NCT02013791

Study 192371-024

Title: A Phase 2, Multi-center, Vehicle- and Sham-controlled, Randomized Study of RESTASIS® X in Patients With Moderate to Severe Dry Eye Disease

Protocol Amendment 6 Date: Jan 19, 2017

Statistical Analysis Plan (SAP) Date: June, 20, 2017

1. Title Page

STATISTICAL ANALYSIS PLAN

A Phase 2, Multicenter, Vehicle- and Sham-controlled, Randomized Study of RESTASIS® X in Patients With Moderate to Severe Dry Eye Disease

Stage 1

Protocol Number:	192371-024
Development Phase:	2
Product Name:	RESTASIS® X
Study Statistician:	[redacted]
Sponsor:	Allergan (North America) 2525 Dupont Drive Irvine, California USA 92612 +1-714-246-4500 +1-800-347-4500

2. Table of Contents

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Table 3-1 Abbreviations and Definitions of Terms

Abbreviation/Term	Definition
AE	adverse event
BCVA	best-corrected visual acuity
CFB	change from baseline
DDE	Drug Dictionary Enhanced
[redacted]	[redacted]
eCRF	electronic case report form
F1	[redacted]
F2	
IOP	intraocular pressure
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
OSDI	Ocular Surface Disease Index
PK	pharmacokinetic
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TEAE	treatment-emergent adverse event
TBUT	tear film break-up time
VAS	visual analog scale
WHO	World Health Organization

4. Introduction

This statistical analysis plan (SAP) details comprehensive, technical specifications of the statistical analyses of the safety, exploratory efficacy, and health outcomes data outlined and/or specified in Protocol 192371-024 Amendment 6, dated 19 Jan 2017. Study 192371-024 is a 2-stage, Phase 2 study. A final database lock will occur after the completion of stage 2. Separate analysis plans will be prepared for the analysis of each stage. This document is the analysis plan for stage 1. Specifications of tables, figures, and data listings are contained in a separate document. The SAP for pharmacokinetic (PK) data will be prepared separately.

This document is organized into 3 main sections as follows:

1. Study overview
2. Statistical methodology and study endpoints
3. Data handling and analysis conventions

4.1 Study Design Summary

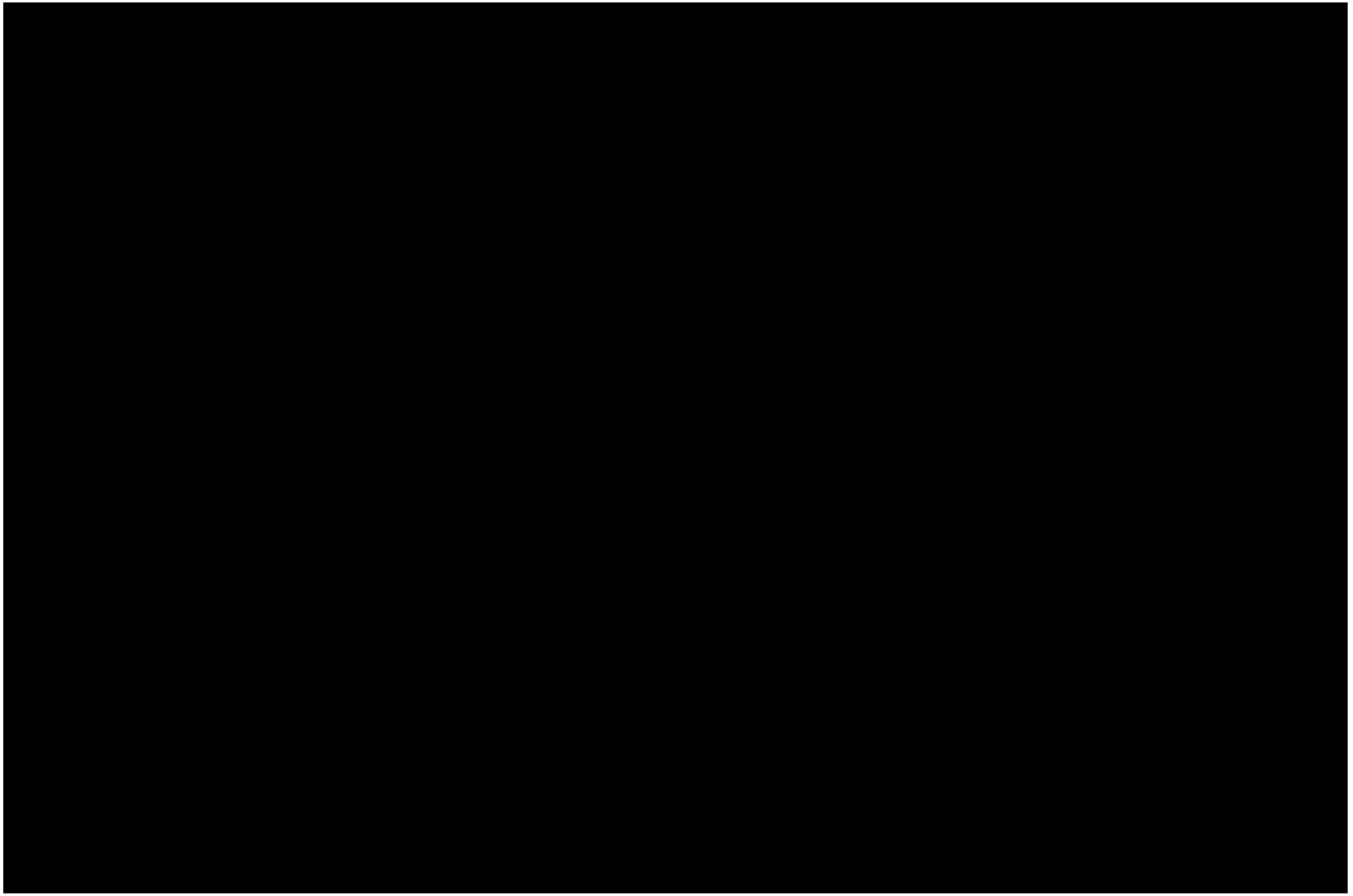
This study is a multicenter, randomized, investigator-masked, 24-week evaluation of the safety, exploratory efficacy, and pharmacokinetics of [redacted] RESTASIS® X in patients with moderate to severe dry eye disease. The study is being conducted in 2 stages.

Stage 1: Single-dose, paired-eye comparison, dose escalation, vehicle-controlled, followed by retreatment (Cohorts 6C and 6D).

Stage 1 will evaluate the safety and ocular and systemic pharmacokinetics of F1 [redacted] and F2 [redacted]

[redacted]

[redacted]



Randomization/Stratification:

Stage 1: Within each cohort, patients will be randomly assigned with respect to the eye, right or left, to receive F1 or F2 (or vehicle for Cohort 1). The contralateral eye will receive vehicle (sham for Cohort 1).

[redacted]

Number of Patients:

Stage 1: Stage 1 will have up to 63 patients and approximately 10 cohorts (Cohorts 1 to 6D). The anticipated numbers of patients per cohort are 3 for Cohort 1; 4 for Cohorts 2, 6C, and 6D; and 8 each for Cohorts 3 through 6B.

4.2 Study Objectives and Assessments

The study objective for stage 1 is presented with corresponding assessments in Table 4-2.

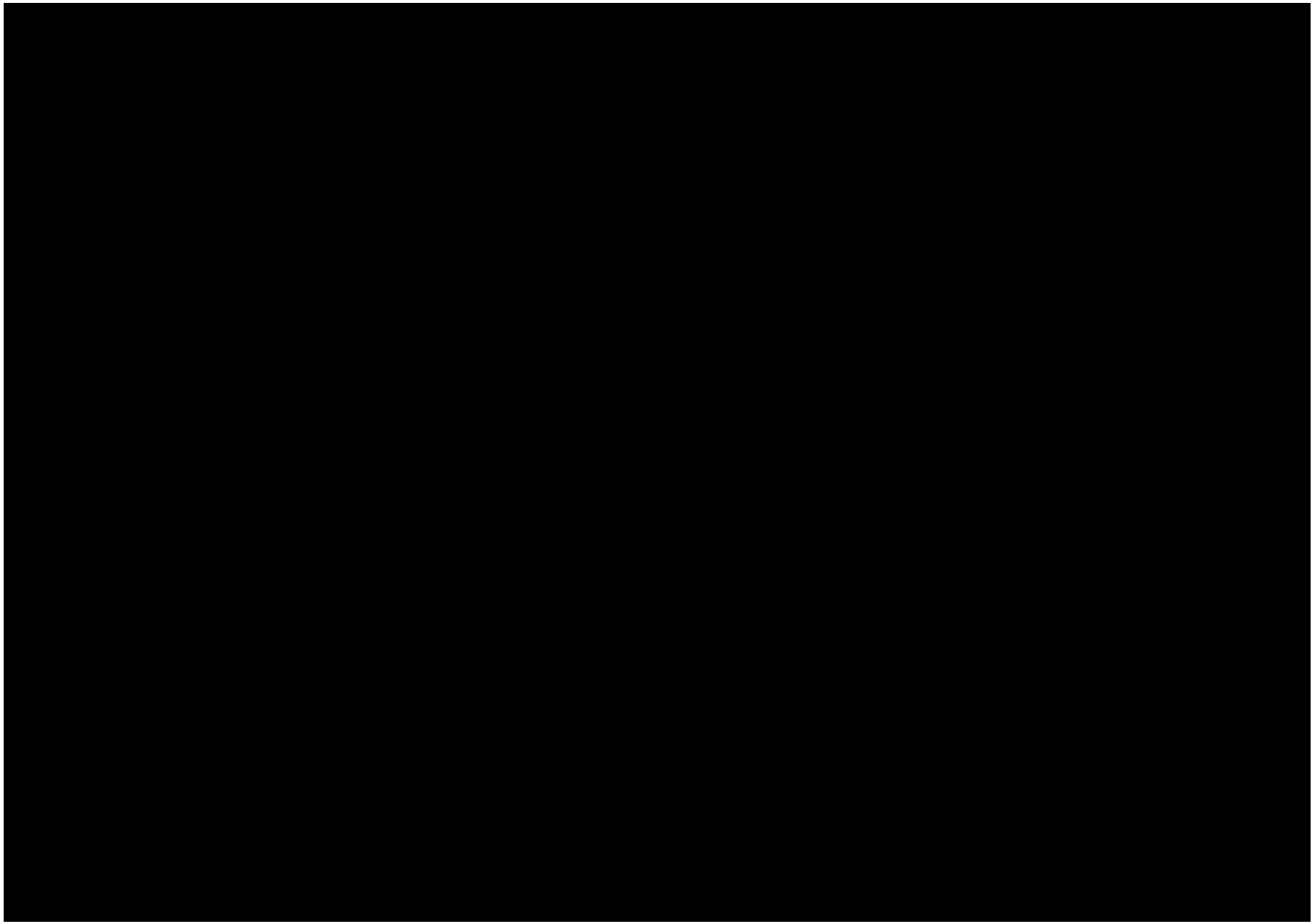
Table 4-2 Study Objective and Corresponding Assessments - Stage 1

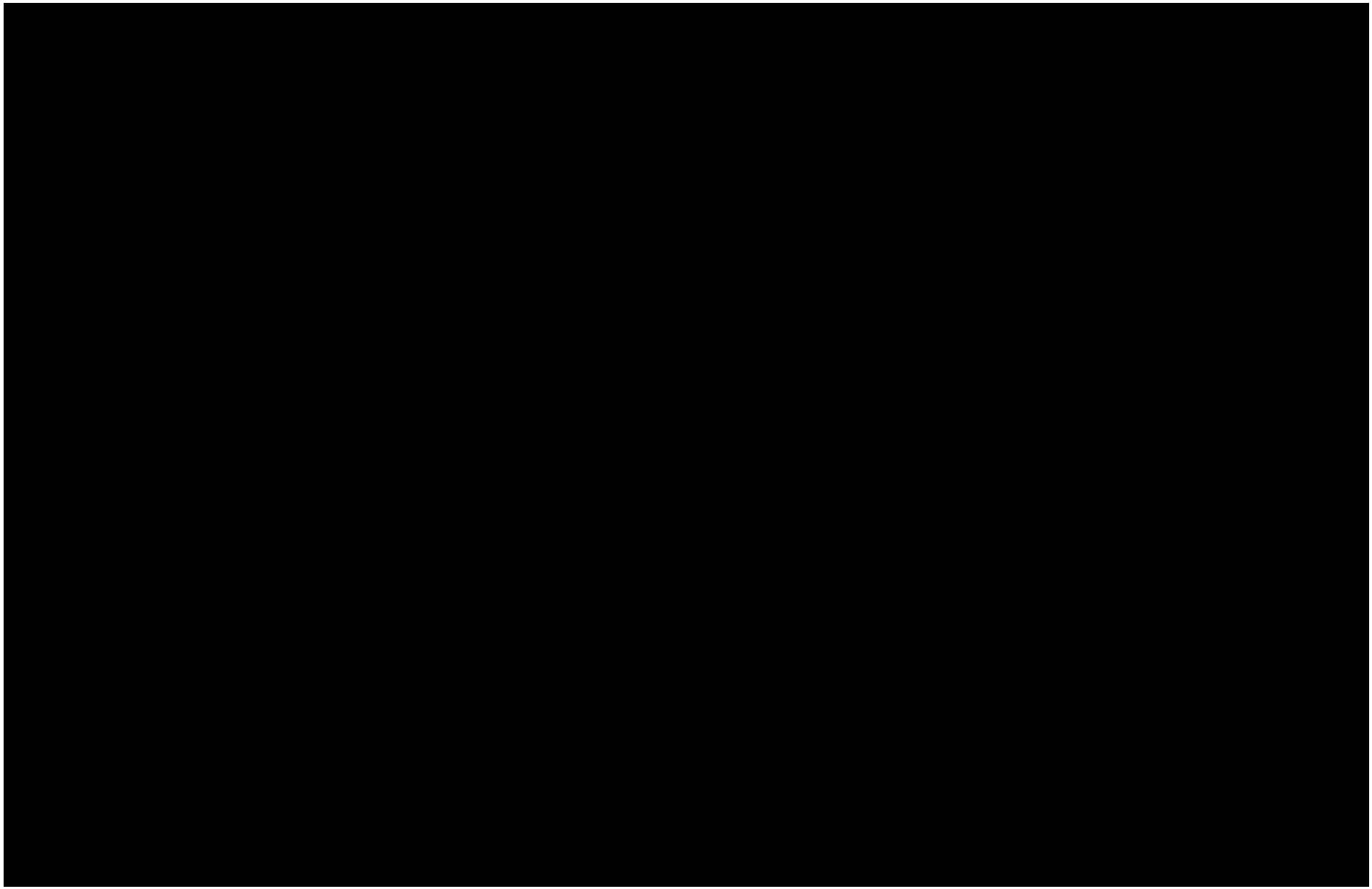
Objective	Assessments
To evaluate the safety, exploratory efficacy, and pharmacokinetics of F1 and F2 administered as a [redacted] in patients with moderate to severe dry eye disease.	Safety Assessments • AEs • BCVA (manifest refraction at screening and exit visits) • Macroscopic hyperemia assessment and slit-lamp biomicroscopy • Dilated ophthalmic exam • Photographic conjunctival hyperemia assessment • IOP • Vital signs • Laboratory tests (chemistry, hematology, urinalysis) • Urine pregnancy test (for females of childbearing potential) Pharmacokinetic Assessments • PK assessments will be detailed in a separate PK analysis plan. [redacted]

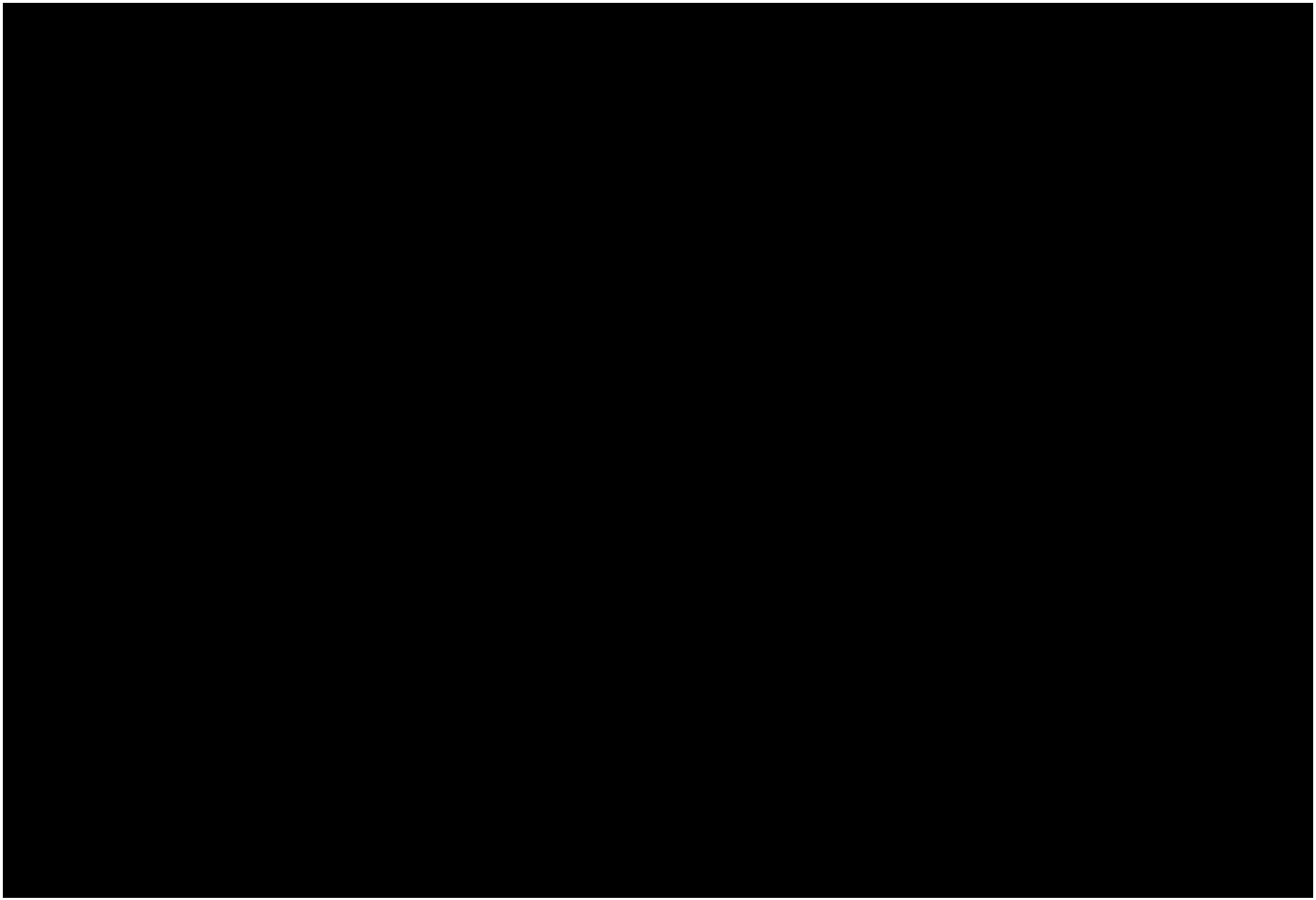
AE = adverse event; BCVA = best-corrected visual acuity; F1 [redacted] F2 = [redacted] IOP = intraocular pressure; OSDI = Ocular Surface Disease Index; PK = pharmacokinetic; TBUT = tear film break-up time; VAS = visual analog scale

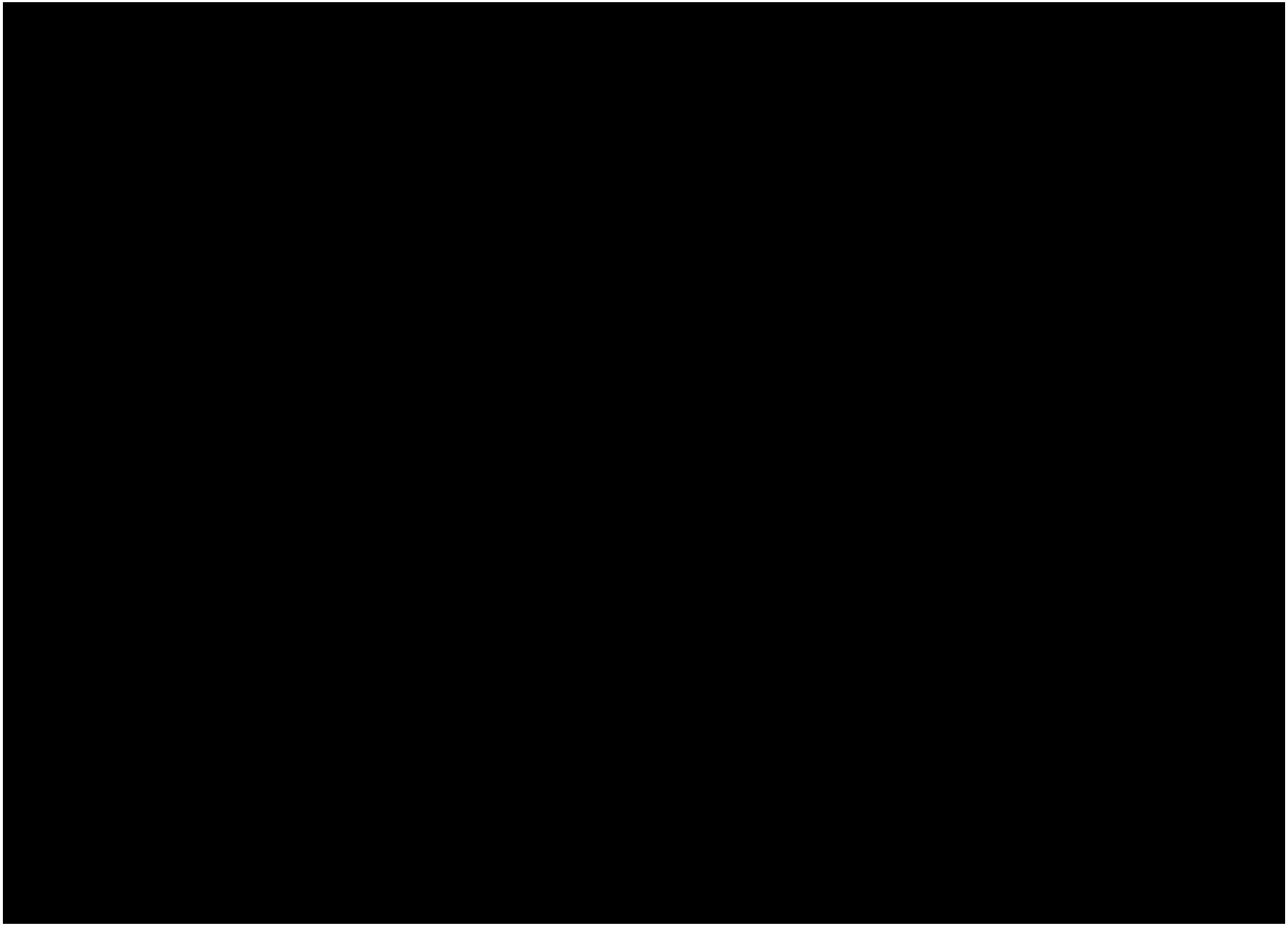
4.3 Schedule of Activities

The schedule of activities is presented in Table 4-3 (stage 1) and Table 4-4 (stage 2). If retreatment is given at Week 12, the stage 1 retreatment schedule will be following the stage 2 retreatment schedule (see post-retreatment follow-up visits in Table 4-4).









5. Statistical Methodology and Study Endpoints

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

This SAP for stage 1 will be approved prior to final 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 clinical study report report as Appendix 16.1.9. Information on the PK analyses can be found in the PK data analysis plan, which is a separate document.

5.1.1 Statistical and Analytical Plans

[redacted]

5.1.1.1 Common Conventions

5.1.1.1.1 Analysis Populations

The analysis populations will consist of patientss as defined in Table 5-1.

Table 5-1 Analysis Populations – Stage 1

Population	Definition	Study Treatment
Safety	All patients who are treated	Actual received[a]
Modified intent-to-treat (mITT)	All randomized patients who have baseline and at least 1 postbaseline assessment for 1 or more of the exploratory efficacy measurements	Randomized assignment

[a] Patients will be summarized according to the first study treatment received or study treatment received for majority of treatment period.

5.1.1.1.2 Study Treatments

The following treatment groups and cohorts are defined for stage 1 in this study:

Cohort	Treatment Group
Cohort 5A	RESTASIS X F1 [redacted]
Cohort 4	RESTASIS X F1 [redacted]
Cohort 6C	RESTASIS X F1 [redacted] with retreatment at week 12
Cohort 3	RESTASIS X F1 [redacted]
Cohort 2	RESTASIS X F1 [redacted]
Cohort 6B	RESTASIS X F2 [redacted]
Cohort 6D	RESTASIS X F2 [redacted] with retreatment at week 12
Cohort 6A	RESTASIS X F2 [redacted]
Cohort 1	Vehicle

Data will be analyzed by treatment group/cohort, unless otherwise specified.

5.1.1.1.3 Statistical Methodology

The methodologies defined in Table 5-2 apply as specified to individual endpoints defined in this SAP for stage 1.

Table 5-2 Statistical Methodology – Stage 1

Methodology	Description
Categorical counts	• Number of patients in individual categories ○ Patients with ≥ 1qualifying event counted once per individual category

Categorical descriptives	• Number and percentage of patients in individual categories
	  ○ Patients with ≥ 1qualifying event counted once per individual category
	• N1 if percentage denominator ≠ number of patients in the population (standard percentage denominator)
	  ○ N1 = patients with nonmissing value

Continuous descriptives	• N1, mean, SD, median, minimum, maximum • N1 = patients with nonmissing value
CFB descriptives	• Continuous descriptives for baseline, postbaseline, and CFB values • N1 = patients with nonmissing values at both baseline and the specified postbaseline analysis visit
Responder	• Categorical descriptives for responders and nonresponders • N1 = patients with nonmissing values at both baseline and the specified postbaseline analysis visit

CFB = change from baseline

Two treatment cycles are defined in this analysis plan. Treatment Cycle 1 includes all visits from study baseline (also called cycle 1 baseline) to Week 24 or Exit visit if a patient receives [redacted] throughout the study, or to the last visit before retreatment if a patient receives [redacted] during the study. For visits in treatment Cycle 1, refer to study windows in Section 6.2. Treatment Cycle 2 applies to patients who receive retreatment, and includes all visits from retreatment and thereafter. Visits in treatment Cycle 2 will be determined based on the study days relative to the retreatment visit using the study windows specified in Section 6.2.

The study baseline value of an assessment will be the measurement prior to the treatment at Day 1 unless it is missing. In that case, the last nonmissing value recorded prior to the treatment (Day 1) will be used instead. The cycle baseline (also called cycle 2 baseline) value of an assessment will be the measurement prior to the retreatment at Week 12 from the first treatment unless it is missing. In that case, the last nonmissing value recorded prior to the retreatment (Week 12) will be used instead.

Ocular evaluation will be summarized by study eye and contralateral eye separately.

Some 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 summarized as follows:

- Missing data will not be imputed and all analyses will be based on observed data.
- Partial dates handling conventions are specified in Section 6.3, but will be listed in the data listings as they appear on the electronic case report forms (eCRFs).

5.1.1.2 Demographics

The safety population will be used to summarize demographics.

5.1.1.2.1 Analysis Populations

The distribution of patients within the analysis populations will be summarized as described in Table 5-3.

Table 5-3 Analysis Population Summaries

Population	Description	Timing	Methodology
mITT and safety populations	Distribution in total and by treatment group	—	Categorical counts

5.1.1.2.2 Patient Disposition

Patient disposition encompasses the distribution of patients who enter, complete, and discontinue each specified analysis period, along with eCRF-reported discontinuation reasons from each respective analysis period. Patient disposition will be summarized as shown in Table 5-4.

Table 5-4 Patient Disposition Summaries

Parameter	Description	Timing	Methodology
Study disposition	Distribution in total and by treatment group	During study	Categorical descriptives
Patient disposition[a] by phase	Distribution in the safety population in total and by treatment group	Treatment Period	Categorical descriptives

[a] Patients who prematurely discontinued will be listed.

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 shown in Table 5-5.

Table 5-5 Protocol Deviation Summary

Parameter	Description	Timing	Methodology
Significant protocol deviations[a]	Distribution in the safety population in total and by treatment group	—	Categorical descriptives

[a] Patients with significant protocol deviations will be listed.

5.1.1.2.4 Demographics

Demographics will be summarized in total and by treatment group for the safety population as shown in Table 5-6.

Table 5-6 Demographic Summaries

Parameter	Description	Timing	Methodology
Age[a]	Age (years) relative to informed consent date	Informed consent	Continuous descriptives
Age group	• < 45 years • 45-65 years • > 65 years	Informed consent	Categorical descriptives

Sex, and race[1]	• eCRF categories
	• Race group 1
	  ○ Caucasian
	  ○ Black
	  ○ Asian
	  ○ Hispanic
	  ○ Other
	• Race group 2
	  ○ Caucasian
	  ○ Non-caucasian
		Screening period	Categorical descriptives

[a] Patient demographics will be listed.

5.1.1.2.5 Medical History

Medical and ophthalmic 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) in total and by treatment group for the safety population as shown in Table 5-7.

Table 5-7 Medical History Summary

Parameter	Description	Timing	Methodology
Medical history	Abnormalities and surgeries	Past	Categorical descriptives
Medical condition at trial initiation	Abnormalities and surgeries	Currently at the time informed consent was obtained	Categorical descriptives
Ophthalmic history	Ophthalmic abnormalities and surgeries	Past	Categorical descriptives
Ophthalmic condition at	Ophthalmic abnormalities and surgeries	Currently at the time	Categorical

Parameter	Description	Timing	Methodology
trial nitiation		informed consent was obtained	descriptives

5.1.1.2.6 Prior and Concomitant Medications

Medications will be coded using the WHO Drug Dictionary Enhanced (DDE), version MAR2016 or newer. Unique patients who reported medications will be summarized by MedDRA SOC, and PT, and WHO DDE drug base preferred name in total and by treatment group for the safety population as shown in Table 5-8.

Table 5-8 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	Categorical descriptives
Concomitant medications	Medications taken ≥ 1 time on or after the study treatment start date, regardless of medication start date	Treatment period	Categorical descriptives

5.1.1.3 Exploratory Efficacy Analyses

[redacted]

5.1.1.3.1 Schirmer's Tear Test (With Anesthesia)

Schirmer's tear test (with anesthesia) will be summarized by treatment group as shown in Table 5-9.

Table 5-9 Schirmer's Tear Test Summaries

Endpoint	Description	Timing	Methodology
Schirmer's tear test score[a]	Summary by analysis visit	Cycle 1: Study baseline (Day 1) and Weeks 4, 8, 12, and 24 Cycle 2: Cycle baseline and Weeks 4R, 8R, and 12R	CFB descriptives
Number (percent) of responders	Summary by analysis visit • Responder defined as ≥ 10 mm/5 min increase from study baseline in Schirmer's tear test score	Cycle 1: Weeks 4, 8, 12, and 24	Categorical descriptives

[a] All schirmer's tear test data will be listed.

5.1.1.3.2 Tear Film Break-Up Time

Tear film break-up time (TBUT) will be summarized by treatment group as shown in Table 5-10.

Table 5-10 Tear Film Break-Up Time Summaries

Endpoint	Description	Timing	Methodology
TBUT	Summary by analysis visit • The average value of 3 measurements in each eye at each visit will be used	Cycle 1: Study baseline (Day 1) and Weeks 4, 8, 12, and 24 Cycle 2: Cycle baseline and Weeks 4R, 8R, and 12R	CFB descriptives

5.1.1.3.3 Sodium Fluorescein Corneal Staining

Sodium fluorescein corneal staining will be summarized by treatment group as shown in Table 5-11.

Table 5-11 Sodium Fluorescein Corneal Staining Summaries

Endpoint	Description	Timing	Methodology
CFB in ordinal scale	Summary by analysis visit	Cycle 1: Study baseline (Day 1) and Weeks 4, 8, 12, and 24 Cycle 2: Cycle baseline and Weeks 4R, 8R, and 12R	CFB descriptives

5.1.1.3.4 Lissamine Green Conjunctival Staining

Lissamine green conjunctival staining will be summarized by treatment group as shown in Table 5-12.

Table 5-12 Lissamine Green Conjunctival Staining Summaries

Endpoint	Description	Timing	Methodology
CFB in ordinal scale of conjunctival staining	Summary by analysis visit and by area (nasal, temporal) and in total • Total is calculated as the sum of areas – nasal and temporal	Cycle 1: Study baseline (Day 1) and Weeks 4, 8, 12, and 24 Cycle 2: Cycle baseline and Weeks 4R, 8R, and 12R	CFB descriptives

Endpoint	Description	Timing	Methodology
CFB in ordinal scale of total corneal and conjunctival staining	Summary by analysis visit • Total corneal and conjunctival staining is the sum of corneal staining plus conjunctival staining (nasal plus temporal)	Cycle 1: Study baseline (Day 1) and Weeks 4, 8, 12, and 24 Cycle 2: Cycle baseline and Weeks 4R, 8R, and 12R	CFB descriptives

5.1.1.3.5 Patient Symptoms (Visual Analog Scale)

A short questionnaire utilizing a VAS to quantify the severity of symptoms of dry eye will be administered. The questions refer to TODAY only including overall ocular discomfort from dry eye disease, level of discomfort experienced from symptoms as specified in Table 6-18. The score will be 0 to 100 with 0 = none and 100 = extreme.

Patient symptoms (VAS) will be summarized by treatment group as shown in Table 5-13.

Table 5-13 Patient Symptoms (Visual Analog Scale) Summaries

Endpoint	Description	Timing	Methodology
Overall VAS score[a]	Summary by analysis visit	Cycle 1: Study baseline (Day 1) and Weeks 12 and 24 Cycle 2: Cycle baseline and Weeks 8R and 12R	CFB descriptives
Worse VAS score[a]	Summary by analysis visit • For each patient, the symptom among all 9 symptoms (specified in Table 6-18) with the worst VAS at baseline (Day 1) will be used. If no single symptom can be identified at baseline (Day 1), the symptom with the worst VAS score at screening will be used.	Cycle 1: Study baseline (Day 1) and Weeks 12 and 24 Cycle 2: Cycle baseline and Weeks 8R and 12R	CFB descriptives

[a] All patient symptoms (VAS) data will be listed.

5.1.1.3.6 Ocular Surface Disease Index

The Ocular Surface Disease Index (OSDI) Questionnaire consists of 12 questions based on which the total score (questions 1-12) and 3 subscales including ocular symptoms (questions 1-3), vision-related functioning (questions 4-9), and environmental triggers (questions 10-12) will be computed. The patients will be asked to rate each symptom using a 5-point scale (0 to 4), where 0 = none of the time, 1 = some of the time, 2 = half of the time, 3 = most of the time, and 4 = all of the time. Seven questions allow a response of not applicable (N/A). A higher score represents greater disability.

The OSDI Questionnaire scores will be summarized by treatment group as shown in Table 5-14.

Table 5-14 Ocular Surface Disease Index Summaries

Endpoint	Description	Timing	Methodology
OSDI score[a]	Summary by analysis visit and by • The total OSDI score • The 3 subscale scores (specified in Table 6-20)	Cycle 1: Study baseline (Day 1) and Weeks 4, 12, and 24 Cycle 2: Cycle baseline and Weeks 4R and Week 12R	CFB descriptives
Number (percent) of responders	Summary by analysis visit • Responder is defined as ≥ 20 point decrease from study baseline in total OSDI score	Cycle 1: Weeks 4, 12, and 24	Categorical descriptives

[a] All ocular surface disease index data will be listed.

5.1.1.3.7 Treatment Assessment by Investigator

The follow-up investigator will complete a global evaluation of the overall effect of investigational medication administered in reference to the Baseline visit (Day 1) prior to the [redacted] of the investigational medication for each eye at the scheduled visits. The global evaluation score will be assessed based on the following scale:

0 = Completely cleared, no sign or symptom of disease
1 = Almost cleared: very significant clearance in disease with only traces of active disease remaining (approximately 90% improvement)
2 = Marked response: significant improvement with some disease remaining (approximately 75% improvement)
3 = Moderate response: intermediate improvement, between slight and marked (approximately 50% improvement)
4 = Slight response: some improvement in disease state but significant disease remains (approximately 25% improvement)
5 = Condition unchanged
6 = Condition worsened

Treatment assessment by investigator will be summarized by treatment group as shown in Table 5-15.

Table 5-15 Treatment Assessment by Investigator Summaries

Endpoint	Description	Timing	Methodology
Global evaluation score	Summary by analysis visit for the raw score	Cycle 1: Weeks 8, 12, and 24 Cycle 2: Week 8R, and Week 12R	Continuous descriptives

5.1.1.4 Safety Analyses

Safety analyses will be based on the safety population.

5.1.1.4.1 Study Treatment Exposure

Study treatment exposure and compliance will be summarized by treatment group for the safety population as shown in Table 5-16.

Table 5-16 Study Treatment Summaries

Parameter	Description	Timing	Methodology
Study treatment exposure (days)	Date of study exit – date of 1st injection + 1	Treatment period	Continuous descriptives

5.1.1.4.2 Adverse Events

Adverse events (AEs) are defined as shown in Table 5-17.

Table 5-17 AE Terms

Term	Description
TEAE	An adverse event recorded on the eCRF would be considered treatment-emergent if either of the following conditions are met: AE onset date ≥ first study treatment date; or AE onset date < first study treatment date and either: • the severity of the event worsened on or after the first study treatment date, or • the event became serious on or after the first study treatment date
SeriousTEAE	An event identified as TEAE that further meets SAE criteria at any time would be a serious TEAE.

SAE = serious adverse event; TEAE = treatment-emergent adverse event

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 for the safety population as shown in Table 5-18.

Table 5-18 AE Summaries

Parameter	Description	Timing	Methodology
Overall summary	Overall summary for the following categories: • TEAEs (ocular vs. non-ocular) • Study drug-related TEAEs (ocular vs. non-ocular) • Study procedure-related TEAEs (ocular vs. non-ocular) • Serious TEAEs (ocular vs. non-ocular) • TEAEs leading to study	From treatment start date until Week 24/Week 12R or early termination date, whichever comes first	Categorical descriptives

Parameter	Description	Timing	Methodology
	discontinuation (ocular vs. non-ocular) • Deaths		
TEAEs[a]	Overall summary and by SOC in alphabetical order, PT and worst severity The worst severity is defined as the greater of the onset severity and maximum severity following onset recorded on the eCRF. If the same TEAE term has been reported more than once for a subject with different severity grades, the worst severity grade will be used in the tabulation.	From treatment start date until Week 24/Week 12R or early termination date, whichever comes first	Categorical descriptives
Ocular TEAEs	Overall summary and by SOC in alphabetical order, PT and worst severity The worst severity is defined as the greater of the onset severity and maximum severity following onset recorded on the eCRF. If the same TEAE term has been reported more than once for a subject with different severity grades, the worst severity grade will be used in the tabulation.	From treatment start date until Week 24/Week 12R or early termination date, whichever comes first	Categorical descriptives
Study drug-related ocular TEAEs	Overall summary and by SOC in alphabetical order and PT	From treatment start date until Week 24/Week 12R or early termination date, whichever comes first	Categorical descriptives
Study procedure-related ocular TEAEs	Overall summary and by SOC in alphabetical order and PT	From treatment start date until Week 24/Week 12R or early termination date, whichever comes first	Categorical descriptives
Serious TEAEs	Overall summary and by SOC in alphabetical order and PT	From treatment start date until Week 24/Week 12R or early termination date, whichever comes first	Categorical descriptives
TEAEs leading to study discontinuation	Overall summary and by SOC in alphabetical order and PT	From treatment start date until Week 24/Week 12R or early termination date, whichever comes first	Categorical descriptives

eCRF = electronic case report form; PT = preferred term; SAE = serious adverse event; SOC = system organ class; TEAE = treatment-emergent adverse event

[a] All AEs including pretreatment AEs and TEAEs, and SAEs will be listed.

5.1.1.4.3 Clinical Laboratory Assessments

Clinical laboratory assessments will be summarized by treatment group for the safety population as shown in Table 5-19.

Table 5-19 Clinical Laboratory Summaries

Endpoint	Description	Timing	Methodology
Descriptives	Summary by laboratory category, parameter and analysis visit • Parameters specified in Table 6-22	Cycle 1: Study baseline (screening), Week 12 (for Cohorts 6C and 6D only), and Week 24 Cycle 2: Cycle baseline and Week 12R	CFB descriptives

5.1.1.4.4 Vital Signs

Vital signs will be summarized by treatment group for the safety population as shown in Table 5-20.

Table 5-20 Vital Signs Summaries

Endpoint	Description	Timing	Methodology
Descriptives	Summary by parameter and analysis visit • Parameters specified in Table 6-23	Cycle 1: Study baseline andWeeks 1, 8, 12 (for Cohorts 6C and 6D only), and 24 Cycle 2: Cycle baseline, Day 1R, and Week 12R	CFB descriptives

5.1.1.4.5 Other Safety Analyses

5.1.1.4.5.1 Best-Corrected Visual Acuity

Manifest refraction will be performed at screening and used for BCVA at all subsequent visits until study exit. If there is a decrease in BCVA, the manifest refraction should be repeated as confirmation. Visual acuity (in Snellen equivalents) will be measured for each eye using a logarithmic visual acuity chart for testing at 10 feet (3 meters) at the scheduled visits.

The visual acuity will be recorded on the eCRF in Snellen equivalent units (eg, 20/63) as the lowest line read with 1 or 0 mistakes.

The line CFB at each evaluation is calculated using the following algorithm:

line change = (10)*[$\log_{10}$ (XB/20) - $\log_{10}$ (XF/20)], where

- XB = denominator of the Snellen equivalent unit at baseline
- XF = denominator of the Snellen equivalent unit at post treatment visit

Each logarithmic value is to be rounded to the nearest tenth before subtraction. A positive value indicates an improvement and a negative value indicates a worsening. For example, the line change for a Snellen equivalent unit of 20/25 at baseline followed by a Snellen equivalent unit of 20/80 at day 2 would be

Line change = 10 x [$\log_{10}$(25/20) – $\log_{10}$ (80/20)] = 10 x (0.1 – 0.6) = -5

which represents a worsening of 5 lines in visual acuity.

BCVA will be summarized by treatment group for the safety population as shown in Table 5-21.

Table 5-21 BCVA Summaries

Endpoint	Description	Timing	Methodology

Line CFB[a]	Summary by analysis visit and line change categories defined below or line change of ≤ -2, -1, 0, +1, or ≥ +2:
	• Better (line changes of ≥ +2)
	• No change (line changes of -1, 0, +1)
	  ○ Line change of +1
	  ○ Line change of 0
	  ○ Line change of -1
	• Worse (line changes of ≤ -2)
		Cycle 1: Day 2 and Weeks 1, 2, 4, 8, 12, and 24
		
		Cycle 2: Day 1R and Weeks 1R, 4R, 8R, and 12R
			Categorical descriptives

CFB = change from baseline
[a] All BCVA will be listed.

5.1.1.4.5.2 Macroscopic Bulbar Hyperemia

The macroscopic (gross) bulbar hyperemia grading consists of global assessments and regional assessments, which will be done under consistent illumination by comparing the appearance of the bulbar conjunctiva to standard photographs (Allergan bulbar conjunctival hyperemia grading guide) at the scheduled visits. Regional assessment includes superior temporal, superior nasal, inferior temporal, and inferior nasal assessment. It will be graded using a 5-point scale described as follows:

0	(None)	=	Normal; vessels of bulbar conjunctiva easily observed
+0.5	(Trace)	=	Trace flush, reddish-pink color
+1	(Mild)	=	Mild flush, reddish color
+2	(Moderate)	=	Bright red color
+3	(Severe)	=	Deep, bright diffuse redness

Macroscopic bulbar hyperemia will be summarized by treatment group for the safety population as shown in Table 5-22.

Table 5-22 Macroscopic Bulbar Hyperemia Summaries

Endpoint	Description	Timing	Methodology
Global assessment: severity grade	Summary by analysis visit	Cycle 1: Study baseline (Day 1), Day 2, and Weeks 1, 2, 4, 8, 12, and 24 Cycle 2: Cycle baseline, Day 1R, and Weeks 1R, 4R, 8R, and 12R	Categorical descriptives

5.1.1.4.5.3 Slit-lamp Biomicroscopy

Slit-lamp biomicroscopy will be summarized by treatment group for the safety population. Biomicroscopy findings will be coded using MedDRA terminology and summarized for each eye by treatment group as shown in Table 5-23.

Table 5-23 Slit-lamp Biomicroscopy Summaries

Endpoint	Description	Timing	Methodology
One or more severity grade increase from baseline	Overall summary and by PT	From treatment start date until Week 24/Week 12R or early termination date, whichever comes first	Categorical descriptives

PT = preferred term

5.1.1.4.5.4 Dilated Ophthalmic Examinations

Ophthalmoscopy findings will be coded using MedDRA terminology.

Cup/disc ratio will be reported using a 0.0 to 1.0 scale. The Armaly chart provided by Allergan provides a pictorial scale of cup/disc ratio of 0.0 to 0.8. Only listing will be provided for cup/disc ratio.

Dilated ophthalmic examinations will be summarized by treatment group for the safety population as shown in Table 5-24.

Table 5-24 Dilated Ophthalmic Examinations Summaries

Endpoint	Description	Timing	Methodology
One or more severity grade increase from baseline	Overall summary and by PT	Week 12 (for Cohorts 6C and 6D only), Week 24/Week 12R or early termination date, whichever comes first	Categorical descriptives

PT = preferred term

5.1.1.4.5.5 Photographic Conjunctival Hyperemia

The photographic conjunctival hyperemia grading consists of global assessments and regional assessments, which will be done using a Canfield camera in each eye at the scheduled visits. Global assessment includes global, global nasal and global temporal assessment, and regional assessment includes superior temporal, superior nasal, inferior temporal, and inferior nasal assessment. It will be graded as 0 = none, +0.5 = trace, +1 = mild, +2 = moderate, +3 = severe, CG = cannot grade, and NE = not evaluated.

Photographic conjunctival hyperemia will be summarized by treatment group for the safety population as shown in Table 5-25.

Table 5-25 Photographic Conjunctival Hyperemia Summaries

Endpoint	Description	Timing	Methodology
Global assessment: severity grade	Summary by analysis visit	Cycle 1: Study baseline (Day 1), Day 2, and Weeks 1, 2, 4, 8, 12, and 24 Cycle 2: Cycle baseline, Day 1R, and Weeks 1R, 4R, 8R, and 12R	Categorical descriptives

5.1.1.4.5.6 Intraocular Pressure

Measurement of intraocular pressure (IOP) will be taken for each eye using the Goldmann applanation tonometer affixed to a slit lamp at the scheduled visits.

IOP will be summarized by treatment group for the safety population as shown in Table 5-26.

Table 5-26 Intraocular Pressure Summaries

Endpoint	Description	Timing	Methodology
IOP[a]	Summary by analysis visit	Cycle 1: Study baseline (Day 1), Week 12 (for Cohorts 6C and 6D only), and Week 24 Cycle 2: Cycle baseline, Week 12R	CFB descriptives

IOP = intraocular pressure
[a] All IOP data will be listed.

5.1.1.4.5.7 REFRESH PLUS Use

REFRESH PLUS use will be summarized by treatment group for the safety population as shown in Table 5-27.

Table 5-27 REFRESH PLUS Use and Compliance Summaries

Endpoint	Description	Timing	Methodology
REFRESH PLUS descriptives	Summary by analysis visit	Cycle 1: Study baseline (Day 1), Day 2, and Weeks 1, 2, 4, 8, 12, and 24 Cycle 2: Cycle baseline, Day 1R, and Weeks 1R, 4R, 8R, and 12R	CFB descriptives

5.1.1.5 Health Outcomes Data Analyses

The Supplemental Dry Eye Patient Reported Outcomes Questionnaire is a series of questions designed to gather information about the types and severity of dry eye symptoms that are experienced by patients in each eye. Health outcomes data will be summarized by treatment group for the mITT Population as shown in Table 5-28.

Table 5-28 Health Outcomes Data Summaries

Endpoint	Description	Timing	Methodology
Treatment satisfaction	Summary of raw score by analysis visit	Cycle 1: Weeks 4, 8, 12, and 24	Continuous descriptives

Endpoint	Description	Timing	Methodology
		Cycle 2: Weeks 4R, 8R, and 12R	

5.1.1.6 Subgroup Analyses

Subgroup analyses are not planned for stage 1.

5.1.1.7 Interim Analyses

An interim database lock of stage 1 will not be conducted until after all patients in Cohorts 1 through 6B complete the study and all patients in Cohorts 6C and 6D complete at least Week 1 following retreatment. Statistical analyses will be performed following the database lock to support the design of future clinical studies.

5.1.2 Determination of Sample Size

The sample size for stage 1 is determined empirically.

Stage 1: Stage 1 will have up to 63 patients and approximately 10 cohorts (Cohorts 1 to 6D). The anticipated numbers of patients per cohort are 3 for Cohort 1; 4 each for Cohorts 2, 6C, and 6D; and 8 each for Cohorts 3 through 6B.

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 definition of modified intent-to-treat (mITT) population is changed to all randomized patients who have baseline and at least 1 postbaseline assessment for 1 or more of the exploratory efficacy measurements from all patients who receive study treatment and have baseline and at least 1 postbaseline assessment for 1 or more of the exploratory efficacy measurements.

6. Data Handling and Analysis Conventions

6.1 Study Treatment Conventions

6.1.1 Analysis Days

Treatment days are defined as shown in Table 6-1.

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
	If analysis date < treatment start date:
	• Day = analysis date – treatment start date
	  ○ Day -1 = day before treatment start date
	  ○ There is no Day 0

6.2 Analysis Visit Windows

All stage 1 analyses will be performed based on the analysis visit windows defined below.

The analysis visit windows for exploratory efficacy and safety endpoints follow the schedule of visits in the protocol and are defined as follows:

6.2.1 Treatment Cycle 1

Table 6-2 Analysis Visit Definitions 1

Analysis Phase	Analysis Visit (Derived)	Target Number of Days from Treatment	Window[a]
Pretreatment	Study Baseline	Day 1	Treatment Day 1
Treatment	Day 2	Day 2	Treatment Day [2, 4]
	Week 1	Day 7	Treatment Day [5, 10]
	Week 2	Day 14	Treatment Day [11, 20]
	Week 4	Day 28	Treatment Day [21, 41]
	Week 8	Day 56	Treatment Day [42, 69]
	Week 12	Day 84	Treatment Day [70, 125]
	Week 24	Day 168	Treatment Day ≥126

For endpoints with scheduled visits of Study Baseline (Day 1), Day 2, Week 1, Week 2, Week 4, Week 8, Week 12, and Week 24.
[a] Study days are calculated based on the visit date – Treatment (Day 1) visit date + 1.

Table 6-3 Analysis Visit Definitions 2

Analysis Phase	Analysis Visit (Derived)	Target Number of Days from Treatment	Window[a]
Pretreatment	Study Baseline	Day 1	Treatment Day 1
Treatment	Week 4	Day 28	Treatment Day [2, 41]

Analysis Phase	Analysis Visit (Derived)	Target Number of Days from Treatment	Window[a]
	Week 8	Day 56	Treatment Day [42, 69]
	Week 12	Day 84	Treatment Day [70, 125]
	Week 24	Day 168	Treatment Day >=126

For endpoints with scheduled visits of Study Baseline (Day 1), Week 4, Week 8, Week 12, and Week 24.
[a] Study days are calculated based on the visit date – Treatment (Day 1) visit date + 1.

Table 6-4 Analysis Visit Definitions 3

Analysis Phase	Analysis Visit (Derived)	Target Number of Days from Treatment	Window[a]
Pretreatment	Study Baseline	Day 1	Treatment Day 1
Treatment	Week 1	Day 7	Treatment Day [2, 31]
	Week 8	Day 56	Treatment Day [32, 69]
	Week 12	Day 84	Treatment Day [70, 125]
	Week 24	Day 168	Treatment Day >=126

For endpoints with scheduled visits of Study Baseline (Day 1), Week 1, Week 8, Week 12, and Week 24.
[a] Study days are calculated based on the visit date – Treatment (Day 1) visit date + 1.

Table 6-5 Analysis Visit Definitions 4

Analysis Phase	Analysis Visit (Derived)	Target Number of Days from Treatment	Window[a]
Pretreatment	Study Baseline	Day 1	Treatment Day 1
Treatment	Week 1	Day 7	Treatment Day [2, 31]
	Week 8	Day 56	Treatment Day [32, 111]
	Week 24	Day 168	Treatment Day >=112

For endpoints with scheduled visits of Study Baseline (Day 1), Week 1, Week 8, and Week 24.
[a] Study days are calculated based on the visit date – Treatment (Day 1) visit date + 1.

Table 6-6 Analysis Visit Definitions 5

Analysis Phase	Analysis Visit (Derived)	Target Number of Days from Treatment	Window[a]
Pretreatment	Study Baseline	Day 1	Treatment Day 1
Treatment	Week 4	Day 28	Treatment Day [2, 55]
	Week 12	Day 84	Treatment Day [56, 125]
	Week 24	Day 168	Treatment Day >=126

For endpoints with scheduled visits of Study Baseline (Day 1), Week 4, Week 12, and Week 24.
[a] Study days are calculated based on the visit date – Treatment (Day 1) visit date + 1.

Table 6-7 Analysis Visit Definitions 6

Analysis Phase	Analysis Visit (Derived)	Target Number of Days from Treatment	Window[a]
Treatment	Week 8	Day 56	Treatment Day [2, 69]
	Week 12	Day 84	Treatment Day [70, 125]
	Week 24	Day 168	Treatment Day >=126

For endpoints with scheduled visits of Week 8, Week 12, and Week 24.
[a] Study days are calculated based on the visit date – Treatment (Day 1) visit date + 1.

Table 6-8 Analysis Visit Definitions 7

Analysis Phase	Analysis Visit (Derived)	Target Number of Days from Treatment	Window[a]
Pretreatment	Study Baseline	Day 1	Treatment Day 1
Treatment	Week 12	Day 84	Treatment Day [2, 125]
	Week 24	Day 168	Treatment Day >=126

For endpoints with scheduled visits of Study Baseline (Day 1), Week 12, and Week 24.
[a] Study days are calculated based on the visit date – Treatment (Day 1) visit date + 1.

Table 6-9 Analysis Visit Definitions 8

Analysis Phase	Analysis Visit (Derived)	Target Number of Days from Treatment	Window[a]
Pretreatment	Study Baseline	Day 1	Treatment Day 1
Treatment	Week 24	Day 168	Treatment Day >=2

For endpoints with scheduled visits of Study Baseline (Day 1), and Week 24.
[a] Study days are calculated based on the visit date – Treatment (Day 1) visit date + 1.

6.2.2 Treatment Cycle 2

Table 6-10 Analysis Visit Definitions 1 (Retreatment)

Analysis Phase	Analysis Visit (Derived)	Target Number of Days from Retreatment	Window[a]
Pre-retreatment	Cycle Baseline	Day 1	Retreatment Day 1 (Week 12 from treatment start)
Retreatment	Day 1R	Day 2	Treatment Day [2, 4]
	Week 1R	Day 7	Treatment Day [5, 17]
	Week 4R	Day 28	Treatment Day [18, 41]
	Week 8R	Day 56	Treatment Day [42, 69]
	Week 12R	Day 84	Treatment Day ≥70

For endpoints with scheduled visits of Cycle Baseline (Day 1), Day 1R, Week 1R, Week 4R, Week 8R, and Week 12R.
[a] Study days from retreatment are calculated based on the visit date – retreatment visit date + 1.

Table 6-11 Analysis Visit Definitions 2 (Retreatment)

Analysis Phase	Analysis Visit (Derived)	Target Number of Days from Retreatment	Window[a]
Pre retreatment	Cycle Baseline	Day 1	Retreatment Day 1 (Week 12 from treatment start)
Retreatment	Week 4R	Day 28	Treatment Day [2, 41]
	Week 8R	Day 56	Treatment Day [42, 69]
	Week 12R	Day 84	Treatment Day ≥ 70

For endpoints with scheduled visits of Cycle Baseline (Day 1), Week 4R, Week 8R, and Week 12R.
[a] Study days from retreatment are calculated based on the visit date – retreatment visit date + 1.

Table 6-12 Analysis Visit Definitions 3 (Retreatment)

Analysis Phase	Analysis Visit (Derived)	Target Number of Days from Retreatment	Window[a]
Pre retreatment	Cycle Baseline	Day 1	Retreatment Day 1 (Week 12 from treatment start)
Retreatment	Day 1R	Day 2	Treatment Day [2, 42]
	Week 12R	Day 84	Treatment Day ≥ 43

For endpoints with scheduled visits of Cycle Baseline (Day 1), Day 1R, and Week 12R.
[a] Study days from retreatment are calculated based on the visit date – retreatment visit date + 1.

Table 6-13 Analysis Visit Definitions 4 (Retreatment)

Analysis Phase	Analysis Visit (Derived)	Target Number of Days from Retreatment	Window[a]
Pre retreatment	Cycle Baseline	Day 1	Retreatment Day 1 (Week 12 from treatment start)
Retreatment	Week 8R	Day 56	Treatment Day [2, 69]
	Week 12R	Day 84	Treatment Day ≥ 70

For endpoints with scheduled visits of Cycle Baseline (Day 1), Week 8R, and Week 12R.
[a] Study days from retreatment are calculated based on the visit date – retreatment visit date + 1.

Table 6-14 Analysis Visit Definitions 5 (Retreatment)

Analysis Phase	Analysis Visit (Derived)	Target Number of Days from Retreatment	Window[a]
Pre retreatment	Cycle Baseline	Day 1	Retreatment Day 1 (Week 12 from treatment start)
Retreatment	Week 4R	Day 28	Treatment Day [2, 55]
	Week 12R	Day 84	Treatment Day ≥ 56

For endpoints with scheduled visits of Cycle Baseline (Day 1), Week 4R, and Week 12R.
[a] Study days from retreatment are calculated based on the visit date – retreatment visit date + 1.

Table 6-15 Analysis Visit Definitions 6 (Retreatment)

Analysis Phase	Analysis Visit (Derived)	Target Number of Days from Retreatment	Window[a]
Pre retreatment	Cycle Baseline	Day 1	Retreatment Day 1 (Week 12 from treatment start)
Retreatment	Week 12R	Day 84	Treatment Day ≥ 2

For endpoints with scheduled visits of Cycle Baseline (Day 1), and Week 12R.
[a] Study days from retreatment are calculated based on the visit date – retreatment visit date + 1.

The following general conventions will apply unless otherwise specified:

- If both scheduled and unscheduled visits occur within a single window, the scheduled visit will be used; unscheduled visits will be used only if there is no scheduled visits available in that window. If multiple visits are eligible for windowing within a single visit window, the visit closest to the target day will be used in the analysis. If multiple visits are equidistant to the target day, the latest visit will be used.
- For clinical laboratory variables, the latest nonmissing assessment within any analysis window will be flagged as the analysis value. This rule will be applied separately for each variable for nonmissing data only. (The exception is because re–runs of laboratory variables may only involve one or a few variables and would thus include missing data for many variables)
- All assessments will be included in respective listings.

6.3 Missing/Incomplete Date Conventions

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

Table 6-16 Imputation Scenarios

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

[a] 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 algorithm show in Table 6-17.

Table 6-17 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.

6.3.1 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

6.3.2 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

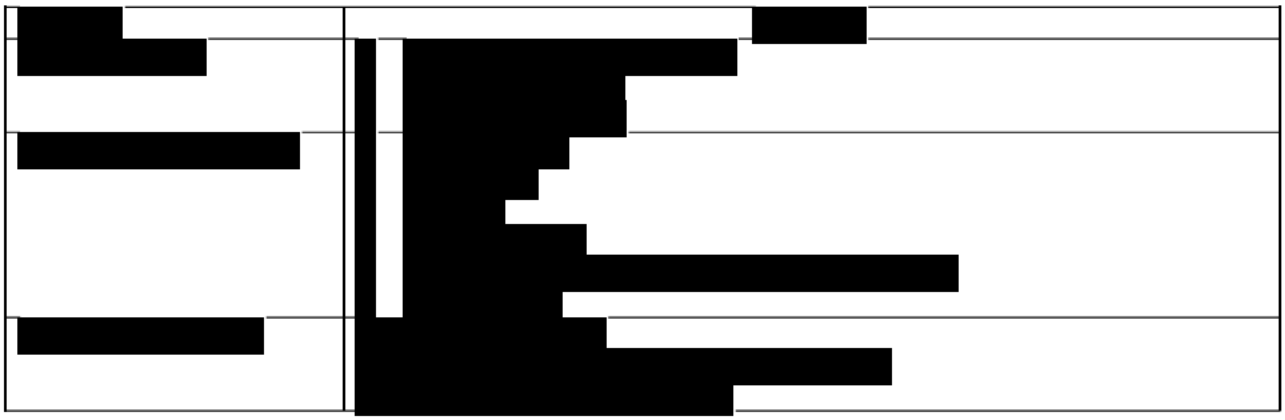
6.3.3 Missing/Incomplete AE/Medication End Date

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

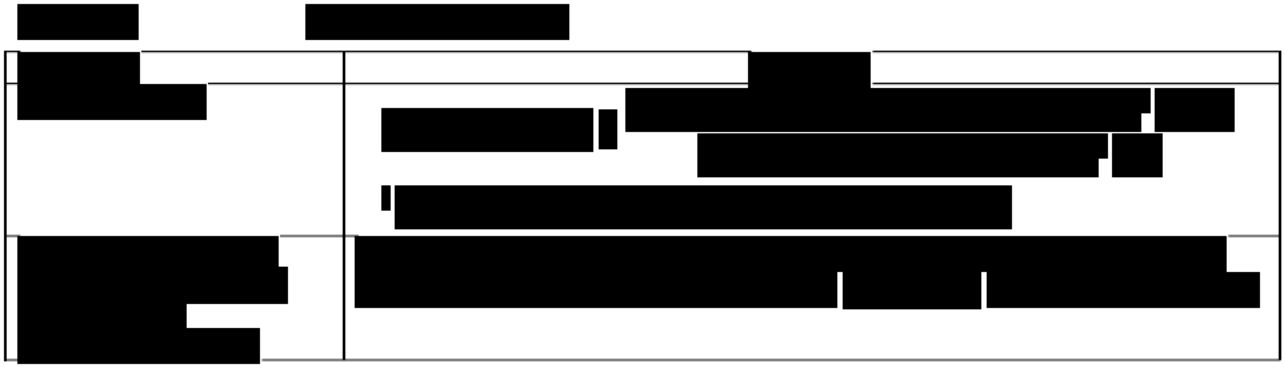
- Initial imputed date, where target date = from treatment start date until Week 24/Week 12R or early termination date, whichever comes first
- Death date

[redacted]

[redacted]



[redacted]



6.5 Safety Endpoint Conventions

6.5.1 Adverse Events

6.5.1.1 Missing Intensity or Relationship

If the investigator is unable to provide the actual values, the imputations will be applied as shown in Table 6-21.

Table 6-21 Missing AE Intensity and Relationship Imputation Algorithms

Missing Value	Imputation	Timing
Intensity	Mild	Screening Period
	Severe	Treatment Period
Relationship	—	Screening Period
	Related	Treatment Period

6.5.2 Clinical Laboratory Assessments

The laboratory parameters will be included as shown in Table 6-22.

Table 6-22 Clinical laboratory Parameters

Category	Parameters
Hematology	Hematocrit, hemoglobin, HbA1c mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelets, red blood cell (RBC) count, RBC morphology, total white blood cell (WBC) count, and differential (neutrophils, bands, lymphocytes, monocytes, basophils, and eosinophils)
Chemistry	Albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartase aminotransferase (AST), gamma-glutamyl transferase (GGT), bicarbonate, calcium, chloride, creatinine, creatine kinase, direct bilirubin, glucose, indirect bilirubin, magnesium, phosphorous, potassium, sodium, total bilirubin, total cholesterol, total protein, urea nitrogen, and uric acid
Urinalysis	Specific gravity, pH, color, protein, glucose, blood, bilirubin, and microscopic examination (WBC, RBC, epithelial cells, bacteria, mucus, casts, crystals)

6.5.3 Vital Signs

The vital sign parameters as shown in Table 6-23 will be summarized.

Table 6-23 Vital Sign Descriptive Parameters

Parameters		
Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Pulse rate (bpm)

6.5.4 Slit-lamp Biomicroscopy

The slit-lamp biomicroscopy examination consists of evaluation of the eye area/condition using a 5-point or 6-point scales, as well as present no or yes, as shown in Table 6-24.

Table 6-24 Slit-lamp Biomicroscopy Scales

Eye Area/Condition	Scale
Eyelids/Eyelid Margins/Lashes • Edema (eyelids) • Erythema Conjunctiva (Bulbar or Palpebral) • Hyperemia • Edema • Subconjunctival Hemorrhage Cornea • Edema • Superficial Punctate Keratopathy	0 (None) +0.5 (Trace) +1 (Mild) +2 (Moderate) +3 (Severe)
Anterior Chamber • Cells	0 = 0 cells +0.5 = 1 to 5 cells (trace) +1 = 6 to 15 cells

Eye Area/Condition	Scale
	+2 = 16 to 25 cells +3 = 26 to 50 cells +4 = > 50 cells
Anterior Chamber • Flare	0 = None: no flare seen +1 = Faint: faint flare seen +2 = Moderate: iris and lens details clear +3 = Marked: iris and lens details hazy +4 = Intense: fibrin or plastic aqueous
Presence of Iris/Pupil Pathology and Other Pathology	Yes No
Other Pathology if present	+0.5 (trace) +1 (mild) +2 (moderate) +3 (severe)

Explanation:

Eyelids/Eyelid Margins/Lashes

Edema (eyelids)

0	(None)	No edema
+0.5	(Trace)	Localized, minimal (trace) swelling
+1	(Mild)	Localized, mild swelling
+2	(Moderate)	Diffuse, moderate swelling
+3	(Severe)	Diffuse, severe swelling

Erythema

0	(None)	No erythema
+0.5	(Trace)	Localized, minimal (trace) flush reddish color
+1	(Mild)	Localized, mild, flush reddish color
+2	(Moderate)	Diffuse reddish color encompassing the entire lid margin
+3	(Severe)	Deep diffuse reddish color of lid margins and superior and/or inferior eyelid

Conjunctiva (Bulbar or Palpebral)

Hyperemia

0	(None)	No hyperemia
+0.5	(Trace)	Minimal (trace) flush, reddish color
+1	(Mild)	Mild flush, reddish color
+2	(Moderate)	Bright red color
+3	(Severe)	Deep, bright diffuse redness

Edema

0	(None)	No edema
+0.5	(Trace)	Localized, minimal (trace) swelling

+1	(Mild)	Localized, mild swelling
+2	(Moderate)	Diffuse, moderate swelling
+3	(Severe)	Diffuse, severe swelling

Subconjunctival Hemorrhage

0	(None)	No hemorrhage
+0.5	(Trace)	Flat hemorrhage ≤ 1 quadrant
+1	(Mild)	Elevated hemorrhage ≤ 1 quadrant, or flat and > 1 quadrant
+2	(Moderate)	Elevated hemorrhage > 1 but ≤ 2 quadrants
+3	(Severe)	Elevated hemorrhage > 2 quadrants

Cornea

Edema

0	(None)	No edema
+0.5	(Trace)	Localized, minimal (trace) epithelial haze
+1	(Mild)	Dull glass appearance of epithelium that may include fine localized microcystic changes
+2	(Moderate)	Dull glass appearance of epithelium with large number of cystic changes with or without stromal edema
+3	(Severe)	Epithelial bullae and/or stromal edema, localized or diffuse, with or without stromal striae

Superficial Punctate Keratopathy

0	=	No superficial punctate keratopathy
+0.5	=	Trace
+1	=	Mild
+2	=	Moderate
+3	=	Severe

Anterior Chamber

Cells

0	=	0 cells
+0.5	=	1 to 5 cells (trace)
+1	=	6 to 15 cells
+2	=	16 to 25 cells
+3	=	26 to 50 cells
+4	=	> 50 cells

Flare

0	=	None: no flare seen
+1	=	Faint: faint flare seen
+2	=	Moderate: iris and lens details clear
+3	=	Marked: iris and lens details hazy
+4	=	Intense: fibrin or plastic aqueous

Iris/Pupil and Other Pathology

The presence of iris/pupil pathology and any other pathology will be evaluated. Other pathology will be graded as +0.5 = trace, +1 = mild, +2 = moderate, and +3 = severe.

6.5.5 Dilated Ophthalmic Examinations

The evaluation of dilated ophthalmic examinations is shown in Table 6-25.

Table 6-25 Dilated Ophthalmic Examinations Grade

Description	Grade

Lens Status:
• Phakic
  ○ Cortical lens opacity
  ○ Nuclear lens opacity
  ○ Posterior Subcapsular lens opacity
• Pseudophakic
• Aphakic
	Severity:
	0 (None)
	1 (Mild)
	2 (Moderate)
	3 (Severe)

Presence of Other Pathology	Yes No
Other pathology if present: • Lens • Vitreous • Fundus • Optic nerve	+0.5 (Trace) +1 (Mild) +2 (Moderate) +3 (Severe) NE (Not Evaluable)

6.6 Health Outcomes Endpoint Conventions

The supplemental dry eye questionnaire will be collected as shown in Table 6-26.

Table 6-26 Supplemental Dry Eye Questionnaire

Dry Eye Symptoms Questionnaire	Score
In the last 7 days, have you experienced the following symptoms in your right (or left) eye? 1. Dryness 2. Sensitivity to light 3. Pain 4. Decreased or blurred vision 5. Tearing 6. Experienced feeling like something doesn't belong in your eye 7. Secretion or discharge 8. Burning or stinging 9. Redness 10. Swelling in the upper eyelid 11. Swelling in the lower eyelid 12. Irritation 13. Grittiness or feeling as if small specks of sand are in your eye 14. Discomfort	Frequency: • 0=All of the time • 1=Most of the time • 2=Half of the time • 3=Some of the time • 4=None of the time Severity: • 0=Very mild • 1=Mild • 2=Moderate • 3=Severe • 4=Very severe
Treatment Satisfaction Questionnaire	

Dry Eye Symptoms Questionnaire	Score
Taking your entire treatment experience into consideration, if given the choice again, how likely would you be to repeat the procedure you received in your right (or left) eye?	• 0=Very unlikely • 1=Unlikely • 2=Neither likely or unlikely • 3=Likely • 4=Very likely Mild

6.7 Imputed Value Listing Conventions

In general, listings will present the actual partial or missing values rather than the imputed values.

ALLERGAN

[redacted]

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