Graybug Vision Inc.

Statistical Analysis Plan

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)

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Statistical Analysis Plan for Interventional Studies

Sponsor Name: Graybug Vision, Inc.

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Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
1.0	04-Nov-2020	[redacted]	Initial Release Version
2.0	23-Dec-2020	[redacted]	Updated to bring in line with the analyses outlined for the core study in Protocol Amendment 3. Also made some minor corrections and added conversion formula for Snellen to ETDRS letters.
3.0	08-Jan-2021	[redacted]	Removed Indices of Tables, Figures, and Listings

I confirm that I have reviewed this document and agree with the content.

Approvals
Syneos Health Approval
[redacted]

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1. Glossary of Abbreviations

Abbreviation	Description
AE	adverse event
AMD	age-related macular degeneration
AREDS	Age-related Eye Diseases Study
ATC	Anatomical Therapeutic Chemical
BCVA	best corrected visual acuity
BDRM	Blind Data Review Meeting
CFP	color fundus photography
CI	confidence interval
CL	confidence limit
CNV	choroidal neovascularization
CST	central subfield thickness
eCRF	electronic case report form
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescein angiography
FAS	full analysis set
IOP	intraocular pressure
IRT	interactive response technology
IVT	intravitreal
LASIK	laser-assisted in situ keratomileusis
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
Nd:YAG	neodymium:yttrium-aluminum-garnet
PK	pharmacokinetic
PKS	pharmacokinetic set
PP	per protocol
PPS	per protocol set
PPS2	Month 6 to month 12 per protocol set
PT	preferred term
SAP	statistical analysis plan

Abbreviation	Description
SD-OCT	spectral domain optical coherence tomography
SOC	system organ class
SS	safety set
TEAE	treatment-emergent adverse event
TFL	tables, figures, and listings
THC	tetrahydrocannibol
µm	micrometer
VEGF	vascular endothelial growth factor

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables, and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives stated in Protocol GBV-102-002 (Phase 2b), Version 4.0, dated 08 September 2020 (Amendment 3). This document addresses only the analyses associated with the core study. The analyses for the extension study will be addressed in a later document.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonization (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the data that will be analyzed and the subject characteristics, pharmacodynamics, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP they may be completed and identified in the clinical study report.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and are responsible for the production and quality control of all tables, figures, and listings.

2.2. Timings of Analyses

An unmasked primary analysis for safety and efficacy is planned at the end of the study after database lock when all subjects complete the Day 360 visit or discontinue prematurely from the study. All data up to Day 360 visit and all data that were to be performed at Day 360 visit but were performed late are also included.

3. Study Objectives

3.1. Primary Objective

The primary objective of the study is to evaluate the safety and duration of the effect of GB-102, as measured by time to first rescue treatment/first fulfillment of rescue treatment criteria 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 (AMD) who have received prior induction with IVT anti-vascular endothelial growth factor (VEGF).

If the need for rescue treatment was identified at a given study visit, a rescue treatment was only given in case no study treatment was scheduled. Due to the imbalance in treatment visits between GB-102 and aflibercept, corresponding comparisons for the time to first rescue treatment may be biased. Therefore analyses of the time to first rescue treatment are limited to the GB-102 treatment arms. Based on a comparison of time to first rescue treatment and time to first fulfillment of a least one rescue criterion (as derived from the recorded BCVA and CST measurements) for the GB-102 treatment arms the consistency between these two endpoints will be assessed, with the objective to establish time to fulfillment of at least one rescue criterion as an alternative endpoint for the assessment of duration of effect versus aflibercept. If the two endpoints are consistent for GB-102, the alternative endpoint can be used to make an unbiased comparison to aflibercept.

3.2. Secondary Objective(s)

The secondary objectives of the study are:

- 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, Early Treatment Diabetic Retinopathy [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

3.3. Brief Description

The study was planned as a Phase 2b, multicenter, visual examiner-masked, randomized active-controlled, parallel-arm design, conducted at approximately 35 study centers in the United States. 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 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 Development Operations) in February 2020. Subsequently, the only unmasked person at the sponsor is the Vice President of Global Clinical Development Operations. The current Chief Medical Officer remains masked to data subsequent to February 2020 analysis. No SAEs have been reported in ALTISSIMO; however, 5 subjects have reported

drug material observed in the AC (N=4, 2 mg; N=1, 1 mg). All reported cases have been 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 only the 1 mg dose of GB-102 for those subjects assigned to GB-102.

As further enrollment was suspended (see above), the resulting number of patients per treatment arm are as follows: :

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)

After baseline (Day 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. Subjects will exit the study following all study assessments on Day 360.

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 and to follow the scheduled dosing regimen at subsequent visits. In the event that a subject meets the criteria for rescue treatment at a scheduled dosing visit, no rescue treatment was to be administered; the subject would just receive the scheduled study treatment.

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.

Subjects should not be withdrawn from the study due to an adverse event (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.

3.4. Subject Selection

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 spectra domain optical coherence tomography (SD-OCT), fluorescein angiography (FA), and color fundus photography (CFP) evaluation of the CNV lesion.

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.

3.4.1. 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 µm)
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 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

3.4.2. 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 (IOP > 25 mm) 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

3.5. Determination of Sample Size

Due to early termination of enrollment, the sample size of this study is not sufficient to support specific statistical hypothesis testing; all analyses and comparisons are descriptive only.

3.6. Treatment Assignment and Masking

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.

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). Originally, the 2 doses of study drug were 1 mg at Baseline and Month 6 and 2 mg at Baseline and Month 6. However, due to emerging uncertainty regarding the safety profile of 2 mg GB-102 (see above), there was a decision to re-dose all patients on GB-102 with the 1 mg dose at Month 6 regardless of the original dose.

Enrolled subjects will be masked to treatment assignment. The visual acuity examiners, the Sponsor (other than the Vice President of Global Clinical Development Operations), the masked contract research organization 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 (but not the treatment scheme).

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.

An unmasked primary analysis for safety and efficacy is planned at the end of study after database lock when all subjects complete the Day 360 visit or discontinue prematurely.

As it pertains to any analysis to be performed, pharmacokinetic (PK) concentration data will be made available only to unmasked Syneos Health statistical personnel.

3.7. Administration of Study Medication

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.

3.8. Study Procedures

The schedule of assessments is provided in Table 2, and includes the expected study day relative to the date of first dose, acceptable ranges of study days for each visit, and visit nomenclature.

Table 2: Schedule of Assessments

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[a]	−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
Intravitreal Depot Color Fundus Photography[k]		SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE	SE

Table 2: Schedule of Assessments

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[a]	−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
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).

4. Endpoints

4.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the time to first rescue treatment/first fulfillment of at least one rescue criterion from Baseline through Month 12.

If the need for rescue treatment was identified at a given study visit, a rescue treatment was only given in case no study treatment was scheduled. Due to the imbalance in treatment visits between GB-102 and aflibercept, corresponding comparisons for the time to first rescue treatment may be biased. Therefore analyses of the time to first rescue treatment are limited to the GB-102 treatment arms. Based on a comparison of time to first rescue treatment and time to first fulfillment of a least one rescue criterion (as derived from the recorded BCVA and CST measurements) for the GB-102 treatment arms the consistency between these two endpoints will be assessed, with the objective to establish time to fulfillment of at least one rescue criterion as an alternative endpoint for the assessment of duration of effect versus aflibercept.

4.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints include:

- Time to first rescue treatment/first fulfillment of at least one rescue criterion starting at the Month 6 visit through Month 12
- 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
- Number of treatments, including both rescue and scheduled treatments (combined and separate) during the study
- Number and percentage of subjects receiving treatment at each visit, including both rescue and scheduled treatments (combined and separate)
- Number of visit intervals during which at least one rescue criterion is met
- Number and percentage of subjects meeting at least one rescue criterion at each visit
- Frequency of subjects with absence of exudation (intra-/sub-retinal fluid/cystoid edema) at each visit

4.3. Exploratory Endpoints

The exploratory endpoints include:

- Change from baseline in BCVA comparing subjects receiving GB-102 to subjects receiving aflibercept at all visits
- Change from baseline in BCVA (EDTRS) to the average of the scores at Month 9 and 10

- Change from baseline in BCVA (EDTRS) to the average of the scores at Month 10 and 11
- Change from baseline in BCVA (EDTRS) to the average of the scores at Month 11 and 12
- Change from baseline in CST comparing subjects receiving GB-102 to subjects receiving aflibercept at all visits
- Change from baseline in CST (µm) to the average of the measurements at Month 9 and 10
- Change from baseline in CST (µm) to the average of the measurements at Month 10 and 11
- Change from baseline in CST (µm) to the average of the measurements at Month 11 and 12
- Change in CST from thickest observed CST (µm) prior to enrollment (pre-enrollment baseline) at all visits
- Change in CST from mean observed CST (µm) prior to enrollment (pre-enrollment baseline) at all visits
- Change from baseline in total lesion area (mm^2) at Months 6 and 12
- Change from baseline in CNV lesion area (mm^2) at Months 6 and 12
- Change from baseline in fluorescein leakage area (mm^2) at Months 6 and 12
- Absolute values and change in BCVA and CST compared to values at the time of first rescue treatment (response to first rescue treatment)
- ALTISSIMO (Core Study) Subject Exit Questionnaire

4.4. Safety Endpoints

The main safety endpoint is the o*ccurrence of ocular and nonocular AEs and serious AEs*. Other safety endpoints include physical examination results, vital signs, laboratory results, intraocular pressure, slit-lamp biomicroscopy, dilated ophthalmoscopy, and the presence and severity of nuclear sclerosis, cortical opacities, and posterior subcapsular opacities.

4.5. Other Endpoints

Other endpoints include study drug exposure, concomitant medication use, the subject exit questionnaire, and plasma levels of sunitinib (ng/mL).

5. Analysis Sets

Protocol deviation management at Syneos Health is detailed in “Processing and Management of Protocol Deviations” (3101.W02). For details on the process for defining analysis datasets refer to “(Blind) Data Review and Definition of Analysis Sets” (SOP 3911).

Analysis sets are defined in the following sections. Subjects to be included within and excluded from each analysis set will be determined at a Blind Data Review Meeting (BDRM) before unmasking. A separate BDRM Preparation Plan will include, as a minimum, (1) the criteria which will be used to determine the subjects to be excluded from the analysis sets, (2) the listings which will be prepared for sponsor review in order to determine the subjects to exclude, and (3) the sponsor review forum (i.e., BDRM).

5.1. Screened Set

The Screened Set will include all subjects screened. Subjects can be re-screened; in such a case, one screening number will be entered into the database with the details of the screening failure, and a second screening number will be used when the subject re-screens. This set will be used only for subject disposition data.

5.2. Randomized Set

The Randomized Set will include all subjects that were randomized. This set will be used for listings of protocol deviations, inclusion/exclusion criteria deviations, exclusions from analysis sets, demographics, and baseline characteristics.

5.3. Safety Set

The Safety Set (SS) will include all randomized subjects who receive at least one dose of study treatment. Subjects who receive rescue treatment during the study will be included in the SS. Analyses will group subjects according to the treatment scheme actually received. The SS will be used for all analyses of safety endpoints and for all non-disposition subject listings.

5.4. Full Analysis Set

The Full Analysis Set (FAS) will include 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 scheme. All efficacy analyses will be conducted on the FAS and these analyses will be considred primary.

5.5. Per Protocol Set

The Per Protocol Set (PPS) will consist of a subset of the FAS and will include subjects with no major protocol violations that would affect the assessment of the primary objective of the study. The PP analyses will be conducted according to assigned treatment scheme. Only analyses of the time to first rescue treatment/first fulfillment of rescue criteria (excluding the Month 6 to Month 12 analyses) and the change from baseline on BCVA and CST will be conducted on the PPS.

Criteria for exclusion from the PPS may include the following important protocol deviations if they are determined to potentially bias the assessment of the duration of treatment effect:

- Inclusion/exclusion violations that could impact efficacy endpoints
- Treatment assignment errors
- Study drug administration errors
- Out of window/missed visits
- Subject's use of prohibited concomitant medication
- Any other deviations determined to potentially bias the efficacy endpoints

Potential protocol deviations will be reviewed during BDRMs during the study. Criteria used to determine subjects to be excluded from specific analysis sets will be defined and documented prior to database lock.

5.6. Month 6 to Month 12 Per Protocol Set

The Month 6 to Month 12 Per Protocol Set (PPS2) will include subjects that received the Month 6 dose with no major protocol violations that would affect the assessment of the primary endpoint of the study after the Month 6 dose. The PP analyses will be conducted according to assigned treatment scheme. Only analyses of the time to first rescue treatment/first fulfillment of rescue criteria from Month 6 to Month 12 will be conducted on the PPS2.

Criteria for exclusion from the PPS2 may include the following important protocol deviations if they are determined to potentially bias the assessment of the duration of treatment effect:

- Inclusion/exclusion violations that could impact efficacy endpoints
- Treatment assignment errors
- Study drug administration errors
- Out of window/missed visits
- Subject's use of prohibited concomitant medication
- Any other deviations determined to potentially bias the efficacy endpoints

Potential protocol deviations will be reviewed during BDRMs during the study. Criteria used to determine subjects to be excluded from specific analysis sets will be defined and documented prior to database lock.

5.7. Non-COVID-19 Full Analysis Set

The Non-COVID-19 Full Analysis Set (NCFAS) will consist of a subset of the FAS and will include subjects with no major protocol violations due to COVID-19 that would affect the assessment of the primary efficacy endpoint of the study. Only analyses of the time to first rescue treatment/first fulfillment of rescue criteria and the change from baseline on BCVA and CST will be conducted on the NCFAS.

Criteria for exclusion from the NCFAS are the same as for the PPS, except that the deviations leading to exclusion should be associated with COVID-19.

5.8. Pharmacokinetic Set

The Pharmacokinetic Set (PKS) will include all subjects in the SS that have at least one quantifiable sunitinib PK concentration measured.

6. General Aspects for Statistical Analysis

6.1. General Methods

Statistical programming and analyses will be performed using SAS® Version 9.4 or higher.

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, and medians will be presented to 1 additional decimal place than reported in the raw values. Standard deviations will be presented to 2 additional decimal places than reported in the raw values. Summaries for discrete variables will include the number of observations (n), frequencies and percentages by categories. All percentages will be rounded to one decimal place (i.e., XX.X%).

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.

The unit of analysis in this study will be the study eye for all efficacy, safety, and pharmacodynamic summaries. According to protocol the study eye is selected 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. Additionally, non-ocular AEs and medical history will be presented at the subject level. Nonstudy eye safety summaries will also be presented as appropriate.

All summaries will be presented by treatment scheme and, where appropriate, by visit. When presenting by treatment scheme, each individual treatment scheme (aflibercept, 1 mg GB-102 followed by 1 mg and 2 mg GB-102 followed by 1 mg dosing) will be presented.

All relevant subject data will be included in listings.

6.2. Key Definitions

Study day, for a particular date, relative to the date of first injection of study medication will be computed as (particular date – date of first injection of study medication) + 1 day if the particular date is on or after the date of first injection of study medication. As a result of this definition, the date of first injection of study medication will by Study Day 1, and the date immediately preceding the date of first injection of study medication will be Study Day -1, thus there will be no Study Day 0.

Baseline is defined as the last nonmissing measurement prior to the first injection of study medication.

Change from baseline will be computed as follow-up value minus baseline value.

6.3. Missing Data

The details regarding the handling of missing data (imputations or calculations for specific endpoints) for efficacy data will be included in the sections specific to each endpoint (Section 8 and associated subsections).

The handling of missing or partial dates related to adverse events is detailed in Section 9.3.

6.4. Visit Windows and Allocation

For parameters which will be summarized by visit, parameters that are associated with a scheduled visit in the CRF will remain allocated to that study visit. If data is missing at a scheduled visit and there is an unscheduled visit or end of study visit (conducted when a subject has early terminated the study) that occurred in the analysis range of study days (Tables 3 through 7) for the missed visit, then the data from the unscheduled visit will be assigned to the missing visit.

A listing of all such imputed visits will be presented, including the study day of the unscheduled or end of study visit used in place of the missing visit.

Table 3: Ranges of Study Days Associated With Each Visit for BCVA, Slit-lamp Biomicroscopy, Intraocular Pressure, Dilated Ophthalmoscopy, SD-OCT, and Intravitreal Depot Color Fundus Photography

Scheduled Visit	Planned Study Day	Targeted Range of Study Days	Analysis Range of Study Days
Screening[a]	--	[-30 to -3]	[-30 to -3]
Baseline	1	1	1
Week 2	14	[12 to 16]	[2 to 22)
Month 1	30	[26 to 34]	[22 to 45)
Month 2	60	[53 to 67]	[45 to 75)
Month 3	90	[83 to 97]	[75 to 105)
Month 4	120	[113 to 127]	[105 to 135)
Month 5	150	[143 to 157]	[135 to 165)
Month 6	180	[173 to 187]	[165 to 195)
Month 7	210	[203 to 217]	[195 to 225)
Month 8	240	[233 to 247]	[225 to 255)
Month 9	270	[263 to 277]	[255 to 285)
Month 10	300	[293 to 307]	[285 to 315)
Month 11	330	[323 to 337]	[315 to 345)
Month 12	360	[353 to 367]	[345 to 375)

[a] Intravitreal Depot Color Fundus Photograpy is not performed at the Screening Visit

Table 4: Ranges of Study Days Associated With Each Visit for Vital Signs

Scheduled Visit	Planned Study Day	Targeted Range of Study Days	Analysis Range of Study Days
Screening	--	[-30 to -3]	[-30 to -3]
Baseline	1	1	1
Week 2	14	[12 to 16]	[2 to 22)
Month 1	30	[26 to 34]	[22 to 45)
Month 2	60	[53 to 67]	[45 to 90)
Month 4	120	[113 to 127]	[90 to 150)
Month 6	180	[173 to 187]	[150 to 210)
Month 8	240	[233 to 247]	[210 to 270)
Month 10	300	[293 to 307]	[270 to 330)
Month 12	360	[353 to 367]	[330 to 390)

Table 5: Ranges of Study Days Associated With Each Visit for Clinical Laboratory Tests

Scheduled Visit	Planned Study Day	Targeted Range of Study Days	Analysis Range of Study Days
Screening	--	[-30 to -3]	[-30 to -3]
Month 4	120	[113 to 127]	[2 to 240)
Month 12	360	[353 to 367]	[240 to 390)

Table 6: Ranges of Study Days Associated With Each Visit for Plasma Pharmacokinetic Samples

Scheduled Visit	Planned Study Day	Targeted Range of Study Days	Analysis Range of Study Days
Baseline	1	1	1
Week 2	14	[12 to 16]	[2 to 22)
Month 1	30	[26 to 34]	[22 to 45)
Month 2	60	[53 to 67]	[45 to 75)
Month 3	90	[83 to 97]	[75 to 105)
Month 4	120	[113 to 127]	[105 to 150)
Month 6	180	[173 to 187]	[150 to 195)
Month 7	210	[203 to 217]	[195 to 225)
Month 8	240	[233 to 247]	[225 to 255)
Month 9	270	[263 to 277]	[255 to 315)
Month 12	360	[353 to 367]	[315 to 375)

Table 7: Ranges of Study Days Associated With Each Visit for Fluorescein Angiography and Color Fundus Photography

Scheduled Visit	Planned Study Day	Targeted Range of Study Days	Analysis Range of Study Days
Screening	--	[-30 to -3]	[-30 to -3]
Month 6	180	[173 to 187]	[2 to 270)
Month 12	360	[353 to 367]	[270 to 390)

6.5. Pooling of Centers

Data collected from different study centers will not be pooled for analysis.

6.6. Subgroups

A subgroup analysis of the BCVA strata (< 60 or >= 60 ETDRS letters at randomization) will be conducted on the FAS for the following endpoints: time to first rescue treatment/first fulfillment of rescue criteria and change from baseline in BCVA and CST. The subgroup analyses will not be conducted on the last-observation-carried-forward (LOCF) values for BCVA and CST (see Section 8.2 for a description of the LOCF analysis).

7. Demographic, Other Baseline Characteristics and Medication

7.1. Subject Disposition and Withdrawals

The number of subjects in each analysis set (SS, FAS, PPS, NCFAS and PKS) will be summarized by treatment scheme.

A subject will have fulfilled the requirements for study completion if/when the subject has completed the Day 360 visit. The number and percentage of subjects who are randomized, who complete the study, who complete each scheduled visit, and who prematurely discontinue the study will be presented for each treatment scheme and overall for the Screened Set.

The primary reasons for study discontinuation as recorded on the disposition pages of the electronic case report form (eCRF) will be summarized (number and percentage) by treatment scheme and overall for the Screened Set.

The number and percentage of subjects with major and minor protocol deviations will be summarized overall and by treatment scheme for the SS. Deviations related to the following categories will be included, with the number of deviations related to COVID-19 in each category also summarized:

- inclusion or exclusion criteria
- withdrawal criteria
- treatment or dose
- concomitant medications
- missing/biased data

All protocol deviations will be reviewed and documented before database lock and unmasking of treatment codes.

7.2. Demographic and Other Baseline Characteristics

Continuous summary statistics will be generated for the quantitative demographic variable (age, in years), tabulated by treatment scheme and overall for the SS and PPS. Discrete summary statistics will be generated for qualitative demographic variables (age category [<65, ≥ 65 to < 75, and ≥ 75], sex, ethnicity, race, and iris color for the study eye) tabulated by treatment scheme for the SS and PPS.

Baseline clinical characteristics and disease history, including baseline BCVA (continuous summary and categories: < 60 ETDRS letters, ≥ 60 ETDRS letters), baseline CST (continuous summary and categories: ≤ 350 µm,> 350 µm), total lesion area, total CNV lesion area, fluorescein leakage area, number of previous anti-vegf medications (< 5 medications, ≥ 5 medications), and presence/absence of subretinal and intraretinal fluid will also be summarized descriptively by treatment scheme and overall for the SS and PPS.

7.3. Medical History and Concomitant Diseases

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0. Medical history will be summarized using number and percent of subjects for each MedDRA system

organ class (SOC) and preferred term (PT) by treatment scheme for the SS. Medical history will be presented separately for ocular conditions in the study eye, ocular conditions in the non-study eye, 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.

Results of prior SD-OCT and visual acuity assessments for the past 18 months are also collected. These will be listed, but not summarized.

7.4. Medication

Prior and concomitant medications will be classified by anatomical therapeutic class 4 (ATC class) and PT using the WHO Drug Dictionary, Global B3 March 2019. Concomitant medications are defined as those medications listed as having been taken: (1) prior to initiation of study drug and continuing for any period of time following the first administration of study drug, or (2) at any time following the first administration of study drug. Prior medications are defined as medications initiated prior to the first administration of study drug, including both those stopped before the first administration of study drug and those continued after the first administration of study drug. Some medications may be classified as both concomitant and prior.

Prior and concomitant medications will be summarized separately using discrete summary statistics for each ATC class and PT by treatment scheme for the SS. Medications will be presented separately for ocular medications in the study eye, ocular medications in the non-study eye, and nonocular medications. Subjects with multiple medications in the same ATC4 or PT will be counted only once for that respective ATC4 or PT.

Separate summaries of on-study anti-VEGF medications and on-study anti-VEGF rescue medications will be presented including the number of treatments and the number of subjects on each medication (along with percentages) for each ATC class and PT by treatment scheme for the SS. Subjects with multiple anti-VEGF medications in the same ATC class or PT will be counted only once for that respective ATC class or drug name.

If the ATC class is not provided, the next lowest classification that is provided in the coding dictionary is used. The PT is defined as the active ingredient; if the active ingredient is not provided or includes more than two ingredients, then the drug name is used instead of the PT.

Anti-VEGF medications taken in the 18 months prior to study start and during study conduct are also collected. These will be listed, but not summarized.

7.5. Study Drug Administration

Data on study drug administration (with differentiation between active and sham injections), post-injection assessments, and follow-up calls after each injection will be listed.

8. Efficacy

All efficacy analyses will be conducted on the FAS. The analyses of the time to first rescue treatment/first fulfillment of rescue criteria and the change from baseline on BCVA and CST will also be conducted on the PPS and the NCFAS.

8.1. Primary Efficacy Endpoint and Analysis

Aflibercept is allowed as rescue treatment at any visit following the Day 30 study assessments in subjects who meet any of the following criteria regarding decrease in BCVA and/or increase in CST:

- Decrease in BCVA (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)

Use of rescue treatment will be recorded in the eCRF.

The primary efficacy endpoint is the time to first rescue treatment/first fulfillment of at least one rescue criterion from Baseline through Month 12.

Time to first rescue treatment/first fulfillment of at least one rescue criterion will be analyzed in the GB-102 treatment schemes using the Kaplan-Meier method. The probability of remaining rescue treatment free will be reported for the Month 6 and Month 12 visits with associated 80% confidence intervals (CI) based on Greenwood's standard error estimate. If calculable, estimates of the median time to fulfillment of at least one rescue criterion and the 25th and 75th percentiles will be calculated with corresponding 80% CIs.

For this analysis, time to first rescue treatment/first fulfillment of at least one rescue criterion is based on interval censoring with regard to the scheduled visits. If a subject receives a rescue treatment/fulfills a rescue criterion during an unscheduled visit, then this event is allocated to the visit interval ending at the next scheduled visit that occurs after the unscheduled visit. Subjects who do not receive rescue medication/fufill rescue criterion will be censored at the last visit interval recorded for the subject.

The Kaplan-Meier curves will be plotted.

No confirmatory hypothesis testing of the primary parameter will be conducted.

To assess the homogeneity (or lack thereof) of the treatment groups regarding the study days on which the scheduled visits occur, descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) of study day will be presented by study visit for each treatment scheme.

The consistency between the two endpoints ("time to first rescue treatment" and "time to first fulfillment of rescue treatment criterion") will be assessed based on 2x2 tables of the rescue treatment vs. fulfillment of

rescue treatment criterion at each study visit.

Exploratory comparisons of time to rescue treatment between each GB-102 scheme and aflibercept 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.

8.2. Secondary and Exploratory Efficacy Endpoints and Analyses

For all secondary and exploratory efficacy endpoints, analyses will be conducted on the observed values at each visit, even if rescue treatment was given at a prior visit.

In addition, all analyses of the BCVA and CST efficacy endpoints will be repeated using a LOCF approach for visits after rescue treatment. For this analysis, the values will be censored at each visit after rescue treatment and replaced by the last value recorded prior to receipt of rescue treatment.

Graphs will be produced to visually compare the two analysis approaches for BCVA and CST. The observed values and the LOCF values will be plotted by visit on the same graph for each treatment scheme. The observed values and LOCF values will also be presented on separate graphs.

8.2.1. Time to First Rescue Treatment/First Fulfillment of Rescue Criteria

The secondary efficacy endpoint related to time to first rescue treatment/first fulfillment of rescue criteria is time to first rescue treatment/first fulfillment of at least one rescue criterion starting at the Month 6 visit through Month 12.

This endpoint will be analyzed the same way that the primary efficacy endpoint is analyzed. The probability of not receiving rescue treatment/not fulfilling rescue criteria at Month 12 will be calculated. Subjects that do not receive the scheduled dose at the Month 6 visit will be excluded from the analyses of time to first rescue treatment/first fulfillment of at least one rescue criterion starting at the Month 6 visit through Month 12.

8.2.2. Best Corrected Visual Acuity

The secondary efficacy endpoints related to BCVA are:

- 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

The exploratory efficacy endpoints related to BCVA are:

- Change from baseline in BCVA (EDTRS) to the average of the scores at Month 9 and 10
- Change from baseline in BCVA (EDTRS) to the average of the scores at Month 10 and 11
- Change from baseline in BCVA (EDTRS) to the average of the scores at Month 11 and 12

Absolute values at each visit and change from baseline values at each follow up visit for BCVA will be

summarized using continuous summary statistics, including 80% CIs around the mean for each treatment scheme.

Comparisons of the change from baseline between each GB-102 group and the aflibercept control group will be made using a linear model adjusting for the baseline category (< 60 letters, >= 60 letters) as a factor and also using 2-sample t-tests.

The proportion of subjects in each BCVA change from Baseline category (<= -15 letters, -14 to -10 letters, -9 to -5 letters, -4 to 4 letters, 5 to 9 letters, 10 to 14 letters, >= 15 letters) and with BCVA worse than 20/200 (Snellen equivalent) at each visit will be summarized using discrete summary statistics. As BCVA is collected only in ETDRS letters, a BCVA worse than 20/200 (Snellen equivalent) is considered equivalent to a BCVA of < 34 ETDRS letters.

Subjects with visual acuity measured by counting fingers or by hand motion will be assigned BCVA of 0 ETDRS letters. If it is required to convert a visual acuity measurement made using the Snellen chart, the following formula will be used:

$$\text{ETDRS letters} = 85+50*\log_{10}(20/xxx),$$

where “20/xxx” is the Snellen visual acuity score.

8.2.3. Central Subfield Thickness

The secondary efficacy endpoint related to CST is the change from baseline in CST (µm) at all visits.

The exploratory efficacy endpoints related to CST are:

- Change in CST from thickest observed CST (µm) prior to enrollment (thickest pre-enrollment baseline) at all visits
- Change in CST from mean observed CST (µm) prior to enrollment (mean pre-enrollment baseline) at all visits
- Change from baseline in CST (µm) to the average of the measurements at Month 9 and 10
- Change from baseline in CST (µm) to the average of the measurements at Month 10 and 11
- Change from baseline in CST (µm) to the average of the measurements at Month 11 and 12

Absolute values at each visit and change from baseline and change from thickest observed CST prior to first dose at each follow up visit for CST will be summarized using continuous summary statistics, including 80% CIs around the mean for each treatment scheme.

Comparisons of the change from baseline between each GB-102 group and the aflibercept control group and will be made using a linear model adjusting for the baseline category (≤ 350 µm,> 350 µm) as a covariate and secondarily using 2-sample t-tests.

8.2.4. Number of Treatments

Mean number of treatments received (including both rescue and scheduled treatments), mean number of

scheduled treatments received, and mean number of rescue treatments received from baseline through Month 12, from baseline to Month 6, and from Month 6 to Month 12 will be summarized using continuous summary statistics, including 80% CIs around the mean for each treatment scheme. Sham injections will not be included.

Total number of treatments received (including both rescue and scheduled treatments), total number of scheduled treatments received, and total number of rescue treatments received from baseline through Month 12, from baseline to Month 6, and from Month 6 to Month 12 will also be summarized categorically, presenting the number and percentage of subjects receiving each total. Sham injections will not be included.The proportion of subjects receiving a scheduled treatment at each visit and the proportion of subjects who received rescue treatment through each visit will be summarized separately using discrete summary statistics, including 80% asymptotic normal CIs for each treatment scheme. A subject will be considered to have received rescue treatment at a particular visit if the rescue treatment was received at any time after the previous scheduled visit up to and including the visit of interest.

8.2.5. Fulfillment of Rescue Criteria

The number of times that a subject meets at least one rescue criterion is a secondary efficacy endpoint.

Mean number of times that a subject met at least one rescue criterion from baseline through Month 12, from baseline to Month 6, and from Month 6 to Month 12 will be summarized using continuous summary statistics, including 80% CIs around the mean for each treatment scheme.

Total number of times that a subject met at least one rescue criterion from baseline through Month 12, from baseline to Month 6, and from Month 6 to Month 12 will also be summarized categorically, presenting the number and percentage of subjects receiving each total.

The proportion of subjects that met at least one rescue criterion through each visit will be summarized using discrete summary statistics, including 80% asymptotic normal CIs for each treatment scheme. A subject will be considered to have met at least one rescue criterion at a particular visit if this occurred at any time after the previous scheduled visit up to and including the visit of interest.

8.2.6. Absence of Exudation

The secondary efficacy endpoint related to absence of exudation is the frequency of subjects with absence of exudation (absence of intra-retinal and sub-retinal fluid) at each visit.

The proportion of subjects with absence of exudation, as well as the proportion of subjects with each finding for intra- and sub-retinal fluid (eg, abset, definite with cystoid involvement, etc) will be summarized at each scheduled visit where this data is collected using discrete summary statistics.

8.2.7. Response to First Rescue Treatment

The exploratory efficacy endpoints associated with assessing the response to first rescue treatment are the absolute values and change in BCVA and CST compared to the values at the time of the first rescue treatment.

Only subjects that received at least one rescue treatment will be included in this analysis. For this

analysis, the rescue baseline for BCVA and CST will be defined as last values obtained prior to the administration of the first rescue treatment.

The timepoints of interest are:

- 2 months prior to rescue treatment. Includes subjects with data collected between 46 and 75 days prior to the first rescue treatment. If there are multiple values, the value collected closest to 60 days prior to the first rescue treatment will be used.
- 1 month prior to rescue treatment. Includes subjects with data collected between 15 and 45 days prior to the first rescue treatment. If there are multiple values, the value collected closest to 30 days prior to the first rescue treatment will be used.
- 1 month after rescue treatment. Includes subjects with data collected between 15 and 45 days after the first rescue treatment. If there are multiple values, the value collected closest to 30 days after the first rescue treatment will be used.
- 2 months after rescue treatment. Includes subjects with data collected between 46 and 75 days after the first rescue treatment. If there are multiple values, the value collected closest to 60 days after the first rescue treatment will be used.

Absolute values at each visit and change from rescue baseline for BCVA and CST will be summarized using continuous summary statistics at rescue baseline and at each timepoint of interest, including 80% CIs around the mean for each treatment scheme.

Change from baseline will be plotted over time for the timepoints of interest and the rescue baseline.

The number and percentage of subjects that received another treatment (either rescue or scheduled) within 1 month and 2 months of the first rescue treatment will also be summarized.

8.2.8. Other Endpoints

The other exploratory efficacy endpoints are:

- Change from baseline in total lesion area (mm^2) at Months 6 and 12
- Change from baseline in CNV lesion area (mm^2) at Months 6 and 12
- Change from baseline in fluorescein leakage area (mm^2) at Months 6 and 12
- ALTISSIMO (Core Study) Subject Exit Questionnaire

Observed values at each visit and change from baseline values at each follow up visit for 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.

The responses to the Subject Exit Quesitonnaire will be listed, but not summarized.

9. Safety

The population used for safety analyses will be the Safety Set (SS). Safety will be assessed on the basis of ocular treatment-emergent adverse events (TEAEs) in the study eye, ocular TEAEs in the non-study eye, and non-ocular TEAEs, study drug exposure, concomitant medication use, laboratory results, vital signs, intra-ocular pressure, slit-lamp biomicroscopy, dilated ophthalmoscopy, physical examination results, and plasma concentrations of sunitinib.

9.1. Extent of Exposure and Treatment Compliance

Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) for the number of scheduled treatments received will be presented by treatment scheme. In addition, a frequency table of the number of scheduled treatments received will be presented by treatment scheme. The number and percentage of subjects that received all treatments per pharmacy manual and the number and percentage of subjects that were treated according to the treatment scheme assigned will also be summarized by treatment scheme.

9.2. Adverse Events

The safety of GB-102 will primarily be assessed by the incidence of TEAEs. An AE will be considered a TEAE if it occurs or worsens on or after initiation of study drug through the Month 12 visit. An AE with a missing start date will be considered a TEAE. If an AE has a partial start date where the partial information does not clearly indicate if the AE started before or after the initiation of study drug, then the AE will be considered a TEAE (eg, if the AE start date is 3 Jan 2019 and the date and time of study drug initiation is 3 Jan 2019 07:31, then the AE would be considered a TEAE).

TEAE summaries will be presented separately for ocular TEAEs in the study eye, ocular TEAEs in the non-study eye, and non-ocular TEAEs.

An overall summary of TEAEs will be presented including the number of events and the number of subjects with at least one event (along with percentages) by treatment scheme for TEAEs in several categories based on severity, relationship to study drug, and relationship to study procedure. Serious TEAEs, TEAEs leading to study drug discontinuation, arteriothromboembolic TEAEs will also be included in the overall summary.

All AEs will be coded to SOC and PT using MedDRA version 22.0. 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.

The following categories of adverse events will be summarized:

- TEAEs
- Treatment related TEAEs
- Procedure-related TEAEs
- Serious TEAEs
- Serious treatment related TEAEs
- TEAEs leading to discontinuation of study drug

- TEAEs by maximum severity
- TEAEs by day of onset (Day 1 to Month 6 and Month 6 to Month 12)

For day of onset, TEAEs that occur on the same date as the Month 6 dose will be included in the Month 6 to Month 12 interval if they are considered related to the procedure; otherwise, they will be included in the Day 1 to Month 6 interval.

Listings will be provided for serious TEAEs, TEAEs leading to discontinuation of study drug, arteriothromboembolic TEAEs, and AEs that occurred prior to treatment exposure.

9.3. Laboratory Evaluations

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)

Chemistry, hematology, and urinalysis results and change from baseline will be summarized by treatment scheme at baseline and at each scheduled post-baseline visit. The number and percentage of subjects with low/normal/high or normal/abnormal values according to the lab normal ranges from baseline to each scheduled post-baseline visit and from baseline to the last visit will be presented in shift tables. Worst case values will also be summarized for chemistry and hematology assessments.

9.4. Vital Signs

Vitals signs will consist of blood pressure and heart rate measurements. Systolic and diastolic blood pressure (mmHg) and heart rate (bpm) will be measured after subjects have been at rest (seated) for at least 5 minutes. Along with the vital signs, height (without shoes) will be measured at Screening and body weight will be measured at Screening and Month 12.

Change from baseline will be summarized by treatment scheme at each scheduled post-baseline visit for applicable parameters.

9.5. 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.

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 and last visit . Discrete categories for changes from baseline in IOP will include ≤ −5, −4 to 4, 5 to 9, 10 to 14, and ≥ 15. The numbers and percentages of eyes with an IOP measurement ≥ 30 mmHg and with an increase from baseline in IOP measurement ≥ 10 mmHg will also be summarized.

9.6. Slit-lamp Biomicroscopy

Slit-lamp biomicroscopy will be performed for each eye by a qualified assessing investigator at each study visit. This procedure 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 Age-related Eye Diseases Study (AREDS) photographic reference scale. For detailed instructions regarding AREDS lens scoring, refer to the separately provided AREDS lens grading scale (Chew 2010) provided in the protocol.

Abnormal slit-lamp biomicroscopy results will be summarized for each treatment scheme for the study eye by visit using discrete summary statistics.

After the IVT injection, it is possible that the microparticles in the depot formation could migrate away from the depot. This migration could result in a higher incidence of AEs or could potentially affect the efficacy of the drug. A narrative will be provided for each subject that experiences the presence of the study medication in the anterior chamber in the study eye.

9.7. 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.

Abnormal dilated ophthalmoscopy results will be summarized for each treatment scheme for the study eye by visit using discrete summary statistics.

9.8. 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.

Abnormal physical examination results will be summarized for each treatment by visit using discrete summary statistics.

9.9. Plasma Concentrations of Sunitinib

Blood samples for plasma analysis will be collected from all subjects and an analysis of all subjects assigned to each sunitinib group will be performed. Any statistical analysis of these values will be done post hoc and is not described in this document.

9.10. Fluorescein Angiography and Color Fundus Photography

The FA imaging 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.

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.

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.

10. Changes from Analysis Planned in Protocol

The following secondary endpoints were modified:

- "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)" was updated to "Time to first rescue treatment/first fulfillment of at least one rescue criterion starting at the Month 6 visit through Month 12"
- "Number of times that at least one rescue criterion is met" was updated to "Number of visit intervals during which at least one rescue criterion is met"

The following secondary endpoints were added:

- Number and percentage of subjects receiving treatment at each visit, including both rescue and scheduled treatments (combined and separate)
- Number of visit intervals during which at least one rescue criterion is met
- Number and percentage of subjects meeting at least one rescue criterion at each visit

The following exploratory endpoints were added:

- Change from baseline in BCVA (EDTRS) to the average of the scores at Month 9 and 10
- Change from baseline in BCVA (EDTRS) to the average of the scores at Month 10 and 11
- Change from baseline in BCVA (EDTRS) to the average of the scores at Month 11 and 12
- Change from baseline in CST (µm) to the average of the measurements at Month 9 and 10
- Change from baseline in CST (µm) to the average of the measurements at Month 10 and 11
- Change from baseline in CST (µm) to the average of the measurements at Month 11 and 12
- Absolute values and change in BCVA and CST compared to values at the time of first rescue treatment (response to first rescue treatment)

In the protocol, "Plasma levels of sunitinib (ng/mL)" was listed as a safety endpoint. In the SAP, this is considered under "Other Endpoints".

Per protocol section 9.6.1, "A primary endpoint analysis will be conducted when all subjects complete the Month 12 (Day 360) visit." This was updated to clarify that the analysis will be conducted when all subjects complete the Month 12 (Day 360) visit or early terminate.

Per protocol section 8.1, "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." Per protocol section 9.7, "An AE will be considered a TEAE if it occurs or worsens on or after initiation of study drug." To resolve the difference in definitions in the protocal, an AE will be considered a TEAE if it occurs or worsens on or after initiation of study drug through the Month 12 visit.

There were no other changes from the analysis planned in the protocol."

11. Reference List

Brown DM, Heier JS, Ciulla T, Benz M, Abraham P, et al. Primary endpoint results of a Phase II study of vascular endothelial growth factor trap-eye in wet age-related macular degeneration. Ophthalmology. 2011; 118(6): 1089-1097.

Chew EY, Kim J, Sperduto RD, Datiles MB, 3rd, Coleman HR, Thompson DJ, et al. Evaluation of the age-related eye disease study clinical lens grading system AREDS report No. 31. Ophthalmology. 2010;117(11):2112-9 e3.

Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. BMJ. 1994;308(6921):81-106.

Heier JS, Boyer D, Nguyen QD, Marcus D, Roth DB, et al. The 1-year results of CLEAR-IT 2, a Phase 2 study of the vascular endothelial growth factor trap-eye dosed as-needed after 12-week fixed dosing. Ophthalmology. 2011; 118(6):1098-1106.

Lachin JM and Foulkes MA. 1986. 'Evaluation of Sample Size and Power for Analyses of Survival with Allowance for Nonuniform Patient Entry, Losses to Follow-up, Noncompliance, and Stratification', Biometrics. 1986;42:507-516.

12. Programming Considerations

All tables, figures, listings (TFLs), and statistical analyses will be generated using SAS for Windows, Release 9.4 (SAS Institute Inc., Cary, NC, USA) or later. Computer-generated table, listing, and figure output will adhere to the following specifications.

12.1. General Considerations

- One SAS program can create several outputs
- Each output will be stored in a separate file.
- Output files will be delivered in Word format.
- Numbering of TFLs will follow ICH E3 guidance

12.2. Table, Listing, and Figure Format

12.2.1. General

- All TFLs will be produced in landscape format on American letter size paper size, unless otherwise specified.
- All TFLs will be produced using the Courier New font, Size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for all TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, Size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

12.2.2. Headers

- All output should have the following header at the top left of each page:

Graybug Vision, Inc., Protocol GBV-102-002 (Syneos Health Study Number 1011627)

Draft/Final Run DD-MMM-YYYY

- All output should have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

12.2.3. Display Titles

- Each TFL is identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended, but sponsor preferences are obtained before final determination. A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title is centered. The analysis set are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(ITT Analysis Set)

12.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment scheme columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment scheme in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.
- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

12.2.5. Body of the Data Display

12.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;
- Whole numbers (e.g., counts) are right-justified; and
- Numbers containing fractional portions are decimal aligned.

12.2.5.2. *Table Conventions*

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment schemes in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups are included.
- An Unknown or Missing category are added to each parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values are output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999

- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment scheme who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data are presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment scheme in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by PT), drugs (by ATC1 code), and adverse events (by PT) are displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated are reported as “-”.

- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment scheme (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject are included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by “(cont)” at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

12.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment schemes as above, subject number, visit/collection day, and visit/collection time.

- Missing data are represented on subject listings as either a hyphen (“-”) with a corresponding footnote (“- = unknown or not evaluated”), or as “N/A”, with the footnote “N/A = not applicable”, whichever is appropriate.

- Dates are printed in SAS DATE9.format (“ddMMMyyyy”: 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as “N/A”, unless otherwise specified.

- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

12.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

12.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with “Note:” if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.
- Subject specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or listing. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., ‘Program : myprogram.sas Listing source: 16.x.y.z’).

13. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures, or statistical analyses. An overview of the development of programs is detailed in Syneos Health SOP Developing Statistical Programs (3907).

Syneos Health SOPs Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (3908) describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency, and commenting and by review of the produced output.

Statistical Analysis Plan for Interventional Studies

Sponsor Name: Graybug Vision, Inc.

Protocol Number: GBV-102-002 (Phase 2b)
Protocol 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)

Extension Study Statistical Analysis Plan

Protocol Version and Date: Version 4.0 / 08 September 2020 (Amendment 3)

Syneos Health Project Code: 1011627

Authors:
[redacted]

Notice of Confidential and Proprietary Information:

Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
1.0 (Extension)	31-Mar-2021	[redacted]	Initial Release Version

I confirm that I have reviewed this document and agree with the content.

Approvals
[redacted]

Table of Contents

1. Glossary of Abbreviations

Abbreviation	Description
AE	adverse event
AMD	age-related macular degeneration
AREDS	Age-related Eye Diseases Study
ATC	Anatomical Therapeutic Chemical
BCVA	best corrected visual acuity
CI	confidence interval
CL	confidence limit
CST	central subfield thickness
DRM	data review meeting
eCRF	electronic case report form
EOAE	extension-onset adverse event
ET	early termination
ETDRS	Early Treatment Diabetic Retinopathy Study
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IOP	intraocular pressure
IVT	intravitreal
MedDRA	Medical Dictionary for Regulatory Activities
OU	both eyes
PT	preferred term
SAP	statistical analysis plan
SAE	serious adverse event
SE	study eye
SD-OCT	spectral domain optical coherence tomography
SOC	system organ class
µm	micrometer/micron
VEGF	vascular endothelial growth factor

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables, and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives stated in Protocol GBV-102-002 (Phase 2b), Version 4.0, dated 08 September 2020 (Amendment 3). This document addresses only the analyses associated with the extension study. The analyses for the core study have been addressed in a separate document (Statistical Analysis Plan, Version 3.0, 08JAN2021).

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonization (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the data that will be analyzed and the subject characteristics, pharmacodynamics, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP they may be completed and identified in the clinical study report.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and are responsible for the production and quality control of all tables, figures, and listings.

2.2. Timings of Analyses

An exploratory analysis of safety and efficacy will be performed at the end of the study after database lock when all subjects have completed the Month 18 visit, ended the study by receiving rescue treatment, or discontinued prematurely from the study. No formal statistical hypothesis testing will be performed.

3. Study Objectives

3.1. Primary Objective

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

3.2. Brief Description

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 (ie, 6 months). There will be no additional treatment with GB-102.

The assessments to be collected include adverse events (AEs), serious adverse events (SAEs), concomitant medications, best corrected visual acuity (BCVA) assessments using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol, slit-lamp biomicroscopy findings, the Age-related Eye Diseases Study (AREDS) lens assessments, intraocular pressure (IOP) measurements, dilated ophthalmoscopy results, retinal central subfield thickness (CST) using spectral domain optical coherence tomography (SD-OCT), color fundus photograpy for depot imaging (ultra-widefield imaging, where available), and date of administration of rescue treatment.

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

3.3. Subject Selection

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

The study eye selected in ALTISSIMO (Core Study) will remain the same for the Extension Study. There will be no randomization in the Extension Study.

3.3.1. 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 angiograpy, 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.

3.3.2. 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)

3.4. Determination of Sample Size

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

3.5. Treatment Assignment and Masking

No treatments are scheduled during the Extension Study. Enrolled subjects will remain masked to their treatment assignment in ALTISSIMO (Core Study).

The visual acuity examiners, the Sponsor (other than the Vice President of Global Clinical Development Operations), the masked contract research organization 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 (but not the treatment scheme) in ALTISSIMO (Core Study).

3.6. Administration of Study Medication

No study medication will be administered during the Extension Study.

3.7. Study Procedures

The schedule of assessments is provided in Table 1, and includes the expected study day relative to the date of first dose in ALTISSIMO (Core Study), acceptable ranges of study days for each visit, and visit nomenclature.

Table 1: Schedule of Assessments

Activity/Assessment	M12 (S/B)[a]	M13	M14	M15	M16	M17	M18/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

S/B = Screening/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

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 study drug at dosing visits.

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. Endpoints

4.1. Exploratory Efficacy Endpoints

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

The exploratory efficacy endpoints for the Extension Study include, but are not limited to:

- Time to first rescue treatment/first fulfillment of at least one rescue criterion from Baseline through Month 18
- Time to first rescue treatment/first fulfillment of at least one rescue criterion starting at the Month 6 visit through Month 18
- Observed values and 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
- Observed values and change from baseline in CST (μm) at all visits
- Number and percentage of subjects receiving rescue treatment at each visit
- Number of visit intervals during which at least one rescue criterion is met
- Number and percentage of subjects meeting at least one rescue criterion at each visit

4.2. Safety Endpoints

The main safety endpoint is the occurrence of ocular and nonocular AEs and serious AEs. Other safety endpoints include intraocular pressure, slit-lamp biomicroscopy, dilated ophthalmoscopy, and the presence and severity of nuclear sclerosis, cortical opacities, and posterior subcapsular opacities.

5. Analysis Sets

Protocol deviation management at Syneos Health is detailed in “Processing and Management of Protocol Deviations” (3101.W02). For details on the process for defining analysis datasets refer to “(Blind) Data Review and Definition of Analysis Sets” (SOP 3911).

Analysis sets are defined in the following sections. Subjects to be included within and excluded from each analysis set will be determined at a Data Review Meeting (DRM) prior to database lock.

5.1. Extension Set

The Extension Set will include all subjects enrolled in the Extension Study; ie, all subjects that met study entry criteria and were determined to be accepatable to the investigator. This set will be used for all of the analyses in the Extension Study.

6. General Aspects for Statistical Analysis

6.1. General Methods

Statistical programming and analyses will be performed using SAS® Version 9.4 or higher.

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

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, and medians will be presented to 1 additional decimal place than reported in the raw values. Standard deviations will be presented to 2 additional decimal places than reported in the raw values. Summaries for discrete variables will include the number of observations (n), frequencies and percentages by categories. All percentages will be rounded to one decimal place (i.e., XX.X%).

The unit of analysis in this study will be the study eye for all efficacy and safety summaries. According to protocol the study eye is selected as the study eye in ALTISSIMO (Core Study).

All summaries will be presented according to the actual treatment scheme from ALTISSIMO (Core Study) and, where appropriate, by visit. When presenting by treatment scheme, each individual treatment scheme (aflibercept, 1 mg GB-102 followed by 1 mg and 2 mg GB-102 followed by 1 mg dosing) will be presented.

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.

All relevant subject data will be included in listings.

6.2. Key Definitions

Study day, for a particular date, relative to the date of first injection of study medication in ALTISSIMO (Core Study) will be computed as (particular date – date of first injection of study medication in ALTISSIMO (Core Study)) + 1 day if the particular date is on or after the date of first injection of study medication. As a result of this definition, the date of first injection of study medication will by Study Day 1, and the date immediately preceding the date of first injection of study medication will be Study Day -1, thus there will be no Study Day 0.

Baseline is defined as the last nonmissing measurement prior to the first injection of study medication in ALTISSIMO (Core Study).

Change from baseline will be computed as follow-up value minus baseline value.

6.3. Missing Data

The handling of missing or partial dates related to adverse events is detailed in Section 9.3.

No other imputation of missing data will be performed.

6.4. Visit Windows and Allocation

For parameters which will be summarized by visit, parameters that are associated with a scheduled visit in the CRF will remain allocated to that study visit. If data is missing at a scheduled visit and there is an unscheduled visit or end of study visit (conducted when a subject has early terminated the study) that occurred in the analysis range of study days (Table 2) for the missed visit, then the data from the unscheduled visit will be assigned to the missing visit. For ranges associated with ALTISSIMO (Core Study) visits, see the SAP Version 3.0, 08Jan2021.

A listing of all such imputed visits will be presented, including the study day of the unscheduled or end of study visit used in place of the missing visit.

Table 2: Ranges of Study Days Associated With Each Visit for BCVA, Slit-lamp Biomicroscopy, Intraocular Pressure, Dilated Ophthalmoscopy, SD-OCT, and Intravitreal Depot Color Fundus Photography

Scheduled Visit	Planned Study Day	Targeted Range of Study Days	Analysis Range of Study Days
Month 13	390	[383 to 397]	[375 to 405)
Month 14	420	[413 to 427]	[405 to 435)
Month 15	450	[443 to 457]	[435 to 465)
Month 16	480	[473 to 487]	[465 to 495)
Month 17	510	[503 to 517]	[495 to 525)
Month 18	540	[533 to 547]	[525 to …)

[a] Intravitreal Depot Color Fundus Photograpy is not performed at the Screening Visit

6.5. Pooling of Centers

Data collected from different study centers will not be pooled for analysis.

7. Demographic, Other Baseline Characteristics and Medication

7.1. Subject Disposition and Withdrawals

A subject will have fulfilled the requirements for study completion if/when the subject has completed the Month 18 visit or when the subject receives rescue treatment. The number and percentage of subjects who enter the Extension Study, who complete the Extension Study, and who prematurely discontinue the Extension Study will be presented for each treatment scheme and overall.

The primary reasons for study discontinuation as recorded on the disposition pages of the electronic case report form (eCRF) will be summarized (number and percentage) by treatment scheme and overall.

The number and percentage of subjects with major and minor protocol deviations will be summarized overall and by treatment scheme. Deviations related to the following categories will be included, with the number of deviations related to COVID-19 in each category also summarized:

- inclusion or exclusion criteria
- withdrawal criteria
- treatment or dose
- concomitant medications
- missing/biased data

All protocol deviations will be reviewed and documented before database lock.

7.2. Demographic and Other Baseline Characteristics

Continuous summary statistics will be generated for the quantitative demographic variable (age, in years), tabulated by treatment scheme and overall. Discrete summary statistics will be generated for qualitative demographic variables (age category [<65, ≥ 65 to < 75, and ≥ 75], sex, ethnicity, race, and iris color for the study eye) tabulated by treatment scheme.

Baseline clinical characteristics and disease history, including baseline BCVA (continuous summary and categories: < 60 ETDRS letters, ≥ 60 ETDRS letters), baseline CST (continuous summary and categories: ≤ 350 µm,> 350 µm), total lesion area, total CNV lesion area, fluorescein leakage area, number of previous anti-vegf medications (< 5 medications, ≥ 5 medications), and presence/absence of subretinal and intraretinal fluid will also be summarized descriptively by treatment scheme and overall.

7.3. Medication and Procedures

Concomitant medications will be classified by anatomical therapeutic class 4 (ATC class) and PT using the WHO Drug Dictionary, Global B3 March 2019. Concomitant medications are defined as those medications which were on-going at the time of the Month 12 visit in the Core Study or that were initiated during the Extension Study.

Concomitant medications will be summarized using discrete summary statistics for each ATC class and PT by treatment scheme. Medications will be presented separately for ocular medications in the study eye, ocular medications in the non-study eye, and nonocular medications. Subjects with multiple

medications in the same ATC4 or PT will be counted only once for that respective ATC4 or PT. Ocular concomitant procedures will be summarized similarly.

A summary of on-study anti-VEGF medications (eg rescue medications) will be presented including the number of treatments and the number of subjects on each medication (along with percentages) for each PT by treatment scheme. Subjects with multiple anti-VEGF medications in the same PT will be counted only once for that drug name. An anti-VEGF medication is considred on-study if it was administered after the Month 12 ALTISSIMO (Core Study) visit.

The PT is defined as the active ingredient; if the active ingredient is not provided or includes more than two ingredients, then the drug name is used instead of the PT.

8. Efficacy

All efficacy analyses will be conducted on the Extension Set.

8.1. Exploratory Efficacy Endpoints and Analyses

For all exploratory efficacy endpoints, analyses will be conducted on the observed values at each visit, even if rescue treatment was given at a prior visit.

8.1.1. Time to First Rescue Treatment/First Fulfillment of Rescue Criteria

The exploratory efficacy endpoints related to time to first rescue treatment/first fulfillment of rescue criteria are

- Time to first rescue treatment/first fulfillment of at least one rescue criterion starting from Baseline through Month 18.
- Time to first rescue treatment/first fulfillment of at least one rescue criterion starting at the Month 6 visit through Month 18. Subjects that did not receive the scheduled dose at the Month 6 visit will be excluded from this analysis.

These endpoints will be analyzed similarly to the primary efficacy endpoint in ALTISSIMO (Core Study).

Aflibercept is allowed as rescue treatment at any visit following the Day 30 study assessments in ALTISSIMO (Core 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)

Use of rescue treatment will be recorded in the eCRF.

Time to first rescue treatment/first fulfillment of at least one rescue criterion will be analyzed in the GB-102 treatment schemes using the Kaplan-Meier method. The probability of remaining rescue treatment free/not fulfilling rescue criteria through Month 18 will be calculated with associated 80% confidence intervals (CI) based on Greenwood's standard error estimate. If calculable, estimates of the median time to fulfillment of at least one rescue criterion and the 25th and 75th percentiles will be calculated with corresponding 80% CIs.

For this analysis, time to first rescue treatment/first fulfillment of at least one rescue criterion is based on interval censoring with regard to the scheduled visits. If a subject receives a rescue treatment/fulfills a rescue criterion during an unscheduled visit, then this event is allocated to the visit interval ending at the next scheduled visit that occurs after the unscheduled visit. Subjects who do not receive rescue

medication/fufill rescue criterion will be censored at the last visit interval recorded for the subject.

The Kaplan-Meier curves will be plotted.

To assess the homogeneity (or lack thereof) of the treatment groups regarding the study days on which the scheduled visits occur, descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) of study day will be presented by study visit for each treatment scheme.

The consistency between the two endpoints ("time to first rescue treatment" and "time to first fulfillment of rescue treatment criterion") will be assessed based on 2x2 tables of the rescue treatment vs. fulfillment of rescue treatment criterion at each study visit.

8.1.2. Best Corrected Visual Acuity

The exploratory efficacy endpoints related to BCVA are:

- Observed values and 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 BCVA (EDTRS) to the average of the scores at Month 9 and 10
- Change from baseline in BCVA (EDTRS) to the average of the scores at Month 10 and 11
- Change from baseline in BCVA (EDTRS) to the average of the scores at Month 11 and 12

Absolute values at each visit and change from baseline values at each follow up visit for BCVA will be summarized using continuous summary statistics, including 80% CIs around the mean for each treatment scheme.

The proportion of subjects in each BCVA change from Baseline category (<= -15 letters, -14 to -10 letters, -9 to -5 letters, -4 to 4 letters, 5 to 9 letters, 10 to 14 letters, >= 15 letters) and with BCVA worse than 20/200 (Snellen equivalent) at each visit will be summarized using discrete summary statistics. As BCVA is collected only in ETDRS letters, a BCVA worse than 20/200 (Snellen equivalent) is considered equivalent to a BCVA of < 34 ETDRS letters.

Subjects with visual acuity measured by counting fingers or by hand motion will be assigned BCVA of 0 ETDRS letters. If it is required to convert a visual acuity measurement made using the Snellen chart, the following formula will be used:

$$\text{ETDRS letters} = 85+50*\log_{10}(20/xxx),$$

where "20/xxx" is the Snellen visual acuity score.

8.1.3. Central Subfield Thickness

The exploratory efficacy endpoints related to CST are:

- Observed values and change from baseline in CST (μm) at all visits.

- Change from baseline in CST (µm) to the average of the measurements at Month 9 and 10
- Change from baseline in CST (µm) to the average of the measurements at Month 10 and 11
- Change from baseline in CST (µm) to the average of the measurements at Month 11 and 12

Absolute values at each visit and change from baseline at each follow up visit for CST will be summarized using continuous summary statistics, including 80% CIs around the mean for each treatment scheme.

8.1.4. Number of Rescue Treatments

Mean number of rescue treatments received from Month 12 to Month 18 will be summarized using continuous summary statistics, including 80% CIs around the mean for each treatment scheme.

Total number of rescue treatments received will also be summarized categorically, presenting the number and percentage of subjects receiving each total. The proportion of subjects who received rescue treatment through each visit will be summarized separately using discrete summary statistics, including 80% asymptotic normal CIs for each treatment scheme. A subject will be considered to have received rescue treatment at a particular visit if the rescue treatment was received at any time after the previous scheduled visit up to and including the visit of interest.

8.1.5. Fulfillment of Rescue Criteria

The number of times that a subject meets at least one rescue criterion is an exploratory efficacy endpoint.

Mean number of times that a subject met at least one rescue criterion from Month 12 to Month 18 will be summarized using continuous summary statistics, including 80% CIs around the mean for each treatment scheme.

Total number of times that a subject met at least one rescue criterion from Month 12 to Month 18 will also be summarized categorically, presenting the number and percentage of subjects receiving each total.

The proportion of subjects that met at least one rescue criterion through each visit will be summarized using discrete summary statistics, including 80% asymptotic normal CIs for each treatment scheme. A subject will be considered to have met at least one rescue criterion at a particular visit if this occurred at any time after the previous scheduled visit up to and including the visit of interest.

9. Safety

The population used for safety analyses will be the Extension Set. Safety will be assessed on the basis of ocular extension-onset adverse events (EOAEs) in the study eye, ocular EOAEs in the non-study eye, and non-ocular EOAEs, concomitant medication use, intra-ocular pressure, slit-lamp biomicroscopy, and dilated ophthalmoscopy,.

9.1. Adverse Events

The safety of GB-102 will primarily be assessed by the incidence of EOAEs. An AE will be considered an EOAE if it occurs or worsens on or after the Month 12 ALTISSIMO (Core Study) visit through study exit. An AE with a missing start date will be considered an EOAE. If an AE has a partial start date where the partial information does not clearly indicate if the AE started before or after the Month 12 visit, then the AE will be considered an EOAE (eg, if the AE start date is 3 Jan 2019 and the date of the Month 12 visit is 3 Jan 2019, then the AE would be considered an EOAE).

EOAE summaries will be presented separately for ocular EOAEs in the study eye, ocular EOAEs in the non-study eye, and non-ocular EOAEs.

An overall summary of EOAEs will be presented including the number of events and the number of subjects with at least one event (along with percentages) by treatment scheme for EOAEs in several categories based on severity, relationship to study drug, and relationship to study procedure. Serious EOAEs, EOAEs leading to study drug discontinuation, arteriothromboembolic EOAEs will also be included in the overall summary.

All AEs will be coded to SOC and PT using MedDRA Version 22.0. The number of EOAEs and the number and percentage of subjects with any EOAEs will be tabulated overall and by SOC and PT within each SOC by treatment scheme.

The following categories of adverse events will be summarized:

- EOAEs
- Treatment related EOAEs
- Serious EOAEs
- Serious treatment related EOAEs
- EOAEs by maximum severity
- Non-serious EOAEs

9.2. 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.

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 for each treatment scheme by visit and last visit . Discrete categories for changes from baseline in IOP will include ≤ −5, −4 to 4, 5 to 9, 10 to 14, and ≥ 15. The numbers and percentages of eyes with an IOP measurement ≥ 30 mmHg and with an increase from baseline in IOP measurement ≥ 10 mmHg will also be summarized.

9.3. Slit-lamp Biomicroscopy

Slit-lamp biomicroscopy will be performed for each eye by a qualified assessing investigator at each study visit. This procedure 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 Age-related Eye Diseases Study (AREDS) photographic reference scale. For detailed instructions regarding AREDS lens scoring, refer to the separately provided AREDS lens grading scale (Chew 2010) provided in the protocol.

Abnormal slit-lamp biomicroscopy results will be summarized for each treatment scheme for the study eye by visit using discrete summary statistics.

After the IVT injection, it is possible that the microparticles in the depot formation could migrate away from the depot. This migration could result in a higher incidence of AEs or could potentially affect the efficacy of the drug. A narrative will be provided for each subject that experiences the presence of the study medication in the anterior chamber in the study eye.

9.4. 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.

Abnormal dilated ophthalmoscopy results will be summarized for each treatment scheme for the study eye by visit using discrete summary statistics.

10. Changes from Analysis Planned in Protocol

There were no changes from the analysis planned in the protocol for the Extension Study.

11. Reference List

Brown DM, Heier JS, Ciulla T, Benz M, Abraham P, et al. Primary endpoint results of a Phase II study of vascular endothelial growth factor trap-eye in wet age-related macular degeneration. Ophthalmology. 2011; 118(6): 1089-1097.

Chew EY, Kim J, Sperduto RD, Datiles MB, 3rd, Coleman HR, Thompson DJ, et al. Evaluation of the age-related eye disease study clinical lens grading system AREDS report No. 31. Ophthalmology. 2010;117(11):2112-9 e3.

Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. BMJ. 1994;308(6921):81-106.

Heier JS, Boyer D, Nguyen QD, Marcus D, Roth DB, et al. The 1-year results of CLEAR-IT 2, a Phase 2 study of the vascular endothelial growth factor trap-eye dosed as-needed after 12-week fixed dosing. Ophthalmology. 2011; 118(6):1098-1106.

Lachin JM and Foulkes MA. 1986. 'Evaluation of Sample Size and Power for Analyses of Survival with Allowance for Nonuniform Patient Entry, Losses to Follow-up, Noncompliance, and Stratification', Biometrics. 1986;42:507-516.

12. Programming Considerations

All tables, figures, listings (TFLs), and statistical analyses will be generated using SAS for Windows, Release 9.4 (SAS Institute Inc., Cary, NC, USA) or later. Computer-generated table, listing, and figure output will adhere to the following specifications.

12.1. General Considerations

- One SAS program can create several outputs
- Each output will be stored in a separate file.
- Output files will be delivered in Word format.
- Numbering of TFLs will follow ICH E3 guidance

12.2. Table, Listing, and Figure Format

12.2.1. General

- All TFLs will be produced in landscape format on American letter size paper size, unless otherwise specified.
- All TFLs will be produced using the Courier New font, Size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for all TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, Size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

12.2.2. Headers

- All output should have the following header at the top left of each page:

Graybug Vision, Inc., Protocol GBV-102-002 (Syneos Health Study Number 1011627)

Draft/Final Run DD-MMM-YYYY

- All output should have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

12.2.3. Display Titles

- Each TFL is identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended, but sponsor preferences are obtained before final determination. A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title is centered. The analysis set are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(ITT Analysis Set)

12.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment scheme columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment scheme in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.
- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

12.2.5. Body of the Data Display

12.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;
- Whole numbers (e.g., counts) are right-justified; and
- Numbers containing fractional portions are decimal aligned.

12.2.5.2. *Table Conventions*

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment schemes in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups are included.
- An Unknown or Missing category are added to each parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values are output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999

- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment scheme who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data are presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment scheme in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by PT), drugs (by ATC1 code), and adverse events (by PT) are displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated are reported as “-”.

- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment scheme (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject are included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by “(cont)” at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

12.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment schemes as above, subject number, visit/collection day, and visit/collection time.

- Missing data are represented on subject listings as either a hyphen (“-”) with a corresponding footnote (“- = unknown or not evaluated”), or as “N/A”, with the footnote “N/A = not applicable”, whichever is appropriate.

- Dates are printed in SAS DATE9.format (“ddMMMyyyy”: 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as “N/A”, unless otherwise specified.

- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

12.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

12.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with “Note:” if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.
- Subject specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or listing. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., ‘Program : myprogram.sas Listing source: 16.x.y.z’).

13. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures, or statistical analyses. An overview of the development of programs is detailed in Syneos Health SOP Developing Statistical Programs (3907).

Syneos Health SOPs Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (3908) describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency, and commenting and by review of the produced output.