NCT02595528

**Study ID**: 199201-009

**Title:** A Phase 2, Multicenter, Double-masked, Randomized, Vehicle-Controlled, Study of the Concurrent Use of AGN-190584 and AGN-199201 in Patients With Presbyopia

**Statistical Analysis Plan Amendment 2 Date**: 09Nov2017

# 1. Title Page

**STATISTICAL ANALYSIS PLAN**

**A Phase 2, Multicenter, Double-masked, Randomized, Vehicle-Controlled, Study of the Concurrent Use of AGN-190584 and AGN-199201 in Patients with Presbyopia**

**Amendment 2.0: 2017-11-09**

| | |
|---|---|
| Study Number: | 199201-009 |
| Development Phase: | 2b |
| Product Name: | AGN-199201 (oxymetazoline hydrochloride ophthalmic solution) and AGN-190584 (pilocarpine hydrochloride ophthalmic solution) |
| Study Statistician: | [redacted] |
| Sponsor: | Allergan (North America)<br>2525 Dupont Drive, Irvine, California USA 92612<br>[redacted] |

## 2. Table of Contents

## 2.1 List of Tables

## 2.2 List of Figures

# 3. List of Abbreviations and Definition of Terms

**Table 3-1 Abbreviations and Definitions of Terms**

| Abbreviation/Term | Definition |
|---|---|
| AE | adverse event |
| AGN | Allergan |
| ANCOVA | analysis of covariance |
| ANOVA | analysis of variance |
| ATC | Anatomical Therapeutic Chemical |
| CFB | change from baseline |
| eCRF | electronic case report form |
| EO | exploratory objective |
| GCP | Good Clinical Practice |
| ICH | International Conference on Harmonisation |
| LOCF | last observation carried forward |
| LS | least squares |
| MedDRA | Medication Dictionary for Regulatory Activities |
| mITT | modified intent-to-treat |
| MMRM | mixed-effects model for repeated measures |
| NEI | national eye institute (NEI) visual function questionnaire - 25 (VFQ-25) |
| OC | observed cases |
| PCS | potentially clinically significant |
| PO | primary objective |
| PP | per-protocol |
| PRO | patient reported outcome |
| PT | preferred term |
| SAE | serious adverse event |
| SADE | serious adverse device effect |
| SAP | statistical analysis plan |
| SID | subject identification |
| SO | secondary objective |
| SOC | system organ class |
| TEAE | treatment-emergent adverse event |
| UDVA | uncorrected distance vision acuity |
| UNVA | uncorrected near vision acuity |
| VAS | visual analog scale |
| VFQ-25 | visual function questionnaire - 25 |
| WHO | World Health Organization |

# 4. Introduction

This statistical analysis plan (SAP) details comprehensive, technical specifications of the statistical analyses of the efficacy and safety data outlined and/or specified in the final protocol of Study 199201-009 (version dated 2015-09-15) and the most recent amendment (version 4 dated 2016-04-04). Specifications of tables, figures, and data listings are contained in a separate document.

This document is organized into 3 main sections:

1. Study overview
2. Statistical Methodology and Study Endpoints
3. Data Handling and Analysis Conventions

## 4.1 Study Design Summary

This study is a phase 2b, multicenter, double-masked, parallel-group, randomized sequence, dose response, vehicle-controlled study in patients with presbyopia. Sixteen unfixed combination of AGN-190584 [redacted] and AGN-199201 ([redacted] and a fixed combination of AGN-190584 [redacted] and AGN-199201 [redacted] solutions will be dosed in the nondominant eye during 5 dosing periods. For 17 different treatment combinations, each dosing period will be once daily for 2 consecutive days, followed by a 7 to 21 day washout before the next 2-day dosing period, until exit after the fifth 2-day dosing period. The study duration will be 39 to 112 days per patient.

Following a screening visit (days -18 to -1) patients will be randomized at a baseline visit (visit 1) in a 1:1:1:1 ratio (stratified by uncorrected near vision acuity at baseline of ≤ 20/80 and > 20/80) to 1 of the following treatment groups:

- Group 1: AGN-199201 [redacted] and AGN-190584 vehicle 0%
- Group 2: AGN-199201 [redacted] and AGN-190584 ophthalmic solution [redacted]
- Group 3: AGN-199201 [redacted] and AGN-190584 ophthalmic solution [redacted]
- Group 4: AGN-199201 [redacted] and AGN-190584 ophthalmic solution [redacted]

All patients will receive the fixed combination of AGN-199201 and AGN-190584 ophthalmic solutions within one of the 5 dosing periods. Vehicle for AGN-190584, vehicle for AGN-199201, and the vehicle for fixed combination ophthalmic solution have the same formulation.

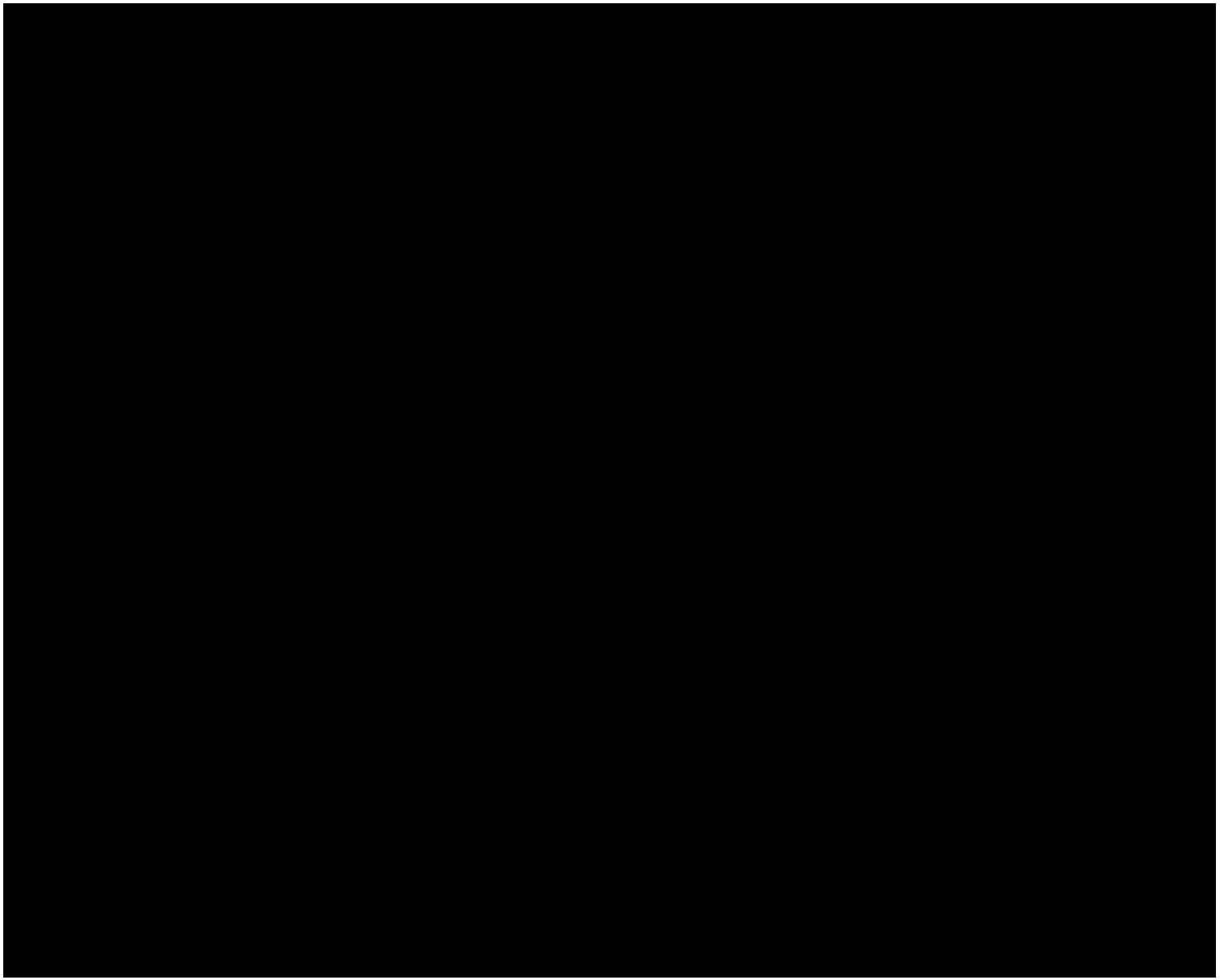
## 4.2 Study Objectives and Endpoints

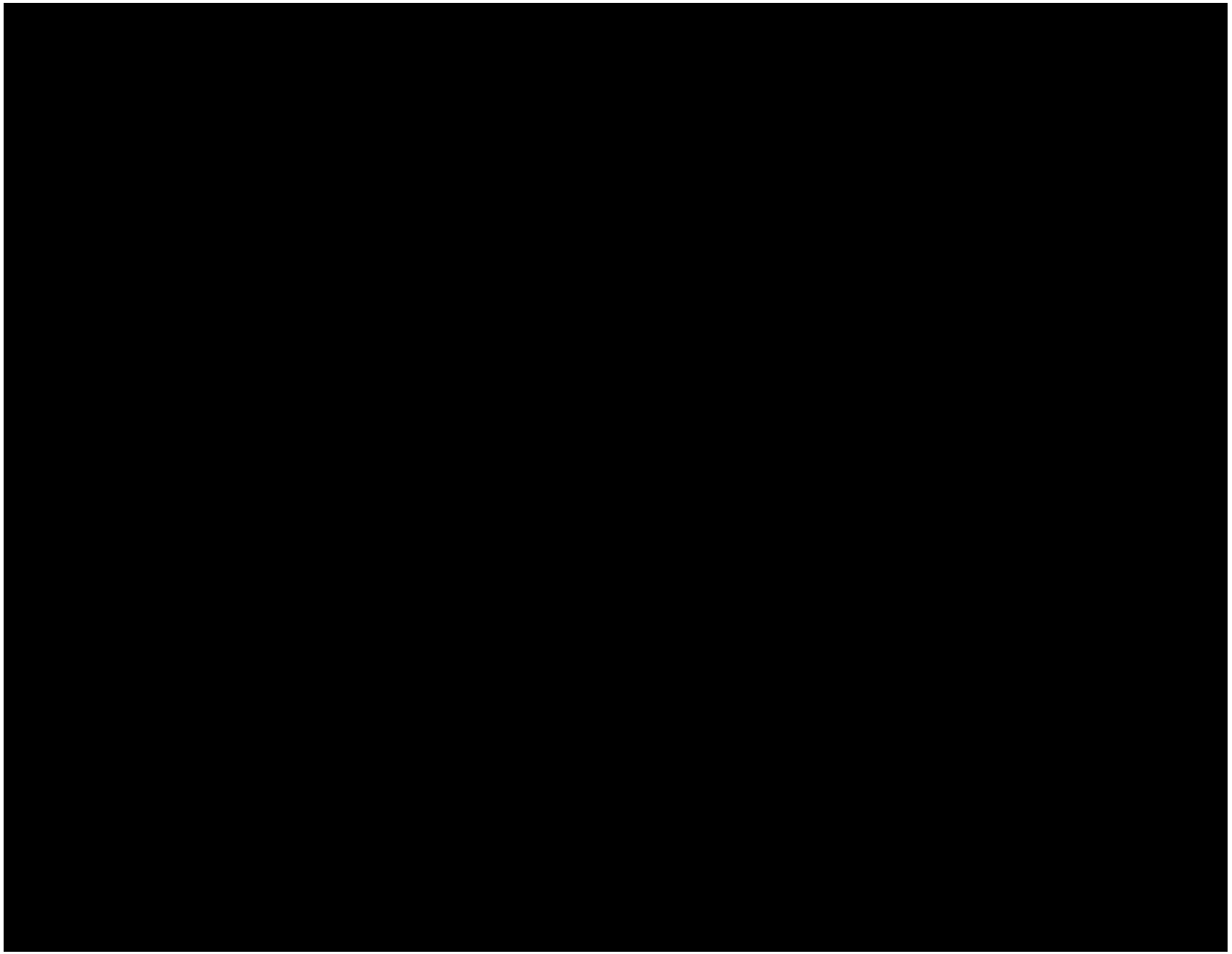
Each study primary objective (PO), secondary objective (SO), and exploratory objective (EO) is presented with corresponding endpoint(s) below:

**Table 4-1 Study Objectives and Corresponding Endpoints**

| Objectives | Endpoints |
|---|---|
| Primary | |
| PO1 To identify the optimum concentrations of AGN-199201 , and AGN-190584 when dosed in combination once a day for the improvement of uncorrected near vision acuity (UNVA) in patients with presbyopia | The primary efficacy variable is the weighted average change from baseline in UNVA letter in the nondominant eye over 2-day periods between hour 1 and hour 10. Baseline will be the hour 0 measure for each dosing period. |

## 4.3 Schedule of Activities





# 5. Statistical Methodology and Study Endpoints

## 5.1 Statistical Methods Planned in the Protocol and Determination of Sample Size

This statistical analysis plan (SAP) will be approved prior to database lock. The SAP expands the statistical section of the protocol and contains a detailed description of methods to analyze data collected in the study. The text portion of the SAP will be included in the CSR report as Appendix 16.1.9.

### 5.1.1 Statistical and Analytical Plans

Statistical analyses will be conducted using [redacted]

#### 5.1.1.1 Common Conventions

##### 5.1.1.1.1 Analysis Populations

The analysis populations will consist of subjects as defined below:

**Table 5-1 Analysis Populations**

| Population | Definition | Study Treatment |
|---|---|---|
| Screened | All screened subjects who sign informed consent | — |
| Modified Intent-to-Treat (mITT) | All randomized subjects with a baseline and at least 1 post baseline assessment of mesopic high contrast UNVA, with baseline vary not more than 3 lines across the 5 dosing period, and will be analyzed as randomized. | Randomized assignment |
| Per Protocol (PP) | All randomized patients who have no significant protocol deviations that affect the primary efficacy variable and complete all study visits for each dosing period. | Actual received |
| Safety | All subjects who received ≥ 1 administration of study treatment | Actual received |

##### 5.1.1.1.2 Study Treatments

The following treatment groups are defined for this study:

- AGN-199201[redacted] AGN-190584[redacted]
- AGN-199201[redacted]+ AGN-190584[redacted]
- AGN-199201[redacted]+ AGN-190584[redacted]
- AGN-199201[redacted] AGN-190584[redacted]
- Fixed Combo + Fixed Combo[redacted]
- AGN-199201 0% + AGN-190584[redacted]
- AGN-199201[redacted]+ AGN-190584[redacted]

- AGN-199201 + AGN-190584
- AGN-199201 + AGN-190584
- AGN-199201 + AGN-190584
- AGN-199201 + AGN-190584
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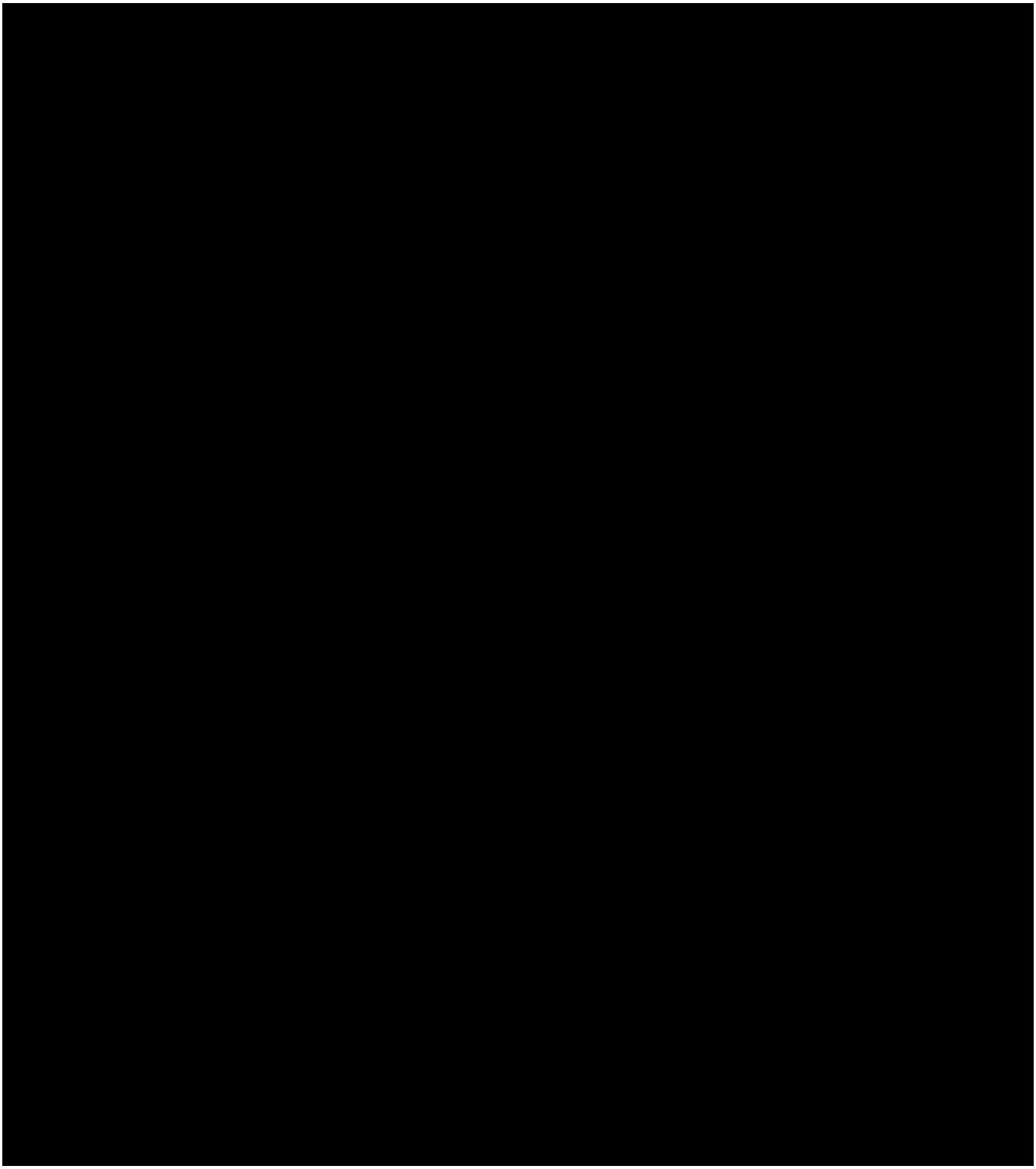
- AGN-199201 + AGN-190584
- AGN-199201 + AGN-190584

The following treatment sequences are defined for this study:



#### 5.1.1.1.3 Statistical Methodology

The methodologies defined below apply as specified to individual endpoints defined in this SAP. When indicated, 95% two-sided confidence intervals and two-sided p-values will be presented.

Individual endpoint analyses may specify exceptions (additions or deletions) to these general definitions.

**Table 5-3 Statistical Methodology**

| Methodology | | Description |
|---|---|---|
| M1 | Categorical counts | • Number of subjects in individual categories<br>  o Subjects with ≥ 1 qualifying event counted once per individual category |
| M2 | Categorical descriptives | • Number and percentage of subjects in individual categories<br>  o Subjects with ≥ 1 qualifying event counted once per individual category<br>• (Optional) N included if percentage denominator ≠ number of subjects in the population (standard percentage denominator). |
| M3 | PCS descriptives | • Number and percentage of subjects meeting potentially clinically significant (PCS) criteria<br>  o Subjects with ≥ 1qualifying event counted once per PCS category<br>• Percentage denominator = number of subjects with non-missing baseline and >=1 non-missing postbaseline assessment<br>• Unevaluable assessments considered missing |
| M4 | Continuous descriptives | • N included, mean, standard deviation (SD), median, minimum, maximum<br>• N included = subjects with non-missing value |
| M5 | CFB descriptives | • Continuous descriptives for baseline, postbaseline, and change from baseline (CFB) values<br>• N included = subjects with non-missing values at both baseline and the specified postbaseline analysis visit |
| M6 | CFB ANCOVA | • Continuous descriptives and standard error (SE) for baseline, postbaseline, and CFB values<br>• Estimates derived from mixed model for CFB value controlling for factors (pilocarpine dose, oxymetazoline dose) and covariates (baseline UNVA severity, iris color)<br>  o Least squares (LS) means and standard errors<br>  o P-values from contrast t-test comparing active AGN-199201 treatment groups vs AGN-199201 vehicle<br>• N included = subjects with non-missing values at both baseline and the postbaseline analysis visit |
| M7 | CFB MMRM | • Continuous descriptives and SE for baseline, postbaseline, and CFB values at each analysis visit<br>  o N included = subjects with non-missing values at both baseline and the postbaseline analysis visit<br>• Estimates derived from mixed model for CFB value controlling for fixed factors (pilocarpine dose, oxymetazoline dose,), covariates (baseline UNVA severity, iris color), and interactions (pilocarpine dose and oxymetazoline dose interaction), with an compound symmetry covariance matrix<br>  o LS means and standard errors<br>  o N included = subjects with non-missing values at both baseline and postbaseline analysis visit |
| M8 | CFB figure | • Plot of CFB LS means and SE bars for each treatment group. |
| M9 | CFB RS figure | • Plot of CFB response surface in 3 dimension. |
| M10 | Responder | • Categorical descriptives for responders and nonresponders<br>  o Nonresponders include:<br>  ▪ Subjects who do not meet responder criteria |

CFB = change from baseline; ANCOVA = analysis of covariance; ANOVA = analysis of variance.
MMRM = mixed model for repeated measures; RS=response surface

Raw and derived data listings will be provided, and will be fully defined in the table, figure, and data listing specification document.

#### 5.1.1.1.4 Missing Data

General missing data handling conventions are specified for methodologies in Section 5.1.1.1.3 and summarized as follows:

**Table 5-4 Missing Data Handling by Endpoint Type**

| Endpoint type | Timing | Missing Data Handling |
|---|---|---|
| Responder | Treatment Period | • All subjects included<br>• Subjects with no postbaseline values will be excluded |
| CFB ANCOVA | Treatment Period | • If missing covariates (including baseline if applicable)<br>  ○ Subject excluded<br>• If missing weighted average change from baseline UNVA letters:<br>  ○ Subject excluded |
| CFB MMRM | Treatment Period | • If missing covariates (including baseline if applicable) or missing values at all postbaseline analysis visits<br>  ○ Subject excluded<br>• If missing weighted average change from baseline UNVA letters:<br>  ○ Subject excluded |
| CFB Posebaseline | Treatment Period | • If missing value at the specified postbaseline analysis visit:<br>  ○ Available cases<br>  ▪ Subject excluded |

#### 5.1.1.1.5 Site Pooling

Data from all sites will be pooled for analysis.

#### 5.1.1.1.6 Other Common Conventions

Ocular adverse events and other ocular evaluations will be summarized using eye as the experimental unit by dosing group and dosing period. Nonocular adverse events and other nonocular assessments will be summarized using patient as the experimental unit by dosing group and dosing period.

### 5.1.1.2 Demographics

#### 5.1.1.2.1 Analysis Populations

The distribution of subjects within the analysis populations will be summarized as follows:

**Table 5-5 Analysis Population Summaries**

| Endpoint | Description | Timing | Methodology |
|---|---|---|---|
| Screened Population | Distribution overall and within countries/regions/sites in total | Screening Period, | Categorical counts |

| | | | |
|---|---|---|---|
| mITT, PP and Safety populations | Distribution overall and within countries/regions/sites in total and by treatment group | Treatment Period | Categorical counts |

#### 5.1.1.2.2 Subject Disposition

Subject disposition encompasses the distribution of subjects who enter, complete, and discontinue each specified analysis period, along with eCRF-reported discontinuation reasons from each respective analysis period. Subject disposition will be summarized as follows:

**Table 5-6 Subject Disposition Summaries**

| Endpoint | Description | Timing | Methodology |
|---|---|---|---|
| Screening and pretreatment disposition | Distribution in the Screened Population in total | Screening Period, Pretreament Period | Categorical descriptives |
| Study disposition | Distribution in the mITT Population in total and by treatment group | Treatment Period | Categorical descriptives |

#### 5.1.1.2.3 Protocol Deviations

Protocol deviations will be defined in a separate document, including importance classification. Protocol deviations will be summarized as follows:

**Table 5-7 Protocol Deviation Summary**

| Endpoint | Description | Timing | Methodology |
|---|---|---|---|
| Important protocol deviations | Distribution in the mITT Population in total and by treatment group | Treatment Period | Categorical descriptives |

#### 5.1.1.2.4 Demographics

Demographics will be summarized for the Screened Population, and in total and by treatment group for the mITT, PP and Safety populations, as follows:

**Table 5-8 Demographic Summaries**

| Endpoint | Description | Timing | Methodology |
|---|---|---|---|
| Age | Age (years) relative to informed consent date | Informed consent | Continuous descriptives |
| Age group | • 40-47 years<br>• 48-51 years | Informed consent | Categorical descriptives |
| Sex, race, and ethnicity | • eCRF categories<br>• Race group<br>  ○ White<br>  ○ Non-white<br>• Ethnicity<br>  ○ Hispanic<br>  ○ Non-hispanic | Screening Period | Categorical descriptives |

### 5.1.1.2.5 Baseline Characteristics

Baseline characteristics will be summarized in total and by treatment group for the mITT, PP and Safety populations as follows:

**Table 5-9 Baseline Characteristics Summaries**

| Endpoint | Description | Timing | Methodology |
|---|---|---|---|
| Baseline characteristics | • Iris color | Latest assessment in Screening Period or Pretreament Period | Categorical descriptives |
| Randomization strata | • UNVA at baseline of ≤ 20/80<br>• UNVA at baseline of > 20/80 | Randomization date | Categorical descriptives |

### 5.1.1.2.6 Medical History

Medical history, encompassing abnormalities and surgeries reported as occurring before the Screening Visit, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.0 or newer. Unique subjects who report medical history events will be summarized by MedDRA system organ class (SOC) and preferred term (PT) in total and by treatment group for the Safety Population as follows:

**Table 5-10 Medical History Summary**

| Endpoint | Description | Timing | Methodology |
|---|---|---|---|
| Medical history | Abnormalities and surgeries occurring before the Screening Visit | Screening Period | Categorical descriptives |

SOCs will be sorted alphabetically; PTs will be sorted in descending frequency in the highest dose group.

### 5.1.1.2.7 Prior and Concomitant Medications

Medications will be listed for the Safety Population as follows:

Medications will be coded using the World Health Organization (WHO) Drug Dictionary, version 14.0 or newer. Unique subjects who reported medications will be summarized by Anatomical Therapeutic Chemical (ATC) 4 class and PT in total and by treatment group for the Safety Population as follows:

**Table 5-11 Medication Summaries**

| Endpoint | Description | Timing | Methodology |
|---|---|---|---|
| Prior medications | Medications taken ≥ 1 time before the study treatment start date, regardless of medication end date | Screening Period, Pretreament Period | Categorical descriptives |
| Concomitant medications | Medications taken ≥ 1 time on or after the study treatment start date, regardless of medication start date<br>• Medications starting 1 day after | Treatment Period | Categorical descriptives |

| Endpoint | Description | Timing | Methodology |
|---|---|---|---|
| | treatment end date will be listed but excluded from analysis | | |

ATC4 classes will be sorted alphabetically; PTs will be sorted in descending frequency in the highest dose group.

#### 5.1.1.2.8 National Eye Institute Visual Function Questionnaire

National eye institute (NEI) visual function questionnaire - 25 (VFQ-25) that will be administered at screening to determine patient-reported near and distance vision functioning. NEI VFQ-25 will be summarized for the Safety Population.

**Table 5-12 NEI VFG-25 Summary**

| Endpoint | Description | Timing | Methodology |
|---|---|---|---|
| NEI VFQ-25 | NEI VFQ-25 questionnaires | Screening Period | Categorical descriptives |

### 5.1.1.3 Efficacy Analyses

Efficacy analyses will be based on the mITT Population. The primary efficacy variable, weighted average change from baseline in UNVA letter, will also be analyzed based on the PP population.

The following efficacy assessments are defined:

[redacted]

[redacted]:

[redacted]

### 5.1.1.3.1 Study Success Criteria

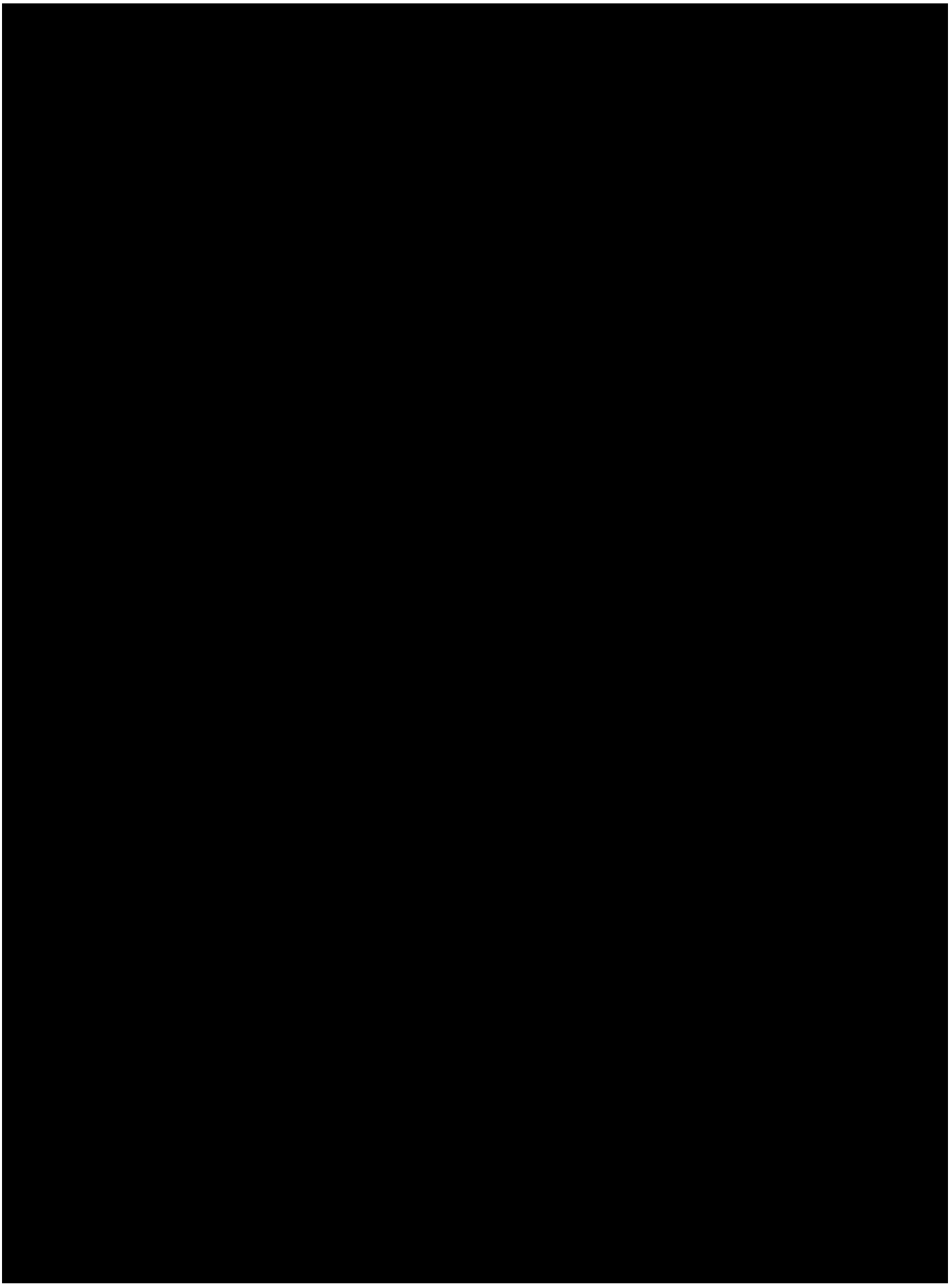
There will be no adjustment of type 1 error rate for the multiple tests.

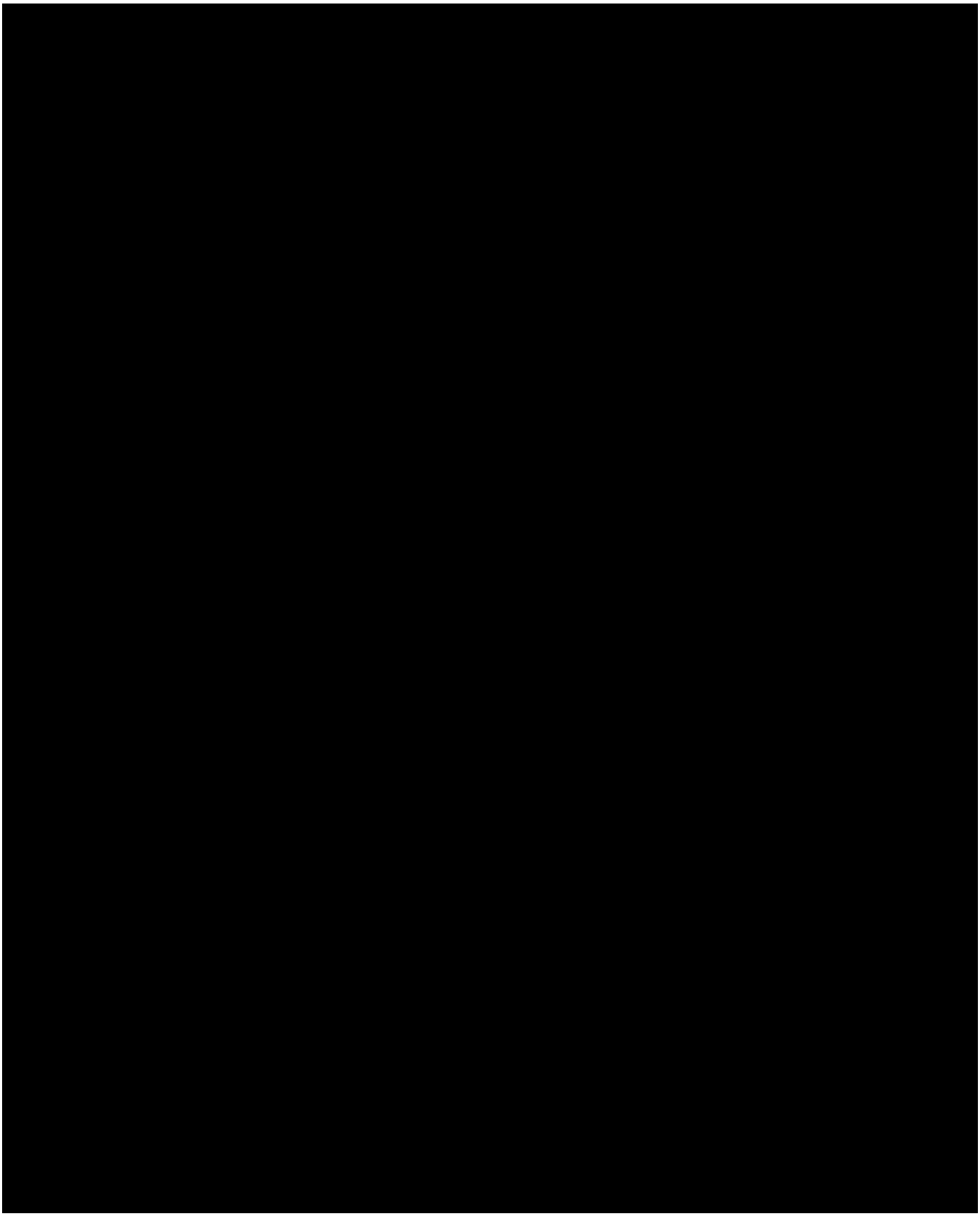
### 5.1.1.3.2 Mesopic, High Contrast UNVA

General description of mesopic, high contrast UNVA endpoints.

**Table 5-15 Mesopic, High Contrast UNVA Analyses**

| Endpoint | Description | Timing | Methodology |
|---|---|---|---|
| Average change from baseline in UNVA letters (Primary efficacy variable) | Average change from baseline in UNVA letters[1] in the nondominant eye over two-day dosing periods between hour 1 and hour 10. | Treatment Period | CFB MMRM[2]<br>CFB ANCOVA[3]<br>CFB RS figure<br>CFB figure |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |





[redacted]

#### 5.1.1.4.2 Adverse Events

The following adverse event (AE) terms are defined:

**Table 5-23 AE Terms**

| Term | Description |
|---|---|
| Treatment-emergent | An event that initially occurs or increases in intensity on or after the treatment start date, where:<br>• Treatment start date ≤ event start date ≤ following washout period before the next 2-day dosing period or last dose date + 30 days |
| On-therapy | An event where:<br>• Treatment start date ≤ event start date ≤ following washout period before the next 2-day dosing period or last dose date + 30 days |

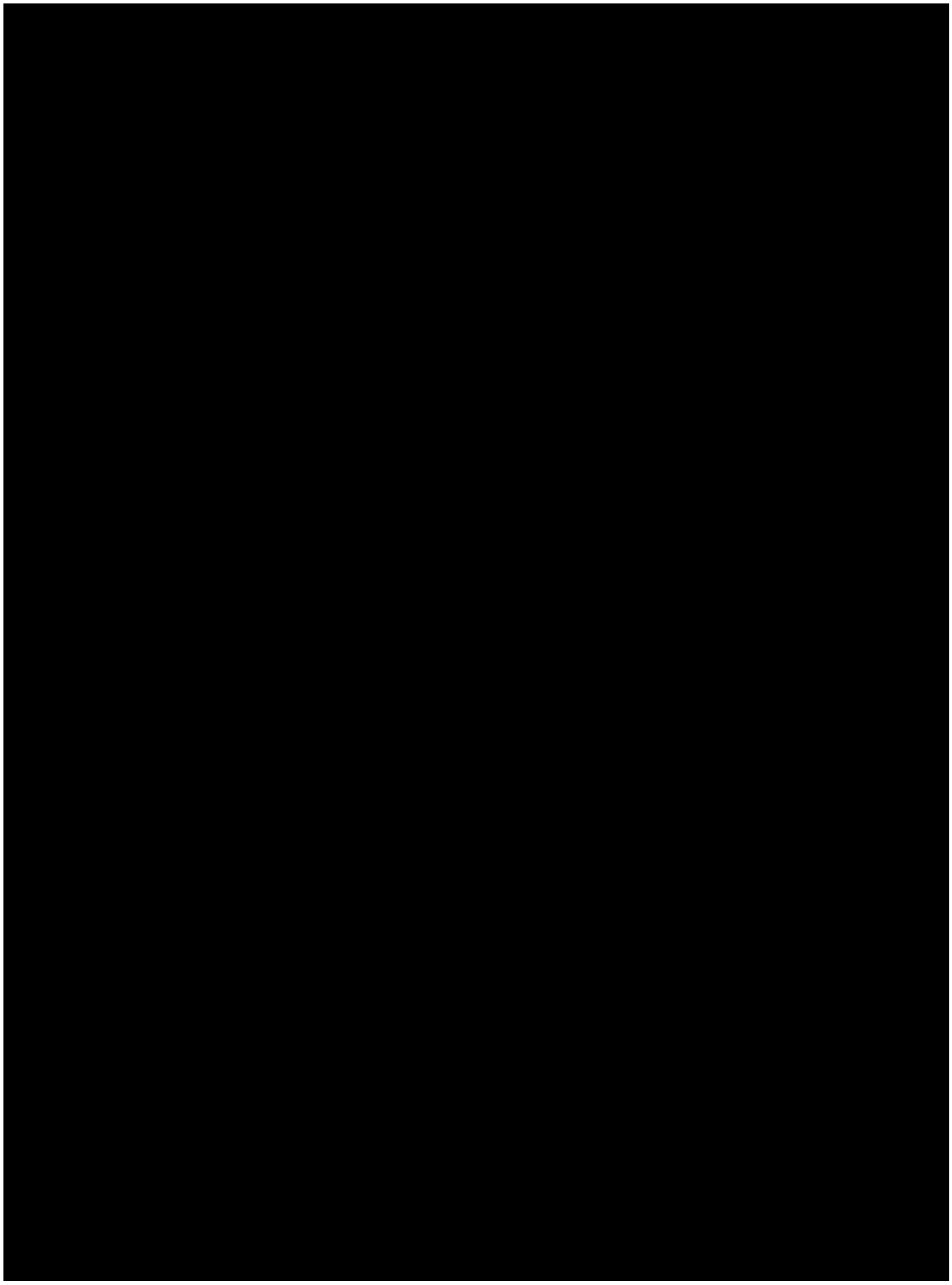
AEs, encompassing abnormalities and surgeries reported as occurring after the Screening Visit, will be coded using MedDRA version 19.0 or newer. Unique subjects reporting AEs in the

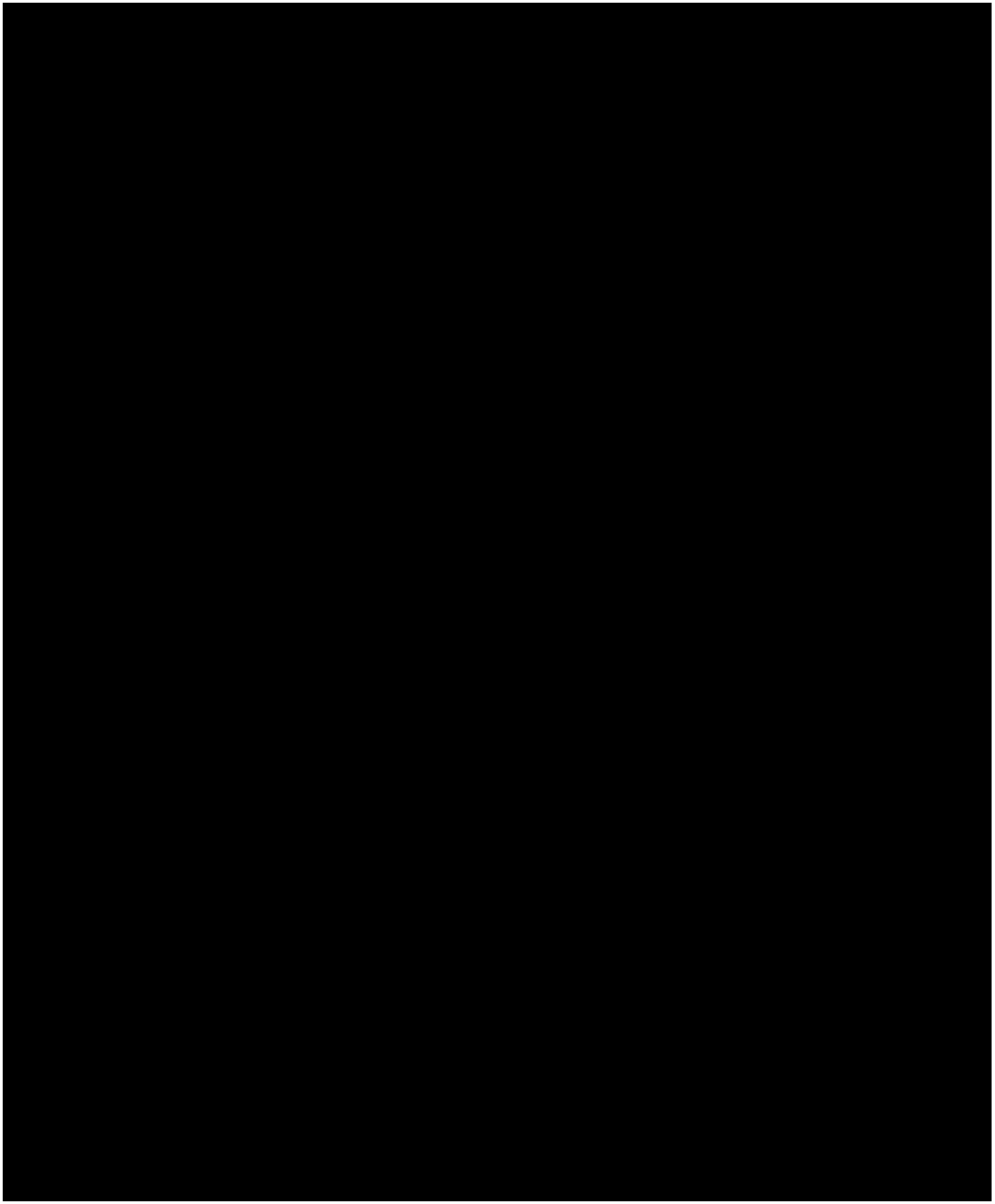
following AE categories will be summarized by treatment group and overall for the Safety Population as follows:

**Table 5-21 AE Summaries**

| Endpoint | Description | Timing | Methodology |
|---|---|---|---|
| Overall summary | Overall summary only for the following categories:<br>• Treatment-emergent AEs (TEAEs)<br>• Treatment-related TEAEs<br>• Study-procedure-related TEAEs<br>• On-therapy serious adverse events (SAEs)<br>• On-therapy fatal SAEs<br>• AEs leading to discontinuation | Treatment Period, Follow-up | Categorical descriptives |
| TEAEs | Overall summary and by SOC and PT | Treatment Period, Follow-up | Categorical descriptives |
| Common TEAEs | Summary by PT<br>• Includes TEAEs occurring in ≥ 5.0% of subjects in any treatment group | Treatment Period, Follow-up | Categorical descriptives |
| TEAEs by intensity | Overall summary and by SOC, PT, and intensity<br>• Subjects categorized overall and within each SOC and PT for the most intense occurrence | Treatment Period, Follow-up | Categorical descriptives |
| Treatment-related TEAEs | Overall summary and by PT | Treatment Period, Follow-up | Categorical descriptives |
| Study-procedure-related TEAEs | Overall summary and by PT | Treatment Period, Follow-up | Categorical descriptives |
| On-therapy SAEs[1] | Overall summary and by PT | Treatment Period, Follow-up | Categorical descriptives |
| On-therapy fatal SAEs[1] | Overall summary and by PT | Treatment Period, Follow-up | Categorical descriptives |
| AEs leading to study discontinuation[1] | Overall summary and by PT | Treatment Period, Follow-up | Categorical descriptives |

[1] Subjects who report ≥ 1 AE in the AE category and all AEs for those subjects will be listed.
SOCs will be sorted alphabetically; PTs will be sorted in descending frequency in the highest dose group.





#### 5.1.1.5 Subgroup Analyses

Subgroup analyses will be performed for the primary efficacy variable by UNVA severity at baseline and iris color (brown or not brown).

#### 5.1.1.6 Interim Analyses

Not applicable.

### 5.1.2 Determination of Sample Size

The study consists of 4 parallel groups and forty patients per each parallel group will be enrolled. With a 1:1:1:1 parallel group allocation and 10% dropout rate, a total of 160 patients are to be enrolled in order to have 144 patients complete the study. The sample size is deemed appropriate to assesses the efficacy profile of the combination relative to monotherapies.

## 5.2 Changes in the Conduct of the Study or Planned Analyses

### 5.2.1 Changes in the Conduct of the Study

Not applicable.

### 5.2.2 Changes to Analyses Prior to Database Lock

The term of 'average change from baseline in UNVA letters' instead of 'weighted average change from baseline in UNVA letters' will be used since weighted average concept only applies when missing mid-timepoint values are imputed. UNVA responder analyses with at least a 2-line improvement in mesopic, high contrast UNVA from baseline at a majority of postdose timepoints (6 or more) in the nondominant eye will be added.

Subgroup analyses by gender, race and ethnicity will be performed .

mITT definition will be change to 'All randomized subjects with a baseline and at least 1 post baseline assessment of mesopic high contrast UNVA, with baseline vary not more than 3 lines across the 5 dosing period, and will be analyzed as randomized.'

# 6. Data Handling and Analysis Conventions

## 6.1 Study Treatment Conventions

### 6.1.1 Analysis Days

Treatments are defined as follows:

**Table 6-1 Analysis Day Definitions**

| Term | Description |
|---|---|
| Treatment Day | Relative to treatment start date<br>If analysis date ≥ treatment start date:<br>• Day = analysis date – treatment start date + 1<br>  o Day 1 = treatment start date |

### 6.1.2 Missing/Incomplete Treatment End Date

If the investigator is unable to provide the treatment end date, treatment end date will be imputed to the last available dosing record date/last available efficacy assessment date.

[redacted]

## 6.3 Site Pooling

Data from all sites will be pooled for analysis.

## 6.4 Missing/Incomplete Date Conventions

Dates may be imputed with year, month, and day values under certain scenarios:

**Table 6-4 Imputation Scenarios**

| Scenario | Complete | | | Imputable |
|---|---|---|---|---|
| | Year | Month | Day | |
| 1 | Yes | Yes | Yes | Complete |
| 2 | Yes | Yes | — | Yes |
| 3 | Yes | — | Yes | No[1] |
| 4 | Yes | — | — | Yes |
| 5 | — | Yes | Yes | No[1] |
| 6 | — | Yes | — | No[1] |
| 7 | — | — | Yes | No[1] |
| 8 | — | — | — | Yes |

[1] Not allowed per database design.

Dates will be imputed initially toward a specified target date for imputable scenarios 2, 4, and 8, and adjusted against the latest reasonable dates. The initial imputed date is determined by the following algorithm:

**Table 6-5 Initial Imputed Date Algorithm**

| Available Year (YYYY) | Available Month (MM) | | | |
|---|---|---|---|---|
| | Missing | < Target Month | = Target Month | > Target Month |
| **Missing** | Target Date | — | | |
| **< Target Year** | YYYY-12-31 | YYYY-MM-LD | | |
| **= Target Year** | Target Date | YYYY-MM-LD | Target Date | YYYY-MM-01 |
| **> Target Year** | YYYY-01-01 | YYYY-MM-01 | | |

YYYY = available start date year; MM = available start date month; LD = last day of the month.

### 6.4.1 Missing/Incomplete AE Start Date

AE start dates will be imputed as the minimum of the following:

- Initial imputed date, where target date = Treatment start date
- Complete end date

### 6.4.2 Missing/Incomplete Medication Start Date

Medication start dates will be imputed as the minimum of the following:

- Initial imputed date, where target date = Treatment start date – 1
- Complete end date

### 6.4.3 Missing/Incomplete AE/Medication End Date

AE and medication end dates will be imputed as the minimum of the following:

- Initial imputed date, where target date = Treatment end date + 30
- Death date

## 6.5 Efficacy Endpoint Conventions

Not applicable.

## 6.6 Safety Endpoint Conventions

### 6.6.1 Adverse Events

#### 6.6.1.1 Missing Intensity or Relationship

If the investigator is unable to provide the actual values, the following imputations will be applied:

**Table 6-6 Missing AE Intensity and Relationship Imputation Algorithms**

| Missing Value | Imputation | Timing |
|---|---|---|
| Intensity | Mild | Screening Period, Pretreatment Period |
| | Severe | Treatment Period |
| Relationship | — | Screening Period, Pretreatment Period |
| | Related | Treatment Period |

#### 6.6.1.2 Possible Distant Spread of Toxin (PDSOT)

Not applicable.

#### 6.6.1.3 AE Group of Interest

Not applicable.

### 6.6.2 Clinical Laboratory Assessments

Not applicable

## 6.7 Imputed Value Listing Conventions

In general, listings will present the actual partial or missing values rather than the imputed values that may be used in endpoint derivation. In instances where imputed values will be presented, imputed values will be flagged. Actual rules will be fully defined in the table, figure, and data listing specification document.

## 6.8 Analysis Plan Amendment 1 Summary

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

| Section | Revision | Rationale |
|---|---|---|
| Section 5.1.1.1.1 | mITT definition is changed to 'All randomized subjects with a baseline and at least 1 post baseline assessment of mesopic high contrast UNVA, with baseline vary not more than 3 lines across the 5 dosing period, and will be analyzed as randomized.' | Correction for the primary efficacy baseline data issue. |
| Section | Age group | Correction |

| Section | Revision | Rationale |
|---|---|---|
| 5.1.1.2.4 | • 40-47 years<br>• 48-51 years | |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| Section 5.2.2 | UNVA responder analyses with at least a 2-line improvement in mesopic, high contrast UNVA from baseline at a majority of postdose timepoints (6 or more) in the nondominant eye will be added. | Added additional analysis |

## 6.9 Analysis Plan Amendment 2 Summary

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

| Section | Revision | Rationale |
|---|---|---|
| [redacted] | [redacted] | [redacted] |

# ALLERGAN

**199201-009 Statistical Analysis Plan**

| Date (DD/MMM/YYYY)/Time (PT) | Signed by: | Justification |
|---|---|---|
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |