Statistical Analysis Plan

Sponsor Name: Gemini Therapeutics, Inc.

Protocol Number: GEM-CL-10311
Protocol Title: A Multicenter, Multiple-Dose Study in Neovascular Age-related Macular Degeneration (nAMD) to Evaluate the Safety, Tolerability, Pharmacodynamics, Immunogenicity, and Clinical Effect of Repeat Intravitreal (IVT) Injections of GEM103 as an Adjunct to Standard of Care Aflibercept Therapy

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

Approvals

Syneos Health Approval

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Name, Title Lead Biostatistician	Signature	Date (DD-Mmm-YYYY)
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Gemini Therapeutics, Inc. Approval

PPD PPD PPD	PPD	17-Feb-2022
Name, Title Sponsor Contact	Signature	Date (DD-Mmm-YYYY)

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1. Glossary of Abbreviations

Abbreviation	Description
ADA	Antidrug antibody(ies)
AE	Adverse Event
AMD	age-related macular degeneration
AP	Alternate pathway
ATC	Anatomical Therapeutic Chemical
BCVA	best corrected visual acuity
CFH	complement factor H
CI	Confidence Interval
Cmax	maximum concentration
CNV	choroidal neovascularization
CRF	Case Report Form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
ECG	Electrocardiogram
eCRF	electronic case report form
EOM	every other month
EOS	end of study
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescein angiography
FAF	fundus autofluorescence
FAS	Full Analysis Set
ICF	Informed consent form
ICH	International Conference on Harmonization
IOP	intraocular pressure
IVT	intravitreal
LLVA	low luminance visual acuity
MA	macular atrophy

Abbreviation	Description
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MNRead	Minnesota Low-vision Reading Test
MRC	Medical Review Committee
nAMD	Neovascular Age-Related Macular Degeneration
N/A	Not Applicable
NA	Not Applicable
NEI-VFQ-25	National Eye Institute Visual Functioning Questionnaire-25
NIR	near infrared reflectance imaging
OCT	optical coherence tomography
OCT-A	optical coherence tomography – angiogram/angiography
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PT	Preferred Term
QC	Quality Control
QTc	Corrected QT Interval
rhCFH	recombinant human CFH
RPE	retinal pigment epithelium
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SD-OCT	spectral domain optical coherence tomography
SE	Standard Error
SI	Standard International System of Units
SOA	schedule of assessments
SoC	standard of care
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
TFL	Table, Figure and Listing

Abbreviation	Description
VA	visual acuity
VEGF	vascular endothelial growth factor
WHO	World Health Organization

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 which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

This SAP is created based on Protocol Number GEM-CL-10311 version 3.0 dated 05 May 2021. The purpose of this SAP is to outline the planned analyses by Syneos Health (SYNH) to support the completion of the Clinical Study Report (CSR). This SAP describes in detail the statistical methodology and the statistical analyses to be conducted for the above mentioned protocol. The planned analyses identified in this SAP is following the Statistical Principles for Clinical Trials such as International Council for Harmonisation (ICH) guidelines, E4, and E9.

2.1. Responsibilities

Syneos Health will perform all statistical analyses, except pharmacokinetics (PK), and is responsible for the production and quality control of all tables, figures and listings.

2.2. Timings of Analyses

The primary analysis of safety and efficacy is planned after all subjects complete the final study visit or terminate early from the main phase of the study. Unless otherwise specified, the analysis includes all data collected in the database through the time of the database lock.

An independent Medical Review Committee (MRC) consisting of Sponsor medical personnel and independent medical expert(s) will meet approximately quarterly to review safety information for the study. No descriptive summaries of safety findings are planned.

Interim data may be summarized for presentation to regulatory authorities or to the scientific community to facilitate discussions and obtain input on late phase study designs.

3. Study Objectives

3.1. Primary Objective

- Describe the safety and tolerability of GEM103+ standard of care (SoC) vs sham+SoC.

3.2. Secondary Objective(s)

- To evaluate total complement factor H (CFH) in aqueous humor after GEM103 intravitreal (IVT) injection, whenever possible
- Describe the effect on best corrected visual acuity (BCVA)
- Describe the effect on macular atrophy (MA) size in subjects with MA present at baseline

3.3. Exploratory Objectives

- To evaluate the immunogenicity of GEM103 in serum after GEM103 IVT injection, whenever possible
- Describe the effect of GEM103 IVT injection on biomarkers in aqueous humor
- Describe the effect on new MA in subjects without MA at baseline
- Describe the effect on choroidal neovascularization (CNV) size
- Describe the effect on thickness of retinal layers
- Describe the effect on subretinal and intraretinal fluid
- Describe the effect on low luminance visual acuity (LLVA)
- Describe the effect on National Eye Institute Visual Functioning Questionnaire 25 item Version (NEI-VFQ-25)
- Describe the effect on Minnesota Low-vision Reading Test (MNRead)

4. Study Details/Design

4.1. Brief Description

This is a Phase 2a, single-masked, sham-controlled, multicenter, multiple-dose study in subjects with neovascular age-related macular degeneration (nAMD) to evaluate the safety, tolerability, immunogenicity, pharmacokinetic/pharmacodynamic, complement biomarkers, and clinical efficacy during 12 months of GEM103 IVT injections every other month (EOM) as an adjunct to standard of care (SoC) aflibercept therapy.

Study drug or sham, along with (SoC) aflibercept, will be administered to 1 eye only, which will be designated during the screening process, based on eligibility, and prior to any baseline measurements. If both eyes meet all eye-specific entry criteria, then the study eye will be determined by the Investigator and the subject together. All assessments will be performed in the study eye as well as the fellow eye whenever feasible.

Detailed assessments of intraocular pressure (IOP), visual acuity (VA) and function, and retinal parameters such as CNV and MA lesion size will be performed for each subject enrolled.

Data will be collected on demographics, medical and ocular history, family history, and concomitant medications. Additionally, ophthalmic anatomic assessments and multimodal imaging, exploratory genetic and biomarker analyses, and aqueous humor sampling will be done for each subject enrolled.

The Investigator will monitor the safety of study procedures according to local institutional policy. All Adverse Events (AEs) will be recorded in the electronic case report form. Accumulating safety data will be reviewed on an ongoing basis. The minimum planned duration of each subject's participation is approximately 13 months: 1 month for screening and 12 months for dosing and follow-up.

4.2. Subject Selection

The target population for this study is subjects with nAMD who are undergoing treatment (at least 1 prior dose) with aflibercept therapy. Approximately 45 subjects (~30 treated with GEM103+SoC and ~15 treated with sham+SoC; SoC defined as aflibercept EOM) are planned for inclusion in the study.

The full list of inclusion and exclusion criteria is provided in section 4.3.1 and 4.3.2 of the protocol.

4.3. Determination of Sample Size

The planned total sample size of approximately 45 subjects (~30 treated with GEM103+SoC, ~15 treated with sham+SoC; SoC defined as aflibercept EOM) is based on feasibility considerations, rather than any specific statistical test.

4.4. Treatment Assignment and Masking

Subjects will be randomly assigned to a treatment cohort in a 2:1 randomization pattern with 2 subjects assigned to treatment with GEM103+SoC (SoC defined as aflibercept EOM) for every 1 subject assigned to treatment with sham+SoC.

Subjects randomized to the sham+SoC treatment group will receive SoC with a sham IVT injection instead of GEM103, to keep the subject masked to their treatment assignment.

4.5. Administration of Study Medication

At each dosing visit, 2 IVT injections (or sham) will be administered; aflibercept and GEM103 (or sham). They will be administered separately to the same eye, with the second injection administered at 90°, or 3 clock hours distance, from the location of the first injection. GEM103 and aflibercept will under no circumstances be administered as 1 combined injection from the same syringe. The intravitreal injections will be administered in accordance with SoC techniques including the use of 5% povidone iodine and a sterile lid speculum. Administer aflibercept (2 mg/50 µL) first, followed by GEM103 (500 µg/50 µL) 15 minutes (±5 minutes) later.

4.6. Study Procedures and Flowchart

The study procedures to be performed as summarized in the Schedule of Assessments table, is provided in the protocol Appendix A, Schedule of Assessments.

5. Endpoints

5.1. Primary Endpoint

- Ocular and non-ocular treatment-emergent adverse events (TEAEs)
- Changes in ophthalmic exams
- Results of visual function assessments

5.2. Secondary Endpoints

- Aqueous humor concentrations of total CFH
- Mean change in BCVA from baseline in Early Treatment Diabetic Retinopathy Study (ETDRS) letters
- Mean change in size of MA evaluated by fundus autofluorescence (FAF)

5.3. Exploratory Endpoints

- Generation of serum GEM103 antidrug antibodies
- Change from baseline in complement protein, complement split products, and related cytokines protein values in aqueous humor
- New MA evaluated by FAF
- Mean reduction from baseline in CNV size as evaluated by fluorescein angiography (FA)
- Mean change from baseline in center point thickness and central subfield thickness in µm as evaluated by spectral domain optical coherence tomography (SD-OCT)
- The proportion of patients with intraretinal or subretinal fluid as evaluated by SD-OCT
- Mean change in low luminance visual acuity (LLVA) from baseline in ETDRS letters
- Mean change in score from baseline on National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25)
- Mean change in maximum reading speed from baseline on Minnesota Low-vision Reading Test (MNRead)

6. Analysis Sets

6.1. Consented Subject Set

The Consented Subject Set (CSS) will include subjects who signed the ICF and will be used to create a diagram to illustrate subject flow from consent through disposition (similar to a Consolidated Standards of Reporting Trials [CONSORT] diagram for a randomized trial).

6.2. Biomarker Set

The Biomarker Set (BS) will include subjects with sufficient data to assess biomarker results.

6.3. Full Analysis Set

The Full Analysis Set (FAS) will include all randomized subjects who receive at least 1 dose of study drug (GEM103 or sham). Safety analyses will be performed on the FAS. Analyses on the FAS are consistent with the intention-to-treat principle. Subjects will be analyzed according to actual treatment received. The FAS will be used for all analyses of primary, secondary and exploratory endpoints.

6.4. Protocol Deviations

All protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management, dosing, and sampling procedures or patient assessment will be listed. The list of protocol deviations will be reviewed by the Sponsor and the principal investigator and finalized before database lock. The final decision with respect to significant protocol violations will be made before database lock. A formal (blind) data review meeting is not necessary.

Protocol deviations will be summarized by the number and percent of subjects with any protocol deviations and with any significant protocol deviations.

7. General Aspects for Statistical Analysis

7.1. General Methods

All analyses and summaries will be produced using Statistical Analysis System (SAS®) version 9.4 or higher. All SAS programs used to generate analytical results will be developed and validated according to SYNH programming standards and SAS validation procedures. Summaries will be presented by treatment group (GEM103+SoC vs Sham+SoC) unless otherwise specified.

Continuous data will be summarized using descriptive statistics (number of subjects (n), arithmetic mean (Mean), standard deviation (SD), median, minimum, and maximum) and, where appropriate, graphic representation, and two-sided 95% confidence intervals (CI). The minimum and maximum will be displayed to the precision with which the data were collected. The mean and median will be displayed to one additional decimal place and the SD will be displayed to two additional decimal places.

Categorical data will be summarized by sample size, proportions, and, where appropriate, two-sided 95% CIs. The total number of subjects with a non-missing value for the given variable will be used as the denominator for percent calculations, unless stated otherwise. All percentages will be presented with one decimal, unless otherwise specified. Percentages equal to 100 will be presented as 100, and percentages will not be presented for zero frequencies.

All relevant subject data will be included in listings. All subjects entered into the database will be included in subject data listings. All pre- and post-dose assessments including repeat and unscheduled assessments will be included in the data listings.

Any reported p-values will be considered part of the descriptive analyses (i.e., hypothesis-generating) and will not be adjusted for multiplicity. The phrase “statistically significant” may be used interchangeably with “nominally statistically significant” to indicate that a nominal p-value was <0.05.

7.2. Key Definitions

7.2.1. Baseline

Unless otherwise specified, baseline is defined as the last non-missing observation prior to the first dose of study drug administration.

7.2.2. Study Day

The day of first dose of study drug administration is defined as study Day 1. Subsequent days are numbered consecutively (Day 2, Day 3, etc.). Prior to the day of first dose of study drug administration, study days are numbered sequentially with negative values (i.e., Day -1, Day -2, etc.). There is no Day 0.

7.3. Missing Data

In general, missing data will not be imputed. All analyses will be based on observed cases. Sections 7.3.1 and 7.3.2 note the situations where missing data will be imputed.

7.3.1. Handling of Missing Dates/Months/Years for Prior/Concomitant Therapies

If the medication cannot be classified into concomitant medications or prior medications due to incomplete date, the rules below will be applied for the classification.

For start date,

- If the year and month are observed but the day is missing, the first day of the month will be used unless month and year are the same as month and year of first dose date then impute using the day of first dose date
- If the year is observed but the month and day are missing, the first day of the year, 01 Jan, will be used unless year is the same as first dose date then the first dose date will be used
- If the start date is completely missing, the medication will be considered concomitant unless the stop date is before study drug administration
- If the start and stop dates are both completely missing, a therapy will be considered concomitant.

For end date,

- If the year and month are observed but the day is missing, the last day of the month will be used unless month and year are the same as month and year of last dose date, then impute the last dose date
- If the year is observed but the month and day are missing, the last day of the year, 31 Dec, will be used unless year is the same as last dose date then the last dose date will be used
- If the end date is completely missing, if medication is still ongoing, then missing end date is not supposed to be imputed. If the medication is not ongoing and the start date is prior to first dose date, the end date will be imputed using 1st dose date.
- If both start and end dates are completely missing, medication will be considered concomitant.

The original partial or missing date will be shown in listings for all prior and concomitant medications.

7.3.2. Adverse Events Dates

For AEs with incomplete dates, the following rules will be used to impute start and/or stop dates for the sole purpose of determining if an AE is treatment-emergent. Imputed dates will not appear in the data listings.

For partial start dates:

- If the month and year of AE onset are provided but day is missing
    - If the month and year match the month and the year of the date of first dosing administration, then the date of first dosing administration will be used and the AE will be considered treatment-emergent.
    - Otherwise, the first of the month will be used.
- If the year of AE onset is provided, but the month and day are missing
    - If the year matches the year of the first dosing administration, then the date of first dosing administration will be used.
    - Otherwise, the first day of the month and the first month of the year will be used.
    - If the stop date is not missing and the imputed onset date is after the stop date, then the stop date will be used.
    - If the onset date is completely missing and the stop date is on or after the date of first dose, the event will be considered a TEAE.
    - If both onset date and stop date are missing, the event will be considered a TEAE. Partial stop dates will not be imputed.

- If the stop date is complete and the imputed start date is after the actual stop date, then the start date will be imputed as the stop date.

7.4. Visit Windows

For all analyses, data will be summarized according to the scheduled visit and time points as outlined in the protocol and by the visit denoted on the electronic case report form (eCRF). There will be no derivation for visit windows in terms of summary assessments. Nominal visits will be used for by-visit tables.

Data collected at unscheduled visits that occurred outside the time windows specified in the protocol will be included in the data listings but will not be included in the analyses unless otherwise stated.

For data with repeated observations at a given visit, for example, laboratory assessments, the earliest of the available non-missing values at a visit should be used in summary tables. Other observations will be considered as unscheduled visits.

7.5. Pooling of Centers

Data from all sites will be summarized together for analyses.

7.6. Subgroups

No subgroup analyses are planned for the study.

8. Demographic, Other Baseline Characteristics and Medication

8.1. Subject Disposition and Withdrawals

A summary table will be produced for all subjects detailing the number of subjects screened, screen failed and randomized, the number and percentages of all subjects in each analysis populations (Consented Subject Set, Biomarker Set, Full Analysis Set), subjects who completed the study, and subjects who prematurely discontinued the study. In addition, reasons leading to discontinuation from study will be summarized for all subjects for each treatment group. A listing of subject disposition will also be provided for all subjects.

Subjects in each analysis population, and those excluded from each analysis population (CSS, BS, FAS) and reasons for exclusion will be listed.

Screen failures are defined as all subjects who sign the informed consent but are not enrolled into the study.

8.2. Demographic and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be tabulated by treatment group for the Full Analysis Set.

The following characteristics will be summarized:

- Study eye
- Age at screening (years)
- Gender
- Childbearing potential for females
- Race
- Ethnicity
- Genetic Profile
- Length of Prior Anti-VEGF Treatment (years)
- Previous anti-VEGF treatment

Genetic profile is based on a blood sample for exploratory genetics and will first be classified by Rare (presence of rare genetic variant) or Complotype Variant. The categories will be Rare, Complotype, 402HH, 402HY, and 402YY. First, the number and percent of subjects with rare genetic variants will be summarized; appearing in the summary table as “Rare”. Second, the number and percent of subjects with Complotype variant (but not Rare) will be summarized. Finally, for subjects that are neither Rare nor Complotype, categories of 402HH, 402HY, and 402YY will be summarized.

Genetic profile for Sub-Type HTRA/ARMS2 Variant will also be summarized.

The following baseline characteristics are observed at screening and/or baseline and will be summarized for the Full Analysis Set. In case of multiple measurements, the last available value before first application of the study drug will be used for summary tables.

- NEI-VFQ-25 composite score
- MNRead score (study eye)
- MNRead score (fellow eye)
- MNRead score (OU)

- MA size (mm^2) (study eye)
- MA size (mm^2) (fellow eye)
- Center Point Thickness (CPT) (study eye)
- Center Point Thickness (CPT) (fellow eye)
- Center Subfield Thickness (CST) (study eye)
- Center Subfield Thickness (CST) (fellow eye)
- BCVA measured by ETDRS letter score (study eye)
- BCVA measured by ETDRS letter score (fellow eye)
- LLVA measured by ETDRS letter score (study eye)
- LLVA measured by ETDRS letter score (fellow eye)
- Total CNV Area (study eye)
- Total CNV Area (fellow eye)
- Total Lesion Area Within ETDRS Grid (study eye)
- Total Lesion Area Within ETDRS Grid (fellow eye)

Descriptive statistics will be provided for each continuous variable; whereas, frequencies and percentages will be provided for categorical variables. Calculation for length of prior anti-VEGF treatment is described below:

- Length of Prior Anti-VEGF Treatment (years) = (End date of prior anti-VEGF treatment - Start date of prior anti-VEGF treatment +1)/365.25

8.3. Medical History

Ocular and Non-Ocular Medical History will be summarized for the Full Analysis Set using Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). The reported medical history terms will be coded using MedDRA Version 23.0 or higher. A subject experiencing a medical history within more than one SOC and PT will be counted only once within that SOC and PT, respectively. Medical History will be sorted by the highest occurrence in the GEM103+SoC treatment group in decreasing order.

Medical history findings will also be listed by subject for the Full Analysis Set.

8.4. Medication and Procedures

All prior and concomitant medications and procedures will be classified using the Anatomical Therapeutic Chemical (ATC) classification codes and preferred drug names from the World Health Organization Drug Dictionary (WHO-DD), September 2020 or later.

Summaries of prior and concomitant medications and procedures will be presented for the Full Analysis Set separately in tabular form using the forth-level ATC term as an upper classification level and the preferred drug name as a lower classification level. All medications and procedures will be summarized and sorted by descending frequency of ATC level 4 and preferred drug name within a given ATC level 4 term. If the medication or procedure does not have an ATC level 4 term, the ATC level 3 term is used. If the ATC level 3 term is also unavailable, the ATC level 2 term is used. The summary will consist of the frequency and percent of subjects who used the medication or procedure at least once. Medications and procedures will be listed separately.

Prior and concomitant anti-VEGF therapy will be summarized by study eye and fellow eye similiary in addition to overall prior and concomitant medications and procedures.

8.4.1. Prior Medication/Procedure

Any medication or procedure that started prior and did not continue on or after the first dose of study treatment will be classified as prior.

8.4.2. Concomitant Medication/Procedure

Any medication or procedure taken during the study period, including those which started before the first dose study treatment, but were reported ongoing at the first administration, will be classified as concomitant.

9. Efficacy

All efficacy parameters will be summarized and presented in tables based on the Full Analysis Set (FAS). Subjects will be analyzed as members of the treatment group to which they were randomized to. All CRF data will be listed, where applicable.

Observed values and changes from baseline for each secondary and exploratory endpoint in Section 5 will be summarized with descriptive statistics at each scheduled time point for the study eye. Subjects will be presented by treatment group. Study eye will be identified during the screening process. If both eyes meet all eye-specific entry criteria, then the study eye will be determined by the Investigator and the subject together.

For continuous data, a two-sided paired t-test will be used to test if the mean change from baseline at a scheduled timepoint is significantly different from zero at a 5% significance level. The 95% confidence interval (CI) for the mean change from baseline, the standard error of the mean, and the t-test p value will be presented. In addition, a two-sample t-test will be used to test if the mean change from baseline is significantly different from zero at a 5% significance level between GEM+SoC and Sham+SoC for best-corrected visual acuity (BCVA), low luminance visual acuity (LLVA), and Macular Atrophy (MA) size.

A figure will be provided for BCVA Score, LLVA Score, and MA size displaying the mean change from baseline and standard error for each treatment group by study eye and fellow eye plotted over time.

9.1. Best Corrected Visual Acuity (BCVA)

Best-corrected visual acuity (BCVA) assessment is done prior to dosing, as applicable. The mean change from baseline in BCVA score will be summarized, along with observed values, at each scheduled timepoint using the Early Treatment Diabetic Retinopathy Study (ETDRS) method for each treatment group, as specified in Section 7.1 for continuous data. Baseline will be taken as the last available non-missing assessment prior to first study drug administration.

The proportion of subjects with an increase from baseline of 15, 10, and 5 letters or more in BCVA using the ETDRS method will be summarized using descriptive statistics. Subjects will be considered to be fulfilling this criterion if they show a change from baseline value in BCVA of greater than or equal to 15, 10, or 5 letters, respectively. The number and proportion of subjects will be calculated for each time point. The denominator of the proportion will be the number of subjects who have a non-missing value for BCVA assessment at the specified visit.

9.2. Low Luminance Visual Acuity (LLVA)

Low luminance visual acuity (LLVA) assessment is done prior to dosing, as applicable. The mean change from baseline in LLVA score will be summarized, along with observed values, at each scheduled timepoint using the Early Treatment Diabetic Retinopathy Study (ETDRS) method for each treatment group, as specified in Section 7.1 for continuous data. Baseline will be taken as the last available non-missing assessment prior to first study drug administration.

The analysis of the proportion of subject with an increase from baseline of 15, 10, and 5 letters or more in BCVA specified in Section 9.1 will be conducted for LLVA.

9.3. Macular Atrophy (MA) Size

Mean change from baseline in size of Macular Atrophy as evaluated by fundus autofluorescence (FAF) will be summarized as a continuous variable for each treatment group for the study eye and fellow eye.

Results for macular atrophy area size will be obtained from the data vendor Eyekor by FAF/NIR Grading Form question "Area and proximity of Hypo FAF" as specified in the Imaging & Grading Charter Revision 1.0, 20-Jan-2021. Area size results will be used to calculate mean change from baseline; the range is from 0-42.00 and the units are mm^2. Results of 0 mm^2 will be included in the calculation of change from baseline. Results of "Cannot Grade", "Not Applicable", or missing will not be used.

If area size is missing but result for question "Macular atrophy presence at center point" is "Absent", area size result of 0 mm^2 will be imputed for that timepoint.

9.4. New Macular Atrophy (MA)

Incidence of new Macular Atrophy as evaluated by Fundus Autofluorescence (FAF) will be summarized using descriptive statistics for each treatment group for the study eye and fellow eye.

Two summaries will be performed:

9.4.1. Presence of Macular Atrophy by Visit

Categorical analyses of presence of MA status derived from FAF will be based on the categorical variable "Macular atrophy presence *Presence of hypo FAF and associated hypertransmission on OCT"* included in the Imaging & Grading Charter. Incidence will be summarized by visit including baseline. Categories will be summarized by "Present" and "Not Present". If results are either "Absent" or "Questionable" then MA is not present. If the results are "Definite" then MA is present. Results of "Cannot Grade", "Not Applicable", or missing will not be used for analysis.

9.4.2. Presence of New Macular Atrophy Since Last Visit

Categorical analyses of presence of new MA status derived from FAF will be based on the categorical variable "*Presence of new macular atrophy *New area(s) of hypo FAF since last visit"* included in the Imaging & Grading Charter. Incidence will be summarized by visit. Categories will be summarized by "Present". Category of "Not Present" will not be summarized. If results are either "Absent" or "Questionable" then MA is not present. If the results are "Definite" then MA is present. Results of "Cannot Grade", "Not Applicable", or missing will not be used for analysis. The denominator will be the number of subjects who have "Absent" or "Questionable" for Presence of Macular Atrophy at Baseline.

9.5. Choroidal Neovascularization (CNV)

Mean reduction from baseline in choroidal neovascularization (CNV) size as evaluated by fluorescein angiography (FA) will be summarized using descriptive statistics for each treatment group for the study eye and fellow eye.

Two analyses of CNV size derived from FA will be performed based on results obtained from the Image & Grading Charter under FA Grading Form question "Total CNV area" and "Total lesion area within ETDRS grid". Area size results will be used to calculate mean change from baseline; the range is from 0-42.00 and the units are mm^2. Results of 0 mm^2 will be included in the calculation of change from baseline. Results of "Cannot Grade", "Not Applicable", or missing will not be used for analysis.

9.6. Retinal Layer Thickness

Mean change from baseline in Center Point Thickness (CPT) and Central Subfield Thickness (CST) in millimeters (mm) as evaluated by Spectral Domain Optical Coherence Tomography (SD-OCT) will be summarized as a continuous variable for each treatment group for the study eye and fellow eye.

Results for retinal layer thickness will be obtained from Image & Grading Charter SD-OCT Grading Form field “Retinal thickness grid”, where variable CENTTHC captures Center Point Thickness and variable THSECC captures Center Subfield Thickness. The range for retinal thickness is from 0-2mm. Results of 0 mm will be included in the calculation of change from baseline. Results of “Cannot Grade”, “Not Applicable”, or missing will not be used.

9.7. Subretinal and Intraretinal Fluid

Proportion of patients with intraretinal and subretinal fluid, IRF and SRF respectively, as evaluated by SD-OCT, will be summarized using descriptive statistics for each treatment group for the study eye and fellow eye.

Three separate analyses of incidence of existing fluid will be performed based on the Image & Grading Charter SD-OCT Grading Form fields “IRF” and “SRF”. They include: Intraretinal Fluid (IRF) presence, Subretinal Fluid (SRF) presence, and combined IRF and SRF presence.

9.7.1. IRF

Results of “Definite, outside center subfield only”, “Definite, only non-cystoid, center subfield involved”, and “Definite, cystoid, center subfield involved” will correspond to present existing fluid, and will be summarized separately by the number and percent of subjects reporting each category. Results of “Absent” or “Questionable” will correspond to no present existing fluid. Results of “Cannot Grade”, “Not Applicable”, or missing will not be used for analysis.

9.7.2. SRF

Results of “Definite, outside center subfield only”, and “Definite, center subfield involved”, will correspond to present existing fluid, and will be summarized separately by the number and percent of subjects reporting each category. Results of “Absent” or “Questionable” will correspond to no present existing fluid. Results of “Cannot Grade”, “Not Applicable”, or missing will not be used for analysis.

9.7.3. IRF or SRF Combined

Results of IRF or SRF will be combined using same derivation of existing fluid specified in section 9.7.1 and 9.7.2. Only “Present” and “Not Present” will be summarized.

9.8. National Eye Institute Visual Functioning Questionnaire 25-item Version (NEI-VFQ-25)

Mean change from baseline in NEI-VFQ-25 will be summarized using descriptive statistics for each treatment group.

The NEI-VFQ-25 composite score and sub-scale scores will be evaluated at each visit (baseline, month 6 – day 181, and month 12 /EOS). The calculation for NEI-VFQ-25 sub-scale scores and composite score will be performed according to the “NEI VFQ-25 Scoring Algorithm – August 2000”. The most important instructions are displayed in appendix 16.1.

The scores and their changes from baseline to all post-baseline visits in the NEI VFQ-25 composite score

will be summarized descriptively, including p-value and 95% confidence intervals for the changes.

9.9. Minnesota Low-vision Reading Test (MNRead)

The MNRead acuity cards are continuous-text reading acuity cards suitable for measuring the reading acuity and reading speed of normal and low-vision subjects. Mean change from baseline in MNRead maximum reading speed will be summarized using descriptive statistics for each treatment group for the study eye, fellow eye, and both eyes (OU). Maximum reading speed is obtained from CRF MNRead Reading Assessment Chart 1, 2, and 3.

Formula for reading speed (words per minute) for each sentence is as follows: *reading speed = 60 x (10 - errors) / (time in seconds)*

10. Safety

The population used for safety analyses will be the Full Analysis Set (FAS). Safety will be assessed based on adverse event (AE), clinical laboratory data (hematology and clinical chemistry), physical examinations, vital signs, best-corrected visual acuity (BCVA), biomicroscopy, intraocular pressure (IOP), and ophthalmoscopy. Unless otherwise specified, table summaries will be presented by treatment group (GEM103+SoC and sham+SoC).

All safety information will be provided in subject listings.

10.1. Extent of Exposure

Study drug exposure will be summarized using the treatment duration (days) and number of doses for the Full Analysis Set for GEM103 or Sham and for Aflibercept administration. Treatment duration is the number of days between first and last study drug injection, defined as last injection date – first injection date + 1. Continuous variables will be summarized with descriptive statistics of mean, SD, median, minimum, and maximum.

10.2. Adverse Events

All adverse events will be classified by System Organ Class (SOC) and Preferred Term (PT) using MedDRA version 23.0.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study treatment or any event already present that worsens in either intensity or frequency after exposure to study treatment.

A treatment-related intraocular adverse event (AE) is defined as any adverse event that is study medication-related and an ocular event, either right eye (OD) or left eye (OS).

An overall summary of TEAEs will be tabulated across all treatment groups, including the number and percent of subjects reporting the following categories:

- TEAEs
- Serious TEAEs
- Study Drug-related Only TEAEs (not Study Procedure-related)
- Study Drug-related Only Serious TEAEs (not Study Procedure-related)
- Study Procedure-related TEAEs (not Study Drug-related)
- Study Procedure-related Serious TEAEs (not Study Drug-related)
- Study Drug- and Study Procedure-related TEAEs
- Study Drug- and Study Procedure-related Serious TEAEs
- TEAEs with a Severity of Severe
- TEAEs leading to Permanent Discontinuation of study medication

Each category will be further summarized by Non-Ocular and Ocular relation. For the TEAEs that are categorized as Ocular-realted, a sub-category will include summarization by Study Eye and Fellow Eye.

A summary table of TEAEs (number and percentage of subjects who experienced an AE) grouped by primary SOC and PT will be presented across all treatment groups for the following categories of events:

- All TEAEs

- All Serious TEAEs
- All Study Drug-related TEAEs
- All Study Drug-related Serious TEAEs
- All Study Procedure-related TEAEs
- All Study Procedure-related Serious TEAEs
- All Study Drug and Study Procedure-related TEAEs
- All Study Drug and Study Procedure-related Serious TEAEs
- All TEAEs by maximum severity
- All TEAEs leading to study drug discontinuation
- All TEAEs by Outcome

All summary tables will include separate summarization by Ocular and Non-Ocular-related TEAEs. For the TEAEs that are categorized as Ocular-realted, they will also be summarized by Study Eye and Fellow Eye.

AEs are assessed with respect to relationship status by the investigator, as not related, unlikely related, possibly related, probably related, and definitely related. An AE would be categorized in statistical presentations as “treatment-related” if it is assessed by the investigator as possibly related, probably related, or definitely related.

A subject with more than one occurrence of the same AE in a particular SOC and PT will be counted only once in the total of subjects experiencing AEs in that particular SOC and PT, respectively. If a subject experiences the same AE at more than one severity, or with more than one relationship category, the most severe rating or the stronger causal relationship will be reported.

Any missing severity or relationship of an AE should be replaced by the worst case as follows:

- If severity is missing, then the AE will be included in the “Severe” category
- If relationship is missing, then the AE will be included as “treatment-related”

The tables will be sorted by descending frequency of SOC and then, within a SOC, by descending frequency of PT based on the subject count for the GEM103+SoC column.

All AEs will be listed by subject and chronologically by date and time of AE onset. This listing will include all data collected in the eCRF and the coded variables. Additional listings of SAEs, study-drug related TEAEs, AEs leading to discontinuation of study treatment, and deaths will be provided.

10.3. Laboratory Evaluations

Clinical laboratory tests will be performed at prespecified time points per the Schedule of Assessments in Appendix A of Protocol.

A central study laboratory will be used for all protocol-specified clinical laboratory parameters.

Laboratory results will be displayed using standard units for all summaries and listings. Laboratory results collected in conventional units will be converted to International System of Units (SI) for all summaries and listings.

Shift tables using categories of low, normal, and high, comparing laboratory test results from Baseline to each visit will be presented with percentages based on subjects with a non-missing value at Baseline and post-baseline visit.

All laboratory values (including values, reference ranges, and possible flags (low, high)) will be presented in the subject data listings.

Clinical safety laboratory assessments include the following: hematology (platelet count, red blood cell count, hemoglobin count, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, percent reticulocytes, and white blood cell count with differential) and clinical chemistry (blood urea nitrogen, creatinine, glucose, potassium, sodium, total calcium, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total and direct bilirubin, total protein, standard electrolytes – magnesium, phosphate, and chloride).

10.4. Vital Signs

Vital sign measurements will consist of systolic and diastolic blood pressures (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), and body temperature (°C). Descriptive summaries (number of subjects, mean, standard deviation, median, minimum, and maximum) of actual values and changes from baseline will be presented for each visit and time point for each treatment group. Vital signs will be performed at prespecified time points per the Schedule of Assessments in Appendix A of the Protocol.

Vital signs data will be listed chronologically by subject and visit for each vital sign parameter.

10.5. ECG

A 12-lead electrocardiogram (ECG) will be taken at screening, after lying supine for 5 minutes, as part of the cardiac examination. The results will be recorded as normal, abnormal not clinically significant, and abnormal clinically significant on the eCRF.

10.6. Physical Examination

A complete physical examination will include examination of the following parameters and body systems: general appearance, skin, HEENT (head, eyes, ears, nose, throat), heart, lungs, abdomen, extremities/joints, and neurological status. Abnormal findings will be recorded in the eCRF and referred for appropriate investigation by a primary care physician or other healthcare provider at the determination of the Investigator. A physical examination summary of abnormal clinically significant findings by assessment visit and body system will be provided.

A by-subject listing will be provided, including body system and result by treatment group.

10.7. Slit Lamp Examination

Ocular Biomicroscopic Examination will be performed with findings reported for Lids/Lashes, Conjunctiva, Cornea, Anterior Chamber, and Iris/Pupil. In addition, Ophthalmoscopy Examation will be performed with findings reported for Vitreous, Optic Nerve, Macula, and Retina Periphery. The findings will be listed by subject.

Lens Status and Opacification will be summarized by the number and proportion of subjects with each status and opacification (Phakic, Pseudophakic, Aphakic). Nuclear Cataract, Cortical Cataract, and Posterior Subcapsular Cataract categories will be further summarized by severity grade. The findings will be listed by subject.

The following Biomicroscopic (BMC) and Ophthalmoscopy (OPH) structures will be summarized by the number and proportion of subjects with each finding:

- BMC – Lids/Lashes
- BMC – Conjuctiva
- BMC – Iris/Pupil
- OPH – Optic Nerve
- OPH – Retina Periphery
- OPH – Macula

The following Biomicroscopic (BMC) and Ophthalmoscopy (OPH) structures will be summarized by the number and proportion of subjects with each finding and severity grade:

- BMC – Anterior Chamber
- BMC – Cornea
- OPH – Vitreous

10.8. Intraocular Pressure (IOP)

The number and proportion of subjects with an increase in intraocular pressure (IOP) of 10 mm Hg or more from each pre-dose assessment will be calculated for each time point for the study eye.

IOP will also be summarized by study visit and change from each pre-dose assessment using descriptive statistics for continious variables.

The findings will be listed by subject.

10.9. Best-corrected Visual Acuity (BCVA)

The proportion of subjects with a loss from baseline of 15, 10, and 5 letters or more in BCVA using the ETDRS method will be summarized using descriptive statistics. Subjects will be considered to be fulfilling this criterion if they show a change from baseline value in BCVA of less than or equal to 15, 10, or 5 letters, respectively. The number and proportion of subjects will be calculated for each time point. The denominator of the proportion will be the number of subjects who have a non-missing value for BCVA assessment at the specified visit.

10.10. Low Luminance Visual Acuity (LLVA)

The proportion of subjects with a loss from baseline of 15, 10, and 5 letters or more in LLVA using the ETDRS method will be summarized using descriptive statistics. Subjects will be considered to be fulfilling this criterion if they show a change from baseline value in BCVA of less than or equal to 15, 10, or 5 letters, respectively. The number and proportion of subjects will be calculated for each time point. The denominator of the proportion will be the number of subjects who have a non-missing value for LLVA assessment at the specified visit.

11. Other Variables

The population used for analyses of variables specified in section 11 will be the Biomarker Set (BS). Unless otherwise specified, table summaries will be presented by treatment group (GEM103+SoC and sham+SoC).

11.1. Plasma and Aqueous Humor Concentrations of Total Complement Factor H (CFH)

Observed continuous total complement factor H (CFH) concentration level in aqueous humor (ng/mL) and plasma data will be summarized by type of biological matrix by treatment group using descriptive statistics. Changes from baseline will also be presented for all continuous parameters by treatment group over time. A two-sided paired t-test and 95% confidence interval (CI) will be summarized for the mean change from baseline as specified in Section 9.

All total CFH values will be presented in the subject data listings.

A figure will be provided for CFH displaying the mean change from baseline and standard error for each treatment group plotted over time.

11.2. Generation of Serum GEM103 Antidrug Antibodies (ADA)

Shift tables using categories of negative, positive, and total, comparing ADA test results from Baseline to each visit will be presented with percentages based on subjects with a non-missing value at Baseline and post-baseline visit.

All ADA values will be presented in the subject data listings.

11.3. Biomarkers in Aqueous Humor

Observed continuous biomarker level data will be summarized type of biological matrix by treatment group using descriptive statistics. Changes from baseline will also be presented for all continuous parameters by treatment group over time. A two-sided paired t-test and 95% confidence interval (CI) will be summarized for the mean change from baseline as specified in Section 9.

All biomarker values will be presented in the subject data listings.

A figure will be provided for Biomarkers displaying the mean change from baseline and standard error for each treatment group plotted over time.

12. Interim Analyses

An interim analysis will be conducted on a subset of endpoints. Given the study is single-masked, where the subject is masked to their treatment assignment, there will not be unmasking activites by Syneos Health. A complete list of TFLs are to be determined.

13. Changes from Analysis Planned in Protocol

Not Applicable.

14. Reference List

Protocol: A Multicenter, Multiple-Dose Study in Neovascular Age-Related Macular Degeneration (nAMD) to Evaluate the Safety, Tolerability, Pharmacodynamics, Immunogenicity, and Clinical Effect of Repeat Intravitreal (IVT) Injections of GEM103 as an Adjunct to Standard of Care Aflibercept Therapy.

Mangione, CM. NEI VFQ-25 Scoring Algorithm – August 2000, Version 2000, The National Eye Institute 25-Item, Visual Function Questionnaire (VFQ-25)

15. Programming Considerations

All TFLs), and statistical analyses will be generated using SAS for Windows, Release 9.4 (SAS Institute Inc., Cary, NC, USA). Computer-generated TFL output will adhere to the following specifications.

15.1. 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 or portable document format pdf
- Numbering of tables, listings and figures (TLFs) will follow International Conference on Harmonisation (ICH) E3 guidance

15.2. Table, Figure, and Listing Format

15.2.1. General

- All TFLs will be produced in landscape format on A4/American letter 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.
- 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 (eg, µ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) 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.

15.2.2. Headers

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

  Gemini Therapeutics, Inc.

Protocol No: GEM-CL-10311

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

15.2.3. Display Titles

- Each TFL are identified by the designation and a numeral. (ie, 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 body.

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

15.2.4. 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 group columns and total column (if applicable).
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group 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 Active comparators first in the case of active comparator trials, followed by a total column (if applicable)

15.2.5. Body of the Data Display

15.2.5.1. *General Conventions*

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

- Alphanumeric values will be left-justified;
- Whole numbers (eg, counts) will be right-justified; and
- Numbers containing fractional portions will be decimal aligned.

15.2.5.2. *Table Conventions*

- Units will be included where available
- For categorical parameters, all categories will be presented in the table, even if n = 0 for all treatment groups in a given category. 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 will be 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 will be printed out to 1 more significant digit than the original values, and standard deviations will be printed out to 2 more significant digits than the original values. The minimum and maximum will report the same significant digits as the original values. For example, systolic blood pressure will be presented as follows:

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

- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (eg, 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 group 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 will be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group 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 AEs (by PT) will be displayed in decreasing order. If incidence for more than 1 term is

identical, they will then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated will be reported as '-'.

- The percentage of subjects will normally be calculated as a proportion of the number of subjects assessed in the relevant treatment group (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. Details will be described in footnotes or programming notes, as necessary.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, a footnote or programming note will be added describing whether the subject is included in the summary statistics for all relevant categories or just 1 category as well as the selection criteria

- Where a category with a subheading (such as SOC) has to be split over more than 1 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

15.2.5.3. *Listing Conventions*

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

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

- All observed time values will 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.

15.2.5.4. *Figure Conventions*

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

15.2.6. 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 will always begin with 'Note:' if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote will start on a new line, where possible.

- Subject specific footnotes are avoided, where possible.

- Footnotes will be used sparingly and add value to the TFL. 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, the date the program was run, and the listing source (ie, 'Program : myprogram.sas Listing source: 16.x.y.z')

- Sources and/or cross-references in footnotes will use the keyword prefix (in singular form) for each reference and will be separated by a comma when multiple cross-references are displayed.
  Example
  Listing source: Listing 16.2.4.1.1, Listing 16.2.4.1.2, Listing 16.2.4.2.1

16. 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 Developing Statistical Programs SOP (3907) .

Syneos Health Developing Statistical Programs SOP (3907), Conducting the Transfer of Biostatistical Deliverables SOP (3908) and the SAS Programming and Validation Plan 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.

17. Appendices

17.1. Calculation of the NEI VFQ-25 scores

The calculation for NEI VFQ-25 sub-scale scores and composite score will be performed according to the "NEI VFQ-25 Scoring Algorithm – August 2000". The most important instructions are displayed below:

The NEI VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question.

The NEI VFQ-25 generates the following vision-targeted subscales (number of questions):

- global vision rating (1),
- difficulty with near vision activities (3),
- difficulty with distance vision activities (3),
- limitations in social functioning due to vision (2),
- role limitations due to vision (2),
- dependency on others due to vision (3),
- mental health symptoms due to vision (4),
- driving difficulties (3),
- limitations with peripheral (1),
- color vision (1), and
- ocular pain (2).

Additionally, the VFQ-25 contains the single general health rating question which has been shown to be a robust predictor of future health and mortality in population-based studies.

Scoring VFQ-25 is a two-step process:

1. First, original numeric values from the survey are re-coded following the scoring rules outlined in Table 16.1. All items are scored so that a high score represents better functioning. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively. In this format scores represent the achieved percentage of the total possible score, e.g. a score of 50 represents 50% of the highest possible score.

2. In step 2, items within each sub-scale are averaged together to create the 12 sub-scale scores. Table 5 indicates which items contribute to each specific sub-scale. Items that are left blank (missing data) are not taken into account when calculating the scale scores. Sub-scales with at least one item answered can be used to generate a sub-scale score. Hence, scores represent the average for all items in the subscale that the respondent answered.

Table 16.1: Scoring Key: Recoding of Items

Item Numbers	Change original response category [a]	To recoded value of:
1,3	1 2 3 4 5	100 75 50 25 0
4, 15c [b]	0 1 2 3 4	100 75 50 25 0
2	1 2 3 4 5 6	100 80 60 40 20 0
5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 16a	0 1 2 3 4 5	100 75 50 25 0 *
17,18,19,20,21, 22,23,24,25	1 2 3 4 5	0 25 50 75 100

(a) Pre-coded response choices as printed in the questionnaire.
(b) Item 15c has four-response levels, but is expanded to a five-levels using item 15b.
Note: If 15b=1, then 15c should be recoded to "0"
If 15b=2, then 15c should be recoded to missing.
If 15b=3, then 15c should be recoded to missing
* Response choice "6" indicates that the person does not perform the activity because of non-vision related problems. If this choice is selected, the item is coded as "missing."

To calculate an overall composite score for the VFQ-25, simply average the vision targeted subscale scores, excluding the general health rating question. By averaging the sub-scale scores rather than the individual items we have given equal weight to each subscale, whereas averaging the items would give more weight to scales with more items.

Table 16.2: Averaging of Items to Generate VFQ-25 Sub-Scales

Scale	Number of items	Items to be averaged (after recoding per Table 16.1)
General Health	1	1
General Vision	1	2
Ocular Pain	2	4, 19
Near Activities	3	5, 6, 7
Distance Activities	3	8, 9, 14
Vision Specific: Social Functioning Mental Health Role Difficulties Dependency	 2 4 2 3	 11, 13 3, 21, 22, 25 17, 18 20, 23, 24
Driving	3	15c, 16, 16a
Color Vision	1	12
Peripheral Vision	1	10

Scoring Example:
Items 5, 6, and 7 are used to generate the near activities sub-scale score (Table 16.2). Each of the items has 6 response choices.

- Response choice 6 indicates that the respondent does not perform the activity because of reasons that are unrelated to vision. If a respondent selects this choice, the answer is treated as missing and an average of the remaining items is calculated.
- Response choice 5 indicates that an activity is so difficult that the participant no longer performs the activity. This extremely poor near vision response choice is recoded to "0" points before taking an average of all three items.
- To score all items in the same direction, Table 16.1 shows that responses 1 through 5 for items 5, 6, and 7 should be recoded to values of 100, 75, 50, 25, and 0 respectively.
- If the respondent is missing one of the items, the person's score will be equal to the average of the two non-missing items.

Formula:
Mean = (Score for each item with a non-missing answer)/Total number of items with non-missing answers
Example: With responses converted: = (25 + 100 + 25) / 3= 50

Note: 100 = Best, 0 = Worst possible score.