NCT02780115

Study ID: 199201-010

Title: A Phase 2, Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety, Efficacy, and Pharmacokinetics of the Fixed Combination of AGN-199201 and AGN-190584 in Patients With Presbyopia

Statistical Analysis Plan Amendment 2 Date: 15Dec2017

1. Title Page

STATISTICAL ANALYSIS PLAN

A Phase 2, Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety, Efficacy, and Pharmacokinetics of the Fixed Combination of AGN-199201 and AGN-190584 in Patients With Presbyopia

Amendment 2.0: 2017-12-15

Study Number:	199201-010
Development Phase:	2
Product Name:	AGN-199201 (oxymetazoline hydrochloride ophthalmic solution) and AGN-190584 (pilocarpine hydrochloride ophthalmic solution)
Study Statistician:	[redacted]
Sponsor:	Allergan PLC 2525 Dupont Drive, Irvine, California USA 92612 +1-714-246-4500

2. Table of Contents

2.1 List of Tables

[redacted]

[redacted]

[redacted]

2.2 List of Figures

[redacted]

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
CMH	Cochran-Mantel-Haenszel
DCNVA	distance corrected near visual acuity
eCRF	electronic case report form
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IOP	intraocular pressure
IxRS	interactive response system
LOCF	last observation carried forward
LS	least squares
MedDRA	Medication Dictionary for Regulatory Activities
mITT	modified intent-to-treat
N	number of patients
N/A	not applicable
NEI	national eye institute
NVPT	near vision presbyopia task
OC	observed cases
OCT	optical coherence tomography
OU	both eyes
PCS	potentially clinically significant
PICO PRO	presbyopia impact and coping questionnaire patient-reported outcome
PO	primary objective
PP	per-protocol
PPSQ PRO	presbyopia patient satisfaction questionnaire patient-reported outcome
PRO	patient-reported outcome
PT	preferred term
QD	once daily
SAE	serious adverse event
SADE	serious adverse device effect
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
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

Abbreviation/Term	Definition
[redacted]	[redacted]
WHO	World Health Organization

4. Introduction

This statistical analysis plan (SAP) details comprehensive, technical specifications of the statistical analyses of the efficacy, safety data and health outcomes outlined and/or specified in the final protocol of Study 199201-010 (version dated 2015-10-28) and the most recent amendment (version 3 dated 2016-08-18). Specifications of tables, figures, and data listings are contained in a separate document. The SAP for pharmacokinetic/pharmacodynamic and/or health economics and outcomes research data will be prepared separately. 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 multicenter, double-masked, randomized, parallel-group, vehicle-controlled study will be a controlled comparison of fixed combinations of AGN-199201 and AGN-190584 at different concentrations to vehicle dosed in both eyes (OU), and the fixed combination of AGN-199201 [redacted] and AGN-190584 [redacted] dosed in OU or in the nondominant eye only. Study medication will be administered once daily (QD) in the morning. During office visits 1 through 5, study medication will be administered at hour 0 (8 AM ± 1 hour). Following the treatment period, all patients will be seen for a 14 ± 2-day follow-up period as shown in Figure 1. The study duration will be 38 to 65 days per patient.

Table 4-1 Study Treatment Group

Treatment Group	AGN-199201 (%)	AGN-190584 (%)	Dosing
1	Vehicle control	Vehicle control	OU
2	[redacted]	[redacted]	OU
3	[redacted]	[redacted]	OU
4	[redacted]	[redacted]	OU
5[a]	[redacted]	[redacted]	Nondominant eye

OU = both eyes

[a] Dominant eye dosed with vehicle

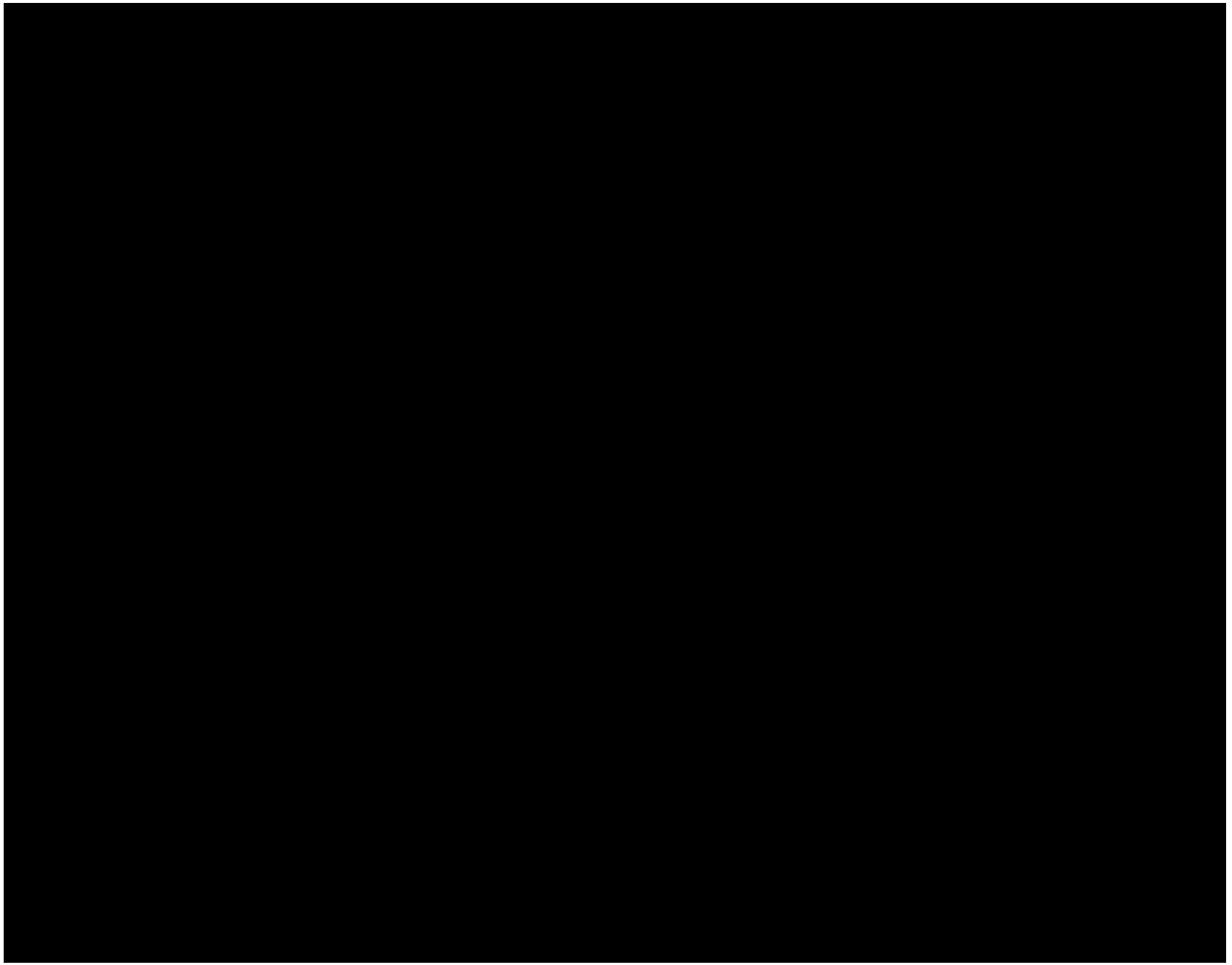
4.2 Study Objectives

Each study primary objective (PO), and secondary objective (SO) are presented below:

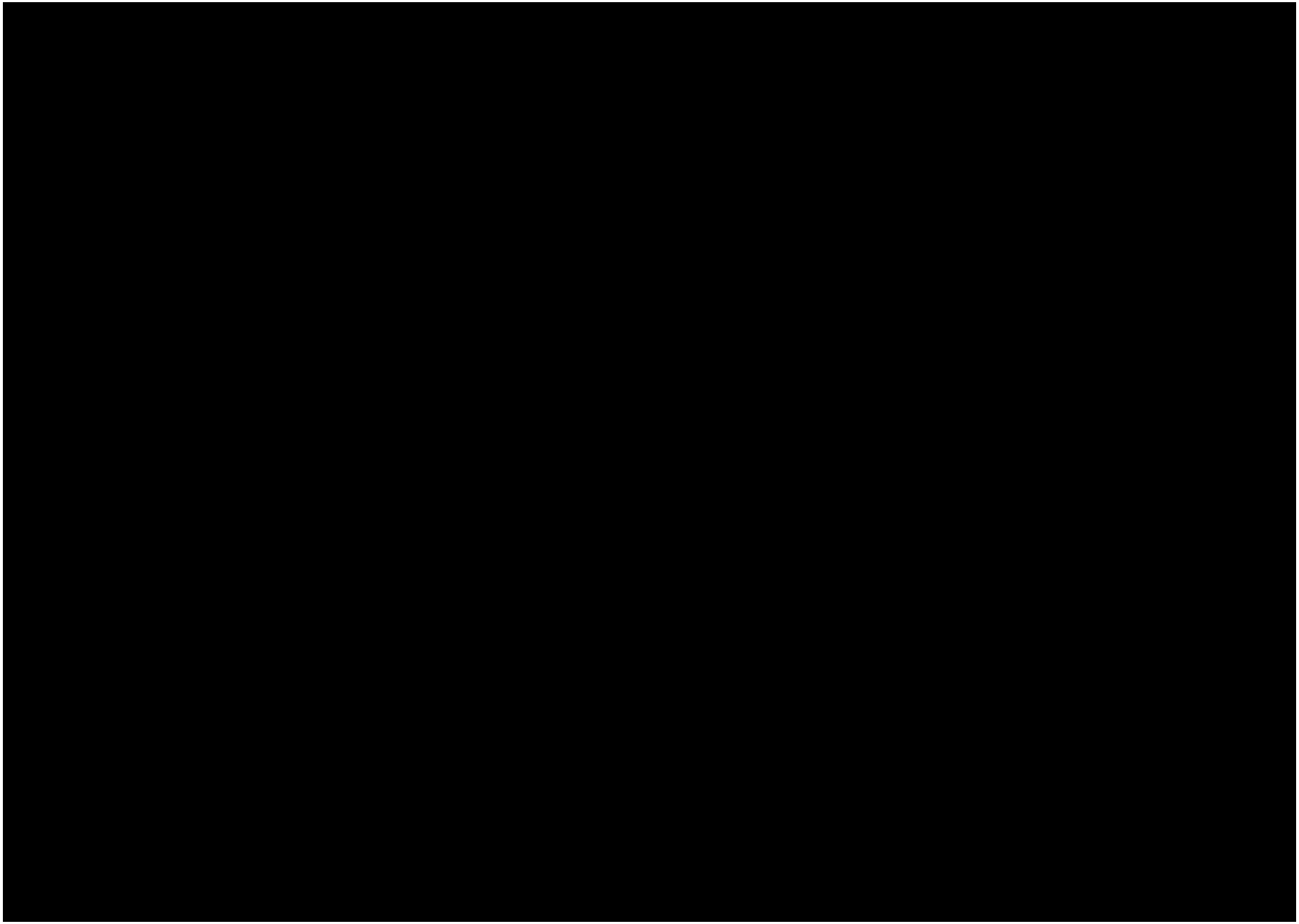
Table 4-2 Study Objectives

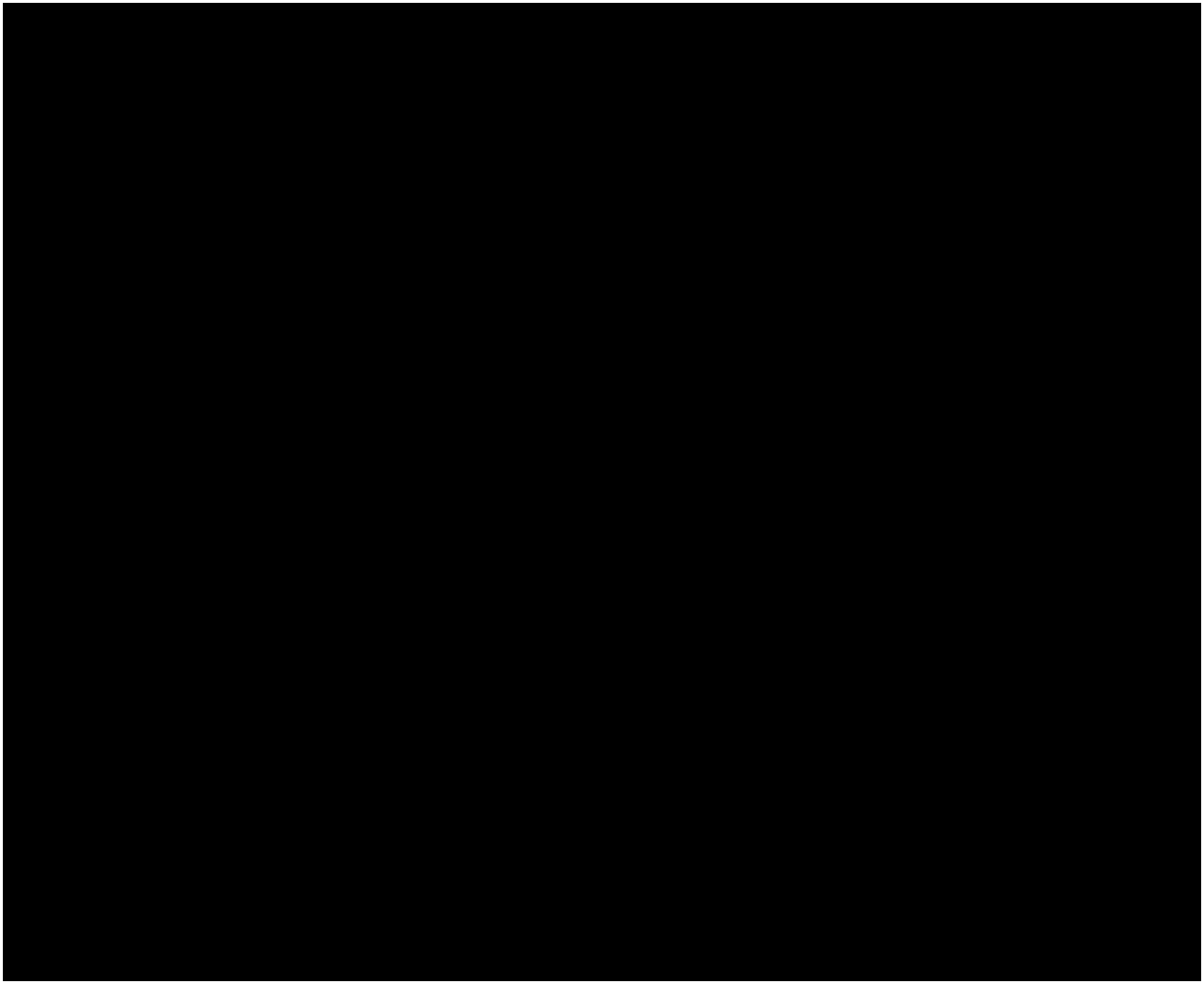
Objectives
PO To evaluate the safety, efficacy, and tolerability of fixed combinations of AGN-199201 and AGN-190584 over a 42-day observation period when administered bilaterally, once daily (QD) for 28 days in patients with presbyopia
SO1 To compare the safety, efficacy, and tolerability of a fixed combination of AGN-199201 [redacted] and AGN-190584 [redacted] when administered monocularly to the nondominant eye versus bilaterally over a 42-day observation period with QD dosing for the first 28 days in patients with presbyopia
SO2 To assess the systemic pharmacokinetics of AGN-199201 [redacted] and AGN-190584 [redacted] following single and multiple (QD for 28 days) ophthalmic administrations as a fixed combination in 1 or both eyes (OU)
SO3 To evaluate the psychometric properties of the de novo patient-reported outcome (PRO) instruments developed for this program, including the near vision presbyopia performance tasks and task-based questionnaire under mesopic and photopic conditions, the presbyopia patient satisfaction questionnaire, and the presbyopia impact and coping questionnaire

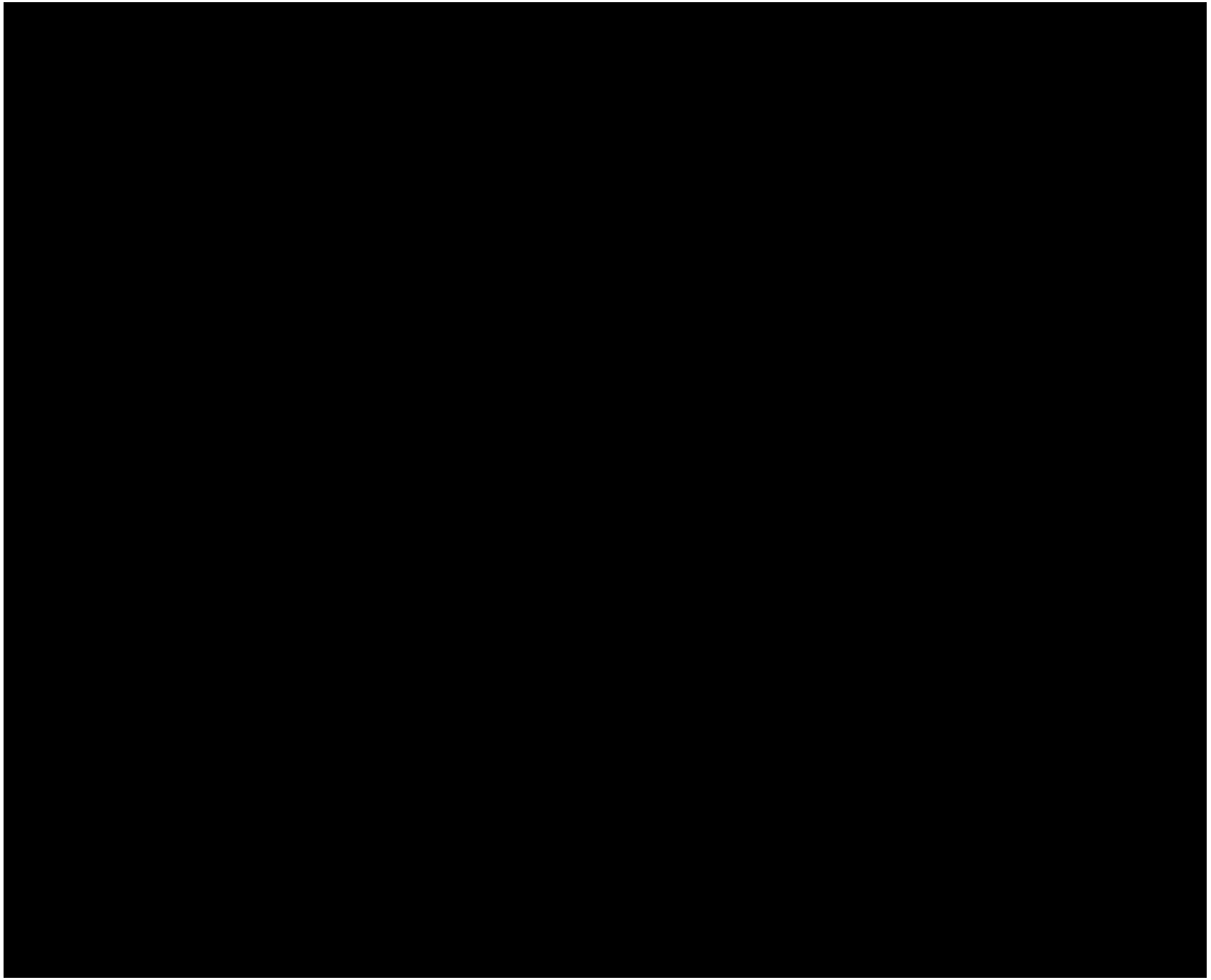
PO = primary objective, SO1 = first secondary objective, SO2 = second secondary objective, SO3 = third secondary objective

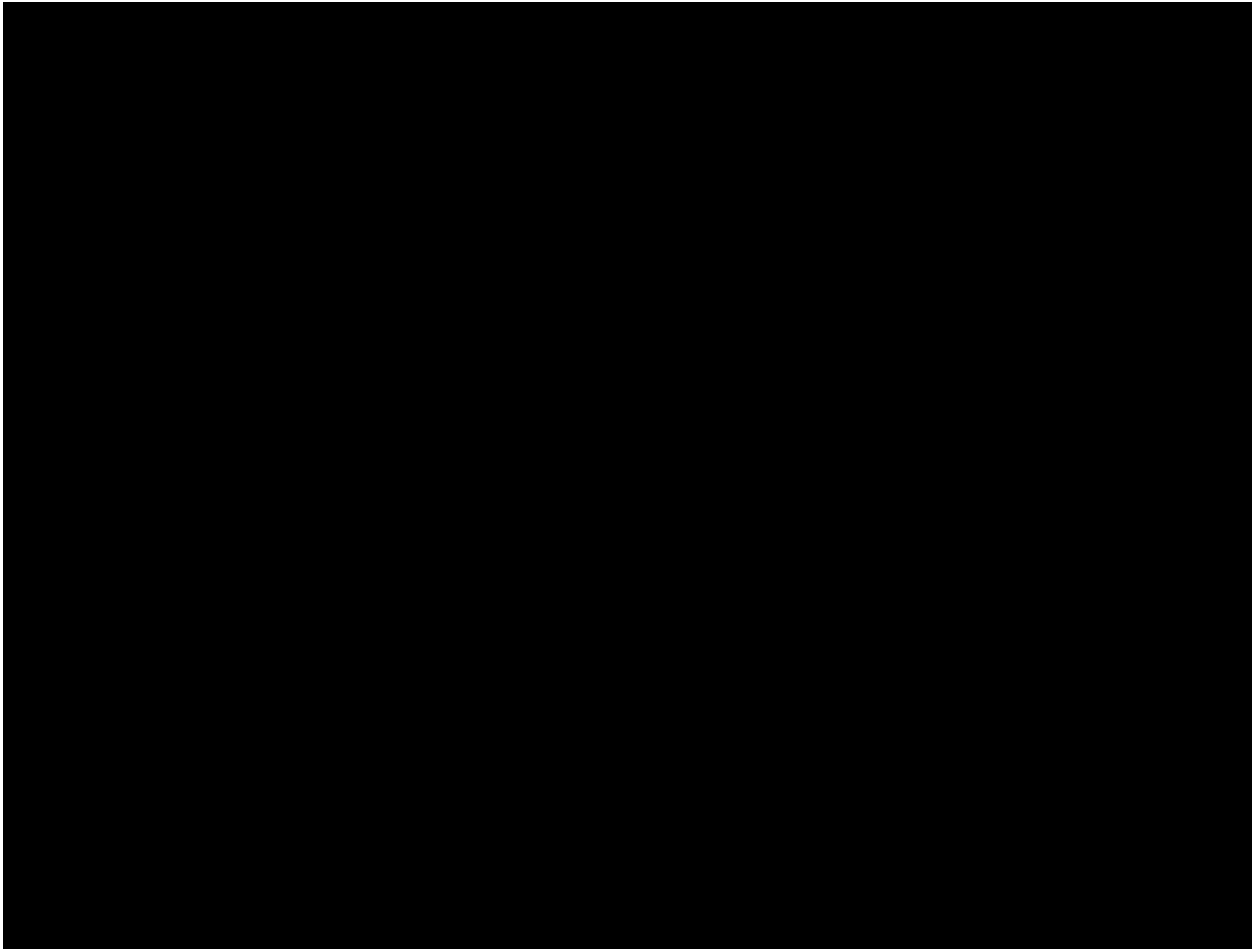


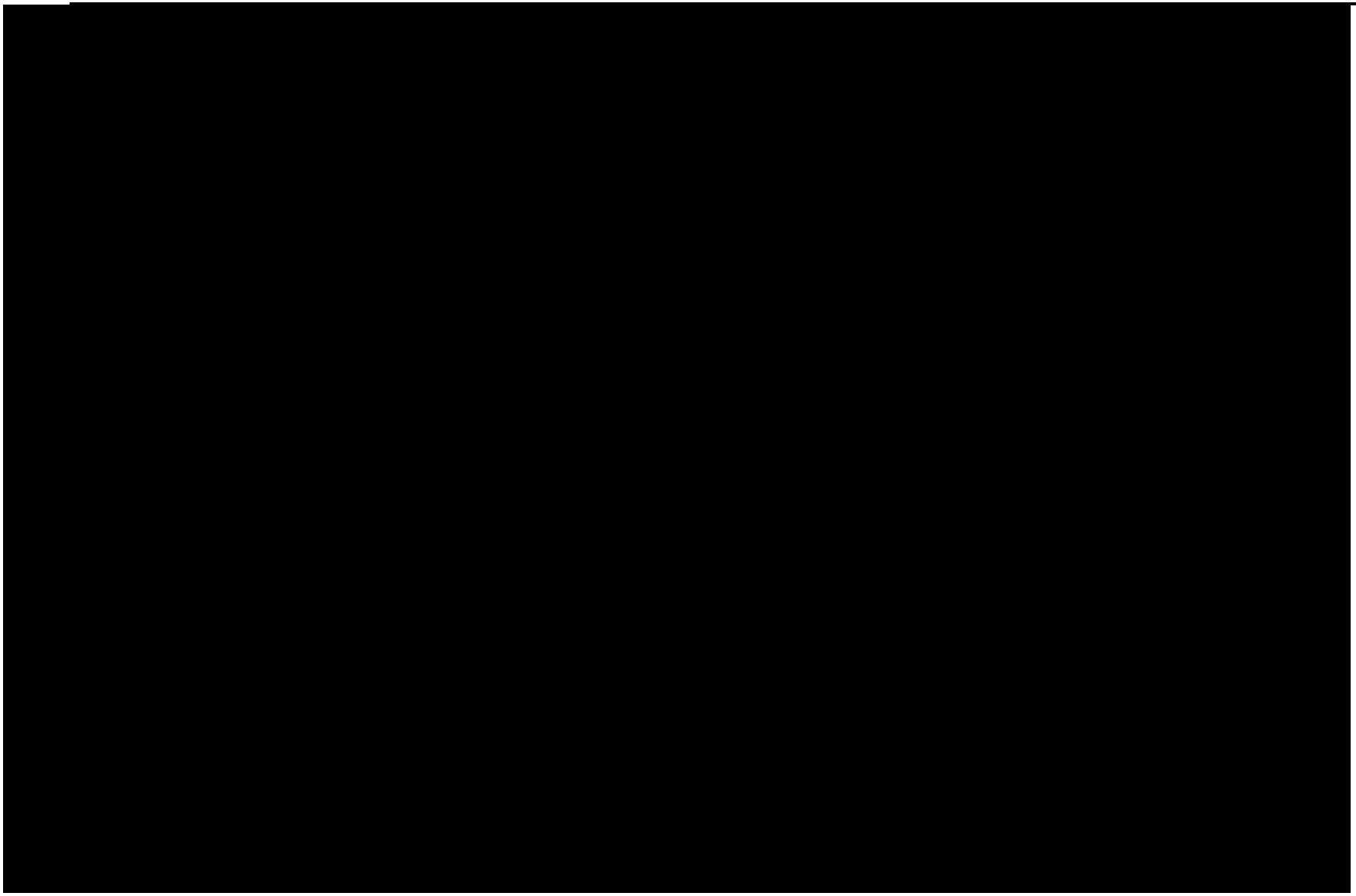
[redacted]











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 patients as defined below: See Table 5-1.

Table 5-1 Analysis Populations

Population	Definition	Study Treatment
Screened	All screened patients who sign informed consent	—
Modified Intent-to-Treat (mITT)	All randomized patients with a baseline and at least 1 post baseline assessment of mesopic, high contrast, UNVA and will be analyzed as randomized	Randomized assignment
Safety	All patients who received ≥ 1 administration of study treatment and will be analyzed as treated	Actual received

The efficacy variables will be analyzed using the mITT population. All safety measures will be analyzed using the safety population.

5.1.1.1.2 Study Treatments

The following treatment groups are defined for this study, also presented in Table 4-1, as group 1, 2, 3, 4 and 5:

- Group 1: Vehicle Control, OU
- Group 2: Fixed combination AGN-199201 [redacted] and AGN-190584 [redacted]), OU
- Group 3: Fixed combination AGN-199201 [redacted] and AGN-190584 [redacted] OU
- Group 4: Fixed combination AGN-199201 [redacted] and AGN-190584 [redacted], OU
- Group 5: Fixed combination AGN-199201 [redacted] and AGN-190584 [redacted]), Non-dominant eye and vehicle to the dominant eye

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 5-2 Statistical Methodology

Methodology		Description
M1	Categorical counts	• Number of patients in individual categories o Patients with ≥ 1 qualifying event counted once per individual category
M2	Categorical descriptives	• Number and percentage of patients in individual categories o Patients with ≥ 1 qualifying event counted once per individual category • (Optional) N included if percentage denominator ≠ number of patients in the population (standard percentage denominator).
M3	PCS descriptives	• Number and percentage of patients meeting potentially clinically significant (PCS) criteria o Patients with ≥ 1qualifying event counted once per PCS category • Percentage denominator = number of patients with non-missing baseline and >=1 non-missing postbaseline assessment • Unevaluable assessments considered missing
M4	Continuous descriptives	• N included, mean, standard deviation (SD), median, minimum, maximum • N included = patients with non-missing value
M5	CFB descriptives	• Continuous descriptives for baseline, postbaseline, and change from baseline (CFB) values • N included = patients 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
		• Estimates derived from mixed model for CFB value controlling for treatment group and covariates (baseline UNVA severity, iris color and age group)
		  o Least squares (LS) means and standard errors
		  o P-values and confidence intervals from contrast t-test comparing active AGN-199201 treatment groups vs AGN-199201 vehicle
		• N included = patients with non-missing values at both baseline and the postbaseline analysis visit

M7	CFB figure	• Plot of CFB LS means and SE bars for each treatment group

M8	Responder	• Categorical descriptives for responders and nonresponders
		  o Nonresponders include:
		  ▪ Patients who do not meet responder criteria
		• CMH test comparing active AGN-199201 treatment groups vs AGN-199201 vehicle

ANCOVA = analysis of covariance; N = number of patients. CMH = Cochran-Mantel-Haenszel

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

There will be no imputation of missing data for all analyses.

Table 5-3 Missing Data Handling by Endpoint Type

Endpoint type	Timing	Missing Data Handling
Responder	Treatment Period	• All patients included • Patients with no postbaseline values will be excluded

CFB ANCOVA	Treatment Period	• If missing covariates (including baseline if applicable)
		  ○ Subject excluded
		• If missing average change from baseline UNVA letters:
		  ○ Subject excluded

CFB Posebaseline	Treatment Period	• If missing value at the specified postbaseline analysis visit:
		  ○ Available cases
		  ▪ Subject excluded

ANCOVA = analysis of covariance; CFB = change from baseline

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 treatment group. Nonocular adverse events and other nonocular assessments will be summarized using patient as the experimental unit by treatment group.

5.1.1.2 Demographics

5.1.1.2.1 Analysis Populations

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

Table 5-4 Analysis Population Summaries

Population	Description	Timing	Methodology
Screened Population	Distribution overall and within countries/regions/sites in total	Screening Period	Categorical counts
mITT 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 Participant Disposition

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

Table 5-5 Subject Disposition Summaries

Parameter	Description	Timing	Methodology
Screening disposition	Distribution in the Screened Population in total	Screening Period	Categorical descriptive
Study disposition	Distribution in the mITT Population in total and by treatment group	Treatment Period	Categorical descriptive

mITT = modified intent-to-treat

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 5-6 Protocol Deviation Summary

Parameter	Description	Timing	Methodology
Important protocol deviations	Distribution in the mITT Population in total and by treatment group	Treatment Period	Categorical descriptive

5.1.1.2.4 Demographics

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

Table 5-7 Demographic Summaries

Parameter	Description	Timing	Methodology
Age	Age (years) relative to informed consent date	Informed consent	Continuous descriptives
Age group	• ≤ 50 years • > 50 years	Informed consent	Categorical descriptives

Sex, race, and ethnicity	• eCRF categories
	• Race group
	  ○ White
	  ○ Non-white
	• Ethnicity
	  ○ Hispanic
	  ○ 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 and Safety populations as follows:

Table 5-8 Baseline Characteristics Summaries

Parameter	Description	Timing	Methodology
Baseline characteristics	• Iris color	Latest assessment in	Categorical

Parameter	Description	Timing	Methodology
		Screening Period or Pretreament Period	descriptives
Randomization strata	• UNVA severity at baseline (≤ 20/80 and > 20/80)	Randomization date	Categorical descriptives
Baseline efficacy	• Mesopic pupil diameter with Grand Seiko sites vs without Grand Seiko sites • UNVA severity at baseline with Grand Seiko sites vs without Grand Seiko sites	Randomization date	Continuous 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 patients who report medical history events will be summarized by MedDRA system organ class (SOC) and preferred term (PT) by treatment group for the Safety Population as follows:

Table 5-9 Medical History Summary

Parameter	Description	Timing	Methodology
Medical and surgical history	Abnormalities and surgeries occurring before the Screening Visit	Screening Period	Categorical descriptive

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

5.1.1.2.7 Ophthalmic History and Ophthalmic Surgical History

Ophthalmic history, encompassing abnormalities and ophthalmic surgeries reported as occurring before the Screening Visit, will be coded using MedDRA, version 19.0 or newer. Unique patients who report ophthalmic history events will be summarized by MedDRA SOC and PT by treatment group for the Safety Population as follows:

Table 5-10 Ophthalmic History and Ophthalmic Surgery History Summary

Parameter	Description	Timing	Methodology
Ophthalmic history and ophthalmic surgery history	Abnormalities and surgeries occurring before the Screening Visit	Screening Period	Categorical descriptive

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

5.1.1.2.8 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 patients who reported medications will be summarized by

Anatomical Therapeutic Chemical (ATC) 4 class and PT by treatment group for the Safety Population as follows:

Table 5-11 Medication Summaries

Parameter	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 • Medications starting 1 day after treatment end date will be listed but excluded from analysis	Treatment Period, Follow-up Period	Categorical descriptives

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

5.1.1.3 Efficacy Analyses

Efficacy analyses will be based on the mITT Population.

The following efficacy assessments are defined:

Baseline assessments for applicable efficacy endpoints defined as follows:

Table 5-13 Efficacy Endpoint Baseline Definitions

Endpoint	Description	Timing
• Mesopic, high contrast UNVA [redacted]	Non-missing measurements at Day 1 Hour 0 • Patients with no Day 1 Hour 0 measurement will be excluded from CFB analyses[1]	Day 1 Hour 0
[redacted]		

5.1.1.3.1 Study Success Criteria

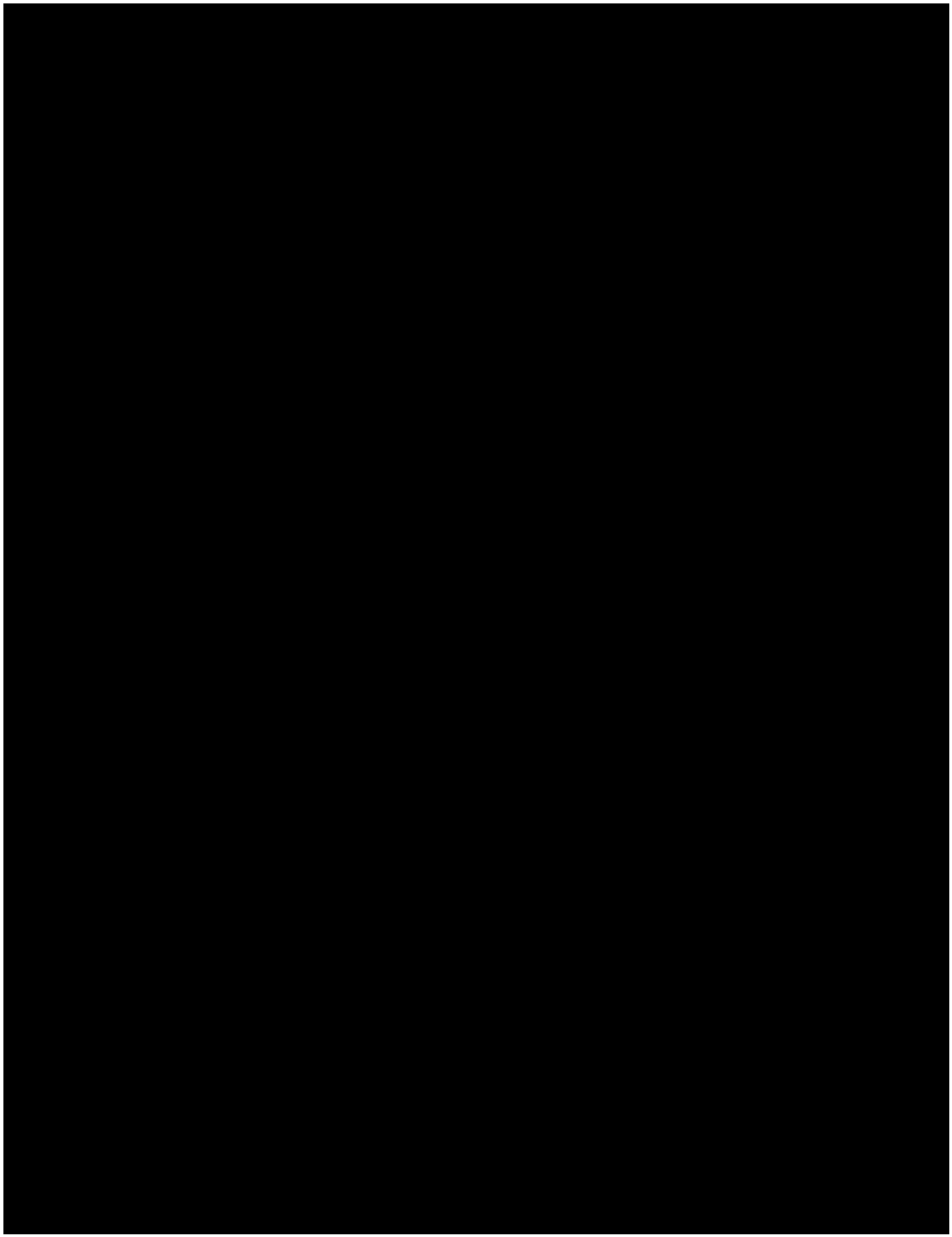
There will be no adjustment of type 1 error rate for the multiple tests. There will be no imputation of missing data for all analyses.

5.1.1.3.2 Mesopic, High Contrast UNVA

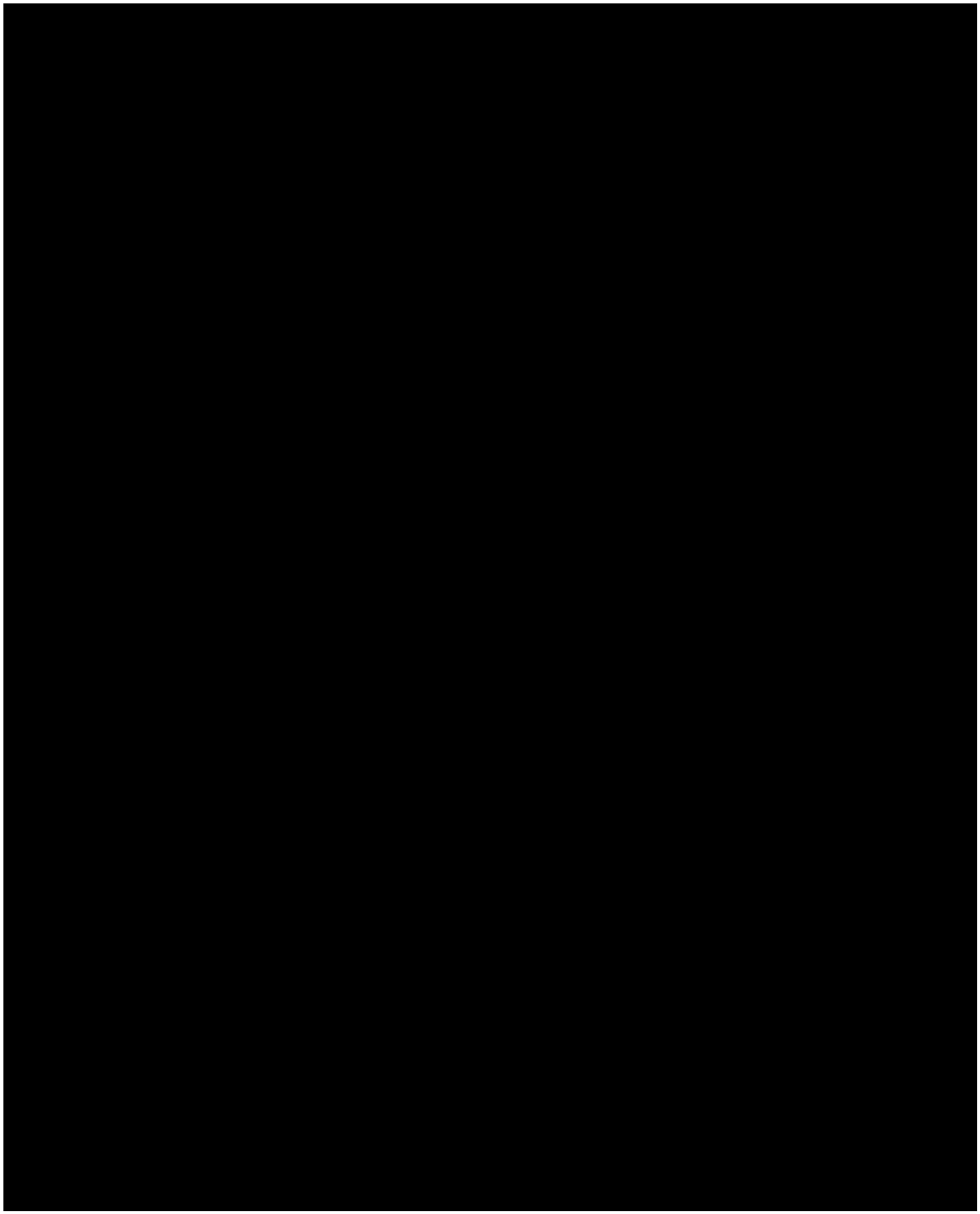
Mesopic, high contrast UNVA endpoints will be summarized by treatment group for mITT Population.

Table 5-14 Mesopic, High Contrast UNVA

Endpoint	Description	Timing	Methodology
Average change from baseline in UNVA letters (Primary efficacy variable)	Average change from baseline in UNVA lines in the nondominant eye at day 28.	Treatment Period Day 28	CFB ANCOVA[1] CFB figure
[redacted]	[redacted]	[redacted]	[redacted]



[redacted]



[redacted]

5.1.1.4.2 Adverse Events

The following adverse event (AE) terms are defined:

Table 5-24 AE Terms

Term	Description
Treatment-emergent	An event that initially occurs or increases in intensity on or after the treatment start date, where: • Treatment start date ≤ event start date ≤ treatment end date + 30
On-therapy	An event where: • Treatment start date ≤ event start date ≤ treatment end date + 30

AEs, encompassing abnormalities and surgeries reported as occurring after the Screening Visit, will be coded using MedDRA version 19.0 or newer. Unique patients reporting AEs in the following AE categories will be summarized by treatment group and overall for the Safety Population as follows:

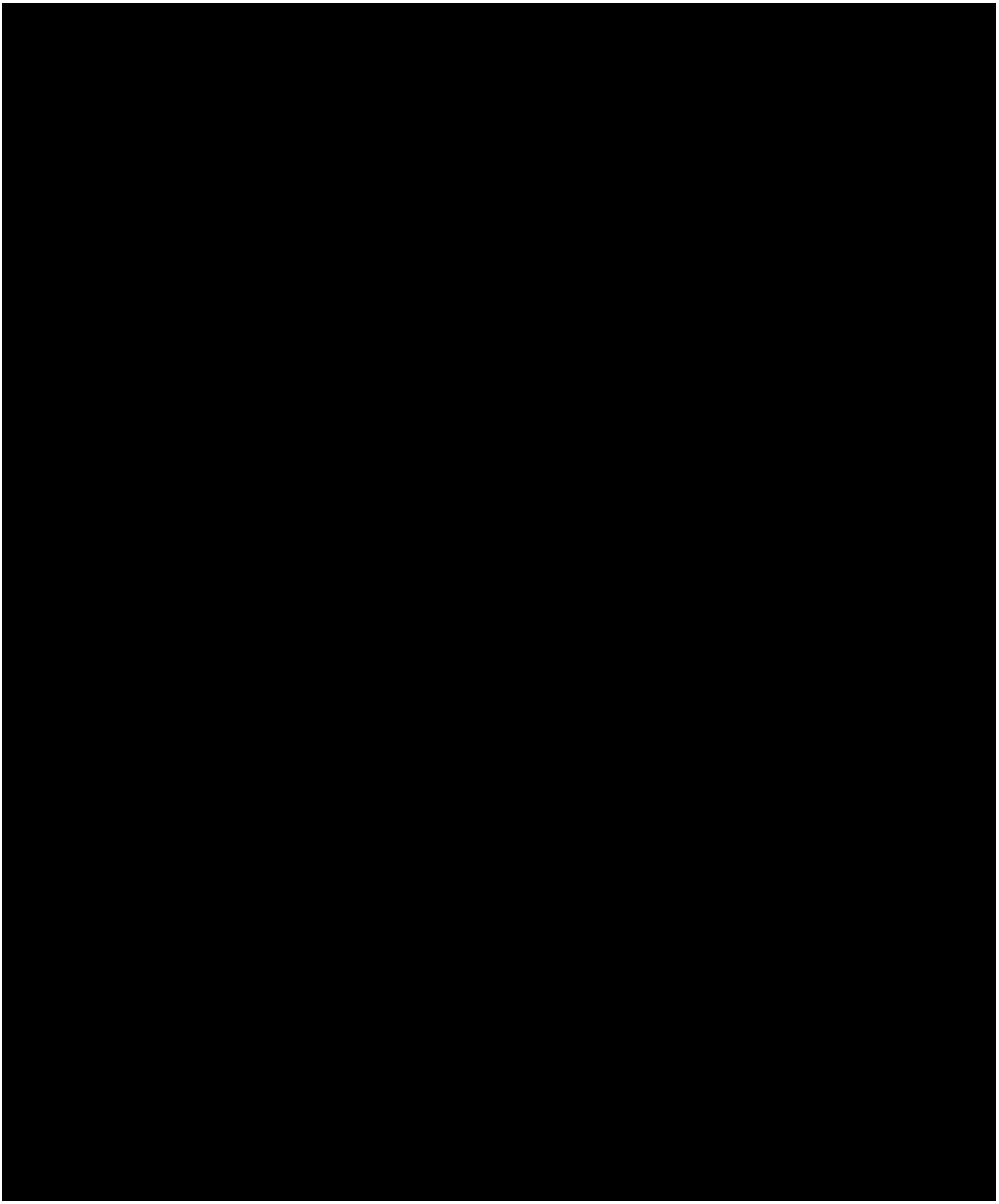
Table 5-25 AE Summaries

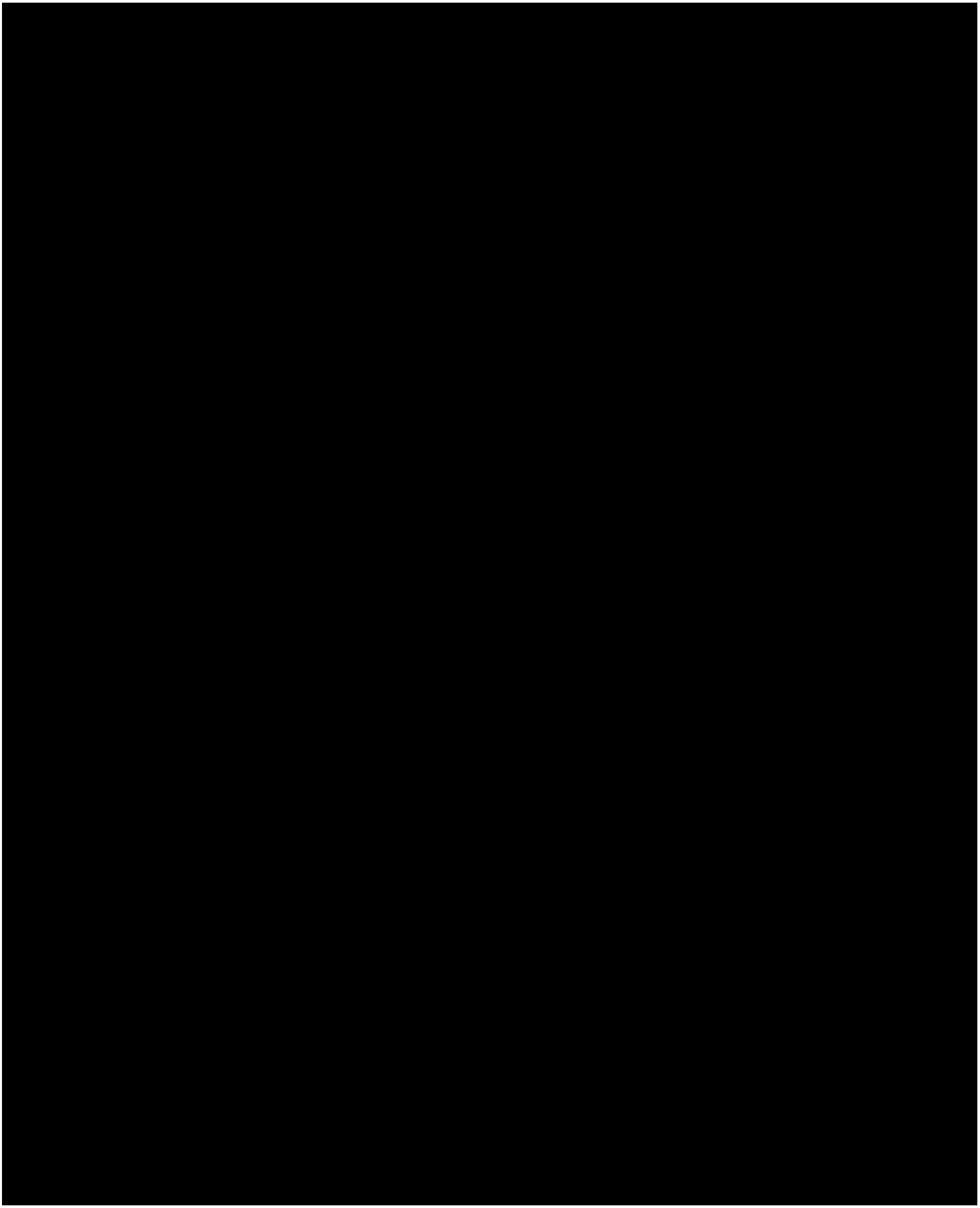
Parameter	Description	Timing	Methodology
Overall summary	Overall summary only for the following categories: • Treatment-emergent AEs (TEAEs) • Treatment-related TEAEs • Study-procedure-related TEAEs • On-therapy serious adverse events (SAEs) • On-therapy fatal SAEs • AEs leading to discontinuation	Treatment Period, Follow-up Period	Categorical descriptives
TEAEs	Overall summary and by SOC and PT	Treatment Period, Follow-up Period	Categorical descriptives
Ocular TEAEs	Summary by SOC and PT for ocular TEAEs dominant eye nondominant eye	Treatment Period, Follow-up Period	Categorical descriptives
Non-ocular TEAEs	Summary by SOC and PT for non-ocular TEAEs	Treatment Period, Follow-up Period	Categorical descriptives
Common TEAEs	Summary by PT • Includes TEAEs occurring in ≥ 5.0% of patients in any treatment group	Treatment Period, Follow-up Period	Categorical descriptives
Common Ocular TEAEs	Summary by PT for common ocular TEAEs dominant eye	Treatment Period, Follow-up Period	Categorical descriptives

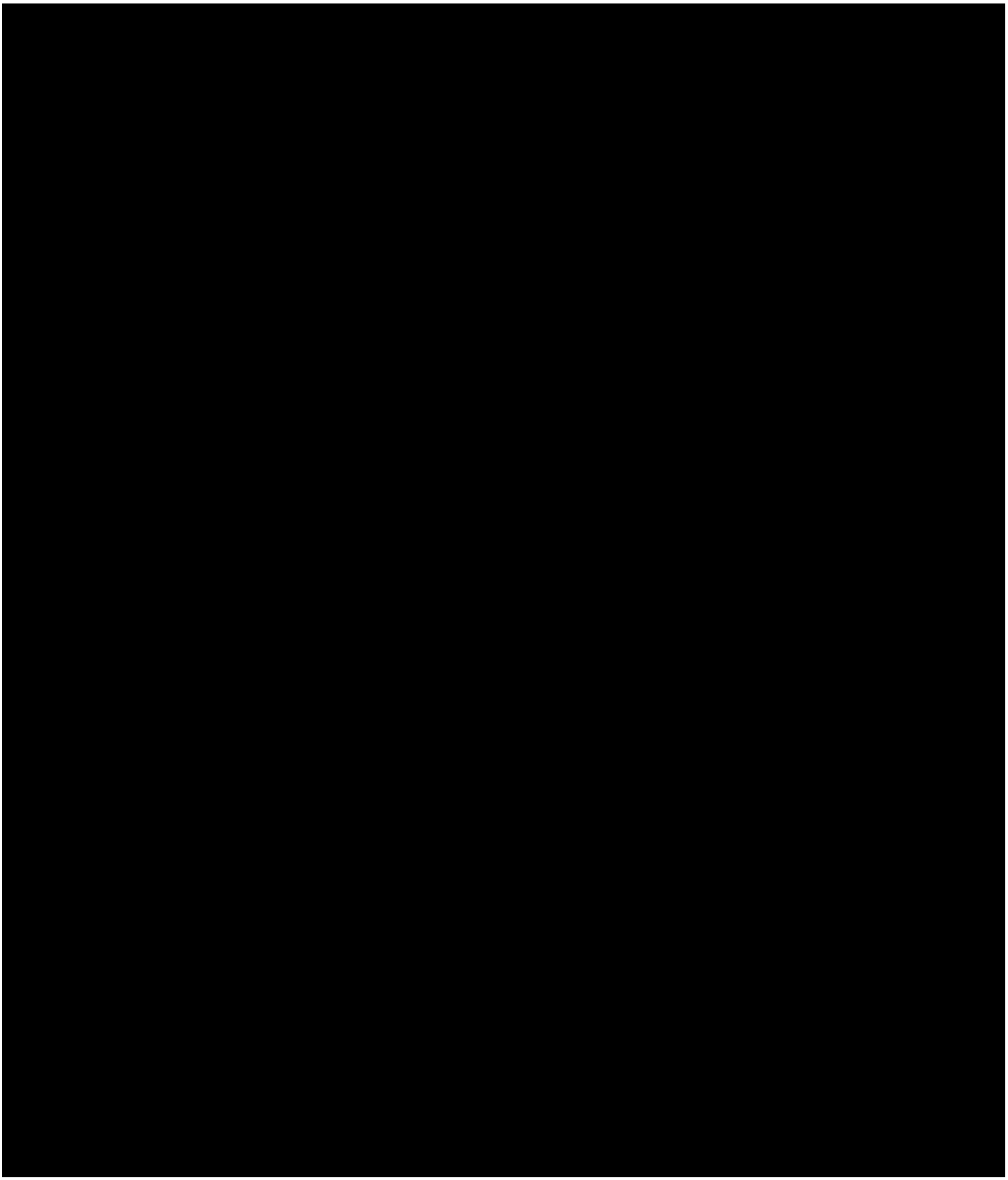
Parameter	Description	Timing	Methodology
	nondominant eye		
Common Non-ocular TEAEs	Summary by PT for common non-ocular TEAEs	Treatment Period, Follow-up Period	Categorical descriptives
TEAEs by intensity	Overall summary and by SOC, PT, and intensity • Patients categorized overall and within each SOC and PT for the most intense occurrence	Treatment Period, Follow-up Period	Categorical descriptives
Ocular TEAEs by intensity	Overall summary and by SOC, PT, and intensity for ocular TEAEs • Patients categorized overall and within each SOC and PT for the most intense occurrence dominant eye nondominant eye	Treatment Period, Follow-up Period	Categorical descriptives
Non-ocular TEAEs by intensity	Overall summary and by SOC, PT, and intensity for non-ocular TEAEs • Patients categorized overall and within each SOC and PT for the most intense occurrence	Treatment Period, Follow-up Period	Categorical descriptives
Treatment-related TEAEs	Overall summary and by PT	Treatment Period, Follow-up Period	Categorical descriptives
Ocular Treatment-related TEAEs	Overall summary and by PT for ocular TEAEs dominant eye nondominant eye	Treatment Period, Follow-up Period	Categorical descriptives
Non-ocular Treatment-related TEAEs	Overall summary and by PT for non-ocular TEAEs	Treatment Period, Follow-up Period	Categorical descriptives
Study-procedure-related TEAEs	Overall summary and by PT	Treatment Period, Follow-up Period	Categorical descriptives
Ocular Study-procedure-related TEAEs	Overall summary and by PT for ocular TEAEs dominant eye nondominant eye	Treatment Period, Follow-up Period	Categorical descriptives
Non-ocular Study-procedure-related TEAEs	Overall summary and by PT for non-ocular TEAEs	Treatment Period, Follow-up Period	Categorical descriptives
On-therapy SAEs[1]	Overall summary and by PT	Treatment Period, Follow-up Period	Categorical descriptives
On-therapy ocular SAEs	Overall summary and by PT for ocular SAEs dominant eye nondominant eye	Treatment Period, Follow-up Period	Categorical descriptives
On-therapy non-ocular SAEs	Overall summary and by PT for non-ocular SAEs	Treatment Period, Follow-up Period	Categorical descriptives
On-therapy fatal SAEs[1]	Overall summary and by PT	Treatment Period, Follow-up Period	Categorical descriptives
On-therapy fatal ocular SAEs	Overall summary and by PT for ocular fatal SAEs dominant eye nondominant eye	Treatment Period, Follow-up Period	Categorical descriptives
On-therapy fatal non-ocular SAEs	Overall summary and by PT for non-ocular fatal SAEs	Treatment Period, Follow-up Period	Categorical descriptives

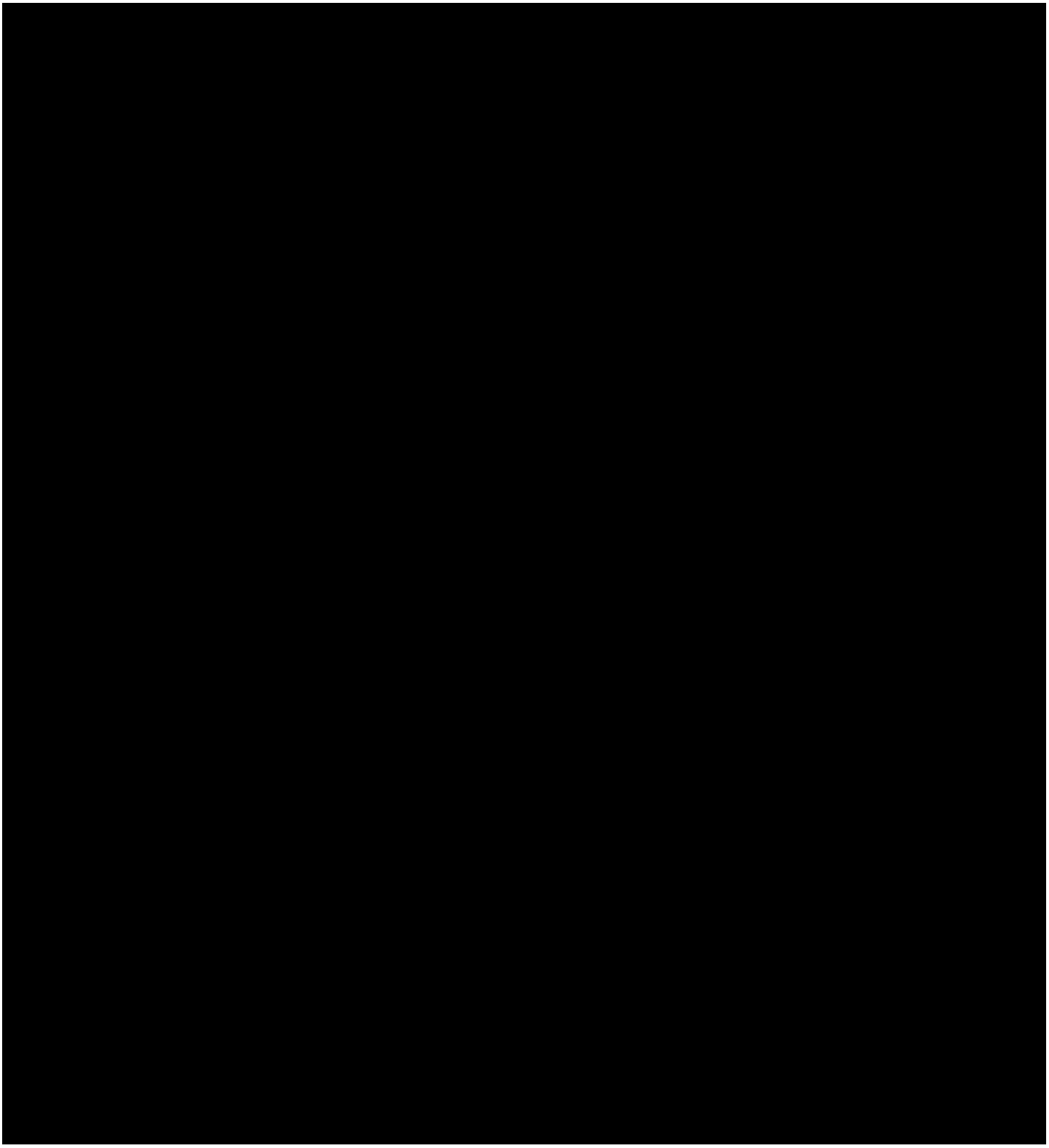
Parameter	Description	Timing	Methodology
AEs leading to study discontinuation[1]	Overall summary and by PT	Treatment Period, Follow-up Period	Categorical descriptives
Ocular AEs leading to study discontinuation	Overall summary and by PT for ocular AEs leading to discontinuation dominant eye nondominant eye	Treatment Period, Follow-up Period	Categorical descriptives
Non-ocularAEs leading to study discontinuation	Overall summary and by PT for non-ocular AEs leading to discontinuation	Treatment Period, Follow-up Period	Categorical descriptives

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









[redacted]

5.1.1.7 Interim Analyses

Not applicable

5.1.2 Determination of Sample Size

A sample size of approximately 150 patients will be randomized in a 1:1:1:1:1 ratio into 1 of the 5 study groups. Approximately two-thirds of the enrolled patients will be younger patients (≤ 50 years old), and approximately one-third of the enrolled patients will be older patients (> 50 years old).

From the Study 199201-007 results, the treatment effect for the younger patients was on average 1.98 lines of change in mesopic, high contrast UNVA, with standard deviations for active and

vehicle of 1.12 and 1.01, respectively. For older patients, the treatment effect was on average 0.72 lines of change in mesopic, high contrast UNVA, with standard deviations for active and vehicle of 1.87 and 1.15, respectively. The treatment effect for the younger patients was on average 1.02 lines of change in photopic, high contrast UNVA, with standard deviations for active and vehicle of 1.42 and 0.67, respectively. For older patients, the treatment effect was on average 0.27 lines of change in photopic, high contrast UNVA, with standard deviations for active and vehicle of 1.10 and 0.93, respectively.

Accounting for a 12.5% dropout rate, 26 patients per treatment group will provide 99% power to observe a difference between an active group and the vehicle group for lines of change from baseline in mesopic, high contrast UNVA, and 68% power for lines of change from baseline in photopic, high contrast UNVA, with a type I error of 0.05

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 not be performed.

6. Data Handling and Analysis Conventions

6.1 Study Treatment Conventions

6.1.1 Analysis Days

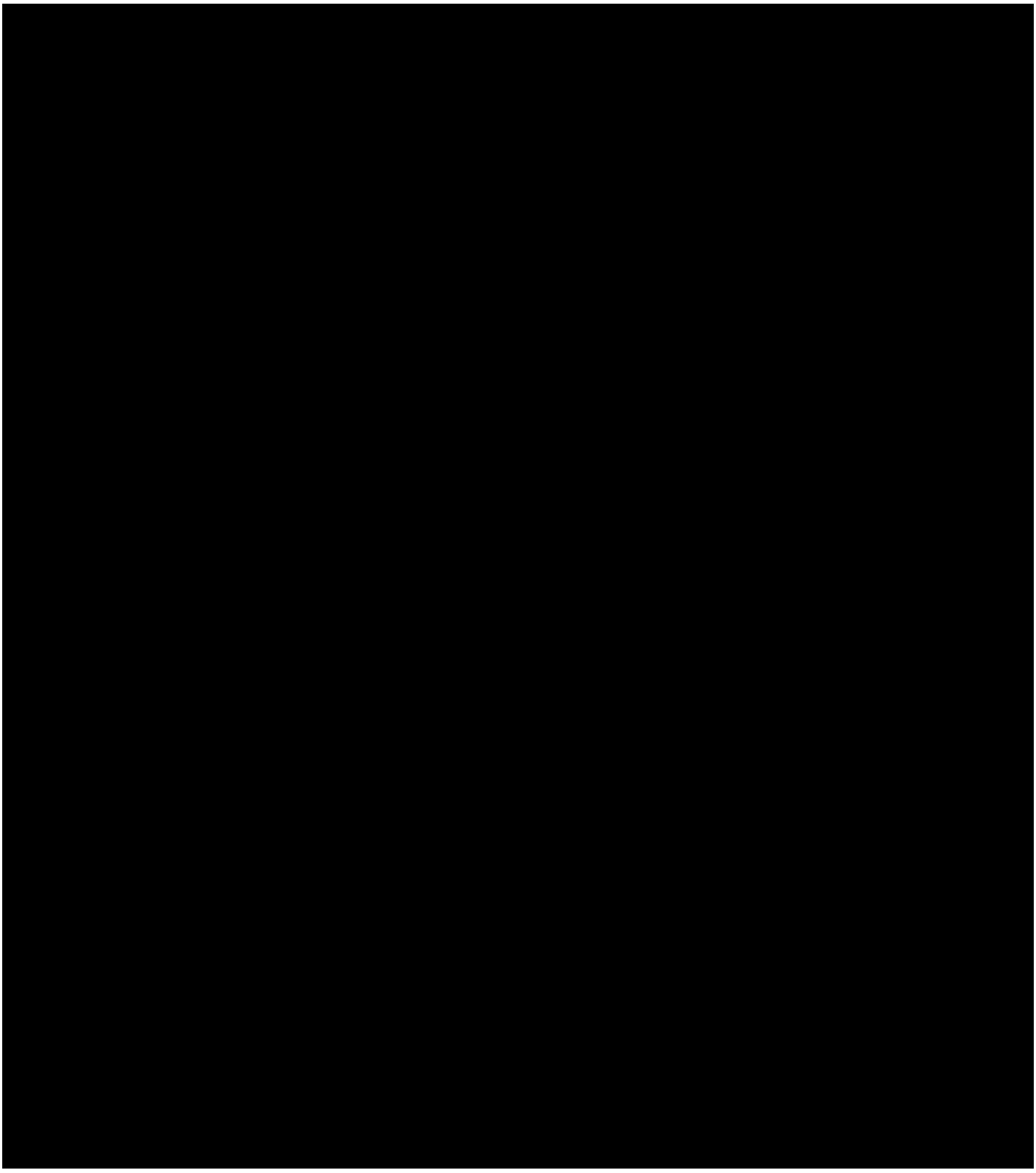
Treatment is defined as follows:

Table 6-1 Analysis Day Definitions

Term	Description
Treatment Day	Relative to treatment start date If analysis date ≥ treatment start date: • Day = analysis date – treatment start date + 1 ○ 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 as the last available dosing record date/last available efficacy assessment date



- [redacted]

[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

[redacted]

[redacted]

6.6.4 Electrocardiograms

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
[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	Added additional analysis

Section	Revision	Rationale
	timepoints (6 or more) in the nondominant eye will be added.	

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
Section 5.1.1.3	Added the baseline of depth of focus	For clarification
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

ALLERGAN

199201-010 Statistical Analysis Plan

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