's medical officer will evaluate the on-going masked safety data.

Masking

The visual acuity examiners, the Sponsor (other than the Vice President of Global Clinical Operations), the masked contract research organization (CRO) personnel, the medical monitor, and other study personnel, including individuals at a central reading center, study coordinators, laboratory vendor, etc. will remain masked relative to the GB-102 treatment scheme. The visual acuity examiners are not allowed to perform any study related activities other than BCVA assessments to maintain masking including obtaining medical histories or attempting to elicit any information regarding treatment, adverse events, or clinical information from the subjects. The same BCVA examiner should be utilized for each subject throughout the study when possible.

Each study center will have at least 2 investigators who are retina specialists; one will serve as the injecting investigator and the other will serve as the assessing investigator. To maintain study masking,

the roles of these investigators should not be switched during the conduct of the study.

- Injecting Investigator: An injecting investigator will perform the study drug (GB-102 or aflibercept), sham, and/or rescue injections, will supervise the preparation and tracking of study drug, and will perform predose and postdose safety assessments for the IVT injections.
- Assessing Investigator: An assessing investigator will supervise and assess the collection of AEs and efficacy parameters. The assessing investigator will determine whether rescue treatment is required.

The SD-OCT, FA, and CFP technicians are masked to treatment scheme; however, collected images may reveal to the assessing investigator or technician which subjects received the GB-102 depot.

Study personnel performing reconstitution of the investigational drug product (GB-102) will be unmasked to treatment assignment but not the treatment scheme. Study drug will be boxed in numbered kits and identical in external appearance and weight. Kits containing GB-102 are identical in physical appearance and drug vial/diluent (pre-filled syringe) configuration, and fully masked as to the dose strength (1 mg or 2 mg) of GB-102.

Rescue Treatment

Rescue treatment (using aflibercept) will be permitted in the study eye in ***any*** of the study arms if the eligibility criteria are met for rescue treatment.

EXTENSION STUDY

The Extension Study is a multicenter, visual examiner-masked study, designed to monitor the safety and duration of effect of IVT GB-102 administered every 6 months compared to IVT aflibercept administered every 2 months in subjects in ALTISSIMO (Core Study) who complete all study visits through Month 12 (Day 360) and who do not require/receive rescue treatment at the Month 12 (Day 360) final study visit.

Enrolled subjects will be followed for monthly visits until they receive rescue treatment or for a maximum of 180 days (i.e, 6 months). There will be no additional treatment with GB-102.

The assessments to be collected include AEs, SAEs, concomitant medications, BCVA assessments using ETDRS protocol, slit-lamp biomicroscopy findings, AREDS lens assessments, IOP measurements, dilated ophthalmoscopy results, retinal CST using

SD-OCT, color fundus photography for depot imaging (ultra-widefield imaging, where available) and date of administration of rescue treatment.

Once a subject meets at least one rescue criteria and all study visit assessments are completed, they may receive an injection of aflibercept and exit the study.

No formal statistical hypotheses testing will be performed. An exploratory analysis of safety and efficacy will be performed after all subjects have completed the study.

Safety Monitoring

A medical monitor (ophthalmologist) and the Sponsor's medical officer will evaluate the on-going masked safety data.

Masking

The visual acuity examiners, the Sponsor (other than the Vice President of Global Clinical Operations), the masked contract research organization (CRO) personnel, the medical monitor, and other study personnel, including individuals at a central reading center, study coordinators, laboratory vendor, etc. will remain masked relative to the GB-102 treatment scheme. The visual acuity examiners are not allowed to perform any study related activities other than BCVA assessments to maintain masking including obtaining medical histories or attempting to elicit any information regarding treatment, adverse events, or clinical information from the subjects. The same BCVA examiner should be utilized for each subject throughout the study when possible.

Each study center will have at least 2 investigators who are retina specialists; one will serve as the injecting investigator and the other will serve as the assessing investigator. To maintain study masking, the roles of these investigators should not be switched during the conduct of the study.

- Injecting Investigator: An injecting investigator will perform the rescue injections, will supervise the preparation and tracking of study drug, and will perform predose and postdose safety assessments for the IVT injections.
- Assessing Investigator: An assessing investigator will supervise and assess the collection of AEs, SAEs, concomitant medications, BCVA assessments using ETDRS protocol, slit-lamp biomicroscopy findings, AREDS lens assessments, IOP measurements, dilated ophthalmoscopy results, and retinal CST

using SD-OCT. The assessing investigator will determine whether rescue treatment is required.

The SD-OCT and color fundus photography imaging (ultra-widefield imaging, where available) technicians are masked to treatment scheme; however, collected images may reveal to the assessing investigator or technician which subjects received the GB-102 depot in ALTISSIMO (Core Study).

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**.

EXTENSION STUDY

The study eye is defined as the eye that was treated in ALTISSIMO (Core Study).

Rescue Treatment Criteria:

Rescue treatment (aflibercept) for all subjects enrolled is allowed at any visit following the Day 30 study assessments in ALTISSIMO (Core Study) or any visit following the Month 13 (Day 390) study assessments in the Extension Study in subjects who meet any of the following criteria regarding decrease in BCVA and/or increase in CST:

- Decrease in BCVA (any of the following criteria):
  - ≥ 5 ETDRS letter decrease compared with the average of last 2 visit BCVA ETDRS letter scores, and/or,
  - ≥ 10 ETDRS letter decrease compared with best on-study BCVA ETDRS letter score
- Increase in CST (any of the following criteria):
  - ≥ 75 μm compared with the average of the last 2 visit CST measurements (μm), and/or,
  - ≥ 100 μm compared with the lowest on-study CST measurement (μm)

Before rescue treatment is administered, the assessing investigator must confirm that the criteria have been met using an interactive database system.

Number of Subjects Planned:

Approximately 15 to 20 subjects per treatment schemes will be randomized (approximately 56 subjects across all treatment schemes combined)

EXTENSION STUDY

There will be no randomization in the Extension Study.

Target Population: Subjects eligible for screening must have an active choroidal neovascularization (CNV) lesion in the **study eye** secondary to AMD that was diagnosed in the 12 weeks to 18 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 21 days of screening.

Eligibility will be confirmed by a central reading center based upon SD-OCT, FA, and CFP evaluation of the CNV lesion.

EXTENSION STUDY

Subjects eligible for screening and enrollment must complete all study assessments at Month 12 (Day 360) including fluorescein angiography, and not require/receive a rescue treatment at the Month 12 (Day 360) final study visit in ALTISSIMO (Core Study).

Duration of Study Participation: Approximately 390 days (up to 30 days for screening and 360 days of treatment/observation)

EXTENSION STUDY

Approximately 180 days of observation after exiting ALTISSIMO (Core Study). During the Extension Study, any subject who meets the rescue criteria at any visit will undergo end of the Extension Study assessments, receive a dose of aflibercept as the rescue medication, and exit the study.

Inclusion Criteria:

1. Verbal and written informed consent obtained from the subject
2. Males or females ≥ 50 years of age
3. Willing and able to give informed consent, comply with all study procedures, and be likely to complete the study
4. Presence of a subfoveal or juxtafoveal CNV lesion secondary to AMD in the **study eye** that was diagnosed in the 12 weeks to 18 months prior to screening and has been treated with at least 3 prior IVT injections of an anti-VEGF agent (aflibercept, bevacizumab, or ranibizumab). The **study eye** and CNV lesion must demonstrate ***all*** of the following features at the Screening Visit (as confirmed by the reading center):
    a. Total lesion size ≤ 12 disc areas (30.5 mm^2)

b. Absence of subfoveal fibrosis, serous pigmented epithelial detachment, retinal pigmented epithelial tear, or subfoveal geographic atrophy

c. If fibrosis is present, it must be ≤ 25% of total lesion area and not involve the center of the fovea

d. If subfoveal hemorrhage is present, it must be < 1 disc area in size and not involve the center of the fovea

e. If subretinal hemorrhage is present, it must be < 50% of total CNV lesion and not involve the center of the fovea

5. Prior pharmacodynamic response of the CNV lesion 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:

   a. Reduction of intraretinal/subretinal fluid by ≥ 30% from the initial diagnosis as determined using SD-OCT

   b. Reduction of excess CST by ≥ 30% from the initial diagnosis as determined using SD-OCT (assuming nominal thickness is 300 microns)

6. Demonstrate a maintained anti-VEGF response (as determined by the investigator) compared with the initial diagnosis (prior to any anti-VEGF treatment) as assessed using SD-OCT following the most recent anti-VEGF injection (defined as a reduction in central subfield thickness, intraretinal/subretinal fluid, or maintenance of dry retina)

7. Screening and baseline BCVA letter score (by ETDRS protocol) of 35 to 88 (20/200 to 20/20 Snellen equivalent) in the **study eye**

8. Availability of prior central subfield thickness (CST) measurements from SD-OCT imaging obtained from the time of initial diagnosis (pre-anti-VEGF therapy) and/or maximal CST thickness obtained any time following anti-VEGF induction

9. 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

10. Most recent dose of anti-VEGF agent administered within 21 days of screening

11. Clear ocular media and adequate pupil dilation in both eyes to permit good quality photographic imaging

12. Women of childbearing potential (ie, not postmenopausal for at least **12 months** or not *surgically sterile* [defined as *bilateral tubal ligation performed at least 12 months previously, hysterectomy, or bilateral oophorectomy*]) must have a negative urine pregnancy test at screening and baseline, and must use adequate birth control throughout the study and until 12 weeks following the last dose of study drug 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

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 > 8.0% at the Screening Visit
4. Chronic renal disease requiring chronic hemodialysis or renal transplantation
5. Any screening laboratory result (hematology, chemistry, or urinalysis) that, in the opinion of the investigator, is not suitable for subject participation in the study
6. 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)
7. Previous participation in an investigational study of GB-102
8. 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
9. 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
10. Presence of any clinically significant epiretinal membrane or vitreomacular traction in the **study eye**

11. History or evidence of any of the following surgeries or procedures in the **study eye**:
    a. Submacular surgery or other surgical intervention for AMD
    b. Prior retinal detachment or macular hole interventions
    c. Vitrectomy
    d. Photodynamic therapy or thermal laser retinal treatment
    e. Intraocular laser treatments for glaucoma (eg, selective laser trabeculoplasty or peripheral iridotomy)
    f. 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
    g. Cataract surgery within the 3 months prior to the Screening Visit
    h. 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.
    i. 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
    j. Corneal transplantation surgery
    k. History of advanced glaucoma with visual field loss encroaching on central fixation
12. Anterior chamber intraocular lens, aphakia, or violation of the posterior capsule in the **study eye**
13. 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. Advanced pre-proliferative diabetic retinopathy (with potential for development of macular edema or macular hemorrhage) or proliferative diabetic retinopathy and/or diabetic macular edema in either eye

b. Any retinal or choroidal vasculopathy, other than AMD, in either eye

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

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

e. Subfoveal hemorrhage that is ≥ 1 disc areas in size (if the blood is under the fovea, the fovea must be surrounded ≥ 270° by visible CNV)

f. Subretinal hemorrhage that is ≥ 50% of the total CNV lesion area

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

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.

14. Any history of active bacterial, viral, fungal, or parasitic infection in either eye within the 30 days prior to the Screening Visit
15. Known allergy to constituents of the study drug formulation, ocular antimicrobicide solutions, or clinically relevant hypersensitivity to fluorescein
16. Women who are pregnant or lactating
17. 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 12 weeks following the last dose of study drug
18. 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 monthly study visits and assessments, or interfere with the interpretation of study results
19. Exposure to tetrahydrocannibol (THC) (eg, recreational or medicinal marijuana containing THC) within the past 12 months

	20. Prior exposure to oral sunitinib malate in the past 6 weeks
EXTENSION STUDY Inclusion Criteria:	1. Verbal and written informed consent for the Extension Study obtained from the subject 2. Completed all study assessments at Month 12 (Day 360) final study visit including fluorescein angiography, and did not require/receive a rescue treatment at the Month 12 (Day 360) final study visit in ALTISSIMO (Core Study) 3. Willing and able to give informed consent, comply with all study procedures, and be likely to complete the Extension Study
EXTENSION STUDY Exclusion Criteria:	1. Subjects who terminated early from ALTISSIMO (Core Study) 2. Subjects who did not complete all study assessments at Month 12 (Day 360) final study visit including fluorescein angiography in ALTISSIMO (Core Study) 3. Subjects who received rescue treatment at the Month 12 (Day 360) final study visit in ALTISSIMO (Core Study)

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

Subjects randomized to receive GB-102 will receive their assigned dose on Day 1 and Day 180. All subjects assigned to GB-102 will receive the 1 mg GB-102 dose at Month 6 (Day 180). To maintain masking to treatment scheme, sham injections will be performed in the study eye on Days 60, 120, 240, and 300 to correspond to the dosing schedule of aflibercept.

EXTENSION STUDY

GB-102 will not be administered during the Extension Study.

Reference Therapy, Dose, and Mode of Administration:

Aflibercept is recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human immunoglobulin (IgG)1 formulated as an iso-osmotic solution for intravitreal administration. The approved aflibercept dose is 2 mg in a 50 µL injection administered every 2 months.

Subjects randomized to receive aflibercept will receive active drug on Days 1, 60, 120, 180, 240, and 300.

EXTENSION STUDY

No doses for any treatment schemes (GB-102 1 mg dose or aflibercept) will be administered during the Extension Study. However, subjects may receive aflibercept for rescue treatment therapy provided they have met the rescue treatment criteria. Once any type of rescue treatment has been administered, the subject will exit the Extension Study after undergoing the end of the Extension Study assessments.

Study Endpoints:

Primary Endpoint

- Time to first rescue treatment (GB-102 only). This would be further validated through assessing time to fufillment of at least one rescue criterion.

Secondary Endpoints

- Time to fulfillment of at least one rescue criterion starting at the Month 6 visit through to the Month 12 visit (excluding any rescue at the Month 12 visit).
- Number of times that at least one rescue criterion is met
- Number of treatments, including both rescue and scheduled study treatments, during the study
- Change from baseline in BCVA (ETDRS) at all visits
- Categorical change from Baseline in BCVA (ETDRS) at all visits
- Frequency of subjects with BCVA worse than 20/200 (Snellen equivalent) at all visits
- Change from baseline in CST (µm) at all visits
- Frequency of subjects with absence of exudation (intra-/sub-retinal fluid/cystoid edema) at all visits

Exploratory Endpoints

- Change from baseline in BCVA comparing all subjects receiving GB-102 to subjects receiving aflibercept at all visits
- Change from baseline in CST comparing all subjects receiving GB-102 to subjects receiving aflibercept at all visits
- Change from baseline in total lesion area (mm^2) at Months 6 and 12 of treatment
- Change from baseline in CNV lesion area (mm^2) at Months 6 and 12 of treatment
- Change from baseline in fluorescein leakage area (mm^2) at Months 6 and 12 of treatment
- Change from thickest observed CST (µm) prior to enrollment (pre-enrollment baseline) at all visits
- Change from average of observed CST (µm) prior to enrollment (pre-enrollment baseline) at all visits
- ALTISSIMO (Core Study) Subject Exit Questionnaire

- The subject exit questionnaire (Appendix 18.6) is not a validated patient reported outcome (PRO) measure and is designed to explore a subject's experience with the medication. All subjects exiting the study on Month 12 (Day 360), regardless of whether or not the subject joins the Extension Study, are required to complete the questionnaire.

Safety Endpoints

- Occurrence of ocular and nonocular AEs and SAEs
- Plasma levels of sunitinib (ng/mL)

EXTENSION STUDY

Exploratory Endpoints

All safety and efficacy data collected beyond Month 12 (Day 360) will be assessed in an exploratory manner.

Statistical Methods:

Analysis Population

- Safety analysis set (SS): Includes all randomized subjects who receive at least one dose of study treatment. Subjects will be analyzed according to actual treatment scheme received.
- Full analysis set (FAS): Includes all randomized subjects who receive at least one dose of study treatment, and complete a 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. All efficacy analyses will be conducted on the FAS and these analyses will be considered primary.
- 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 primary efficacy endpoint of the study. Analyses conducted on the PP set will be considered secondary.

Primary Endpoint and Analysis

The primary efficacy endpoint is the time to first rescue treatment (GB-102 only). This would be further validated throught assessing time to fulfillment of at least one rescue criterion.

Time to first rescue treatment/fulfillment of at least one rescue criterion will be analyzed using the Kaplan-Meier method. The probability of remaining rescue treatment free/not fulfilling at least one rescue criterion will be reported for the Month 6 and Month 12 visits with associated 80% confidence intervals (CI) based on Greenwood's standard error estimate. Kaplan-Meier curves will be produced. If calculable, estimates of the median time to fulfillment of at least on rescue criterion and the 25th and 75th percentiles will be calculated with corresponding 80% CIs. The FAS will be the primary population used for analysis of the primary efficacy endpoint.

For this analysis, the interval censored nature of the time to first rescue treatment/fulfillment of at least one rescue criterion with regard to the scheduled study visits is considered: If a subject receives a rescue treatment/fulfills a rescue criterion during an unscheduled visit, then the subject will be considered to have met the event of interest in the visit interval which ends at the next scheduled study visit that occurs after the unscheduled visit. Subjects who do not receive rescue medication/fulfill a rescue criterion will be censored on last scheduled study visit recorded for the subject.

Exploratory comparisons between each GB-102 scheme and aflibercept and between the combined GB-102 schemes versus aflibercept regarding time to first fulfillment of at least one rescue criterion will be conducted using a log-rank test stratified by baseline BCVA (< 60 letters vs ≥ 60 letters), as defined at the time of randomization. The Peto method will be used to estimate the hazard ratio and asymptotic 80% confidence interval based on the stratified log rank test statistic.

A primary endpoint analysis will be conducted when all subjects complete the Month 12 (Day 360) visit.

Secondary Endpoint Analyses

The change from baseline in BCVA and CST will be presented by treatment scheme with associated 80% confidence intervals (CI) for all visits. A similar analysis will be done for absolute values and change in BCVA and CST relative to the time of first rescue treatment (response to rescue treatment). Time to fulfillment of at least one rescue criterion starting at the Month 6 visit through Month 12 will be summarized using descriptive statistics including 80% CIs and will be presented for the number of rescue treatments, number of scheduled treatments, number of total of rescue and scheduled treatments, and number of times that at least one rescue criterion is met from baseline through Month 12.

Absence of exudation (intra-/sub-retinal fluid/cystoid edema), categories of change from Baseline in BCVA, and BCVA worse than 20/200 (Snellen equivalent) will be summarized at each visit using discrete summary statistics, including 80% asymptotic normal CIs for each treatment scheme.

Further details on the analysis of the secondary efficacy endpoints will be provided in the SAP.

Exploratory Efficacy Endpoints

Observed values at each visit and change from baseline values at each follow up visit for BCVA, CST, total lesion area, CNV lesion area, and fluorescein leakage area will be summarized using continuous summary statistics, including 80% CIs around the mean for each treatment scheme, as well as the combined GB-102 groups and the aflibercept control group. For CST, the change from the thickest pre-enrollment value (µm) and change from average pre-enrollment value (µm) at each visit will be similarly summarized.

For BCVA and CST, comparisons between each GB-102 group and the aflibercept control group and between the combined GB-102 groups and the aflibercept control group will be made primarily for each visit using a linear model adjusting for the baseline value as a covariate/class variable and secondarily using 2 sample t-tests.

Safety Analyses

All reported adverse events will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock. Treatment-emergent adverse events will be summarized by system organ class (SOC) and preferred term (PT). Frequencies and percentages will be provided by treatment scheme for subjects with TEAEs, treatment related TEAEs, serious TEAEs, serious treatment related TEAEs, TEAEs leading to premature study discontinuation, TEAEs by maximum severity, TEAEs by day of onset, and arteriothromboembolic TEAEs using Antiplatelet Trialists' Collaboration criteria (ATC 1994). Separate analyses will be performed for ocular AEs in the study eye, ocular AEs in the non-study eye, and nonocular AEs.

Sunitinib systemic exposure will be summarized by descriptive statistics by dose group and time points. An analysis of approximately 20% of the subjects assigned to each sunitinib group will be performed.

Sample Size Considerations

The sample size of this study was not selected to support specific statistical hypothesis testing as all comparisons are exploratory.

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. However, if the amount of missing post-baseline values for a particular endpoint are substantial, multiple imputation methods will be considered for the imputation of missing values.

Sensitivity analyses of primary and secondary efficacy endpoints will be conducted using the per protocol population. Additional sensitivity analyses will be specified in the statistical analysis plan.

EXTENSION STUDY

All safety and efficacy data collected beyond Month 12 (Day 360) will be presented in listings and summarized as appropriate using descriptive statistics.

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GLOSSARY OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AC	anterior chamber
ADL	activities of daily living
AE	adverse event
AMD	age-related macular degeneration
ANCOVA	analysis of covariance
AREDS	age-related eye diseasesStudy
ATC	antiplatelet trialists' collaboration
BCVA	best corrected visual acuity
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
CST	central subfield thickness
DLT	dose limiting toxicity
ETDRS	early treatment diabetic retinopathy study
EU	endotoxin units
FA	fluorescein angiography
FAS	full analysis set
FDA	food and drug administration
GCP	good clinical practice
GLP	good laboratory practice
HD	high dose
HIPAA	health insurance portability and accountability act
HSC	human stem cell
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
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
OU	both eyes
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
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
THC	tetrahydrocannibol
TKI	tyrosine kinase inhibitor
T_{max}	peak exposure
US	united states
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WOCF	worst observation carried forward

1 INTRODUCTION

1.1 Background

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness among people who are 50 years of age or older in the industrialized world (Wong 2014). For more than a decade, intravitreally administered anti-vascular endothelial growth factor (VEGF) agents targeting VEGF-A have revolutionized the treatment of neovascular (wet) AMD with the use of aflibercept (EYLEA® Injection), ranibizumab (LUCENTIS® Intravitreal Injection), or off-label intravitreal (IVT) bevacizumab (AVASTIN® Solution, Collet 2013, Eandi 2016). Despite the dramatic clinical sight-saving success of these drugs, the need for frequent IVT injections has emerged as a burdensome consequence for both patients and retinal specialists. Intravitreal injections have become the most commonly performed ophthalmic procedure in the United States (US), surpassing cataract extraction, with an estimated 6 million injections performed in 2016 alone and a projected annual growth rate of approximately 10% (Williams 2014). Randomized clinical studies have uniformly demonstrated that maximum gains in visual acuity can be achieved through regimented monthly IVT injections of anti-VEGF drugs (CATT Research Group 2011, Heier 2012, Rosenfeld 2006). However, mandated life-long monthly injections are impractical and unsustainable due to costs, disruption in quality-of-life (eg, appointments, travel, waiting times), and the clinical staffing required to manage an ever increasing number of patients with the disease (Prenner 2015). Furthermore, approximately 20% to 30% of treated patients exhibit persistent fluid in the retina despite maximal treatments, suggesting the need for newer pharmacologic approaches with broader mechanisms of action beyond VEGF-A suppression alone (Jaffe 2016). Given a decade of clinical experience in treating patients with wet AMD, retinal practitioners recently surveyed by the American Society of Retinal Specialists responded that the top 3 greatest unmet needs are: “long-acting sustained (drug) delivery” (74% of respondents); “reduced treatment burden” (72% of respondents); and “new treatment mechanisms of action” (45% of respondents) (ASRS 2016).
To address the unmet medical need in patients with AMD, Graybug Vision has developed a proprietary drug product (GB-102) intended to reduce the frequency of IVT injections and provide a mechanism of action involving blockade of multiple VEGF receptor targets associated with angiogenesis, vascular permeability, cellular proliferation, which are key biologic processes associated with the progression of choroidal neovascularization (CNV), the hallmark lesion in neovascular AMD.

1.2 Investigational Product

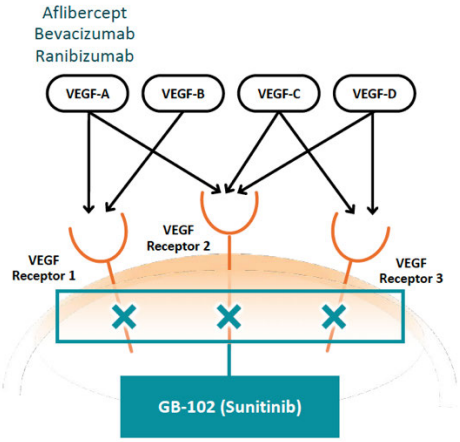
GB-102 is a depot formulation of sunitinib malate intended for IVT injection. The formulation consists of microparticles made from poly(lactic-co-glycolic) acid (PLGA) and methoxy-polyethylene glycol (mPEG)-PLGA. The mPEG component provides a hydrophilic, biocompatible property. During production, the 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 preclinical studies, theoretically enabling dosing twice yearly as described in Section 1.3.1.

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 (SUTENT® Capsules) and represents a class of small molecules referred to as receptor tyrosine kinase inhibitors (TKIs).

Sunitinib 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 nAMD. 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



1.3 General Information

1.3.1 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.

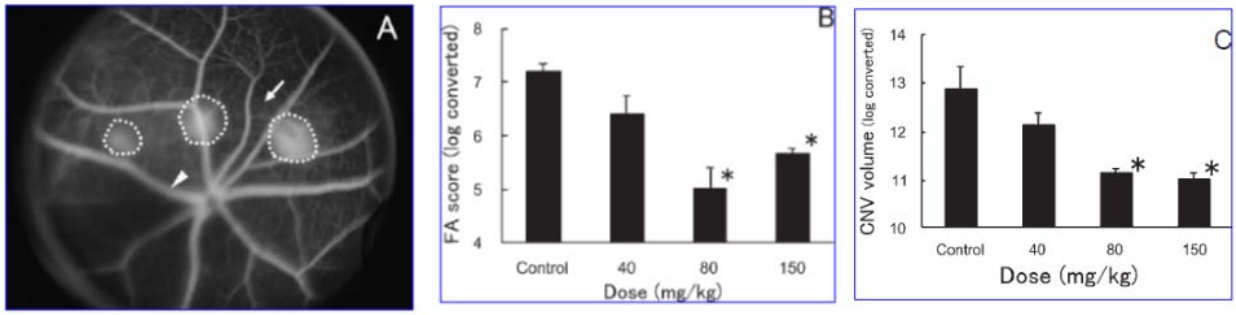
1.3.1.1 Primary Pharmacology – Ocular

Sunitinib has demonstrated evidence of inhibiting angiogenesis, vascular permeability, proliferation, and fibrosis – key findings associated with choroidal neovascular lesions in nAMD. Sunitinib has also demonstrated neuroprotective effects.

Oral Sunitinib Malate Inhibits 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 1-2).

Figure 1-2. Oral Dosing of Sunitinib Reduces Laser-Induced Choroidal Neovascularization in a Murine Model

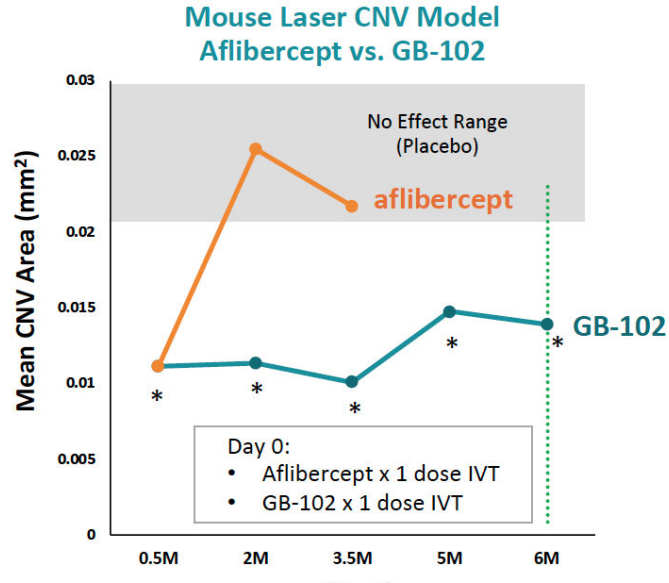


CNV = choroidal neovascularization; FA = fluorescein angiogram
(A) FA
(B) FA scores
(C) CNV histology scores
Source: (Takahashi 2006)

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 (Tsujinaka 2018). 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 1-3). 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 1-3. Sustained Reduction in Laser-Induced CNV Following Single Injection of IVT GB-102 Compared to IVT Aflibercept



(Tsujinaka 2018) * p<0.05 (GB-102 or aflibercept vs. fellow eye control)

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

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 (Ruiz 2005, Sharma 2011). Sunitinib also promotes photoreceptor survival and function as demonstrated in a murine light damage model of retinal degeneration (Kim 2015).

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

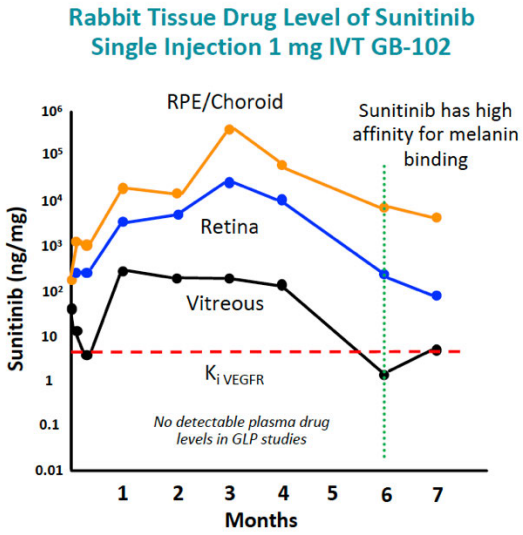
Single Intravitreal Injection of GB-102 Sustains Inhibitory Levels of Drug in the Retinal Pigment Epithelium-Choroid up to 6 Months in Pigmented Rabbits up to 6 Months

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 1-4). 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 1-4. 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.

1.3.1.3 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.

1.4 Clinical Studies

Three clinical studies with GB-102 have been conducted or are ongoing as follows (Table 1-1).

Table 1-1. Summary of Clinical Studies with GB-102

Protocol	Title	Design	Subjects	Status
GBV-102-001	A Phase 1/2 multicenter study evaluating the safety, tolerability and efficacy of an intravitreal depot formulation of sunitinib male (GB-102) in subjects with neovascular age-related macular degeneration	Single injection, open-label, sequentially-enrolled, escalating dose cohorts followed for 8 months	GB-102: 0.25 mg (N=8) 0.5 mg (N=8) 1 mg (N=8) 2 mg (N=8)	Completed
GBV-102-003	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) ands retinal vein occlusion (RVO)	Single injection, open-label, concurrently-enrolled parallel dose arms followed for 6 months	GB-102: 1 mg (N=10) 2 mg (N=11)	Active. Enrollment completed.
GBV-102-002	A Phase 2b multicenter dose-ranging study evaluating the safety and efficacy of a long-acting intravitreal sunitinib malate depot formulation (GB-102) compared to intravitreal aflibercept in subjects with neovascular (wet) age-related macular degeneration (ALTISSIMO study)	Repeat injection, randomized, double-masked, parallel arm study followed for 12 months	GB-102: 1 mg (N=21) 2 mg (N=22) Aflibercept:* 2 mg (N=13)	Active. Enrollment completed.

*EYLEA®, aflibercept (2 mg) for intravitreal injection (Regeneron, Inc.)

A summary of the clinical studies are provided below.

1.4.1 Protocol GBV-102-001 (Part 1)

Objectives. Part 1 of the Phase 1/2a protocol GBV-102-001 was the first-in-human evaluation study of GB-102. The primary study objective was to assess safety, tolerability, and pharmacodynamic parameters (BCVA, CST) following a single IVT injection of GB-102.

[Note: Part 2 of Protocol GBV-102-001 was a planned randomized, controlled, 3-arm study comparing 2 doses levels of GB-102 administered every 6 months to aflibercept administered every 2 months. This portion of the study was not be conducted but replaced with Phase 2b dose-ranging study (Protocol GBV-102-002)].

Study Population. Subjects with the diagnosis of nAMD within the past 18 months, had at least 3 prior IVT injections of any anti-VEGF agent (aflibercept, bevacizumab, or ranibizumab), showed a response to prior treatment, and had evidence of retinal fluid and/or leakage on fluorescein angiography at the time of screening.

Methods. Following confirmation of lesion qualification by a third-party reading center, eligible subjects were assigned to receive a single IVT injection of GB-102 in 1 of 4 consecutively initiated, open-label, dose cohorts in the designated study eye (Table 1-2):

Table 1-2. Disposition of Subjects by Cohort and Dose

Cohort	Dose of GB-102 (mg)	Number of Subjects
A	0.25	8
B	0.5	8
C	1	8
D	2	8

GB-102 was administered on Day 1 in all cohorts. Subjects returned to the study center on targeted Days 3 (sentinel subjects only), 14, 30, 60, 90, 120, 150, 180, 210, and 240 for safety, clinical, and imaging assessments. Subjects exited the study following all study assessments on Day 240 (Month 8). Rescue treatment (aflibercept) was available to subject who met protocol-specified criteria.

The safety parameters collected included adverse events (AEs), BCVA assessments (ETDRS protocol), and full ophthalmic examination (slit lamp biomicroscopy, intraocular pressure (IOP) measurements, and dilated ophthalmoscopy results). Plasma samples were obtained on all subjects to characterize systemic exposure to sunitinib.

Functional and pharmacodynamic assessments included BCVA (ETDRS protocol), CST measurements (SD-OCT), fluorescein angiograms (FA), and color fundus photography (CFP). Imaging data was interpreted by an independent third-party reading center.

The intent-to-treat (ITT) population is defined as all subjects who received any study treatment at baseline, have a baseline BCVA and CST measurement, and at least one post-baseline BCVA and CST measurement in the study eye, and includes subjects who have received rescue. The per protocol analysis set (PP) population in this report is defined the same as the ITT population but excludes subjects with major protocol violations that would affect the assessment of the primary efficacy endpoint of the study. The safety population are any subjects who have received study treatment.

Results. Seventy-one (71) subjects were screened, and 32 subjects were enrolled from 8 study sites in the United States (Table 1-3). The first subject was enrolled on August 29, 2017 and the last subject completed the study on January 16, 2019. Four (4) subjects (Cohort A, N=1; Cohort B, N=3) were early terminations: 1 subject died secondary to metastatic gastric cancer (not previously diagnosed) and 3 subjects withdrew consent (hardships in complying with monthly visits from remote locations). The total cumulative subject-days exposed to GB-102 was approximately 7374 days.

A summary of the study population at baseline is provided in Table 1-3. The mean age was 74.2 years with a baseline BCVA of approximately 20/50 (estimated Snellen equivalent), central subfield thickness of 294 µm, mean number of prior anti-VEGF injections of 4.8, and approximately 60 days since the last anti-VEGF dose to first dose of GB-102.

Table 1-3. Protocol GBV-102-001 – Part 1: Subject Demographics at Baseline

	0.25 mg N=8	0.5 mg N=8	1 mg N=8	2 mg N=8	Total N=32
Mean Age, years (SD) Range	74.4 (11.6) 59-89	78.3 (9.4) 60–90	73.1 (7.6) 60–83	70.9 (9.9) 59–84	74.2 (9.7) 59–90
Sex, n (%) Female	5 (62.5%)	5 (62.5%)	5 (62.5%)	4 (50.0%)	19 (59.4%)
Mean BCVA [ETDRS letters] (SD) Estimated Snellen equivalent	56.5 (11.1) 20/80	65.1 (9.9) 20/50	67.9 (7.5) 20/50	63.8 (14.3) 20/50	63.3 (11.3) 20/50
Mean CST, µm (SD)	279 (84.3)	310 (75.9)	276 (57.4)	308 (53.2)	294 (68.7)
Mean number of prior anti-VEGF injections (SD) Range	3.5 (0.9) 3–5	4.5 (1.1) 3–6	5.0 (3.4) 3–11	6.3 (3.1) 3–13	4.8 (2.5) 3–13
Mean Days since last anti-VEGF injection (SD) Range	45.3 (20.1) 19–82	74.9 (65.7) 30–218	62.4 (42.8) 31–163	54.6 (28.8) 27–112	59.3 (42.3) 19–218

1.4.1.1 Ocular Adverse Events

There were no ocular serious adverse events (SAEs) or dose-limiting toxicity events including inflammatory events (eg, sterile endophthalmitis, vitritis, uveitis, or corneal decompensation). A summary of drug-related treatment emergent ocular AEs > 1 subject are presented in Table 1-4.

Table 1-4. Treatment Emergent Drug-Related Ocular Adverse Events > 1 Subject

Reported Event	0.25 mg N=8	0.5 mg N=8	1 mg N=8	2 mg N=8	Total N=32
Ocular SAEs	0	0	0	0	0
Dose-limiting toxicity events	0	0	0	0	0
Medication in anterior chamber	0	2 (25%)	3 (38%)	4 (50%)[a]	9 (28%)
Vitreous floaters	1 (12%)	2 (25%)	1 (12%)	4 (50%)	8 (25%)
Medication residue present	0	3 (38%)	1 (12%)	4 (50%)	8 (25%)
Elevated IOP[a]	0	2 (25%)	1 (12%)	2 (25%)	5 (16%)
Visual impairment	0	1 (12%)	2 (25%)	2 (25%)	4 (12%)
Anterior chamber cell[b]	0	0	1 (12%)	2 (25%)	3 (9%)
Eye pain	0	0	0	2 (25%)	2 (6%)
Photophobia	0	0	0	2 (25%)	2 (6%)
Vision blurred	0	0	0	2 (25%)	2 (6%)
Vitreous haze[b]	0	1 (12%)	1 (12%)	0	2 (6%)

[a]Includes preferred term ocular hypertension. Subjects presented with IOP in the range of 25-38 mmHg
[b]Diagnosis confounded by drug particle dispersion in the AC and/or vitreous

The most frequently reported AE was the observation of microparticles migrating into the anterior chamber (AC). The cause was due to incomplete aggregation of the injected microparticles to form a solid depot allowing free-floating microparticles to move from the vitreous into the AC. Medication residue present were transient subjective reports from subjects whereby the investigator was able to identify floating microparticles in the visual axis that might possibly explain the subject's symptoms. While migration of intravitreal drug-eluting implants into the anterior chamber can occur in aphakic or pseudophakic subjects (Collet 2013), the occurrence of microparticle AC migration in phakic subjects was unexpected and may be related to age-related changes in the zonules, similar to observations in patients receiving intravitreal steroid suspensions (Ruiz-Moreno 2005).

Mildly elevated IOP was observed in 5 subjects that also had microparticles in the anterior chamber. AC migration presented generally 2 to 3 months following IVT GB-102; IOP elevation presented generally 1 to 2 months later. The cause for elevated IOP may be due, in part, to partial obstruction of the trabecular meshwork; however, the use of topical steroid eye drops to prevent corneal decompensation is a confounder.

The management of particles in the AC was either AC lavage (N=3) or observation alone (N=6). With observation alone, the particles dissolved spontaneously approximately 1 to 2 months following the diagnosis. Thus, AC migration appears self-limited, reversible, with no long-term sequelae. IOP responded to topical IOP-lowering drops.

The vast majority of ocular drug-related AEs were from the subjects that experienced AC migration (N=9) compared to subjects that did not have this event (N=23) as shown in Table 1-5.

In summary, the reported drug-related ocular adverse events were within expectations of an intravitreal delivery of a microparticle formulation with the exception of migration of drug product into the anterior chamber in phakic subjects and the presence of mildly elevated IOP. The event of AC migration is self-limited and reversible with conservative management and use of topical IOP-lowering eye drops as needed.

Table 1-5. Treatment Emergent Drug-Related Ocular AEs > 1 Subject Comparing AC Migration Subjects (N=9) versus No AC Migration Subjects (N=23)

Reported Event	0.25 mg N=8	0.5 mg N=8	1 mg N=8	2 mg N=8	Total N=32
AC Migration Subjects (N=9)					
Medication in anterior chamber	0	2 (25%)	3 (38%)	4 (50%)	9 (28%)
Medication residue present	0	2 (25%)	1 (12%)	4 (50%)	7 (22%)
Elevated IOP[a]	0	2 (25%)	1 (12%)	2 (25%)	5 (16%)
Visual impairment	0	1 (12%)	2 (25%)	2 (25%)	5 (16%)
Vitreous floaters	0	0	1 (12%)	2 (25%)	3 (9%)
Anterior chamber cell[b]	0	0	1 (12%)	2 (25%)	3 (9%)
Eye pain	0	0	0	2 (25%)	2 (6%)
Photophobia	0	0	0	2 (25%)	2 (6%)
Vision blurred	0	0	0	2 (25%)	2 (6%)
Vitreous haze[b]	0	1 (12%)	1 (12%)	0	2 (6%)
No AC Migration Subjects (N=23)					
Medication in anterior chamber	0	0	0	0	0
Vitreous floaters	1 (12%)	2 (25%)	0	2 (25%)	5 (16%)
Medication residue present	0	1 (12%)	0	0	1 (3%)

[a]Includes preferred term ocular hypertension. Subjects presented with IOP in range of 25-38 mmHg
[b]Diagnosis confounded by drug particle dispersion in the AC and/or vitreous

1.4.1.2 Non-ocular Adverse Events

There were 4 non-ocular SAEs reported in 3 subjects: 1 subject (0.5 mg) was hospitalized for ascites and later died of metastatic gastric cancer (2 SAE events); 1 subject (0.5 mg) was hospitalized secondary to multiple injuries following a motor vehicle accident (subject was a passenger); 1 subject (0.5 mg) was hospitalized for colitis. None of these events were reported as drug-related.

The most frequently reported non-ocular AEs (> 5%) were abdominal pain, systolic pressure increased, and dehydration. None of these events were reported as drug-related.

1.4.1.3 Systemic Exposure to Sunitinib

In all subjects, plasma levels of sunitinib were evaluated on Day 1 (1 and 2 hours post-injection), Day 14, Months 1, 2, 3, 4, and 8. All samples were below the limit of quantitation on all subjects at all time points [LLQ > 0.3 ng/mL].

1.4.1.4 Functional and Pharmacodynamic Parameters

Mean BCVA and CST at all visits for each dose cohort are presented in Figure 1-5 and Figure 1-6, respectively. Pooled results are presented in Figure 1-7. The CST values include historic (pre-study) worst observation measurements during the anti-VEGF induction period.

GB-102 appears to maintain and stabilize visual acuity and retinal thickness in subjects who have received at least 3 prior doses of anti-VEGF. The pooled CST results demonstrate nominal statistical significance ($P<0.05$) at all visits relative to the historic pre-study CST values.

Particle dispersion can interfere with visual acuity and was observed particularly in the 2 mg cohort as demonstrated by a U-shaped decline in BCVA at approximately month 3 to 4 when AC migration was reported (Figure 1-5).

Overall, the results are consistent with outcomes observed in masked randomized controlled studies evaluating sustained-release of anti-VEGF (Awh 2018 [LADDER]).

Figure 1-5. Mean BCVA (ETDRS) For Each Cohort at All Visits

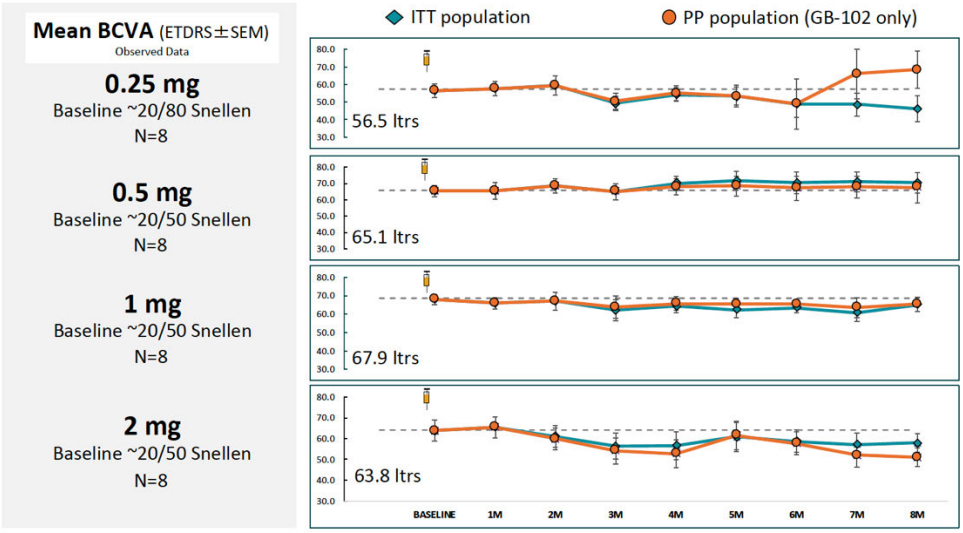


Figure 1-6. Mean CST (µm) For Each Cohort at All Visits

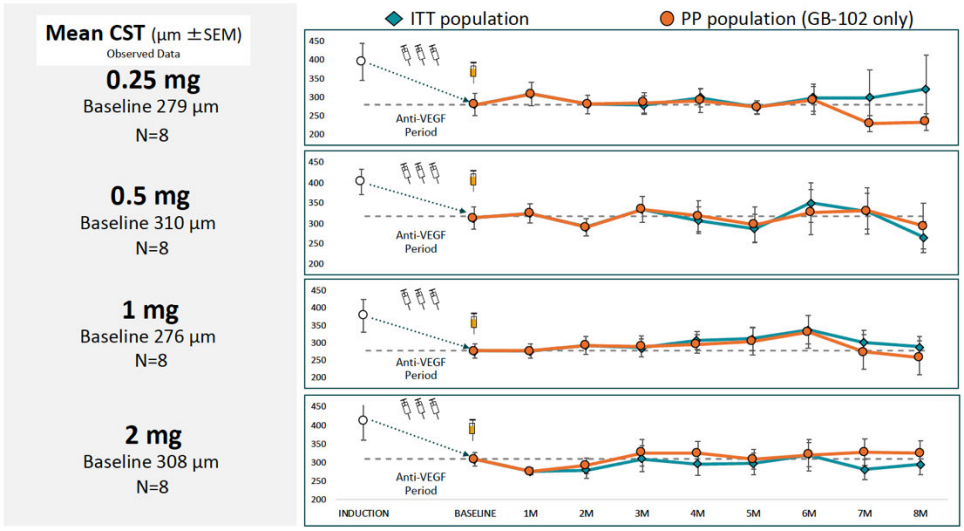
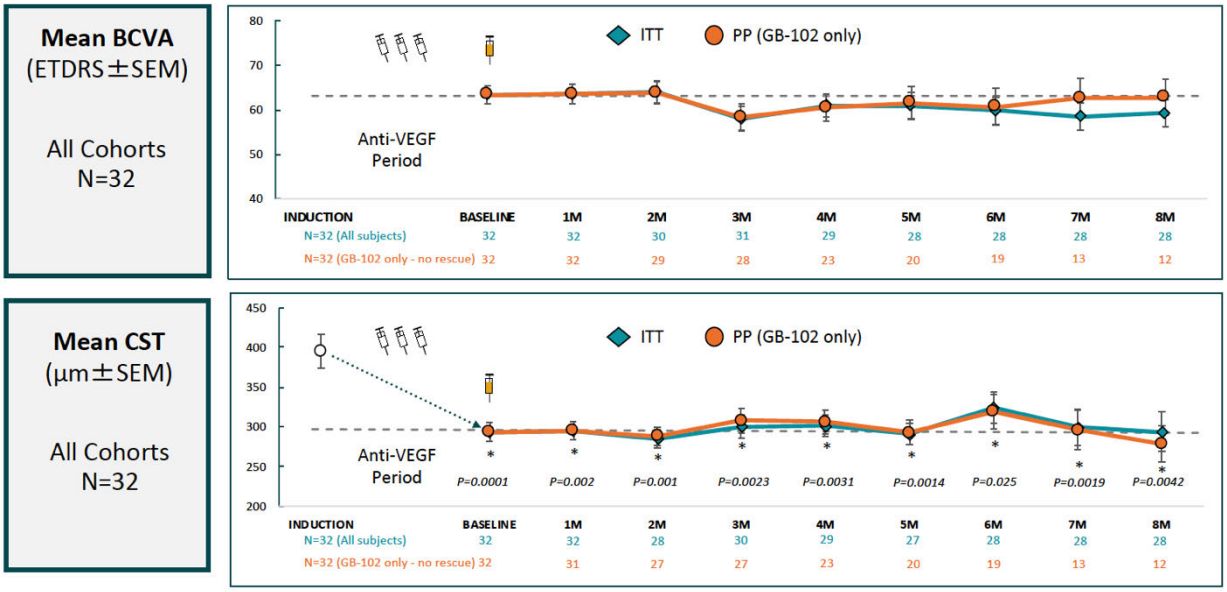


Figure 1-7. Pooled Results (All Cohorts) for BCVA and CST at All Visits

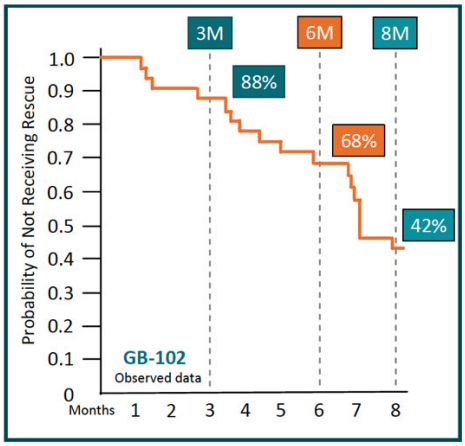


1.4.1.5 Rescue

Protocol-specified criteria for rescue with aflibercept were: > 10 letter loss in BCVA with retinal fluid that, in the opinion of the investigator, was the cause of the BCVA loss, and/or > 75 µm increase in CST, and/or vision-threatening hemorrhage due to underlying nAMD.

Kaplan-Meier survival curves were used to assess rescue-free survival rates. Overall, 88%, 68%, and 42% of the study population was rescue-free through Month 3, 6 and 8, respectively (Figure 1-8).

Figure 1-8. Rescue Free Survival (Pooled Data)



1.4.1.6 Conclusions

Part 1 of the Phase 1/2a study met its primary endpoint of safety and tolerability. There were no ocular SAEs or dose-limiting toxicity events. The most commonly reported ocular AEs related to particle migration into the anterior chamber that may be associated with mild elevation in IOP; however, these events can be managed conservatively (biodegradation) and are self-limited, reversible, with no long-term sequelae.

There is a clear and durable pharmacodynamic effect of GB-102 based on analyses of BCVA, CST, and rescue rates with ≥ 6-month dosing duration achieved in a majority of subjects.

Overall, the results support continued development of GB-102.

1.4.2 Protocol GBV-102-003 (Phase 2a)

The purpose of this study is to assess the safety, tolerability, and pharmacodynamic response of two dose strengths (1 mg and 2 mg) of GB-102 administered as a single injection in subjects with refractory macular edema (ME) secondary to DME or RVO. This study is active and fully enrolled with a total of 21 subjects (N=10, 1 mg; N=11, 2 mg). Study completion is anticipated 1H 2020.

A single subject had a reported 2 drug-related ocular serious adverse events (SAEs).

The subject with the ocular SAEs is a 61-year-old male with history of central retinal vein occlusion, bilateral cataract extraction with posterior intraocular lens placement, and glaucoma. No prior history of laser capsulotomy. On Day 1, the 2 mg GB-102 injection procedure was uncomplicated with a normal appearing drug depot. At the Month 2 visit, the subject experienced migration of drug material to the AC with partial blockage of the visual axis at the pupil, which resulted in the first SAE of decreased visual acuity. Associated findings included posterior uveitis with dispersed vitreous opacities from free-floating drug material. The investigator elected to remove the medication in the AC via AC lavage/washout followed by a pars plana vitrectomy to remove the dispersed drug in the vitreous. Per the investigator, the consistency

(firmness) of the study drug in the AC was unexpected resulting in difficulty in extracting the drug material. The vigorous and prolonged surgical lavage resulted in post-operative corneal edema (the second SAE) and reduction in vision to hand motion. The post-operative corneal edema is being managed with topical steroids and the SAE event is reported as resolving/recovering.

There were also 3 non-ocular SAEs reported in 2 subjects: 1 subject was hospitalized twice for gastrointestinal hemorrhage twice, and 1 subject was hospitalized for non-ST elevated myocardial infaction. None of these events were reported as drug-related.

1.4.3 Protocol GBV-102-002 (Phase 2b, ALTISSIMO Study)

The purpose of this study is to assess the efficacy and safety of two different dosing schemes of GB-102 administered every 6 months (1 mg followed by 1 mg or 2 mg followed by 1 mg) compared with a fixed regimen of 2 mg aflibercept administered every 2 months. The study is active, and enrollment is complete.

The first subject enrolled was September 2019 with a planned sample size of 160 subjects. Due to the reported SAE in Protocol GBV-102-003 on December 17, 2019, enrollment in the ALTISSIMO study was voluntarily suspended by the Sponsor on December 19, 2019 as a safety precaution after a total of 56 subjects had been enrolled. An unmasked limited interim safety review was conducted by the Sponsor (Chief Medical Officer and the Vice President of Global Clinical Operations) in February 2020. During this safety review, no SAEs had been reported in ALTISSIMO; however, 5 subjects had a report of drug material observed in the AC (N=4, 2 mg; N=1, 1 mg). All reported cases were mild-to-moderate in severity. One subject who received the 2 mg dose developed a moderate pseudohypopyon and was managed with elective AC lavage and pars plana vitrectomy without complication. The subjects remain in the study and are under observation alone or undergoing treatment with a short course of prophylactic topical steroids.

The Sponsor elected to stop further enrollment in ALTISSIMO and to re-dose (Month 6 visit) only the 1 mg dose of GB-102 for those subjects assigned to GB-102.

EXTENSION STUDY

The purpose of this portion of the ALTISSIMO study is to monitor the safety and duration of effect of IVT GB-102 administered every 6 months compared to IVT aflibercept administered every 2 months in subjects in ALTISSIMO (Core Study) who complete all study visits through Month 12 (Day 360) and who do not require/receive rescue treatment at the Month 12 (Day 360) final study visit. Enrolled subjects will be followed for monthly visits until they receive rescue treatment or for a maximum of 180 days (i.e, 6 months). There will be no additional treatment with GB-102. With this amendment, the ALTISSIMO study is divided into the ALTISSIMO (Core Study) and the Extension Study. Unless otherwise specified, all segments of the protocol refer to the ALTISSIMO (Core Study).

1.5 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 ALTISSIMO (Core Study): Objectives

With this amendment, the ALTISSIMO Study is divided into the ALTISSIMO (Core Study) and the Extension Study. Unless otherwise specified, all segments of the protocol refer to ALTISSIMO (Core Study).

2.1.1 Primary Objective

To evaluate the safety and duration of the effect of GB-102, as measured by time to first rescue treatment across two different dosing schemes of GB-102 administered every 6 months (1 mg followed by 1 mg or 2 mg followed by 1 mg) as compared to intravitreal (IVT) aflibercept administered every 2 months in subjects with neovascular (wet) age-related macular degeneration who have received prior induction with IVT anti-VEGF.

2.1.2 Secondary Objectives

- To evaluate the efficacy of two different dosing schemes of IVT GB-102 administered every 6 months in maintenance of best-correct visual acuity (BCVA, ETDRS letter score) compared to subjects receiving IVT aflibercept every 2 months
- To evaluate the efficacy of two different dosing schemes of IVT GB-102 administered every 6 months in maintenance of central subfield thickness (CST, μm) compared to subjects receiving IVT aflibercept every 2 months

2.2 Extension Study: Objective

To monitor the safety and duration of effect of IVT GB-102 administered every 6 months compared to IVT aflibercept administered every 2 months in subjects in ALTISSIMO (Core Study) who complete all study visits through Month 12 (Day 360) and who do not require/receive rescue treatment at the Month 12 (Day 360) final study visit.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design Summary

3.1.1 ALTISSIMO (Core Study): Overall Study Design Summary

This is a Phase 2b, multicenter, visual examiner-masked, randomized active-controlled, parallel-arm design.

Subjects eligible for screening must have an active CNV lesion in the **study eye** secondary to AMD that was diagnosed in the 12 weeks to 18 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 21 days of screening. Eligibility will be confirmed by a central reading center based upon SD-OCT, FA, and color fundus photography (CFP) evaluation of the CNV lesion.

Eligible subjects will be randomly assigned (3:3:2) to receive 50-µL IVT injections of 1 of 2 doses of study drug or aflibercept, respectively, in the study eye using a stratified, blocked randomization scheme. Stratification will include baseline BCVA (< 60 letters vs ≥ 60 letters). Approximately 15 to 20 subjects per group, 56 subjects total, will be randomized to one of the following treatment arms:

Group 1: 1 mg GB-102 at baseline and Month 6 and sham at Months 2, 4, 8, and 10 (N=21)

Group 2: 2 mg GB-102 at baseline and 1 mg GB-102 at Month 6 and sham at Months 2, 4, 8, and 10 (N=22)

Group 3: 2 mg aflibercept q 2 months at baseline, Months 2, 4, 6, 8 and 10 (N=13)

Assigned study drug will be administered on Day 1 (Appendix 18.1). Subjects will return to the study center on Days 14, 30, 60, 90, 120, 150, 180, 210, 240, 300, 330, and 360 for safety, clinical, and imaging assessments (Table 3-1). Subjects will exit the study following all study assessments on Day 360.

An interim safety analysis was conducted when approximately 50% of subjects had 3-months of accrued data to determine if any changes to the protocol were needed prior to the Month 6 re-dosing schedule. Unmasking of the interim safety data was made available only to the Sponsor's Chief Medical Officer and the Vice President of Global Clinical Operations. The interim analysis showed no serious ocular adverse events. Four subjects experienced medication in the anterior chamber (AC) in the GB-102, 2 mg dose arm as compared to 1 subject in the GB-102, 1 mg dose arm. Based on this safety analysis, the sponsor decided to terminate the development of the GB-102 2 mg dose, and amended the protocol to use GB-102 1 mg for re-dosing of all subjects on GB-102 at the Month 6 visit, regardless of their original dose assignment. The enrollment was capped at 56 subjects and the primary endpoint was shifted

from Month 10 to Month 12 based on suggested feedback from the Food and Drug Administration (FDA).

An unmasked primary analysis for safety and efficacy is planned when all subjects complete the Day 360 visit.

The safety parameters to be collected include adverse events (AEs), serious adverse events (SAEs), physical examination findings, clinical laboratory test results, vital sign measurements, best corrected visual acuity (BCVA) assessments using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol, slit-lamp biomicroscopy findings, Age-related Eye Disease Study (AREDS) lens assessments, intraocular pressure (IOP) measurements, dilated ophthalmoscopy results, and date of administration of rescue treatment.

Efficacy parameters will be measured by means of rescue treatment, BCVA (using the ETDRS protocol), retinal central subfield thickness (CST) using spectral domain-optical coherence tomography (SD-OCT), fluorescein angiography (FA), and color fundus photography (CFP).

The systemic exposure will be based on subjects assigned to each sunitinib treatment group. An analysis of approximately 20% of the subjects assigned to each sunitinib group will be performed.

3.1.2 Extension Study: Overall Study Design Summary

The Extension Study is a multicenter, visual examiner-masked study, designed to monitor the safety and duration of effect of IVT GB-102 administered every 6 months compared to IVT aflibercept administered every 2 months in subjects in ALTISSIMO (Core Study) who complete all study visits through Month 12 (Day 360) and who do not require/receive rescue treatment at the Month 12 (Day 360) final study visit.

Enrolled subjects will be followed for monthly visits until they receive rescue treatment or for a maximum of 180 days (i.e, 6 months). There will be no additional treatment with GB-102.

The assessments to be collected include AEs, SAEs, concomitant medications, BCVA assessments using ETDRS protocol, slit-lamp biomicroscopy findings, AREDS lens assessments, IOP measurements, dilated ophthalmoscopy results, retinal CST using SD-OCT, color fundus photography for depot imaging (ultra-widefield imaging, where available) and date of administration of rescue treatment.

Once a subject meets at least one rescue criteria and all study visit assessments are completed, they may receive an injection of aflibercept and exit the study.

No formal statistical hypotheses testing will be performed. An exploratory analysis of safety and efficacy will be performed after all subjects have completed the study.

3.2 Safety Monitoring

A medical monitor (ophthalmologist) and the Sponsor's medical officer will evaluate the on-going masked safety data.

3.3 Masking

3.3.1 ALTISSIMO (Core Study) and Extension Study: Masking

The visual acuity examiners, the Sponsor (other than the Vice President of Global Clinical Operations), the masked CRO personnel, the medical monitor, and other study personnel, including individuals at a central reading center, study coordinators, laboratory vendor, etc. will remain masked relative to GB-102 scheme. The visual acuity examiners are not allowed to perform any study related activities other than BCVA assessments to maintain masking including obtaining medical histories or attempting to elicit any information regarding treatment, adverse events, or clinical information from the subjects. The same BCVA examiner should be utilized for each subject throughout the study when possible.

Each study center will have at least 2 investigators who are retina specialists; one will serve as the injecting investigator and the other will serve as the assessing investigator. To maintain study masking, the roles of these investigators should not be switched during the conduct of the study.

3.3.2 ALTISSIMO (Core Study): Masking

- Injecting Investigator: An injecting investigator will perform the study drug (GB-102 or aflibercept), sham, and/or rescue injections, will supervise the preparation and tracking of study drug, and will perform predose and postdose safety assessments for the IVT injections.

- Assessing Investigator: An assessing investigator will supervise and assess the collection of AEs and efficacy parameters. The assessing investigator will determine whether rescue treatment is required.

The SD-OCT, FA, and CFP technicians are masked to treatment scheme; however, collected images may reveal to the assessing investigator or technician which subjects received the GB-102 depot.

Study personnel performing reconstitution of the investigational drug product (GB-102) will be unmasked to treatment assignment but not the treatment scheme. Study drug will be boxed in numbered kits and identical in external appearance and weight. Kits containing GB-102 are identical in physical appearance and drug vial/diluent (pre-filled syringe) configuration, and fully masked as to the dose strength (1 or 2 mg) of GB-102.

3.3.3 Extension Study: Masking

- Injecting Investigator: An injecting investigator will perform the rescue injections, will supervise the preparation and tracking of study drug, and will perform predose and postdose safety assessments for the IVT injections.
- Assessing Investigator: An assessing investigator will supervise and assess the collection of AEs, SAEs, concomitant medications, BCVA assessments using ETDRS protocol, slit-lamp biomicroscopy findings, AREDS lens assessments, IOP measurements, dilated ophthalmoscopy results, and retinal CST using SD-OCT. The assessing investigator will determine whether rescue treatment is required.

The SD-OCT and color fundus photography imaging (ultra-widefield imaging, where available) technicians are masked to treatment scheme; however, collected images may reveal to the assessing investigator or technician which subjects received the GB-102 depot in ALTISSIMO Core Study.

3.4 Rescue Treatment

Rescue treatment (using aflibercept) will be permitted in the study eye in ***any*** of the study arms if the eligibility criteria are met for rescue treatment. Subjects receiving rescue treatment will continue to be evaluated at scheduled study visits.

The nonstudy eye may receive IVT anti-VEGF treatment (aflibercept, bevacizumab, or ranibizumab) for the treatment of wet AMD at the discretion of the investigator.

3.5 Study Design Rationale

3.5.1 ALTISSIMO (Core Study): Study Design Rationale

The proposed study is designed to assess the efficacy and safety of two different dosing schemes of GB-102 (1 mg followed by 1 mg or 2 mg followed by 1 mg) administered every 6 months compared with a fixed regimen of aflibercept every 2 months.

The medical monitor (ophthalmologist) and the Sponsor's medical officer will evaluate masked safety data on an on-going basis.

An interim safety analysis was conducted when approximately 50% of subjects had 3-months of accrued data to determine if any changes to the protocol were needed prior to the Month 6 re-dosing schedule. Unmasking of the interim safety data was made available only to the Sponsor's Chief Medical Officer and the Vice President of Global Clinical Operations.

Use of at least 2 retinal physician investigators at each study center, including an assessing investigator and an injecting investigator, is a well-established method for conducting registrational drug studies in subjects with wet AMD (CATT Research Group 2011, Heier 2012, Rosenfeld 2006).

The subjects, visual acuity examiners, the Sponsor (other than the Vice President of Global Clinical Operations), the medical monitor, and other study personnel, including individuals at a central reading center, study coordinators, laboratory vendor, etc. will remain masked relative to GB-102 scheme. Though the GB-102 depot may be visible initially upon ocular examination, the observer will be masked as to the treatment scheme. The depot is expected to fully bioabsorb after approximately 4 to 6 months. Sham injections are incorporated in the study plan to maintain subject masking.

The planned study assessments (eg, AEs, abbreviated physical examinations, clinical laboratory tests, vital sign measurements, BCVA assessments, slit-lamp biomicroscopy examinations, AREDS lens assessments, SD-OCT, FA, CFP, dilated ophthalmoscopy evaluations, and systemic exposure) are conventional parameters used to evaluate the safety and pharmacodynamic activity of pharmacologic agents in retinal disease.

The sample size of this study (56 subjects randomized 3:3:2 to two GB-102 dosing schemes and the aflibercept group, respectively) was not selected to support specific statistical hypothesis testing; however, approximately 12 evaluable subjects in the full analysis set are planned for the aflibercept group, and 20 evaluable subjects in the full analysis set per GB-102 group will be sufficient to establish estimates of serious ocular event rates related to GB-102. Details regarding the determination of sample size are described in Section 9.8.

Rescue treatment with aflibercept for the study eye and the frequency of monthly injections is within the standard-of-care for subjects with wet AMD for the maintenance of visual acuity and/or the prevention of vision loss.

3.5.2 Extension Study: Study Design Rationale

The Extension Study is designed to monitor the safety and duration of effect of IVT GB-102 administered every 6 months compared to IVT aflibercept administered every 2 months in subjects in ALTISSIMO (Core Study) who complete all study visits through Month 12 (Day 360) and who do not require/receive rescue treatment at the Month 12 (Day 360) final study visit.

In order to maintain masking of the treatment schemes for ALTISSIMO (Core Study), all subjects from all treatment schemes on ALTISSIMO (Core Study) will be allowed to enroll in the Extension Study provided all entry criteria are met prior to study entry.

3.6 Appropriateness of Measurements

3.6.1 ALTISSIMO (Core Study): Appropriateness of Measurements

The primary aim of the data analyses in this study is to assess the safety and exploratory efficacy of two different GB-102 treatment schemes in subjects with wet AMD.

The safety and pharmacodynamic parameters to be evaluated in this study are consistent with landmark, randomized, multicenter, registrational drug studies of IVT agents used to treat wet AMD (CATT Research Group 2011, Heier 2012, Rosenfeld 2006).

Additional safety parameters intended to assess systemic AEs related to sunitinib exposure include clinical laboratory tests (eg, chemistry, hematology, and urinalysis).

Systemic PK will be evaluated to characterize systemic exposure from IVT sunitinib administration.

3.6.2 Extension Study: Appropriateness of Measurements

The aim of the Extension Study is to monitor the safety and duration of effect of two different GB-102 treatment schemes in subjects with wet AMD.

No additional safety parameters intended to assess systemic AEs related to sunitinib exposure or systemic PK will be evaluated in the Extension Study.

Table 3-1. Study Plan and Schedule of Assessments: ALTISSIMO (Core Study)

Activity/Assessment	S[a]	B	W 2	M 1	M 2	M 3	M 4	M 5	M 6	M 7	M 8	M 9	M 10	M 11	M 12 (ET)
Visit Day ± Window[n]	−30 to −3	1	14±2	30±4	60±7	90±7	120±7	150±7	180±7	210±7	240±7	270±7	300±7	330±7	360±7
Informed Consent/HIPAA	X														
Inclusion/Exclusion Criteria	X														
Demographics Data	X														
Medical/Medication History	X														
Physical Examination	X														X
Pregnancy Testing[b]	X	X													X
Clinical Laboratory Tests[c]	X						X								X
Plasma PK[d]		X	X	X	X	X	X		X	X	X	X			X
Adverse Events	X	X[e]	X	X	X[d]	X	X[d]	X	X[d]	X	X[d]	X	X[d]	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[o]	X	X	X	X	X		X		X		X		X		X
BCVA (ETDRS)[f]	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
Slit-lamp Biomicroscopy[g]	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
IOP[h]	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
Dilated Ophthalmoscopy	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
SD-OCT[i]	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
Fluorescein Angiography[j]	OU								OU						OU
Color Fundus Photography[j]	OU								OU						OU

Activity/Assessment	S[a]	B	W 2	M 1	M 2	M 3	M 4	M 5	M 6	M 7	M 8	M 9	M 10	M 11	M 12 (ET)
Visit Day ± Window[n]	**−30 to −3**	**1**	**14±2**	**30±4**	**60±7**	**90±7**	**120±7**	**150±7**	**180±7**	**210±7**	**240±7**	**270±7**	**300±7**	**330±7**	**360±7**
Intravitreal Depot Color Fundus Photography[k]		SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE
GB-102 Dosing/ Sham Injection[l]		SE			sham		sham		SE		sham		sham		
Aflibercept Dosing[l]		SE			SE		SE		SE		SE		SE		
Postinjection Assessment[m]		SE			SE		SE		SE		SE		SE		
Follow-Up Call[e]		+1 day			+1 day		+1 day		+1 day		+1 day		+1 day		
Subject Exit Questionnaire[p]															X

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; PK = pharmacokinetic; 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 and that the reading center has confirmed eligibility.

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

c **Chemistry** (nonfasting blood): sodium, potassium, chloride, bicarbonate, albumin, alkaline phosphatase, aspartate amino transferase, alanine amino transferase, bilirubin direct, bilirubin indirect, total bilirubin, creatinine, blood urea nitrogen, total protein, calcium, phosphorus, and hemoglobin A1c. **Hematology** (complete blood count with differential): white blood cell count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width, platelet count, and mean platelet volume. **Urinalysis** (dipstick): glucose, protein, and pH. Urine drug screen will be taken at Screening Visit only.

d All subjects in each group will have blood drawn for sunitinib systemic exposure assessment. An analysis of approximately 20% of the subjects assigned to each sunitinib group will be performed. Blood collection on Day 1 and Day 180 will be 1 hour ± 15 minutes after intravitreal injection. For all other visits, blood samples can be collected at any time. Blood samples are immediately processed for plasma and stored frozen until shipped.

e All subjects will receive a telephone call for the day after the intravitreal or sham injection following visits at Baseline and Months 2, 4, 6, 8, and 10 to assess for any significant complaints or adverse events.

f 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.

g The Age-Related Disease Study lens assessment will be conducted and graded by the investigator as part of the biomicroscopy examination.

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 dosing visits.

i CST thickness measurements from SD-OCTs prior to enrollment (eg, initial diagnosis and /or during anti-VEGF induction) will be collected for up to 18 months prior to screening, if applicable

j Fluorescein angiography and color fundus photography will be conducted prior to intravitreal injection at Month 6.

k Additional color fundus photography of the intravitreal GB-102 depot will be obtained following the dilated ophthalmic examination at all visits. 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 where rescue treatment is administered. The photographs may be used to document the general appearance and rate of bioabsorbability of the depot. For detailed instructions regarding collection of the intravitreal depot CFP imaging, refer to the separately provided guideline. Select sites will collect additional intravitreal depot color fundus photography using the Zeiss Clarus 500 or Optos California Ultra-widefield Fundus Imaging system at all visits after initial dosing at Baseline and at any unscheduled visits where rescue treatment is administered.

l For all dosing procedures (intravitreal or sham), subject should remain seated for approximately 15 minutes post-injection with minimal to no movement of the head. Aflibercept dosing to be conducted per instructions in prescribing information by the injecting physician. All subjects receiving GB-102 at baseline will receive 1 mg GB-102 at Month 6.

m 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 or ophthalmoscopy, per discretion of the investigator) prior to going home.

n 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.

o Along with the vital signs, height (without shoes) will be measured at Screening and body weight will be measured at Screening and Month 12. The same arm and method of obtaining blood pressure and heart rate should be used throughout the study.

p Each subject that completes a Month 12 (Day 360) visit must complete the subject exit questionnaire before exiting the ALTISSIMO (Core Study).

Table 3-2. Study Plan and Schedule of Assessments: Extension Study

Activity/Assessment	M12 (S/B)[a]	M 13	M 14	M 15	M 16	M 17	M 18/ET
Visit Day ± Window[f]	**360**	**390±7**	**420±7**	**450±7**	**480±7**	**510±7**	**540±7**
Informed Consent/HIPAA	X						
Inclusion/Exclusion Criteria	X						
Adverse Events		X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X
BCVA (ETDRS)[b]		OU	OU	OU	OU	OU	OU
Slit-lamp Biomicroscopy[c]		OU	OU	OU	OU	OU	OU
IOP[d]		OU	OU	OU	OU	OU	OU
Dilated Ophthalmoscopy		OU	OU	OU	OU	OU	OU
SD-OCT		OU	OU	OU	OU	OU	OU
Intravitreal Depot Color Fundus Photography[e]		SE	SE	SE	SE	SE	SE

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

a Screening/Baseline Visit of the Extension Study to occur on the same day as Month 12 (Day 360) in ALTISSIMO (Core Study).

b 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.

c The Age-Related Disease Study lens assessment will be conducted and graded by the investigator as part of the biomicroscopy examination.

d 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 rescue treatment.

e Additional color fundus photography of the intravitreal GB-102 depot will be obtained following the dilated ophthalmic examination at all visits and conducted through (and include) the final study visit and any unscheduled visits where rescue treatment is administered. The photographs may be used to document the general appearance and rate of bioabsorbability of the depot. For detailed instructions regarding collection of the intravitreal depot CFP imaging, refer to the separately provided guideline. Select sites will collect additional intravitreal depot color fundus photography using the Zeiss Clarus 500 or Optos California Ultra-widefield Fundus Imaging system at all visits and at any unscheduled visits where rescue treatment is administered.

f 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.

4 SUBJECT POPULATION

4.1 Number of Subjects and Subject Selection

4.1.1 ALTISSIMO (Core Study): Number of Subjects and Subject Selection

Subjects eligible for screening must have an active CNV lesion in the **study eye** secondary to AMD that was diagnosed in the 12 weeks to 18 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 21 days of screening. Eligibility will be confirmed by a central reading center based upon SD-OCT, FA, and color fundus photography (CFP) evaluation of the CNV lesion. The complete inclusion and exclusion criteria are presented, respectively, in Section 4.3 and Section 4.4.

The study is planned to be conducted at approximately 35 study centers in the US and will include approximately 15 to 20 subjects per treatment scheme (approximately 56 subjects across all treatment schemes combined).

4.1.2 Extension Study: Number of Subjects and Subject Selection

Subjects eligible for screening and enrollment must complete all study assessments at the Month 12 (Day 360) including fluorescein angiography, and not require/receive a rescue treatment at the Month 12 (Day 360) final study visit in ALTISSIMO (Core Study). The complete inclusion and exclusion criteria are presented, respectively, in Section 4.5 and Section 4.6.

There will be no randomization in the Extension Study.

4.2 Study Eye Determination

4.2.1 ALTISSIMO (Core Study): 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.

4.2.2 Extension Study: Study Eye Determination

The study eye is defined as the eye that was treated in the ALTISSIMO (Core Study).

4.3 Inclusion Criteria: ALTISSIMO (Core Study)

Subjects must meet all 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 ≥ 50 years of age
3. Willing and able to give informed consent, comply with all study procedures, and be likely to complete the study
4. Presence of a subfoveal or juxtafoveal CNV lesion secondary to AMD in the **study eye** that was diagnosed in the 12 weeks to 18 months prior to screening and has been treated with at least 3 prior IVT injections of an anti-VEGF agent (aflibercept, bevacizumab, or ranibizumab). The **study eye** and CNV lesion must demonstrate ***all*** of the following features at the Screening Visit (as confirmed by the reading center):
    a. Total lesion size ≤ 12 disc areas (30.5 mm^2)
    b. Absence of subfoveal fibrosis, serous pigmented epithelial detachment, retinal pigmented epithelial tear, or subfoveal geographic atrophy
    c. If fibrosis is present, it must be ≤ 25% of total lesion area and not involve the center of the fovea
    d. If subfoveal hemorrhage is present, it must be < 1 disc area in size and not involve the center of the fovea
    e. If subretinal hemorrhage is present, it must be < 50% of total CNV lesion and not involve the center of the fovea
5. Prior pharmacodynamic response of the CNV lesion 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:
    a. Reduction of intraretinal/subretinal fluid by ≥ 30% from the initial diagnosis as determined using SD-OCT
    b. Reduction of excess CST by ≥ 30% from the initial diagnosis as determined using SD-OCT (assuming nominal thickness is 300 microns)
6. Demonstrate a maintained anti-VEGF response (as determined by the investigator) compared with the initial diagnosis (prior to any anti-VEGF treatment) as assessed using SD-OCT following the most recent anti-VEGF injection (defined as a reduction in central subfield thickness, intraretinal/subretinal fluid, or maintenance of dry retina)
7. Screening and baseline BCVA letter score (by ETDRS protocol) of 35 to 88 (20/200 to 20/20 Snellen equivalent) in the **study eye**
8. Availability of central subfield thickness (CST) measurements from SD-OCT imaging obtained from the time of initial diagnosis (pre-anti-VEGF therapy) and/or maximal CST thickness obtained any time following anti-VEGF induction
9. 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
10. Most recent dose of anti-VEGF agent administered within 21 days of screening

11. Clear ocular media and adequate pupil dilation in both eyes to permit good quality photographic imaging
12. Women of childbearing potential (ie, not postmenopausal for at least **12 months** or not *surgically sterile* [defined as *bilateral tubal ligation performed at least 12 months previously, hysterectomy, or bilateral oophorectomy*]) must have a negative urine pregnancy test at screening and baseline, and must use adequate birth control throughout the study and until 12 weeks following the last dose of study drug 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

4.4 Exclusion Criteria: ALTISSIMO (Core Study)

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study.

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 > 8.0% at the Screening Visit
4. Chronic renal disease requiring chronic hemodialysis or renal transplantation
5. Any screening laboratory result (hematology, chemistry, or urinalysis) that, in the opinion of the investigator, is not suitable for subject participation in the study
6. 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)
7. Previous participation in an investigational study of GB-102
8. 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
9. 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
10. Presence of any clinically significant epiretinal membrane or vitreomacular traction in the **study eye**
11. History or evidence of any of the following surgeries or procedures in the **study eye**:
    a. Submacular surgery or other surgical intervention for AMD
    b. Prior retinal detachment or macular hole interventions
    c. Vitrectomy
    d. Photodynamic therapy or thermal laser retinal treatment
    e. Intraocular laser treatments for glaucoma (eg, selective laser trabeculoplasty or peripheral iridotomy)
    f. 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
    g. Cataract surgery within the 3 months prior to the Screening Visit
    h. 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

i. 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

j. Corneal transplantation surgery

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

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

13. 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. Advanced pre-proliferative diabetic retinopathy (with potential for development of macular edema or macular hemorrhage) or proliferative diabetic retinopathy and/or diabetic macular edema in either eye

    b. Any retinal or choroidal vasculopathy, other than AMD, in either eye

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

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

    e. Subfoveal hemorrhage that is ≥ 1 disc areas in size (if the blood is under the fovea, the fovea must be surrounded ≥ 270° by visible CNV)

    f. Subretinal hemorrhage that is ≥ 50% of the total CNV lesion area

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

    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.

14. Any history of active bacterial, viral, fungal, or parasitic infection in either eye within the 30 days prior to the Screening Visit

15. Known allergy to constituents of the study drug formulation, ocular antimicrobicide solutions, or clinically relevant hypersensitivity to fluorescein

16. Women who are pregnant or lactating

17. 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 12 weeks following the last dose of study drug

18. 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 monthly study visits and assessments, or interfere with the interpretation of study results
19. Exposure to tetrahydrocannibol (THC) (eg, recreational or medicinal marijuana containing THC) within the past 12 months
20. Prior exposure to oral sunitinib malate in the past 6 weeks

4.5 Inclusion Criteria: Extension Study

1. Verbal and written informed consent for the Extension Study obtained from the subject
2. Completed all study assessments at Month 12 (Day 360) final study visit including fluorescein angiography, and did not require/receive a rescue treatment at the Month 12 (Day 360) final study visit in ALTISSIMO (Core Study).
3. Willing and able to give informed consent, comply with all study procedures, and be likely to complete the study for the Extension Study

4.6 Exclusion Criteria: Extension Study

1. Subjects who terminated early from ALTISSIMO (Core Study).
2. Subject who did not complete all study assessments at Month 12 (Day 360) final study visit including fluorescein angiography in ALTISSIMO (Core Study).
3. Subjects who received rescue treatment at the Month 12 (Day 360) final study visit in ALTISSIMO (Core Study).

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. This technician will be unmasked to treatment assignment but not the treatment scheme of GB-102. 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. Aflibercept (EYLEA®, 2.0 mg) and associated administration supplies will be provided by the Sponsor for subjects randomized to receive aflibercept.

Each study center will have at least 2 retinal physician investigators, and to maintain masking, their roles should not be switched for an individual subject during the conduct of the study. Information regarding the 2 physician investigators is presented in Section 3.1.

Adequate topical anesthesia and eye preparation materials (eg, povidone iodine solution) will be given prior to the IVT or sham injection per the injecting investigator's standard-of-care. All IOP measurements will be obtained before each injection. 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.

The comparator product (aflibercept) and the sham injection should be prepared and administered as follows:

Aflibercept (2 mg): The comparator product will be prepared and administered in a manner consistent with the approved package insert for EYLEA®.

Sham injections: To maintain masking for subjects, the injecting investigator will conduct the standard preparations for IVT injection of the eye (topical anesthesia and eye preparation). The injecting investigator will press the tip of a sterile 1-cc Luer Lock syringe, without a needle, against the globe in a manner similar to an IVT injection.

5.2 Treatment Assignment

5.2.1 Subject Identification Numbers

5.2.1.1 ALTISSIMO (Core Study): Subject Identification Numbers

After signing the informed consent form, each subject will be assigned a unique screening number via interactive response technology (IRT). 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 via IRT and assigned a randomization number. The screening numbers will be used to identify all enrolled subjects throughout the study.

5.2.1.2 Extension Study: Subject Identification Numbers

The subject identification number assigned in the ALTISSIMO (Core Study) for each subject will be the same number used to identify the subject in the Extension Study.

5.2.2 Enrollment and Method of Assigning Subjects to Treatment Cohorts/Groups

5.2.2.1 ALTISSIMO (Core Study): Enrollment and Method of Assigning Subjects to Treatment Cohorts/Groups

The visual acuity examiners, the Sponsor (other than the Vice President of Global Clinical Operations), the masked CRO personnel, the medical monitor, and other study personnel, including individuals at a central reading center, study coordinators, laboratory vendor, etc. will remain masked relative to treatment assignment during the randomization process and to the GB-102 treatment scheme post-randomization throughout the study.

Eligible subjects will be randomly assigned (3:3:2) to receive 50-µL IVT injections of 1 of 2 doses of study drug or aflibercept, respectively, in the study eye using a stratified, blocked randomization scheme. Stratification will include baseline BCVA (< 60 letters vs ≥ 60 letters).

The study eye will be selected based upon the study qualification criteria and will be used for stratification into the IRT at randomization.

An independent, unmasked designee who is not otherwise involved in the study will generate the randomization code used by the IRT, which subsequently will be used to assign masked study kit

numbers for dispensing to each enrolled subject at Baseline and Months 2, 4, 6, 8 and 10. A new kit will be dispensed at each study visit based on the subject's randomization.

5.2.2.2 Extension Study: Enrollment and Method of Assigning Subjects to Treatment Cohorts/Groups

The visual acuity examiners, the Sponsor (other than the Vice President of Global Clinical Operations), the masked CRO personnel, the medical monitor, and other study personnel, including individuals at a central reading center, study coordinators, laboratory vendor, etc. will remain masked relative to treatment assignment during randomization process for the ALTISSIMO (Core Study) and to the GB-102 treatment scheme post-randomization throughout the Extension Study.

The study eye selected in the ALTISSIMO (Core Study) will remain the same for the Extension 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.

Sham and sham ancillary supply kits will be provided in identical medication kits and medication ancillary supply kits, respectively, to maintain masking to the subject.

The control treatment, aflibercept (EYLEA®) will be supplied in commercial packaging (including filter needle, syringe, and needle for injection) and provided in identical medication kits for masking purposes.

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. Aflibercept must be stored per the EYLEA® label.

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 (aflibercept) is allowed as rescue treatment at any visit following the Day 30 study assessments in ALTISSIMO (Core Study) or any visit following the Month 13 (Day 390) study assessments in the Extension Study in subjects who meet any of the following criteria regarding disease in BCVA and/or increase in CST:

- Decrease in BCVA (any of the following criteria):
    - $\geq$ 5 ETDRS letter decrease compared with the average of last 2 visit BCVA ETDRS letter scores, and/or,
    - $\geq$ 10 ETDRS letter decrease compared with best on-study BCVA ETDRS letter score
- Increase in CST (any of the following criteria):

- ≥ 75 μm compared with the average of the last 2 visit CST measurements (μm), and/or,
- ≥ 100 μm compared with the lowest on-study CST measurement (μm)

Before rescue treatment is administered, the assessing investigator must confirm that the criteria have been met using an interactive database system.

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 (aflibercept, bevacizumab, or ranibizumab)
- Any exposure to a prior investigational drug product that is fully washed out (at least 5 half-lives)

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**
- Use of THC (eg, recreational or medicinal marijuana containing THC)

5.7 Other Study Supplies

Graybug Vision or its designee will make provisions (directly or indirectly) to supply the study centers with standard photographs for AREDS lens grading, 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.

A bulk supply of urine pregnancy tests and lab kits for collection of clinical laboratory analyses will be provided by a central laboratory.

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.

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 for the ALTISSIMO (Core Study) and Table 3-2 for the Extension Study; 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. 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.

6.1 Subject Entry Procedures

6.1.1 ALTISSIMO (Core Study): Subject Entry Procedures

Prospective subjects who meet the entry criteria (inclusion/exclusion criteria) defined in Section 4.3 and Section 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 have entered the study at the time of administration of the first dose on Day 1.

Subject eligibility based on lesion characteristics must be confirmed by the central reading center prior to subject randomization/treatment assignment. In addition, all screening laboratory tests must be performed, and the results must be evaluated and determined to be acceptable to the investigator prior to subject randomization into the study. Screening laboratory tests may be repeated once at the discretion of the investigator or the Sponsor.

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

6.1.2 Extension Study: Subject Entry Procedures

Prospective subjects who meet the entry criteria (inclusion/exclusion criteria) defined in Section 4.5 and Section 4.6 will be considered for inclusion in this study.

The study will be discussed with each subject and a subject willing 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 for the Extension Study will be assigned the same subject identification number assigned in ALTISSIMO (Core Study) that will be used on all source documentation throughout the study.

A subject is considered enrolled into the Extension Study once all study entry criteria for the study have been met and determined to be acceptable by the investigator.

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 reading center 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 blood chemistry and hematology
- Collect urine samples for urinalysis and urine drug screen
- 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 with AREDS lens assessment of both eyes (to be conducted and graded by the investigator as part of the biomicroscopy examination)
- 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 FA and CFP for 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

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 with AREDS lens assessment of both eyes (to be conducted and graded by the investigator as part of the biomicroscopy examination)
- 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, the Medical Monitor has confirmed eligibility based on ocular inclusion criteria, and the investigator has confirmed subject eligibility based on the results from the screening blood chemistry, hematology, urinalysis, and urine pregnancy tests, as well as BCVA assessments, use the IRT for randomization/assignment of treatment. For subjects assigned to receive aflibercept, dosing will be conducted per the prescribing information for EYLEA by the injecting investigator.

- Perform the IVT injection 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; 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
- Draw blood samples for plasma PK (systemic exposure) analyses 1.0 hour ± 15 minutes post-IVT injection
- When medically appropriate, dispense pre-injection and postinjection anti-infectives according to standard clinic procedure at the study center
- 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, 5, 6, 7, 8, 9, 10, and 11

The visits windows are as follows: Week 2 (Day 14 ± 2) and Months 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11 (Day 30 ± 4, Day 60 ± 7, Day 90 ± 7, Day 120 ± 7, Day 150 ± 7, Day 180 ± 7, Day 210 ± 7, Day 240 ± 7, Day 270 ± 7, Day 300 ± 7, and Day 330 ± 7, respectively).

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

- Review concomitant medications and procedures
- Query for AEs
- Assess BCVA (using the ETDRS protocol with manifest refraction) in both eyes
- Perform the slit-lamp biomicroscopy with AREDS lens assessment of both eyes (to be conducted and graded by the investigator as part of the biomicroscopy examination)
- Measure IOP (via Goldmann applanation tonometry or Tono-Pen) in both eyes (must be performed prior to the IVT injection of study drug at relevant study visit)
- 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

Additional procedures to be performed at specific visits are as follows:

- At Month 4 *only*: obtain blood and urine samples for clinical laboratory tests
- At the Week 2, and Months 1, 2, 4, 6, 8, and 10 study visits *only*: obtain vital signs (blood pressure and pulse rate)
- At the Month 6 study visit *only*: perform FA and CFP for both eyes (this procedure must be completed prior to study drug administration)

- At the Week 2, and Months 1, 2, 3, 4, 6, 7, 8, and 9 study visits *only*: draw blood samples for plasma PK (systemic exposure). (The Month 6 blood sample must be obtained 1.0 hour ± 15 minutes post-IVT injection)
- At Months 2, 4, 6, 8, and 10 *only*:
  - Perform the IVT injection 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; if needed, the subject can be examined [eg, additional IOP or ophthalmoscopy] per the discretion of the injecting investigator prior to going home)
  - When medically appropriate, dispense pre-injection and postinjection anti-infectives according to standard clinic procedure at the study center
  - All subjects will receive a telephone call from qualified study center personnel as a safety follow-up the day after the IVT injection procedure

6.2.4 Month 12 (Day 360 ± 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
- Draw blood samples for blood chemistry and hematology
- Draw blood samples for plasma PK (systemic exposure)
- Collect urine samples for urinalysis
- 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 with AREDS lens assessment of both eyes (to be conducted and graded by the investigator as part of the biomicroscopy examination)
- 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 FA and CFP of both eyes; document the position of the depot and the status of the visual axis in the study eye
- Have the subject complete the subject exit questionnaire (Appendix 18.6)
- Exit the subject from ALTISSIMO (Core Study)

- Determine if the subject is willing to participate in the Extension Study and if so, perform the procedures noted in Section 6.2.4.1

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 visibly detectable GB-102 depot on ophthalmic examination at this visit should be followed until the depot is no longer observed.

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

6.2.4.1 Month 12 (Day 360 ± 7 – Screening/Baseline) – Extension Study

The Screening/Baseline visit for the Extension Study is the same day as the Month 12 (Day 360) visit for ALTISSIMO (Core Study). If the subject is willing to participate in the Extension Study the following procedures are to be performed at this visit after the subject has exited ALTISSIMO (Core Study):

- Obtain informed consent and authorization
- Assess the subject regarding the inclusion/exclusion criteria
- If the subject meets the entry criteria, schedule the subject to return for the Month 13 (Day 390) visit, otherwise, exit the subject from the Screening portion of the Extension Study

6.3 Months 13, 14, 15, 16, and 17 (Extension Study)

The visits windows are as follows: Months 13, 14, 15, 16, and 17 (Day 390 ± 7, Day 420 ± 7, Day 450 ± 7, Day 480 ± 7, and Day 510 ± 7, respectively).

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

- Review concomitant medications and procedures
- Query for AEs
- Assess BCVA (using the ETDRS protocol with manifest refraction) in both eyes
- Perform the slit-lamp biomicroscopy with AREDS lens assessment of both eyes (to be conducted and graded by the investigator as part of the biomicroscopy examination)
- Measure IOP (via Goldmann applanation tonometry or Tono-Pen) in both eyes (must be performed prior to the IVT injection of study drug at relevant study visit)
- 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

6.4 Month 18 (Day 540 ± 7) / Early Termination (Extension Study)

The following procedures are to be performed:

- Review concomitant medications and procedures
- Query for AEs
- Assess BCVA (using the ETDRS protocol with manifest refraction) in both eyes
- Perform the slit-lamp biomicroscopy with AREDS lens assessment of both eyes (to be conducted and graded by the investigator as part of the biomicroscopy examination)
- Measure IOP (via Goldmann applanation tonometry or Tono-Pen) in both eyes (must be performed prior to the IVT injection of study drug at relevant study visit)
- 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 visibly detectable GB-102 depot on ophthalmic examination at this visit should be followed until the depot is no longer observed.

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

6.5 Screen Failures

Subjects who miss a scheduled visit prior to randomization or do not qualify for enrollment in the study will be considered screen failures.

6.6 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

6.7 Subject Discontinuation

6.7.1 ALTISSIMO (Core Study): 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.

6.7.2 Extension Study: 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, receiving a rescue treatment (aflibercept or any other type of rescue treatment [i.e., anti-VEGF therapy]) or being lost to follow-up.

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/s 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.

6.8 Subject Replacement

One rescreening of a nontreated screen failure subject may be allowed. However, rescreening is not allowed in the Extension Study.

Subjects will not be replaced for any reason.

6.9 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 and Table 3-2 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 CNV 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 18 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, Hematology, and Urinalysis

Blood and urine samples for routine clinical laboratory tests will be collected. Samples should be obtained prior to administration of study drug. Screening laboratory tests may be repeated once at the discretion of the investigator. The minimum tests to be performed include the following:

- Nonfasting chemistry (blood): sodium, potassium, chloride, bicarbonate, albumin, alkaline phosphatase, aspartate amino transferase, alanine amino transferase, bilirubin direct, bilirubin indirect, total bilirubin, creatinine, blood urea nitrogen, total protein, calcium, phosphorus, and hemoglobin A1c
- Hematology (complete blood count with differential): white blood cell count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width, platelet count, and mean platelet volume
- Urinalysis (dipstick): glucose, protein, and pH
- Urine drug screen (Screening visit only)

For detailed instructions regarding the collection of laboratory tests, refer to the separately provided Laboratory Manual.

7.6 Plasma Pharmacokinetics (Systemic Exposure)

A descriptive statistical summary of plasma concentration of sunitinib and concentration time plots will be generated. Blood samples for plasma analysis will be collected from all subjects and an analysis of approximately 20% of subjects assigned to each sunitinib group will be performed.

For detailed instructions regarding the collection of plasma samples, refer to the separately provided Laboratory Manual.

7.7 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 12.

7.8 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 visual acuity examiners are not allowed to perform any study related activities other than BCVA assessments to maintain masking including obtaining medical histories or attempting to elicit any information regarding treatment, adverse events, or clinical information from the subjects. The same BCVA examiner should be utilized for each subject throughout the study when possible.

7.9 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.

In addition, the lens will be graded by the assessing investigator for the presence and severity of nuclear, cortical, and posterior subcapsular lens opacities using the AREDS photographic reference scale. For detailed instructions regarding AREDS lens scoring, refer to the separately provided AREDS lens grading scale (Chew 2010).

7.10 Intraocular Pressure

At each study visit, IOP will be measured according to routine clinical practice using Goldmann applanation tonometry or Tono-Pen in both eyes at all study visits (must be performed prior to dilation and the IVT injection of study drug at dosing visits). 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.

7.11 Dilated Ophthalmoscopy

Dilated fundus examination of both eyes will be performed in all subjects by designated qualified study center personnel. The following will be observed for the presence of abnormalities:

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

If any findings are abnormal, exact findings should be specified and noted as either clinically or not clinically significant. All abnormal findings that are clinically significant will be described and noted as AEs.

7.12 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).

7.13 Fluorescein Angiography

The FA imaging (after IVT administration of fluorescein dye) of both eyes will be performed to examine the circulation of the retina and characteristics of the CNV lesion in the study eye according to standard FA image capture protocol. The FA images will be obtained using a digital camera by designated certified study center personnel. For detailed instructions regarding collection of FA imaging, refer to the separately provided IAG.

7.14 Color Fundus Photography

The CFP of both eyes will be performed to assess characteristics of the retina. The photographs will be obtained using a digital fundus camera and will be performed by certified study center personnel. For detailed instructions regarding collection of CFP imaging, refer to the separately provided Image Acquisition Guidelines (IAG).

7.15 Intravitreal Depot Color Fundus Photography

Supplemental 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 or Optos California Ultra-widefield 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 to confirm that the depot is not interfering with the visul axis. For detailed instructions regarding collection of the IVT depot CFP imaging, refer to the separately provided guideline.

7.16 Postinjection Assessments

Following the IVT injection procedure or sham injection procedure, the injecting investigator will assess postinjection safety using count fingers or hand motion vision within 15 minutes after injection. The injecting investigator can conduct additional safety assessments (eg, additional IOP and ophthalmoscopy), prior to the subject leaving the clinic if needed. 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 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
- Laboratory abnormality, 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 the end of study and at least 30 days after the last dose of study drug, 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 the Pharmacovigilance at Syneos Health using email notification: safetyreporting@syneoshealth.com or
fax number: 1 (877) 464-7787. Pharmacovigilance will notify the medical monitor and the Sponsor immediately (within 24 hours).

Alternatively, the investigator may contact the medical monitor directly:

Steven Gross, MD
Medical Monitor
Phone: 813-695-9151
Email: steven.gross@syneoshealth.com

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 and, as applicable, European Union Directives 2001/83/EC and 2001/20/EC).

Expedited reports will also be distributed to investigators. Upon receiving such notices, the investigator must review the IB and 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 within 30 days after the subject's last administration of study drug, and that becomes known to the investigator, must be reported to the Sponsor even if the subject is withdrawn from the study.

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.

A visibly detectable GB-102 depot on ophthalmic examination at the final study visit is not considered an AE. Nevertheless, the investigator should follow the subject until the depot is no longer observed.

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

9 STATISTICAL CONSIDERATIONS

A separate statistical analysis plan (SAP) will provide a detailed description of the planned statistical analyses.

9.1 General Methods of Analysis

9.1.1 ALTISSIMO (Core Study): General Methods of Analysis

Summaries for continuous variables will include the number of observations (n), arithmetic mean, standard deviation, median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means, standard deviations, and medians will be presented to 1 additional decimal place than reported in the raw values.

Summaries for discrete variables will include frequencies and percentages. Differences between treatment schemes will be calculated as GB-102 minus aflibercept and change from baseline will be calculated as the value at follow-up study visit minus the value at Baseline (Day 1). The baseline visit will be defined as the last nonmissing measure prior to initiation of study drug.

All summaries will be presented by treatment scheme and, where appropriate, by visit. When presenting by treatment scheme, a combined GB-102 group will be presented (all subjects dosed to 1 mg GB-102 followed by 1 mg dosing and all subjects dosed to 2 mg GB-102 followed by 1 mg dosing) along with each individual treatment scheme (aflibercept, 1 mg GB-102 followed by 1 mg and 2 mg GB-102 followed by 1 mg dosing).

9.1.2 Extension Study: General Methods of Analysis

All safety and efficacy data collected beyond Month 12 (Day 360) will be presented in listings and summarized as appropriate using descriptive statistics.

9.2 Study Endpoints

9.2.1 Primary Endpoint

- Time to first rescue treatment (GB-102 only). This would be further validated through assessing time to fufillment of at least one rescue criterion.

9.2.2 Secondary Endpoints

- Time to fulfillment of at least one rescue criterion starting at the Month 6 visit through to the Month 12 visit (excluding any rescue at the Month 12 visit).
- Number of times that at least one rescue criterion is met
- Number of treatments, including both rescue and scheduled study treatments, during the study

- Change from baseline in BCVA (ETDRS) at all visits
- Categorical change from Baseline in BCVA (ETDRS) at all visits
- Frequency of subjects with BCVA worse than 20/200 (Snellen equivalent) at all visits
- Change from baseline in CST (μm) at all visits
- Frequency of subjects with absence of exudation (intra-/sub-retinal fluid/cystoid edema) at all visits

9.2.3 Exploratory Endpoints

- Change from baseline in BCVA comparing all subjects receiving GB-102 to subjects receiving aflibercept at all visits
- Change from baseline in CST comparing all subjects receiving GB-102 to subjects receiving aflibercept at all visits
- Change from baseline in total lesion area (mm^2) at Months 6 and 12 of treatment
- Change from baseline in CNV lesion area (mm^2) at Months 6 and 12 of treatment
- Change from baseline in fluorescein leakage area (mm^2) at Months 6 and 12 of treatment
- Change from thickest observed CST (μm) prior to enrollment (pre-enrollment baseline) at all visits
- Change from average of observed CST (μm) prior to enrollment (pre-enrollment baseline) at all visits

ALTISSIMO (Core Study) Subject Exit Questionnaire

- The subject exit questionnaire (Appendix 18.6) is not a validated patient reported outcome (PRO) measure and is designed to explore a subject's experience with the medication. All subjects exiting the study on Month 12 (Day 360), regardless of whether or not the subject joins the Extension Study, are required to complete the questionnaire.

9.2.3.1 Exploratory Endpoints: Extension Study

- All safety and efficacy data collected beyond Month 12 (Day 360) will be assessed in an exploratory manner.

9.2.4 Safety Endpoints

- Occurrence of ocular and nonocular AEs and SAEs
- Plasma levels of sunitinib (ng/mL)

9.3 Analysis Populations

Three analysis sets will be defined as follows:

- Safety analysis set (SS): Includes all randomized subjects who receive at least one dose of study treatment. Analyses will group subjects according to the treatment scheme actually received.
- Full analysis set (FAS): Includes all randomized subjects who receive at least one dose of study treatment, and complete a 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. All efficacy analyses will be conducted on the FAS and these analyses will be considered primary.
- 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 primary efficacy endpoint of the study. Analyses conducted on the PP set will be considered secondary.

9.4 Subject Demographics and Baseline Characteristics

Continuous summary statistics will be generated for the quantitative demographic variable (age, in years), tabulated by treatment scheme for the SS and FAS. Discrete summary statistics will be generated for qualitative demographic variables (age category, sex, ethnicity, race, and iris color for the study eye), tabulated by treatment scheme for the SS and FAS.

Baseline clinical characteristics and disease history, such as baseline BCVA, CST, and SD-OCT measurements, fluorescein angiography values, and color fundus photography values, will also be summarized descriptively by treatment group for the SS and FAS.

Medical history will be coded using the current version of MedDRA at the time of database lock. Medical history will be summarized using discrete summary statistics for each MedDRA SOC and preferred term (PT) by treatment scheme for the SS and FAS. Medical history will be presented separately for ocular and nonocular conditions. Subjects with multiple medical histories in the same SOC or PT will be counted only once for that respective SOC or PT.

9.5 Analysis of Imaging Parameters

Data from a central reading center will be used for descriptive summaries of imaging parameters based upon SD-OCT, FA, and CFP. Descriptive summary statistics will be provided and exploratory inference testing will be described in the SAP.

9.6 Efficacy Analyses

A separate SAP will provide a detailed description of the planned statistical analyses. Efficacy parameters will be summarized and analyzed for the FAS (primary population for analysis) and PP (secondary/sensitivity population for analysis).

9.6.1 Primary Efficacy Analysis

The primary efficacy endpoint is the time to first rescue treatment (GB-102 only). This would be further validated through assessing time to fulfillment of at least one rescue criterion.

Time to first rescue treatment/fulfillment of at least one rescue criterion will be analyzed using the Kaplan-Meier method. The probability of remaining rescue treatment free/not fulfilling at least one rescue criterion will be reported for the Month 6 and Month 12 visits with associated 80% confidence intervals (CI) based on Greenwood's standard error estimate. Kaplan-Meier curves will be produced. If calculable, estimates of the median time to fulfillment of at least on rescue criterion and the 25th and 75th percentiles will be calculated with corresponding 80% CIs. The FAS will be the primary population used for analysis of the primary efficacy endpoint.

For this analysis, the interval censored nature of the time to first rescue treatment/fulfillment of at least one rescue criterion with regard to the scheduled study visits is considered: If a subject receives a rescue treatment/fulfills a rescue criterion during an unscheduled visit, then the subject will be considered to have met the event of interest in the visit interval which ends at the next scheduled study visit that occurs after the unscheduled visit. Subjects who do not receive rescue medication/fulfill a rescue criterion will be censored on last scheduled study visit recorded for the subject.

Exploratory comparisons between each GB-102 scheme and aflibercept and between the combined GB-102 schemes versus aflibercept regarding time to first fulfillment of at least one rescue criterion will be conducted using a log-rank test stratified by baseline BCVA (< 60 letters vs ≥ 60 letters), as defined at the time of randomization. The Peto method will be used to estimate the hazard ratio and asymptotic 80% confidence interval based on the stratified log rank test statistic.

A primary endpoint analysis will be conducted when all subjects complete the Month 12 (Day 360) visit.

9.6.2 Secondary Efficacy Analysis

The change from baseline in BCVA and CST will be presented by treatment scheme with associated 80% confidence intervals (CI) for all visits. A similar analysis will be done for absolute values and change in BCVA and CST relative to the time of first rescue treatment (response to rescue treatment). Time to fulfillment of at least one rescue criterion starting at the Month 6 visit through Month 12 will be summarized using descriptive statistics including 80% CIs and will be presented for the number of rescue treatments, number of scheduled treatments, number of total of rescue and scheduled treatments, and number of times that at least one rescue criterion is met from baseline through Month 12.

Absence of exudation (intra-/sub-retinal fluid/cystoid edema), categories of change from Baseline in BCVA, and BCVA worse than 20/200 (Snellen equivalent) will be summarized at each visit using discrete summary statistics, including 80% asymptotic normal CIs for each treatment scheme.

Further details on the analysis of the secondary efficacy endpoints will be provided in the SAP.

9.6.3 Exploratory Efficacy Analysis

Observed values at each visit and change from baseline values at each follow up visit for BCVA, CST, total lesion area, CNV lesion area, and fluorescein leakage area will be summarized using continuous summary statistics, including 80% CIs around the mean for each treatment scheme, as well as the combined GB-102 groups and the aflibercept control group. For CST, the change from the thickest pre-enrollment value (μm) and change from average pre-enrollment value (μm) at each visit will be similarly summarized.

For BCVA and CST, comparisons between each GB-102 group and the aflibercept control group and between the combined GB-102 groups and the aflibercept control group will be made primarily for each visit using a linear model adjusting for the baseline value as a covariate/class variable and secondarily using 2-sample t-tests.

9.6.3.1 Exploratory Efficacy Analysis: Extension Study

All safety and efficacy data collected beyond Month 12 (Day 360) will be presented in listings and summarized as appropriate using descriptive statistics.

9.7 Safety Analyses

All safety analyses will be performed on the safety analysis set.

Adverse Events

The safety of GB-102 will primarily be assessed by the incidence of treatment emergent AEs (TEAE). An AE will be considered a TEAE if it occurs or worsens on or after initiation of study drug. An overall summary of TEAEs will be presented including the number of events and the number of subjects with events (along with percentages) by treatment scheme for TEAEs in several categories based on location, seriousness, relationship to study drug, and severity.

All AEs will be coded to system organ class (SOC) and preferred term (PT) using the current version of MedDRA at the time of database lock. The number of TEAEs and the number and percentage of subjects with any TEAEs will be tabulated overall and by SOC and PT within each SOC by treatment scheme and over all treatment schemes.

The following categories of adverse events will be summarized separately for ocular TEAEs in the study eye, ocular TEAEs in the non-study eye, non-ocular TEAEs, and all TEAEs combined, with full detail provided in the SAP:

- TEAEs
- Treatment related TEAEs
- Serious TEAEs

- Serious treatment related TEAEs
- TEAEs leading to premature study discontinuation
- TEAEs by maximum severity
- TEAEs by day of onset
- Arteriothromboembolic TEAEs using ATC criteria

Descriptive summaries will be provided for SAEs, SUSARs, and AEs leading to study discontinuation.

Plasma Levels of Sunitinib

Plasma concentrations will be summarized at each visit using continuous descriptive statistics.

Other Safety Endpoints

Study drug exposure, concomitant medication use, physical examination results, vital signs, and laboratory results will be summarized by treatment scheme.

IOP measurements will be summarized by treatment scheme separately for the study eye and for the nonstudy eye. The IOP data will be summarized by visit using both continuous and discrete summaries. Changes from baseline will also be summarized continuously and discretely. Discrete categories for IOP measurements will include (in mmHg) ≤ 5, 6 to 14, 15 to 21, 22 to 29, and ≥ 30. These categories will be used to summarize results by visit and to summarize shifts from baseline IOP for each treatment scheme by visit. Discrete categories for changes from baseline in IOP will include ≤ −5, −4 to 0, 1 to 4, 5 to 9, 10 to 14, and ≥ 15. The numbers and percentages of eyes with an IOP measurement ≥ 30 mmHg and the numbers and percentages of eyes with an increase from baseline in IOP measurement ≥ 10 mmHg will also be summarized.

Slit-lamp biomicroscopy and dilated ophthalmoscopy results will be summarized for each treatment scheme for the study eye and nonstudy eye by visit using discrete summary statistics.

Presence and severity of nuclear sclerosis, cortical opacities, and posterior subcapsular opacities evaluated according to the AREDS protocol will be summarized by treatment scheme.

9.8 Sample Size Determination

The sample size of this study was not selected to support specific statistical hypothesis testing as all comparisons are exploratory.

9.9 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. However, if the amount of missing post-baseline values for a particular endpoint are substantial, multiple imputation methods will be

considered for the impution of missing values and details will be included in the statistical analysis plan.

Sensitivity analyses of primary and secondary efficacy endpoints will be conducted using the per protocol population. Additional sensitivity analyses will be specified in the statistical analysis plan.

9.10 Subjects Receiving Rescue Treatment

Subjects receiving rescue treatment will continue to be evaluated at scheduled visits. Rescued subjects will be included in all analyses sets. Descriptive analyses will be conducted including time to first rescue treatment (GB-102 only), time to fulfillment of at least one rescue criterion from Baseline to Month 6 and Month 12, and number of rescue injections.

9.11 Units of Analysis

The unit of analysis will be the individual study eye for assessments performed by eye, or the subject for assessments performed at the subject level.

9.12 Changes in the Conduct of the Study or Planned Analyses

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.

Note: If discrepancies exist between minor features of the statistical analysis as planned in the protocol and as described in the final SAP, a protocol amendment will not be issued and the SAP will prevail.

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 randomization 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.

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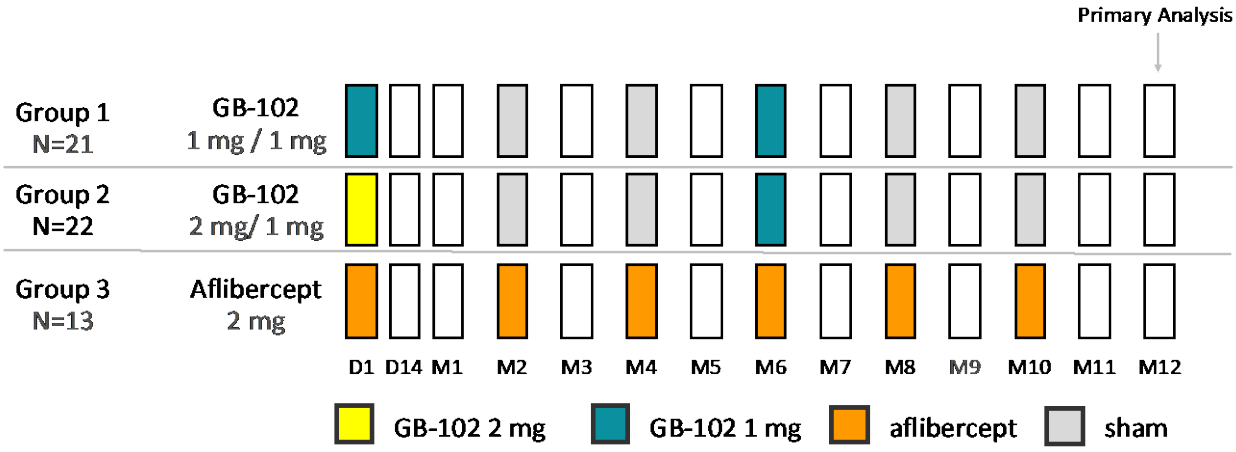
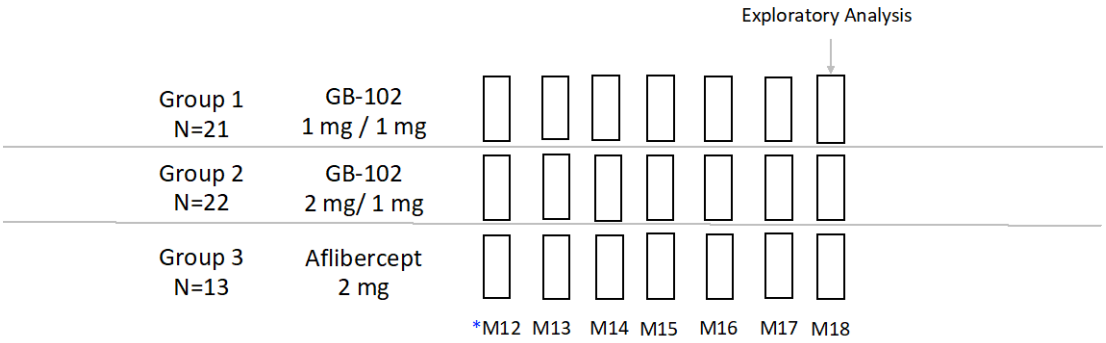
18 APPENDICES

18.1 Study Schema Protocol GBV-102-002

18.1.1 ALTISSIMO (Core Study)



18.1.2 Extension Study



**Screening/Baseline Visit occurs at M12 for the Phase 2b (ALTISSIMO Study)*

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

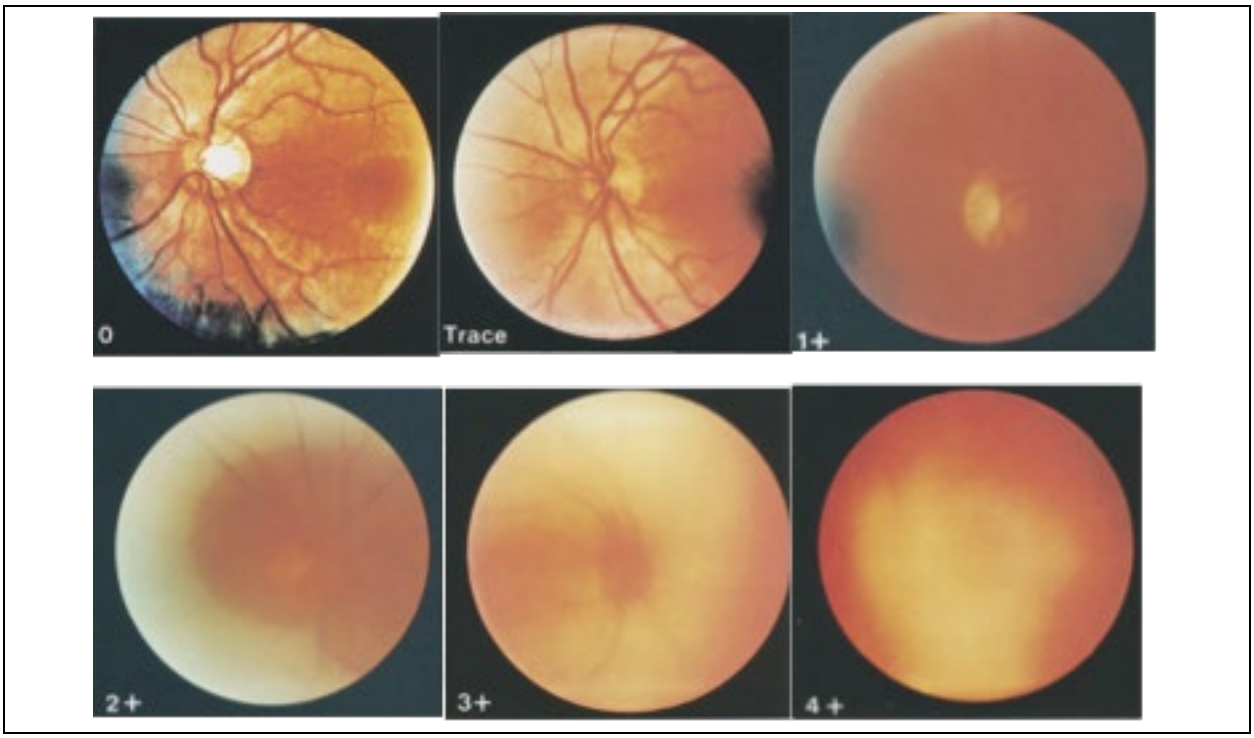
Grade	**Hemorrhage Size (Disc Areas)**
0	None present
+1	< 3
+2	3 to 6 (inclusive)
+3	> 6

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 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

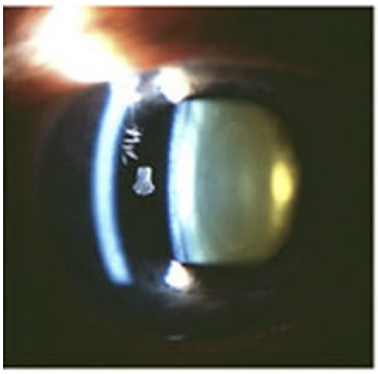
Grade	Description
+1	Opacity is absent
+2	Opacity is present, but less than Cortical Standard Photograph #2
+3	Opacity is present, and as severe or worse than Cortical Standard Photograph #2

Source: (Chew 2010)

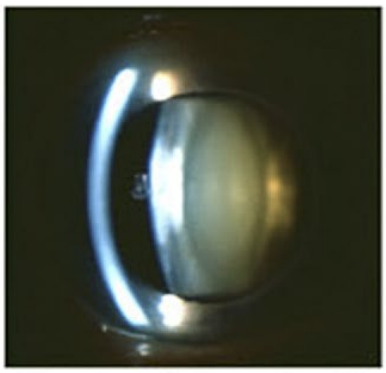
18.5.3 Posterior Subcapsular Opacities

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

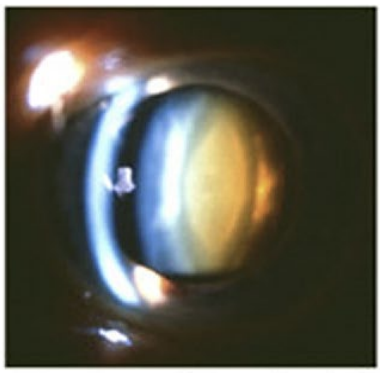
PSC = posterior subcapsular opacity
Source: (Chew 2010)



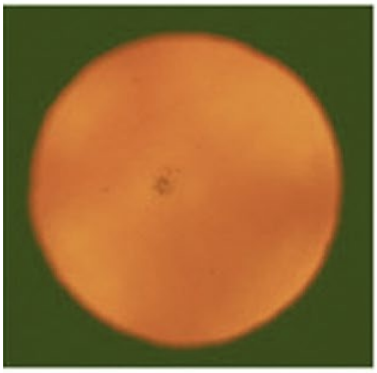
Nuclear Standard 1



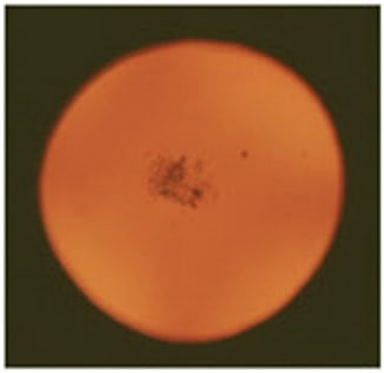
Nuclear Standard 2



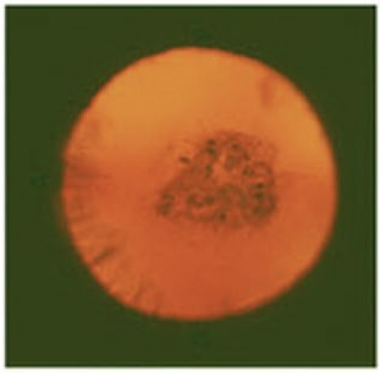
Nuclear Standard 3



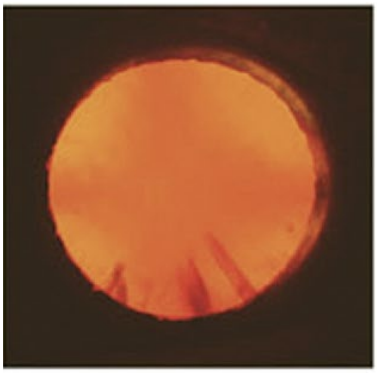
PSC Standard 1



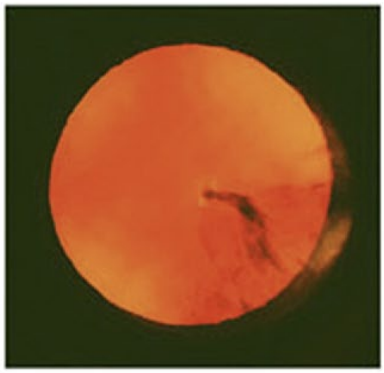
PSC Standard 2



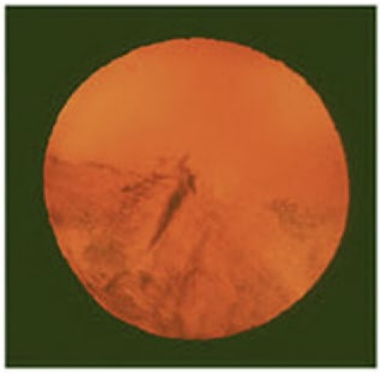
PSC Standard 3



Cortical Standard 1



Cortical Standard 2



Cortical Standard 3

18.6 ALTISSIMO (Core Study) Subject Exit Questionnaire

Each subject will be asked to complete a study subject exit questionnaire about their experience in the Phase 2b GBV-102-002 ALTISSIMO (Core Study). This questionnaire must be completed by each subject who completes the Month 12 (Day 360) visit before exiting the study. This questionnaire is not a validated patient reported outcome (PRO) assessment and is designed to explore the subject's experience with the study drug treatment.

Questions

1. What was your experience with the assigned study drug treatment you received in the ALTISSIMO Study? Please circle one answer that best describes your experience and provide comments:

    1. Dissatisfied
    2. Slightly dissatisfied
    3. Satisfied
    4. Moderately satisfied
    5. Very satisfied

    Please also provide comments on your experience:

    _____
    _____
    _____

2. How did the assigned study drug treatment you received in the ALTISSIMO Study compare with the treatment(s) you received before entering the study? Please circle one answer that best describes your experience and provide comments:

    1. Much worse
    2. Slightly worse
    3. About the same
    4. Slightly better
    5. Much better

    Please also provide comments on your experience:

    _____
    _____
    _____

3. Did you notice any difference in your experience with the study drug treatment between the first 6 months of the ALTISSIMO Study versus the last 6 months of the ALTISSIMO Study? Please circle one answer that best describes your experience and provide comments:

    1. First 6 months were better than the last 6 months
    2. Last 6 months were better than the first 6 months
    3. Last 6 months were the same as the first 6 months

    Please also provide comments on your experience:

    _____
    _____
    _____

4. Based on your experience in this study, how likely are you to request from your physician to receive a long-acting treatment for wet AMD (approximately 4-6 months between treatment injections) if it means less frequent injections? Please circle one answer that best describes your experience and provide comments:

    1. Extremely unlikely
    2. Unlikely
    3. Neutral
    4. Likely
    5. Extremely likely

    Please also provide comments on your experience:

    _____
    _____
    _____

18.7 Protocol Amendment Summary

This summary includes changes made to Protocol Amendment 3 GBV-102-002 (Version 4.0 dated 08 September 2020.

Graybug Vision, Inc. has decided to include an option for subjects completing the GBV-102-002 Phase 2b ALTISSIMO (Core Study) to enter an Extension Study. The Extension Study is designed to follow subjects who complete all study visits through Month 12 (Day 360), complete all study assessments at Month 12 (Day 360) including fluorescein angiography, and do not receive a rescue treatment at the Month 12 (Day 360) final study visit on ALTISSIMO (Core Study). Subjects who enter the Extension Study will be followed for safety until administered rescue treatment as per the rescue treatment criteria or until study completion at Month 18 (Day 540).

Additionally, the definition of the primary and secondary endpoints and statistical plans were further clarified. In particular, the primary endpoint was updated from probability of receiving rescue treatment through Month 12 to time to first rescue treatment (GB-102 only) in order to avoid potential bias in the assessment of the duration of effect.

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

Section	Revision	Rationale
Title Page	Updated the name and contact information on the title page to reflect the change in Chief Medical Officer for Graybug Vision, Inc.	Sponsor decision
Synopsis, Sections 2, 3, 4, 5.2, 6, and 9	Updated the objectives, study design, masking, number of subjects, study endpoints and statistical methods & considerations, enrollment and method for assigning subjects to treatment cohorts/groups, study assessments to describe the activities planned in the Extension Study.	Sponsor decision

Synopsis and Section 9	Updated the Study Endpoints and Statistical Methods for ALTISSIMO (Core Study)	Sponsor decision
Section 1.4	Provided updated information regarding the status of ongoing studies and added in the purpose of and plan for the extension study.	Updated information
Table 3.1, Section 6.2.4 and 18.6	Added a subject exit questionnaire to explore the subject's experience with the study medication in ALTISSIMO (Core Study).	Sponsor decision
Appendix 18.1.2	Added Study Schema for the Extension Study	Sponsor decision