NCT Number: NCT04139122

Protocol Number: SJP-0132/1-01

Study Title:
A Randomized, Double-Masked, Single-Center, Placebo-Controlled Single and Multiple Ascending Dose Study to Assess Safety, Tolerability, Pharmacokinetics, and Efficacy of SJP-0132 in Subjects with Dry Eye Disease

Protocol Version: Version 3.0: 12 December, 2019

Protocol Title:

A Randomized, Double-Masked, Single-Center, Placebo-Controlled Single and Multiple Ascending Dose Study to Assess Safety, Tolerability, Pharmacokinetics, and Efficacy of SJP-0132 in Subjects with Dry Eye Disease

Protocol Number: SJP-0132/1-01

Version Number： 3.0

Compound Number: SJP-0132

Short Title:

Safety, PK, and efficacy of SJP-0132 in subjects with dry eye disease

Phase of Development: 1/2

Sponsor Name and Legal Registered Address:

Senju Pharmaceutical Co., Ltd.

3-1-9, Kawara-machi, Chuo-ku, Osaka 541-0048, Japan

[redacted]

Approval Date: 12 December, 2019

PROTOCOL APPROVAL — Sponsor Signatory

Study Title	A Randomized, Double-Masked, Single-Center, Placebo-Controlled Single and Multiple Ascending Dose Study to Assess Safety, Tolerability, Pharmacokinetics, and Efficacy of SJP-0132 in Subjects with Dry Eye Disease
Protocol Number	SJP-0132/1-01
Protocol Date	Protocol Version 3.0; 12 December 2019

Protocol accepted and approved by:

Sponsor's Responsible Representative

Name:	[redacted]
Institution and Address:	[redacted]
Telephone number:	[redacted]

Signature: _____ Date: _____
(Day Month Year)

PROTOCOL APPROVAL — Principal Investigator

Study Title	A Randomized, Double-Masked, Single-Center, Placebo-Controlled Single and Multiple Ascending Dose Study to Assess Safety, Tolerability, Pharmacokinetics, and Efficacy of SJP-0132 in Subjects with Dry Eye Disease
Protocol Number	SJP-0132/1-01
Protocol Date	Protocol Version 3.0; 12 December

Protocol accepted and approved by:

Principal Investigator

Name:	[redacted]
Institution and Address:	[redacted]
Telephone number:	[redacted]

Signature: _____ Date: _____
(Day Month Year)

INVESTIGATOR AGREEMENT

I have read and understood all sections of the protocol entitled "A Randomized, Double-Masked, Single-Center, Placebo-Controlled Single and Multiple Ascending Dose Study to Assess Safety, Tolerability, Pharmacokinetics, and Efficacy of SJP-0132 in Subjects with Dry Eye Disease" and the accompanying Investigator's Brochure, Version 2.0.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 3.0, dated 12 December 2019, the International Council for Harmonisation harmonised tripartite guideline E6: Good Clinical Practice, and all applicable government regulations. I will not make changes to the protocol before consulting with Senju Pharmaceutical Co., Ltd., nor will I implement protocol changes without independent ethics committee approval, except to eliminate an immediate risk to subjects. I agree to administer study treatment only to subjects under my personal supervision or the supervision of a subinvestigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Subject identity will not be disclosed to third parties or appear in any study report or publication.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Senju Pharmaceutical Co., Ltd.

Principal Investigator

Name:	[redacted]
Institution and Address:	[redacted]
Telephone number:	[redacted]

Signature: _____ Date: _____
(Day Month Year)

STUDY ADMINISTRATION

Study Role	**Name, title, contact information**
Sponsor	Senju Pharmaceutical Co., Ltd.
Sponsor Signatory	[redacted]
Sponsor Pharmacovigilance	[redacted]
Contract Research Organization	WCCT Global, Inc. 5630 Cerritos Ave. Cypress, CA 90630 United States
Principal Investigator	[redacted]
Medical Monitor	[redacted]
Clinical laboratory	[redacted]

Bioanalytical laboratory (PK-analysis)	[redacted]

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 1 (Protocol Version 3.0)	12 Dec 2019
Revision (Protocol Version 2.0)	21 Aug 2019
Original Protocol (Protocol Version 1.0)	29 July 2019

Amendment 1 (12 Dec 2019)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The timing of some of the End-of-Study assessments for Part B was modified.

Section # and Name	**Description of Change**	**Brief Rationale**
2, Schedule of Activities, Part B, EOS	Shifted hematology, serum chemistry, urinalysis, and serum pregnancy test to 2h postdose. Shifted physical examination, weight, and vital signs to 4h postdose. Shifted visual acuity (Snellen), slit lamp biomicroscopy w/out mydriatics, Schirmer I w/o anesthesia, intraocular pressure, slit lamp biomicroscopy w/ mydriatics (lens observation), and ophthalmoscopy to 8h postdose.	Adjustments to timing of assessments to occur after dosing.
9, Study Assessments and Procedures, Part B, Day 29 ±2, EOS	Timing of assessments modified according to Schedule of Activities	Consistency

Revision 1 (21 Aug 2019)

Minor editorial changes only. This version was submitted to the US Food and Drug Administration.

Table of Contents

In-Text Tables

1. Synopsis

Protocol Title:

A Randomized, Double-Masked, Single-Center, Placebo-Controlled Single and Multiple Ascending Dose Study to Assess Safety, Tolerability, Pharmacokinetics, and Efficacy of SJP-0132 in Subjects with Dry Eye Disease

Short Title:

Safety, PK and efficacy study of SJP-0132 in subjects with dry eye disease

Phase of Development: 1/2

Rationale:

This is the first study in humans to evaluate the effectiveness of SJP-0132 in the treatment of dry eye disease. [redacted]

Objectives and Endpoints

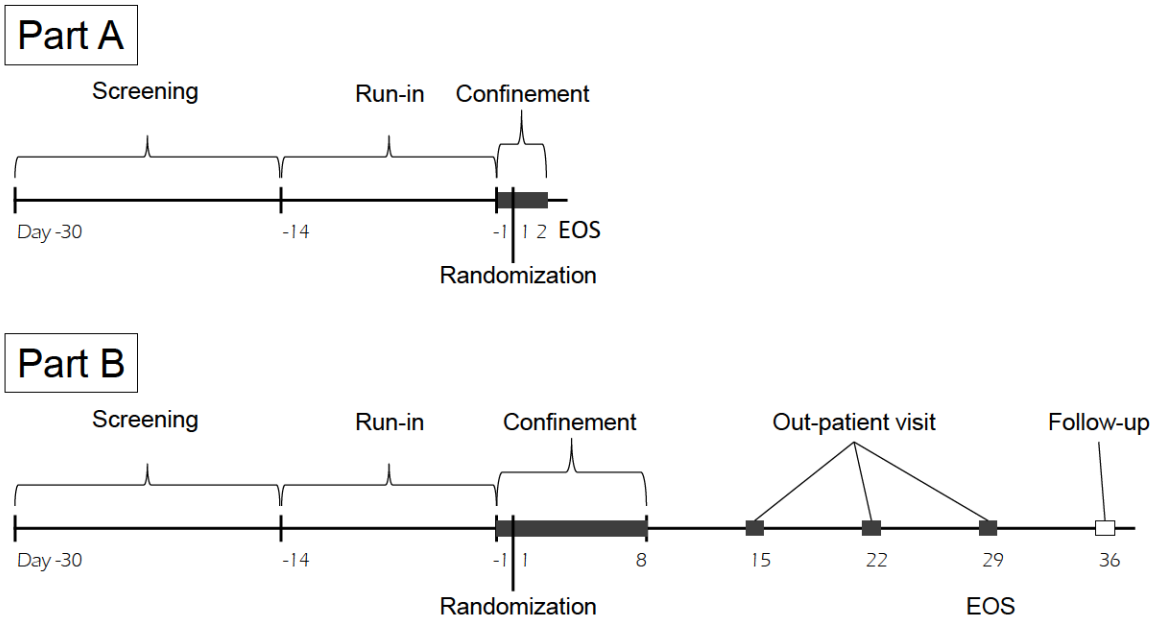
Objectives	Endpoints
Primary	
• Safety and tolerability of SJP-0132	• The number and severity of AEs including abnormal changes from baseline in clinical laboratory results, vital signs, and physical and ophthalmologic examinations
• Pharmacokinetic (PK) profiles of SJP-0132	• Part A: C_{max}, t_{max}, t_{last}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}\infty}$, $t_{1/2}$, $AUC_{\%extrap}$, $AUMC_{0\text{-}last}$, $AUMC_{0\text{-}\infty}$, $MRT_{0\text{-}last}$, $MRT_{0\text{-}\infty}$, Vd/F, CL/F, $C_{max,norm}$, $AUC_{0\text{-}last,norm}$, and $AUC_{0\text{-}\infty,norm}$ • Part B: C_{max}, t_{max}, t_{last}, $AUC_{0\text{-}last}$, $C_{max,norm}$, and $AUC_{0\text{-}last,norm}$ on Day 1, C_{trough} on Days 2, 4 and 8, and Rac
• Efficacy of SJP-0132	• Change from baseline (predose on Day 1) in eye dryness symptom (visual analog scale [VAS]) at 4 hours on Day 29 • Change from baseline (predose on Day 1) in corneal fluorescein staining (CFS) score at the central zone on Day 29
Secondary	
• Efficacy of SJP-0132	• Changes from baseline in dry eye signs: CFS scores at the central, superior, inferior, nasal, temporal and total zones,

	conjunctival lissamine green staining (CLGS) scores at each of 3 nasal and 3 temporal zone and total zone of bulbar conjunctiva, lid wiper epitheliopathy score, and tear film break-up time (TFBUT) at each time point tested • Changes from baseline in dry eye symptoms (VAS [ie, severity of eye dryness, discomfort, burning/stinging, sticky feeling, foreign body sensation, itching, pain, blurred vision, and sensitivity to light], ocular surface disease index [OSDI®], Dry eye Questionnaire 5 [DEQ-5] scores) at each time point tested • Biomarker (Matrix Metalloproteinase-9 (MMP-9), InflammaDry®)

Overall Design:

This is a randomized, double-masked, placebo-controlled single and multiple ascending dose study of SJP-0132 in subjects with dry eye disease who have frequent ocular discomfort or dryness. Non-Japanese subjects will be enrolled in Part A and both Japanese and non-Japanese subjects will be enrolled in Part B.

After Screening (including review of laboratory results), placebo medication will be dispensed to all eligible subjects to be instilled as one drop in each eye [redacted] (Placebo Run-In Phase). Subjects will be admitted to the study center on Day -1 and undergo physical and ophthalmic examinations as shown in Section 2, Schedule of Activities.



Part A

In Part A, 32 non-Japanese subjects will be admitted to the study center on Day -1 and discharged on Day 2 after completion of assessments and blood collections. Subjects will be randomized to receive a single dose of placebo or SJP-0132 ophthalmic [redacted] concentrations of 0.03%, 0.1%, 0.3%, or 1% on Day 1 after confirmation of continued eligibility. All treatments will be administered in both eyes.

Blood for PK measurements will be collected before dosing and at the timepoints specified in the Schedule of Activities (SoA). Eye and safety assessments will be done as indicated below.

After each cohort completes the single dose of SJP-0132 ophthalmic [redacted] or placebo, the Investigator and the Sponsor will assess the data to confirm adequate safety and tolerability while the next cohort begins the Run-in Phase. A written report will be provided.

After completion of the single dose cohorts, a safety review will be conducted to identify the maximum acceptable dose and the second maximum acceptable dose of study drug. The maximum and second maximum acceptable doses of study drug will be selected for the multiple dose study (Part B) in subjects with dry eye disease. Maximum acceptable dose is the highest dose at which no more than 1 subject experiences a severe drug-related AE.

Part B

In Part B, 60 Japanese and non-Japanese subjects will be admitted to the study center on Day -1 and discharged on Day 8 after completion of assessments and blood collections. Subjects will be randomized to receive placebo or SJP-0132 ophthalmic [redacted] on Day 1 after confirmation of continued eligibility.

The first cohort randomized in Part B (Cohort 5) will receive the second maximum acceptable concentration of SJP-0132 ophthalmic [redacted] or placebo [redacted] for 4 weeks. The second cohort randomized in Part B (Cohort 6) will receive the maximum acceptable dose of SJP-0132 ophthalmic [redacted] or placebo [redacted] for 4 weeks. All treatments will be administered in both eyes.

After Cohort 5 completes the 7-day inpatient assessment of SJP-0132 ophthalmic [redacted] or placebo, the Investigator and the Sponsor will assess the data (AEs, clinical laboratory results, vital signs, ophthalmic examinations) to confirm adequate safety and tolerability before allowing a cohort of the next dose level (Cohort 6) to begin. A written report will be provided.

All subjects who complete the Day 29 ±2 EOS visit, will receive a follow-up telephone call on Day 36 ±2 to review AEs and medication use.

For any subjects who receive at least one dose of study drug and discontinue or withdraw from study participation prior to the Day 29 ±2 EOS visit, subjects should complete the EOS visit at the time of discontinuation/withdrawal. Discontinued/withdrawn subjects will also be contacted by telephone 7 days later for follow-up.

Pharmacokinetic (PK) blood draws will be collected prior to dosing on Days 1, 2, 4, and 8, and after dosing on Day 1 at timepoints specified in SoA.

For all subjects in Part A and Part B, the following eye assessments will be done according to the SoA: VAS, visual acuity (by Snellen), corneal aesthesiometry (Cochet-Bonnet),DEQ-5, OSDI®,

slit-lamp biomicroscopy, VAS with anesthesia, intraocular pressure (iCare), fluorescein staining (Baylor Scales), lissamine green staining (Baylor Scales +lid margins [lid wiper epitheliopathy]), Schirmer I test (without anesthesia), tear film break up time (TFBUT), ophthalmoscopy, and matrix metalloproteinase-9 (MMP-9). All ocular exams will be completed for both eyes (study eye and non-study eye) at all timepoints.

For all subjects in Part A and Part B, the following safety assessments will include changes in vital signs (blood pressure, heart rate, oral body temperature (°C), respiratory rate), clinical laboratory results (hematology, clinical chemistry, and urinalysis), adverse events (AEs), concomitant medication use, physical examinations. Additionally, the subjects' overall ocular irritation will be assessed.

In case any medically significant suspected adverse reactions or findings are observed, the Data and Safety Monitoring Board (i.e., consisting of the Investigator, Sponsor, and pharmacovigilance physician) will make a decision for future course of action.

Number of Subjects:

Approximately 226 subjects will be screened to achieve 32 completers in treatment in Part A and 60 completers in Part B.

Treatment Groups and Duration:

Part A: 4 cohorts consisting of 8 subjects each (non-Japanese), with 6 subjects randomized to SJP-0132 ophthalmic [redacted] and 2 randomized to placebo.

- Cohort 1: 0.03% SJP-0132 / Placebo
- Cohort 2: 0.1% SJP-0132 / Placebo
- Cohort 3: 0.3% SJP-0132 / Placebo
- Cohort 4: 1% SJP-0132 / Placebo

Part B: 2 cohorts consisting of 30 subjects each (9 Japanese and 21 non-Japanese) 20 randomized to SJP-0132 ophthalmic [redacted] and 10 randomized to placebo

Cohort#	Active		Placebo		Total
	JP	Non-JP	JP	Non-JP	
5	6	14	3	7	30
6	6	14	3	7	30
Total	12	28	6	14	60

JP = Japanese

For Part A, subject participation will be approximately 32 days, including Screening. For Part B, subject participation will be approximately 9 weeks, including Screening. Total study duration is anticipated to be 3 months.

Investigational Product, Dose, and Mode of Administration

One drop of SJP-0132 ophthalmic [redacted] instilled in both eyes [redacted]

Statistical Methods

The primary statistical analysis of the data will be descriptive in nature. For continuous variables this means calculation of the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by subject counts and related percentages. For ordinal-scaled variables, a combination of the above may be employed as appropriate: frequency and percentage of observations within a category and means and standard deviations of the scores of the categories. For categorical and ordinal variables, percentages will be calculated based on non-missing data.

Sample Size Determination:

No formal sample size and/or power calculations were performed for the study, however a sample size was chosen based on feasibility to allow total of 92 randomized subjects for Part A (n=32) and Part B (n=60). Approximately 32 subjects are expected to complete Part A and 60 subjects are expected to complete Part B.

Safety Analysis:

Safety assessments and changes from baseline in vital signs, clinical laboratory results, adverse events (AEs), will be summarized using descriptive statistics (mean, standard deviation, coefficient of variation (%CV), median, minimum, and maximum). Concomitant medications and physical examination findings will be listed.

Efficacy Analysis:

The study eye will be the eye with the greater central zone corneal fluorescein staining. If both eyes meet all of the inclusion and none of the exclusion criteria and the central zone corneal fluorescein staining scores are equal, the right eye (OD) will be designated as the study eye for the duration of this study.

The fellow eye (non-study eye) will be treated with the product as per the assigned dosing schedule.

Change in eye assessments will be summarized using descriptive statistics (mean, standard deviation, coefficient of variation (%CV), median, minimum, and maximum). The primary endpoint is the difference between SJP-0132 and placebo in changes in eye dryness symptom (visual analog scale [VAS]). Secondary endpoints are changes in dry eye signs (vital staining of cornea, conjunctiva and lid margin, tear film break-up time (TFBUT), and changes in dry eye symptoms (VAS [ie, severity of eye dryness, discomfort, burning/stinging, sticky feeling, foreign body sensation, itching, pain, blurred vision, and sensitivity to light], ocular surface disease index [OSDI®], Dry eye Questionnaire 5 [DEQ-5] scores).

Pharmacokinetic Analysis:

Plasma samples will be analyzed to determine the concentration of SJP-0132. Pharmacokinetic variables will be calculated using non-compartmental analysis. Part A: C_{max}, t_{max}, t_{last}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}\infty}$, $AUC_{\%extrap}$, $t_{1/2}$, $AUMC_{0\text{-}last}$, $AUMC_{0\text{-}\infty}$, $MRT_{0\text{-}last}$, $MRT_{0\text{-}\infty}$, Vd/F, CL/F, $C_{max,norm}$, $AUC_{0\text{-}last,norm}$, $AUC_{0\text{-}\infty,norm}$. Part B: C_{max}, t_{max}, t_{last}, $AUC_{0\text{-}last}$, $C_{max,norm}$, and $AUC_{0\text{-}last,norm}$ on Day 1, C_{trough} on Days 2, 4 and 8, and Rac. The PK data will be summarized using descriptive statistics and will also be displayed graphically as appropriate.

2. Schedule of Activities (SoA)

Part A (SAD)	**Screen**	**Run-in**	**Check In**	**Treatment Phase**								**Check Out**
Procedure ***All 0h assessments will be performed prior to Drug administration.***	**Day -30 to Day -15**	**Day -14 (+2)[5] to Day -2**	**Day -1**	**Day 1**								**Day 2**
				0 h	**0.25 h**	**0.5 h**	**1 h**	**2 h**	**4 h**	**8 h**	**12 h**	**0 h**
Informed Consent / HIPAA	X											
Demography	X											
Medical / Surgical History	X		X									
Inclusion/Exclusion Criteria	X		X									
Physical Examination[1]	X			X			X					X
Height	X											
Weight	X		X									
Vital signs[2]	X		X	X		X	X	X	X	X	X	X
DEQ-5 [3]	X		X									
VAS [3]	X		X	X		X	X	X	X	X	X	X
OSDI© [3]	X		X									
Hematology, Serum Chemistry, Urinalysis	X		X									X
Serology (HIV, HBsAg, HCV)	X											
Serum pregnancy test and FSH (WOCBP only)	X											
Pharmacokinetic Sampling				X	X	X	X	X	X	X	X	
Urine drug and alcohol screen	X		X									
Urine Pregnancy Test			X									
Visual Acuity (Snellen)	X		X								X	X
Slit lamp biomicroscopy (w/out mydriatics)	X			X			X	X			X	X
Matrix Metalloproteinase-9 (MMP-9)[4]	X		X									
TFBUT	X			X				X			X	X
Corneal fluorescein staining (Baylor)	X		X	X				X			X	X
Lissamine green staining (Baylor + Lid Margin)	X			X								
Aesthesiometer	X											
Schirmer I w/o anesthesia	X		X								X	X
VAS w/ anesthesia	X											
Intraocular Pressure (iCare tonometer)	X			X				X			X	X
Slit lamp biomicroscopy (w/ mydriatics; lens observation)	X		X								X	X
Ophthalmoscopy	X		X								X	X
Record and assess adverse events		Continuous										
Concomitant Medications		Continuous										
Confinement Period		X										
Randomization				X								
Drug Administration		Placebo[6]	Placebo[6]	X								

HIPAA = Health Information Portability and Accountability Act; VAS = Visual Analog Scale; TFBUT = Tear film break-up time; OSDI = Ocular Surface Disease Index; WOCBP = women of child-bearing potential

[1] Physical Examination includes head-eye-ears-nose-throat, cardiovascular, respiratory, gastrointestinal, dermatologic, and neurologic examinations.

[2] Blood pressure, heart rate, respiratory rate, oral temperature.

[3] Questionnaires will be completed prior to lab or PK timepoints. Ophthalmic assessments will follow lab or PK timepoints.

[4] 30 minutes before staining tests

[5] Day -14 can be completed within +2 days (Day -14 to Day -16), however Placebo Run-In dosing will begin on Day -14 per protocol

[6] For Placebo Run-In (Day -14 visit) subjects will be dispensed placebo and educated in administration and dosing diary completion.

Part B (MAD) (3 pages)	**Screen**	**Run-In**	**Check In**	**Treatment Period**															
Procedure ***All 0h assessments will be performed prior to Drug administration.***	**Day -30 to Day -15**	**Day -14 (+2)[5] to Day -2**	**Day –1**	**Day 1**								**Day 2**				**Day 3**			
				0 h	**0.25 h**	**0.5 h**	**1 h**	**2 h**	**4 h**	**8 h**	**12 h**	**0 h**	**4 h**	**8 h**	**12 h**	**0 h**	**4 h**	**8 h**	**12 h**
Informed Consent/HIPAA	X																		
Demography	X																		
Medical/Surgical history	X		X																
Inclusion/Exclusion Criteria	X		X																
Physical examinations[1]	X			X			X					X				X			
Height	X																		
Weight	X		X																
Vital signs[2]	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
DEQ-5 [3]	X		X																
VAS [3]	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
OSDI© [3]	X		X																
Hematology, Serum Chemistry, Urinalysis	X		X																
Serology (HIV, HBsAg, HCV)	X																		
Serum pregnancy test and FSH (WOCBP only)	X																		
Pharmacokinetic Sampling				X	X	X	X	X	X			X							
Urine drug and alcohol screen	X		X																
Urine pregnancy test			X																
Visual acuity (Snellen)	X		X								X	X				X			
Slit lamp biomicroscopy (w/out mydriatics)	X			X			X	X			X	X			X	X			X
Matrix Metalloproteinase-9 (MMP-9)[4]	X		X																
TFBUT	X			X				X			X	X			X	X			X
Corneal fluorescein staining (Baylor)	X		X	X				X			X	X			X	X			X
Lissamine green staining (Baylor +Lid Margin)	X			X							X	X			X	X			X
Aesthesiometer	X																		
Schirmer I w/o anesthesia	X		X								X	X							
VAS w/ anesthesia	X																		
Intraocular pressure (iCare tonometer)	X			X							X	X				X			
Slit lamp biomicroscopy (w/ mydriatics; lens observation)	X		X								X								
Ophthalmoscopy	X		X								X								
Record and assess adverse events		Continuous																	

Part B (MAD) (3 pages)	**Screen**	**Run-In**	**Check In**	**Treatment Period**															
Procedure ***All 0h assessments will be performed prior to Drug administration.***	**Day -30 to Day -15**	**Day -14 (+2)[5] to Day -2**	**Day –1**	**Day 1**								**Day 2**				**Day 3**			
				0 h	**0.25 h**	**0.5 h**	**1 h**	**2 h**	**4 h**	**8 h**	**12 h**	**0 h**	**4 h**	**8 h**	**12 h**	**0 h**	**4 h**	**8 h**	**12 h**
Concomitant medications		Continuous																	
Confinement Period			Day -1 until Day 8																
Randomization				X															
Drug administration		Placebo[6]	Placebo[6]	X					X	X	X	X	X	X	X	X	X	X	X

HIPAA = Health Information Portability and Accountability Act; VAS = Visual Analog Scale; TFBUT = Tear film break-up time; OSDI = Ocular Surface Disease Index; WOCBP = women of childbearing potential; FSH = follicle stimulating hormone

[1] Physical Examination includes head-eye-ears-nose-throat, cardiovascular, respiratory, gastrointestinal, dermatologic, and neurologic examinations.

[2] Blood pressure, heart rate, respiratory rate, oral temperature.

[3] Questionnaires will be completed prior to lab or PK timepoints. Ophthalmic assessments will follow lab or PK timepoints.

[4] 30 minutes before staining tests

[5] Day -14 can be completed within +2 days (Day -14 to Day -16), however Placebo Run-In will begin on Day -14, per protocol

[6] For Placebo Run-In (Day -14 visit) subjects will be dispensed placebo and will be educated in self -administration and dosing diary completion.

Part B (MAD) (3 Pages)	**Treatment Period (continued)**																				**EOS**				**Follow Up**
Procedure ***All 0h assessments will be performed <u>prior to</u> Drug administration.***	**Day 4 to Day 7**							**Day 8 (Check Out)**				**Day 9 to Day 28 dosing**				**Outpatient Visit Days 15±2, 22±2**				**Day 29±2**				**Day 36±2**
	0 h	**0.5 h**	**1h**	**2h**	**4h**	**8h**	**12h**	**0 h**	**4 h**	**8 h**	**12 h**	**0 h**	**4 h**	**8 h**	**12 h**	**0 h**	**4 h**	**8 h**	**12 h**	**0 h**	**2 h**	**4 h**	**8 h**	
Physical examinations[1]	X							X								X						X		
Weight																						X		
Vital signs[2]	X							X								X						X		
DEQ-5 [3]																				X				
VAS[3,4]	X	X	X	X	X	X	X	X								X	X	X		X		X	X	
OSDI[© 3]								X								X				X				
Hematology, Serum Chemistry, Urinalysis								X													X			
Serum pregnancy test (for WOCBP only)																					X			
Pharmacokinetic Sampling	X[5]							X																
Visual Acuity (Snellen)	X							X								X							X	
Slit lamp biomicroscopy w/out mydriatics	X						X	X								X							X	
Matrix Metalloproteinase-9 (MMP-9)[6]																				X				
TFBUT	X						X	X								X				X				
Corneal fluorescein staining (Baylor)	X						X	X								X				X				
Lissamine green staining (Baylor +Lid Margin)	X						X	X								X				X				
Schirmer I w/o anesthesia								X															X	
Intraocular pressure (iCare tonometer)								X								X							X	
Slit lamp biomicroscopy w/ mydriatics (lens observation)								X															X	
Ophthalmoscopy								X															X	
Record and assess adverse events	Continuous																							
Concomitant medications	Continuous																							
Confinement Period	X							Out[7]																
Drug administration	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Telephone call																								X

EOS = End of Study Assessments; VAS = Visual Analog Scale; TFBUT = Tear film break-up time; OSDI = Ocular Surface Disease Index; WOCBP = women of childbearing potential

[1] Physical Examination includes head-eye-ears-nose-throat, cardiovascular, respiratory, gastrointestinal, dermatologic, and neurologic examinations.

[2] Blood pressure, heart rate, respiratory rate, oral temperature.

[3] Questionnaires will be completed prior to lab or PK timepoints. Ophthalmic assessments will follow lab or PK timepoints.

[4] VAS assessment completed on Day 4 & 7 at 0h, 0.5h, 1h, 2h, 4h, 8h, 12h timepoints. VAS on Days 5 & 6 at 0, 4, 8, and 12 h

[5] Day 4 only

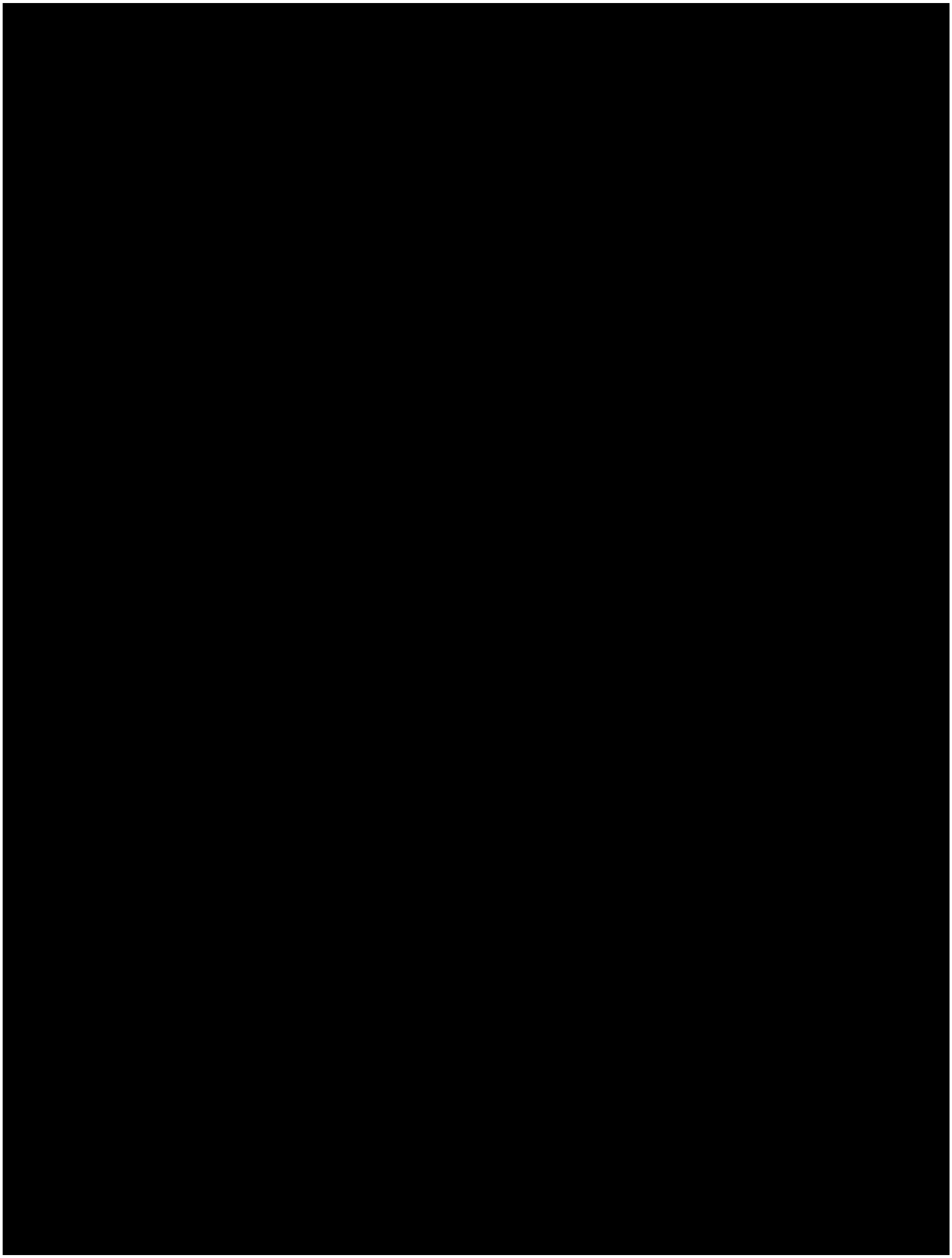
[6] 30 minutes before staining tests

[7] Check-out after completion of all Day 8 assessments and 0 h dosing

3. Introduction

Dry Eye Disease (DED) is defined by the International Dry Eye Workshop (DEWS) as a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles. It is one of the most frequently encountered ocular morbidities. Twenty-five percent of patients who visit ophthalmic clinics report symptoms of dry eye, making it a growing public health problem and one of the most common conditions seen by eye care practitioners (Gayton 2009). DED is seen with increased prevalence in patients with autoimmune diseases (Fox 1984), which affect approximately 8% of the population, of whom 78% are women (Fairweather 2008). DED also affects postmenopausal women (Schaumberg 2003) and the elderly (Moss 2000, Lin 2003). The prevalence of symptomatic dry eye in the United States is about 7% in women and 4% in men over the age of 50 years (Schaumberg 2003). These numbers translate into approximately 3.2 million women and 1.05 million men with DED in the United States (Schaumberg 2002). The prevalence of DED in Japan is estimated to be 33% (Shimmura 1999).

Initial treatments for DED are recommended environmental and lifestyle changes, and the use of artificial tears, Restasis®, or topical steroids. Steroids help control DED-associated inflammation, but they should not be used long term because of their possible role in elevating intraocular pressure (IOP) and causing cataracts. The two main issues associated with the use of Restasis are burning, which is very significant in some patients, and the relatively long onset of action that does not provide immediate relief.



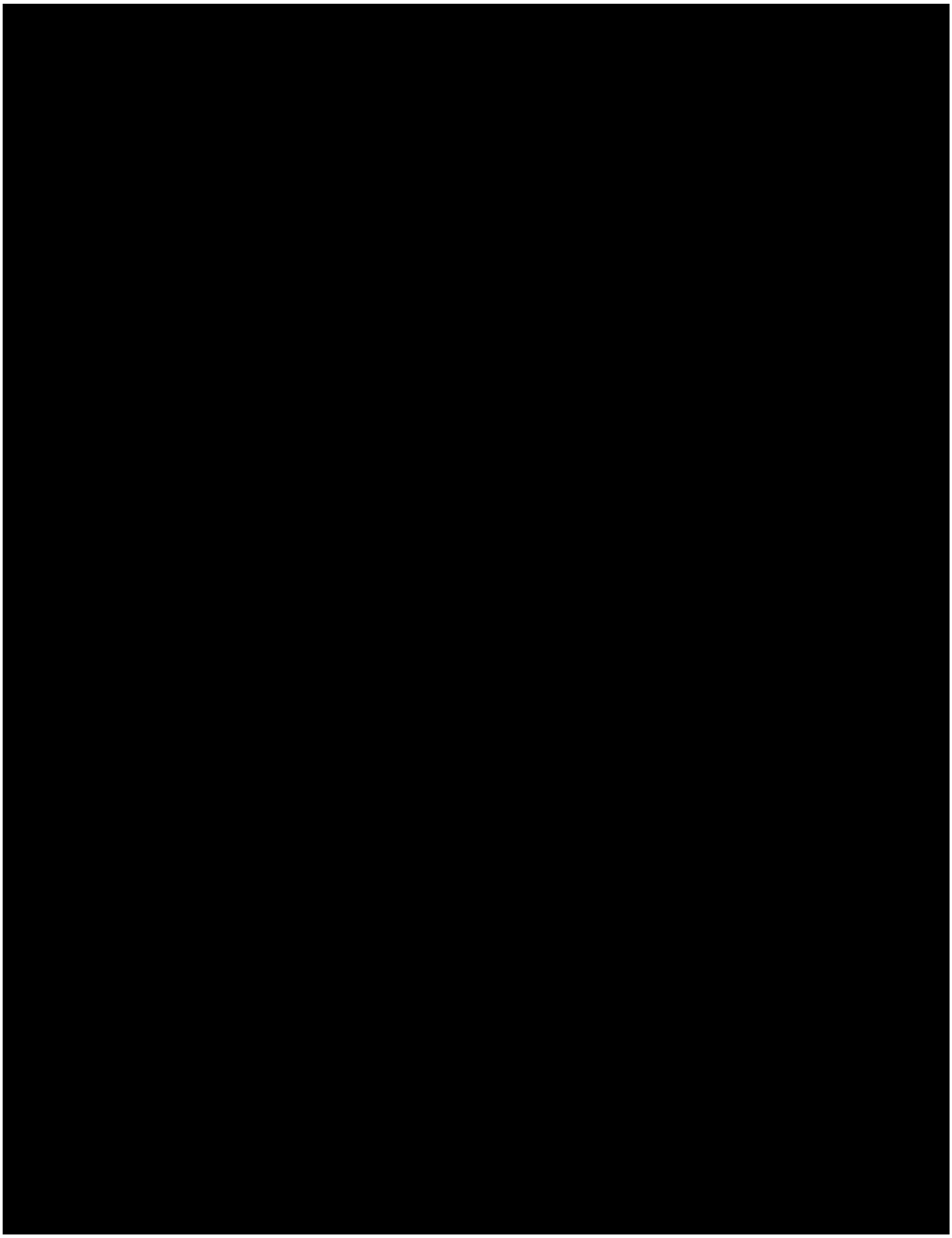
[redacted]

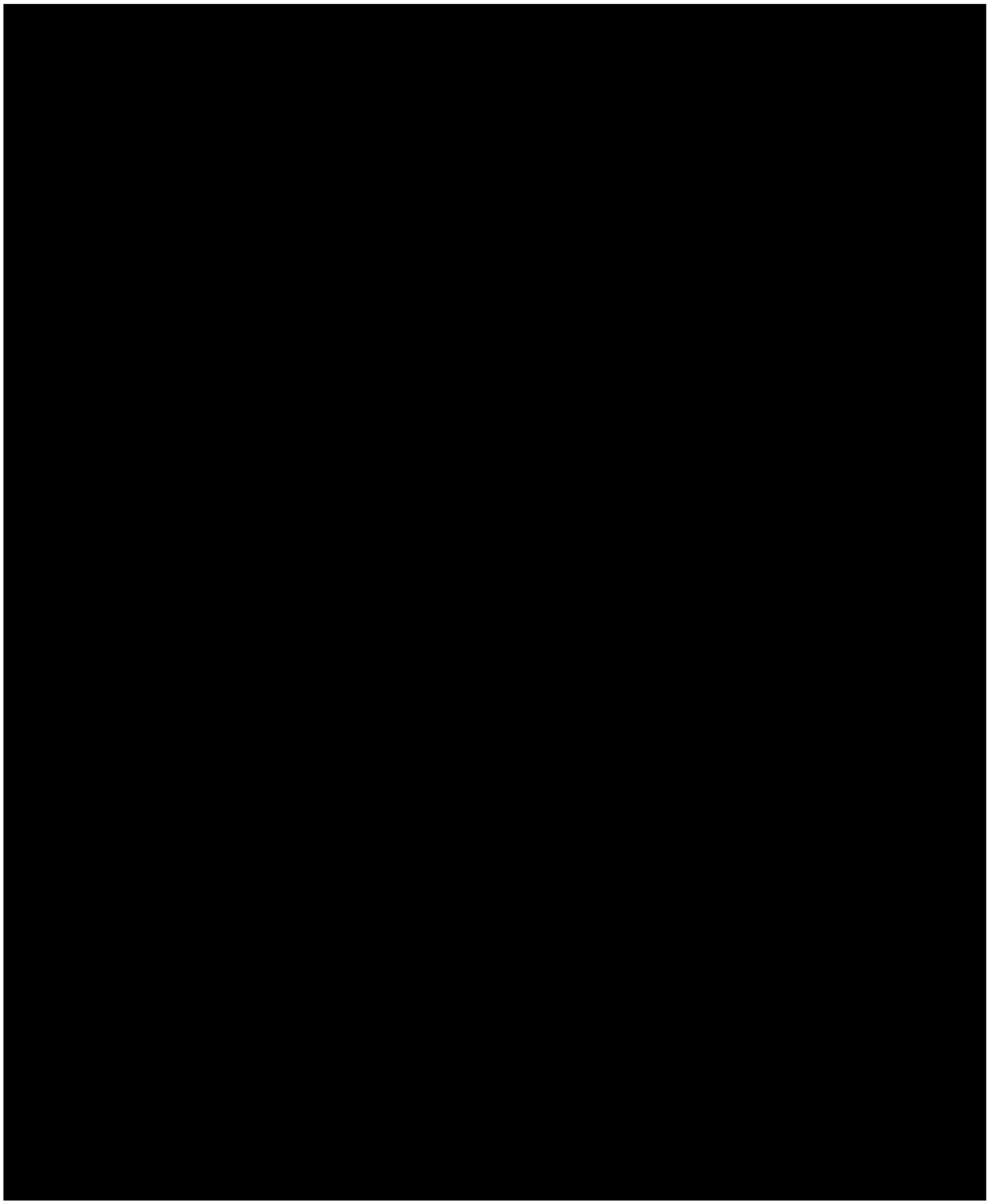
3.1. Study Rationale

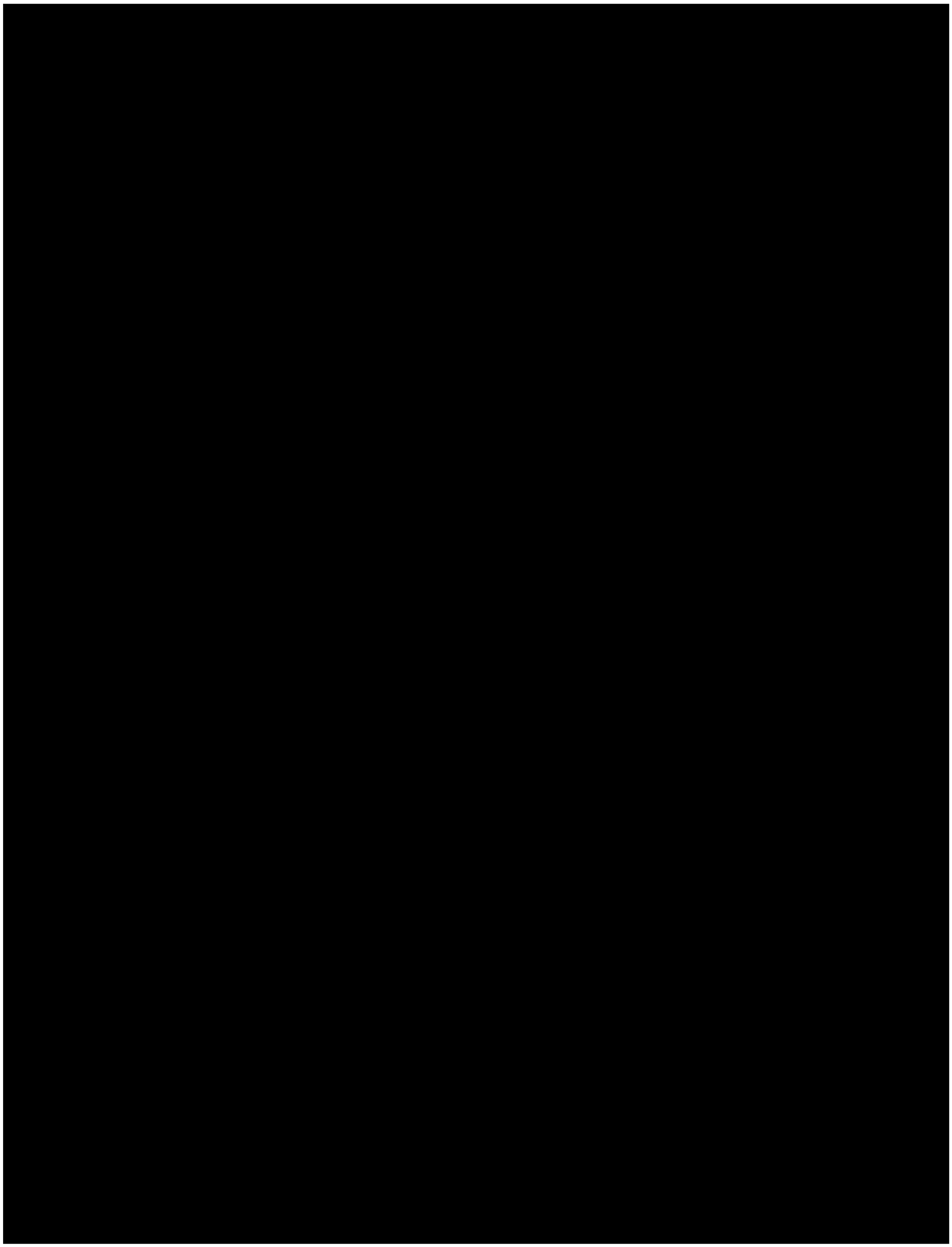
This is the first study in humans to evaluate the efficacy of SJP-0132 in the treatment of dry eye disease. This study will evaluate the safety, tolerability, efficacy, and pharmacokinetics (PK) of single- and multiple-dose regimens of SJP-0132 [redacted]

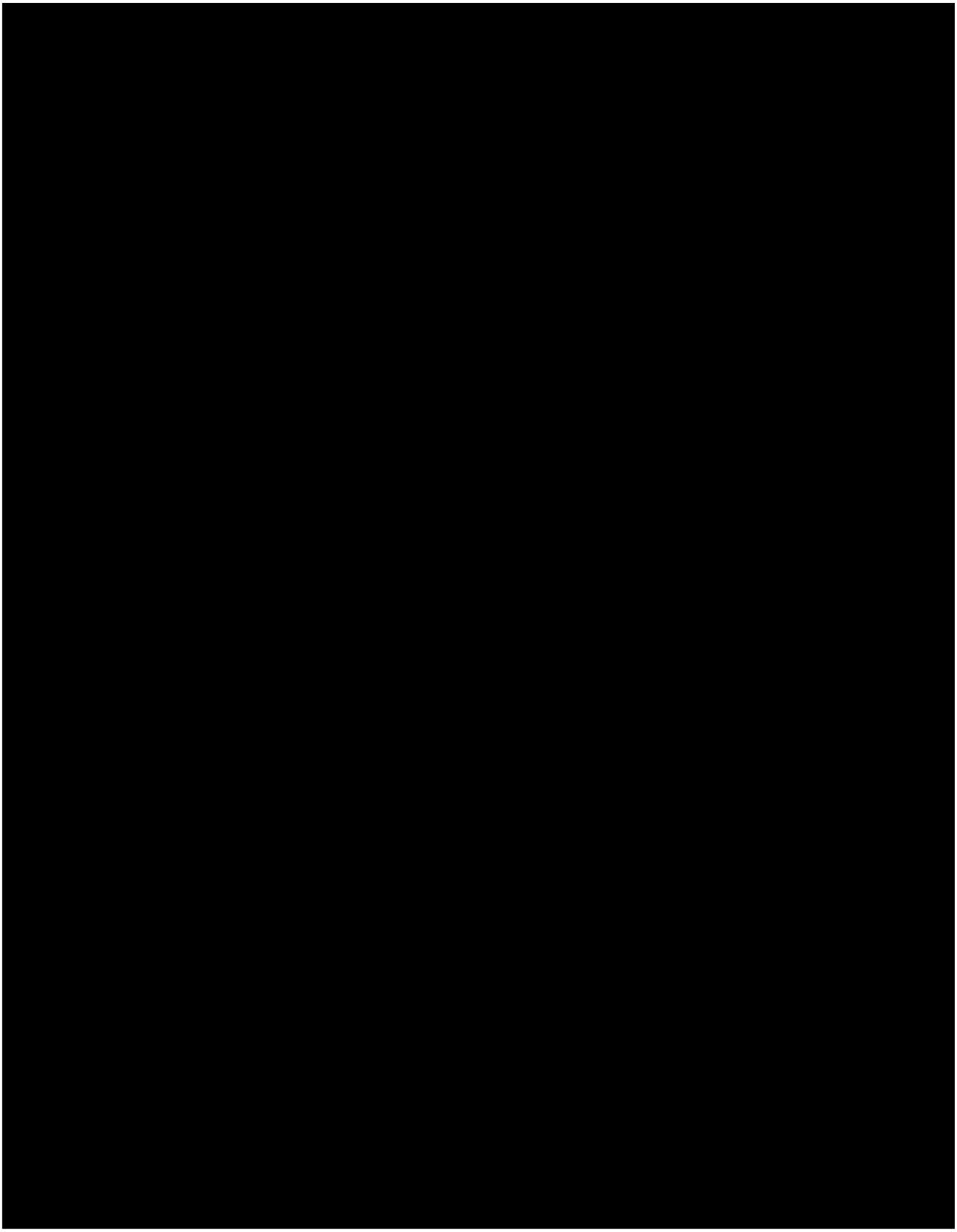
3.2. Background

[redacted]









4. Objectives and Endpoints

Objectives	Endpoints
Primary	
• Safety and tolerability of SJP-0132	• The number and severity of AEs including abnormal changes in clinical laboratory results, vital signs, and physical and ophthalmologic examinations
• Pharmacokinetic (PK) profiles of SJP-0132	• Part A: C_{max}, t_{max}, t_{last}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}\infty}$, $t_{1/2}$, $AUC_{\%extrap}$, $AUMC_{0\text{-}last}$, $AUMC_{0\text{-}\infty}$, $MRT_{0\text{-}last}$, $MRT_{0\text{-}\infty}$, Vd/F, CL/F, $C_{max,norm}$, $AUC_{0\text{-}last,norm}$, and $AUC_{0\text{-}\infty,norm}$ • Part B: C_{max}, t_{max}, t_{last}, $AUC_{0\text{-}last}$, $C_{max,norm}$, and $AUC_{0\text{-}last,norm}$ on Day 1, C_{trough} on Days 2, 4 and 8, and Rac
• Efficacy of SJP-0132	• Change from baseline (predose on Day 1) in eye dryness symptom (visual analog scale [VAS]) at 4 hours on Day 29 • Change from baseline (predose on Day 1) in corneal fluorescein staining (CFS) score at the central zone on Day 29
Secondary	
• Efficacy of SJP-0132	• Changes from baseline in dry eye signs: CFS scores at the central, superior, inferior, nasal, temporal and total zones, conjunctival lissamine green staining (CLGS) scores at each of 3 nasal and 3 temporal zone and total zone of bulbar conjunctiva, lid wiper epitheliopathy score, and tear film break-up time (TFBUT) at each time point tested • Changes from baseline in dry eye symptoms (VAS [ie, severity of eye dryness, discomfort, burning/stinging, sticky feeling, foreign body sensation, itching, pain, blurred vision, and sensitivity to light], ocular surface disease index [OSDI®], Dry eye Questionnaire 5 [DEQ-5] scores) at each time point tested • Biomarker (Matrix Metalloproteinase-9 (MMP-9), InflammaDry®)

5. Study Design

5.1. Overall Design

This is a randomized, double-masked, placebo-controlled single and multiple ascending dose study of SJP-0132 in subjects with dry eye disease who have frequent ocular discomfort or dryness. Non-Japanese subjects will be enrolled in Part A and both Japanese and non-Japanese subjects will be enrolled in Part B.

After Screening (including review of laboratory results), placebo medication will be dispensed to all eligible subjects to be instilled [redacted] (Placebo Run-In) Subjects will be admitted to the study center on Day -1 and undergo physical and ophthalmic examinations as shown in Section 2, Schedule of Activities.

Part A

In Part A, 32 non-Japanese subjects will be admitted to the study center on Day -1 and discharged on Day 2 after completion of assessments and blood collections. Subjects will be randomized to receive a single dose of placebo or SJP-0132 ophthalmic [redacted] concentrations of 0.03%, 0.1%, 0.3%, or 1% on Day 1 after confirmation of continued eligibility. All treatments will be administered in both eyes.

Blood for PK measurements will be collected before dosing and at the timepoints specified in the Schedule of Activities (SoA). Eye and safety assessments will be done as indicated below.

After each cohort completes the single dose of SJP-0132 ophthalmic [redacted] or placebo, the Investigator and the Sponsor will assess the data to confirm adequate safety and tolerability while the next cohort begins the Run-in Phase. A written report will be provided.

After completion of the single dose cohorts, a safety review will be conducted to identify the maximum acceptable dose and the second maximum acceptable dose of study drug. The maximum and second maximum acceptable doses of study drug will be selected for the multiple dose study (Part B) in subjects with dry eye disease. Maximum acceptable dose is the highest dose at which no more than 1 subject experiences a severe drug-related AE.

Part B

In Part B, 60 Japanese and non-Japanese subjects will be admitted to the study center on Day -1 and discharged on Day 8 after completion of assessments and blood collections. Subjects will be randomized to receive placebo or SJP-0132 ophthalmic [redacted] on Day 1 after confirmation of continued eligibility.

The first cohort randomized in Part B (Cohort 5) will receive the second maximum acceptable concentration of SJP-0132 ophthalmic [redacted] or placebo [redacted] for 4 weeks. The second cohort randomized in Part B (Cohort 6) will receive the maximum acceptable dose of SJP-0132 ophthalmic [redacted] or placebo [redacted] for 4 weeks. All treatments will be administered in both eyes.

After Cohort 5 completes the 7-day inpatient assessment of SJP-0132 ophthalmic [redacted] or placebo, the Investigator and the Sponsor will assess the data (AEs, clinical laboratory results, vital signs, ophthalmic examinations) to confirm adequate safety and tolerability before allowing a cohort of the next dose level (Cohort 6) to begin. A written report will be provided.

All subjects who complete the Day 29 ±2 EOS visit, will receive a follow-up telephone call on Day 36 ±2 to review AEs and medication use.

For any subjects who receive at least one dose of study drug and discontinue or withdraw from study participation prior to the Day 29 ±2 EOS visit, subjects should complete the EOS visit at the time of discontinuation/withdrawal. Discontinued/withdrawn subjects will also be contacted by telephone 7 days later for follow-up.

Pharmacokinetic (PK) blood draws will be collected prior to dosing on Days 1, 2, 4, and 8, and after dosing on Day 1 at timepoints specified in SoA.

For all subjects in Part A and Part B, the following eye assessments will be done according to the SoA: VAS, visual acuity (by Snellen), corneal aesthesiometry (Cochet-Bonnet), DEQ-5, OSDI®, slit-lamp biomicroscopy, VAS with anesthesia, intraocular pressure (iCare), fluorescein staining (Baylor Scales), lissamine green staining (Baylor Scales +lid margins [lid wiper epitheliopathy]), Schirmer I test (without anesthesia), and tear film break up time (TFBUT), ophthalmoscopy, and matrix metalloproteinase-9 (MMP-9). All ocular exams will be completed for both eyes (study eye and non-study eye) at all timepoints.

For all subjects in Part A and Part B, the following safety assessments will include changes in vital signs (blood pressure, heart rate, oral body temperature (°C), respiratory rate), clinical laboratory results (hematology, clinical chemistry, and urinalysis), adverse events (AEs), concomitant medication use, physical examinations. Additionally, the subjects' overall ocular irritation will be assessed.

In case any medically significant suspected adverse reactions or findings are observed, the Data and Safety Monitoring Board (i.e., consisting of the Investigator, Sponsor, and pharmacovigilance physician) will make a decision for future course of action.

5.2. Subject and Study Completion

Approximately 226 subjects will be screened to achieve 32 completers in treatment in Part A and 60 completers in Part B.

5.3. End of Study Definition

A subject is considered to have completed the study if he/she has completed all phases of the study, ie, Day 2 EOS for Part A and Day 29 EOS for Part B.

The end of the study (EOS) is defined as the date of the last visit for the last subject, including the follow-up telephone call.

5.4. Scientific Rationale for Study Design

Studies comparing the pharmacokinetics and safety of a drug product in Japanese and non-Japanese (eg, Caucasian) subjects allow for extrapolation of clinical data across regions. Randomization and masking minimizes bias in the assessment of safety and interpretation of results. Safety and tolerability can be clearly assessed as each subject in Part A will receive only a single dose of SJP-0132 in an ascending fashion.

6. Study Population

A sufficient number of subjects will be screened and will participate in the study. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Signed the informed consent form which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol
2. Man or woman, ≥18 years of age (inclusive) at the time of signing the informed consent form
3. Body mass index (BMI) within 18.5 to 30.0 kg/m^2 (inclusive) and body weight between 45 kg and 100 kg
4. Generally healthy as determined by medical history, physical examinations, clinical laboratory examination, and ophthalmologic examinations performed at Screening.
5. Have a subject reported history of Dry Eye Disease in both eyes for at least 6 months prior to Screening.
6. Dry eye symptoms at Screening and Day -1:
   - Baseline eye dryness VAS score ≥40 mm
   - Baseline DEQ 5 ≥6
7. Dry eye signs at Screening and Day -1:
   - Baseline central corneal staining (Baylor scale) of 2 to 4 in at least 1 eye (designated study eye)
8. Non-smoker or ex-smoker for >12 months
9. If male, must agree to use contraception during the treatment period and for at least 7 days, after the last dose of study treatment and refrain from donating sperm during this period
10. If a woman of child-bearing potential (WOCBP), she must agree to use a highly effective form of contraception during the study and for 30 days after the last dose.
11. For Japanese cohort subjects, subjects must be of Japanese descent.

Note: Retesting of abnormal lab values that may lead to exclusion will be allowed once. Retesting will take place during an unscheduled visit in the screening phase.

6.2. Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

1. Have clinically significant systemic or ophthalmic disease
2. Have allergies to [redacted] or to any of the SJP-0132 ophthalmic [redacted] ingredients.
3. Has a positive serum pregnancy test at Screening or urine pregnancy test at Day -1.
4. Have had significant blood loss or have donated or received one or more units (450 mL) of blood or plasma within 30 days before randomization.

5. Have used or anticipates use of any prescription or over-the-counter medication, including topical medications such as ophthalmic solutions (except an ophthalmic solution specially provided by Sponsor, mydriatics, and stain used for trial examinations), nasal drops or spray, vitamins, alternative and complementary medicines (including herbal formulations) within 14 days or 5 half-lives (whichever is longer) before randomization or at any time during the study.
6. Use or anticipates use of prescribed dry eye medications (e.g. Restasis and Xiidra) within 28 days prior to randomization or at any time during the study.
7. Have used or anticipates use CYP3A4 inducers, such as St. John's Wort, within 14 days before randomization or at any time during the study.
8. Have consumed red wine, grapefruit or grapefruit juice, Seville oranges, star fruit, or any products containing these items, or any foods that may inhibit CYP3A4, within 48 hours before randomization and throughout the duration of the study
9. Have a positive urine alcohol test at Screening or Day –1
10. Have a positive urine drug test at Screening or Day –1
11. Has history of, or evidence of, alcohol or drug abuse within past 6 months prior to Screening
12. Have a positive HBsAg, HCV antibody, or HIV test at Screening
13. Have received another investigational medication within 90 days before randomization
14. Contact lens wearers who cannot discontinue the wear over the trial period (i.e., from Screening to EOS)
15. Have undergone eye surgery (including laser surgery) within the last 12 months or whom the Investigator considers unsuitable
16. Subjects whom the Investigator considers are unable or unlikely to comply with the trial protocol or scheduled Screening or Admission (e.g., planned travel outside of the trial area for a substantial portion of the trial period, scheduled hospitalization during the trial period)
17. Have a family history of sudden death
18. Have cardiac disease (e.g., cardiac arrest, ischemic cardiac disease)
19. Have abnormal serum electrolytes according to the judgment of the Investigator
20. Have a BCVA worse than 20/100 in either eye.
21. Current use of punctal plugs or anticipated insertion during study period.
22. History of permanent punctal occlusion (cautery or laser).
23. Any corneal abnormality or disease which might impact normal tear film spreading (eg: cornea scarring, keratoconus or pterygia).
24. Active or history of significant corneal disease (recurrent erosions or herpetic keratitis).
25. Known allergy or sensitivity to fluorescein, lissamine green or any of the study medications.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

1. Refrain from consumption of red wine, grapefruit or grapefruit juice, Seville oranges, star fruit, or any products containing these items, or any foods that may inhibit CYP3A4, within 48 hours before randomization and throughout the duration of the study.

6.3.2. Caffeine, Alcohol, and Tobacco

1. Subjects will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 24 hours prior to the start of dosing on Day 1 of Part A and Days 1, 2, 4, and 8 of Part B, and for the remainder of the confinement period until after collection of the final pharmacokinetic (PK). Subjects will also abstain 24 hours prior to each weekly outpatient visit.
2. Subjects will abstain from alcohol for 24 hours before the start of dosing on Day 1 of Part A and Days 1, 2, 4, and 8 of Part B until after collection of the final pharmacokinetic (PK).
3. Use of tobacco products will not be allowed from screening until after the final follow-up visit.

6.3.3. Activity

1. Subjects will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (eg, watching television, reading).
2. Subjects will be asked to refrain from the following for 24 hours prior to their visits:
    - Dangerous sport activities (eg, skiing, mountain climbing, etc.)
    - Swimming in a chlorinated pool
    - Challenging climates (eg, smoking rooms, sauna, etc.)

6.4. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

7. Treatments

7.1. Treatments Administered

[redacted]

For both Part A and Part B, starting at Day -14 (Placebo Run-In), subjects will instill 1 drop of Placebo into each eye [redacted]

In Part A, subjects will instill 1 drop of SJP-0132 or placebo into each eye (one time only).

In Part B, subjects will instill 1 drop of SJP-0132 or placebo into each eye [redacted]

7.2. Investigational Product Information

The amount of SJP-0132 per mL [redacted]:

0.03% = 0.3 mg

0.1% = 1 mg

0.3% = 3 mg

1% = 10 mg

Non-active excipients include tyloxapol, boric acid, sodium borate, and United States Pharmacopeia (USP) purified water.

7.3. Preparation/Handling/Storage/Accountability

[redacted]

Doses and dosing times while at the clinic will be recorded in the subject source document.

For each instance where study drug is dispensed, site will provide subject education on self-administration, storage, and handling of study drug.

When the subjects self-medicate at home, they will record the date and time of each dose in a diary. The diary will be collected and reviewed at each clinic visit.

At each visit, the study site will remind each subject to bring study drug with them to the next visit, for study drug return and dispensing.

In the instance that a bottle of study drug is lost, the subject should contact the site immediately, and schedule to return to the site for a replacement bottle to be dispensed.

7.4. Dose Modification

Dose modification is not permitted.

7.5. Method of Treatment Assignment

Subjects will be randomly assigned to SJP-0132 or placebo using a computer-generated randomization scheme.

Part A: 4 cohorts consisting of 8 subjects each (non-Japanese), with 6 subjects randomized to SJP-0132 ophthalmic [redacted] and 2 randomized to placebo.

- Cohort 1: 0.03% SJP-0132 / Placebo
- Cohort 2: 0.1% SJP-0132 / Placebo
- Cohort 3: 0.3% SJP-0132 / Placebo
- Cohort 4: 1% SJP-0132 / Placebo

Part B: 2 cohorts consisting of 30 subjects each (9 Japanese and 21 non-Japanese) 20 randomized to SJP-0132 ophthalmic [redacted] and 10 randomized to placebo:

Cohort#	Active		Placebo		Total
	JP	Non-JP	JP	Non-JP	
5	6	14	3	7	30
6	6	14	3	7	30
Total	12	28	6	14	60

JP = Japanese

Doses selected for Part B will be determined after evaluation of safety and tolerability in Part A. The first cohort randomized in Part B (Cohort 5) will receive the second maximum acceptable concentration of SJP-0132 ophthalmic [redacted] or placebo [redacted] 4 weeks. The second cohort randomized in Part B (Cohort 6) will receive the maximum acceptable dose of SJP-0132 ophthalmic [redacted] or placebo [redacted] for 4 weeks.

7.6. Masking

Subjects will be randomly assigned to receive study treatment. Investigators will remain masked to each subject's assigned study treatment throughout the course of the study. In order to maintain this mask, an otherwise uninvolved 3rd party will be responsible for the reconstitution and dispensation of all study treatment and will endeavor to ensure that there are no differences in time taken to dispense following randomization.

This 3rd party will instruct the subject to avoid discussing the taste, color, dosing frequency, or packaging of the study treatment with the investigator.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unmasked study treatment records at the site(s) to verify that randomization/dispensing has been done accurately.

The mask may be broken if, in the opinion of the investigator, it is in the subject's best interest for the investigator to know the study treatment assignment. The sponsor must be notified before the mask is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific masked study treatment will affect the immediate management of the subject's condition. In this case, the sponsor must be notified within 24 hours

after breaking the mask. The date and reason that the mask was broken must be recorded in the source documentation and CRF, as applicable.

7.7. Missed Doses

If a dose is missed, the subject should dose as soon as they remember and adjust subsequent doses for that calendar day at 4-hour intervals, resuming protocol-indicated dosing on the next calendar day. Subject will record Date and time of actual dosing in the provided diary.

7.8. Concomitant Therapy

7.8.1. Recording Prior and Concomitant Medications

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.8.2. Prohibited Concomitant Medications, Treatments, and Procedures

Subjects must abstain from taking prescription or nonprescription drugs (including topical medications such as ophthalmic solutions [except an ophthalmic solution specially provided by Sponsor, mydriatics, and stain used for trial examinations], nasal drops or spray, vitamins, alternative and complementary medicines [including herbal formulations]) within 14 days or 5 half-lives (whichever is longer) before randomization until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study. Subjects must refrain from use of CYP3A4 inducers, such as St. John's Wort, for 14 days before randomization or at any time during the study. Subjects must abstain from prescribed dry eye medications (e.g. Restasis and Xiidra) for 28 days before randomization or at any time during the study.

7.8.3. Rescue Medicine

No rescue medication will be provided.

7.9. Treatment after the End of the Study

Study medication will not be provided after the end of the study.

8. Discontinuation/Withdrawal Criteria

A subject may voluntarily discontinue participation in this study at any time. It is important to document whether the withdrawal of consent is primarily due to an AE or other reason. The Investigator may also, at his or her discretion, discontinue the subject from participating in this study at any time. Withdrawn subjects will not be replaced.

Subjects may be prematurely discontinued from the study for any of the following reasons:

- Subject non-compliance
- Investigator non-compliance
- Subject requires concurrent prohibited medication during the course of the study. If, in the opinion of the Investigator and the study medical monitor, such medication will not interfere with the conduct or interpretation of the study or compromise the safety of the subject, then the subject may continue to receive study medication. If the subject is discontinued from study medication, they would remain in the study for safety assessments as needed.
- Pregnancy of female subject
- Discontinuation of the study at the request of the Sponsor, regulatory agency or an Institutional Review Board / Independent Ethics Committee
- Grade 3 or 4 clinical AE considered causally related to treatment.

If a subject meets a withdrawal criterion during treatment, procedures listed in the SoA for Part A check-out or Part B Day 29 EOS will be required.

8.1. Discontinuation of Study Treatment

If a clinically significant finding is identified after enrollment, the investigator or qualified designee will determine if the subject can continue in the study and if any change in subject management is needed. Any new clinically relevant finding should be reported as an AE.

Procedures listed in the SoA for Part A check-out or Part B Day 29 EOS should be completed at the time of treatment discontinuation.

8.2. Withdrawal from the Study

- A subject may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

- At the time of study discontinuation the End-of-Study procedures need to be completed.

8.3. Lost to Follow Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- Details for completion of each assessment will be included in the Study Manual.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Table 9-1: Volume of Blood to be Collected from Each Subject

Type of Sample	Volume per Sample (mL)	No. of Samples/ Subject		Total Volume of Blood (mL)[a]	
		Part A	Part B	Part A	Part B
Safety (including screening and post treatment assessments)					
- Hematology	4.0	3	4	12.0	16.0
- Serum chemistry	8.5	3	4	25.5	34.0
serology (HIV, HBsAg, HCV)	8.5	1	1	8.5	8.5
serum β-hCG pregnancy test (WOCBP only)	4.9	1	2	4.9	9.8
Pharmacokinetic samples	2.0	8	9	16.0	18.0
Loss by use of indwelling intravenous cannula	1.0	8	9	8.0	9.0
Total				74.9	95.3

a Calculated as number of samples multiplied by amount of blood per sample.

Note: An indwelling intravenous cannula may be used for blood sample collection. If a mandarin (obturator) is used, blood loss due to discard is not expected.

- If blood samples are collected via an indwelling cannula, an appropriate amount (i.e., 1 mL) of fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with saline and charged with a volume equal to the dead space volume of the lock.
- The approximate amount of blood collected from subjects in Part A and Part B will be 75 mL and 95 mL, respectively. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Daily Procedures – Part A

Screening (Day -30 to Day -15)

- Sign ICF
- Record medical and medication history and demographic information (age, sex, race, iris color)
- Review inclusion/exclusion criteria
- Physical examination
- Height (cm) and weight (kg)
- Vital signs
- DEQ-5
- VAS
- OSDI
- Clinical laboratory tests (hematology, serum chemistry, urinalysis)
- Serology (HIV, HBsAg, HCV)
- Serum pregnancy test for WOCBP; FSH for post-menopausal women
- Urine drug and alcohol screens
- Visual acuity (Snellen)
- Slit lamp biomicroscopy (w/out mydriatics)
- MMP-9 (30 minutes before TFBUT and staining tests)
- TFBUT
- Corneal fluorescein staining (Baylor)
- Lissamine green (Baylor + Lid Margin)
- Aesthesiometer
- Schirmer I without anesthesia
- VAS with anesthesia

- Intraocular Pressure (iCare tonometer)
- Slit lamp biomicroscopy (w/ mydriatics; lens observation)
- Ophthalmoscopy

Run-in (Day -14 +2 to Day -2)

- Educate subject in self-administration and dosing diary completion
- Dispense placebo. Subjects will instill one drop in each eye [redacted](First dose may be administered in office as part of self-administration education, if visit is completed on Day -14, otherwise subject should be instructed to begin dosing on Day -14.)
- Review AEs and concomitant medications

Day -1 (Check-in)

- Review medical and medication history
- Review inclusion/exclusion criteria
- Weight
- Vital signs
- DEQ-5
- VAS
- OSDI
- Clinical laboratory tests (hematology, serum chemistry, urinalysis)
- Urine drug and alcohol screens
- Urine pregnancy test for WOCBP
- Visual acuity (Snellen)
- MMP-9 (30 minutes before staining tests)
- Corneal fluorescein staining (Baylor)
- Schirmer I without anesthesia
- Slit lamp biomicroscopy (w/ mydriatics; lens observation)
- Ophthalmoscopy
- Review AEs and concomitant medications
- Administer placebo [redacted]as during run-in

Day 1, Predose

- Review AEs and concomitant medications
- Physical examination

- Vital signs
- VAS
- PK sampling
- Slit lamp biomicroscopy (without mydriatics)
- TFBUT
- Corneal fluorescein staining (Baylor)
- Lissamine green (Baylor + Lid Margin)
- Intraocular Pressure (iCare tonometer)
- Randomize to study treatment

Day 1, 0 hour

- Administer study drug

Day 1, Postdose

- Review AEs and concomitant medications
- Physical examination at 1 hour
- Vital signs at 0.5, 1, 2, 4, 8, and 12 hours
- VAS at 0.5, 1, 2, 4, 8, and 12 hours
- PK sampling at 0.25, 0.5, 1, 2, 4, 8, and 12 hours
- Visual acuity at 12 hours
- Slit lamp biomicroscopy (without mydriatics) at 1, 2, and 12 hours
- TFBUT at 2 and 12 hours
- Corneal fluorescein staining (Baylor) at 2 and 12 hours
- Schirmer I without anesthesia at 12 hours
- Intraocular Pressure (iCare tonometer) at 2 and 12 hours
- Slit lamp biomicroscopy (w/ mydriatics; lens observation) at 12 hours
- Ophthalmoscopy at 12 hours

Day 2, 24 hours Postdose

- Review AEs and concomitant medications
- Physical Examination
- Vital signs
- VAS

- Clinical laboratory tests (chemistry, hematology, urinalysis)
- Visual Acuity (Snellen)
- Slit lamp biomicroscopy (w/out mydriatics)
- TFBUT
- Corneal fluorescein staining (Baylor)
- Schirmer I w/o anesthesia
- Intraocular Pressure (iCare tonometer)
- Slit lamp biomicroscopy (w/ mydriatics; lens observation)
- Ophthalmoscopy
- Check-out of clinic

Part B

Screening (Day -30 to Day -15)

- Sign ICF
- Record medical and medication history and demographic information
- Review inclusion/exclusion criteria
- Physical examination
- Height (cm) and weight (kg)
- Vital signs
- DEQ-5
- VAS
- OSDI
- Clinical laboratory tests (hematology, serum chemistry, urinalysis)
- Serology (HIV, HBsAg, HCV)
- Serum pregnancy test for WOCBP; FSH for post-menopausal women
- Urine drug and alcohol screens
- Visual acuity (Snellen)
- Slit lamp biomicroscopy (w/out mydriatics)
- MMP-9 (30 minutes before TFBUT and staining tests)
- TFBUT

- Corneal fluorescein staining (Baylor)
- Lissamine green (Baylor + Lid Margin)
- Aesthesiometer
- Schirmer I without anesthesia
- VAS with anesthesia
- Intraocular Pressure (iCare tonometer)
- Slit lamp biomicroscopy (w/ mydriatics; lens observation)
- Ophthalmoscopy

Run-in (Day -14 +2 to Day -2)

- Educate subject in self-administration and dosing diary completion
- Dispense placebo. Subjects will instill one drop in each eye [redacted](First dose may be administered in office as part of self-administration education, if visit is completed on Day -14, otherwise subject should be instructed to begin dosing on Day -14)
- Review AEs and concomitant medications

Day -1 (Check-in)

- Review medical and medication history
- Review inclusion/exclusion criteria
- Weight
- Vital signs
- DEQ-5
- VAS
- OSDI
- Clinical laboratory tests (hematology, serum chemistry, urinalysis)
- Urine drug and alcohol screens
- Urine pregnancy test for WOCBP
- Visual acuity (Snellen)
- MMP-9 (30 minutes before staining tests)
- Corneal fluorescein staining (Baylor)
- Schirmer I without anesthesia
- Slit lamp biomicroscopy (w/ mydriatics; lens observation)
- Ophthalmoscopy

- Review AEs and concomitant medications
- Administer placebo [redacted] as during run-in

Day 1, Predose

- Review AEs and concomitant medications
- Physical examination
- Vital signs
- VAS
- PK sampling
- Slit lamp biomicroscopy (without mydriatics)
- TFBUT
- Corneal fluorescein staining (Baylor)
- Lissamine green (Baylor + Lid Margin) at 12 hours
- Intraocular Pressure (iCare tonometer)
- Randomize to study treatment

Day 1, 0 hour

- Administer study drug

Day 1, Postdose

- Review AEs and concomitant medications
- Physical examination at 1 hour
- Vital signs at 0.5, 1, 2, 4, 8, and 12 hours
- VAS at 0.5, 1, 2, 4, 8, and 12 hours
- PK sampling at 0.25, 0.5, 1, 2, and 4 hours
- Visual acuity at 12 hours
- Slit lamp biomicroscopy (without mydriatics) at 1, 2, and 12 hours
- TFBUT at 2 and 12 hours
- Corneal fluorescein staining (Baylor) at 2 and 12 hours
- Lissamine green (Baylor + Lid Margin) at 12 hours
- Schirmer I without anesthesia at 12 hours
- Intraocular Pressure (iCare tonometer) at 12 hours
- Slit lamp biomicroscopy (w/ mydriatics; lens observation) at 12 hours

- Ophthalmoscopy at 12 hours
- Administer study drug at 4, 8, and 12 hours

Days 2 and 3

- Review AEs and concomitant medications
- Physical examination at 0 hour
- Vital signs at 0, 4, 8, and 12 hours
- VAS at 0, 4, 8, and 12 hours
- Visual acuity at 0 hours
- PK sampling at predose on Day 2 (ie, Day 1, 24 hours)
- Slit lamp biomicroscopy (without mydriatics) at 0 and 12 hours
- TFBUT at 0 and 12 hours
- Corneal fluorescein staining (Baylor) at 0 and 12 hours
- Lissamine green (Baylor + Lid Margin) at 0 and 12 hours
- Schirmer I without anesthesia at 0 hours on Day 2
- Intraocular Pressure (iCare tonometer) at 0 hour
- Administer study drug at 0, 4, 8, and 12 hours

Days 4 through 7

- Review AEs and concomitant medications
- Physical examination at 0 hour
- Vital signs at 0 hour
- VAS on Day 4 and on Day 7 at 0, 0.5, 1, 2, 4, 8, and 12 hours; VAS on Days 5 and 6 at 0, 4, 8, and 12 hours
- PK sampling at 0 hour on Day 4
- Visual acuity at 0 hours
- Slit lamp biomicroscopy without mydriatics at 0 and 12 hours
- TFBUT at 0 and 12 hours
- Corneal fluorescein staining (Baylor) at 0 and 12 hours
- Lissamine green staining (Baylor +Lid Margin) at 0 and 12 hours
- Administer study drug at 0, 4, 8, and 12 hours

Day 8, Check Out

- Review AEs and concomitant medications

- Physical examination at 0 hour
- Vital signs at 0 hour
- VAS at 0 hour
- OSDI at 0 hour
- PK sampling at 0 hour
- Clinical laboratory tests (hematology, serum chemistry, urinalysis) at 0 hour
- Visual Acuity (Snellen) at 0 hour
- Slit lamp biomicroscopy without mydriatics at 0 hour
- TFBUT at 0 hour
- Corneal fluorescein staining (Baylor) at 0 hour
- Lissamine green staining (Baylor +Lid Margin) at 0 hour
- Schirmer I without anesthesia at 0 hour
- Intraocular pressure (iCare tonometer) at 0 hour
- Slit lamp biomicroscopy w/ mydriatics (lens observation) at 0 hour
- Ophthalmoscopy at 0 hour
- Administer study drug at 0 hour
- Dispense study drug for administration at home
- Dispense diary and complete refresher education on completion of diary and self-administration of study drug
- Discharge subjects from clinic
- Subjects self-administer study drug at 0, 4, 8, and 12 hours each day
- Subjects record dosing times in diary

Day 9 through Day 28

- Subjects self-administer study drug at 0, 4, 8, and 12 hours each day
- Subjects record dosing times in diary

Day 15 ±2 and Day 22 ±2

Subjects come to clinic for the following assessments (at 0 hour unless otherwise noted):

- Review AEs and concomitant medications
- Physical examination at 0 hour
- Vital signs at 0 hour
- VAS at 0, 4, and 8 hours

- OSDI at 0 hour
- Visual acuity at 0 hour
- Slit lamp biomicroscopy w/out mydriatics at 0 hour
- TFBUT at 0 hour
- Corneal fluorescein staining (Baylor) at 0 hour
- Lissamine green staining (Baylor +Lid Margin) at 0 hour
- Intraocular Pressure (iCare tonometer) at 0 hour
- Subjects self-administer study drug at 0, 4, 8, and 12 hours each day
- Subjects record dosing times in diary
- Dispense study drug for administration at home

Day 29 ±2, EOS

- Review AEs and concomitant medications
- DEQ-5 at 0 hour
- VAS at 0, 4, and 8 hours
- OSDI at 0 hour
- MMP-9 at 0 hour (30 minutes before TFBUT and staining tests)
- TFBUT at 0 hour
- Corneal fluorescein staining (Baylor) at 0 hour
- Lissamine green staining (Baylor +Lid Margin) at 0 hour
- Drug administration at 0 hour
- Clinical laboratory tests (hematology, serum chemistry, urinalysis) at 2 hours
- Serum pregnancy test for WOCBP only at 2 hours
- Physical examination, including weight at 4 hours
- Vital signs at 4 hours
- Visual Acuity (Snellen) at 8 hours
- Slit lamp biomicroscopy without mydriatics at 8 hour
- Schirmer I without anesthesia at 8 hours
- Intraocular pressure (iCare tonometer) at 8 hours
- Slit lamp biomicroscopy w/ mydriatics (lens observation) at 8 hours
- Ophthalmoscopy at 8 hours

Day 36 ±2

- Follow-up telephone call to review AEs and concomitant medications

9.1. Efficacy Assessments

The following ocular assessments will be done during Part A at the time points listed:

DEQ-5	Screening, Day -1
VAS	Screening, Day -1, Day 1 (0 (predose), 0.5, 1, 2, 4, 8, 12, 24 hours)
OSDI©	Screening, Day -1
MMP-9 (InflammaDry)	Screening, Day -1
TFBUT	Screening, Day 1 (0, 2, 12, 24 hours)
Corneal fluorescein staining (Baylor)	Screening, Day -1, Day 1 (0, 2, 12, 24 hours)
Lissamine green staining (Baylor +Lid Margin [lid wiper epitheliopathy])	Screening, Day 1 (0 hour)

The following ocular assessments will be done during Part B at the time points listed:

DEQ-5	Screening, Day -1, Day 29
VAS	Screening, Day -1, Day 1 (0, 0.5, 1, 2, 4, 8, 12 hours), Days 2 and 3 (0, 4, 8, 12 hours), Days 4 and 7 (0, 0.5, 1, 2, 4, 8, 12 hours), Days 5 and 6 (0, 4, 8, 12 hours) Day 8 (0 hour), Days 15, 22 and 29 (0, 4, 8 hours)
OSDI©	Screening, Day -1, Days 8, 15, 22 and 29 at 0 hour
MMP-9 (InflammaDry)	Screening, Day -1, and 29 (0 hour)
TFBUT	Screening, Day 1 (0, 2 and 12 hours), Days 2 through 7 (0 and 12 hours) Days 8, 15, 22, and 29 (0 hour)
Corneal fluorescein staining (Baylor)	Screening, Day -1, Day 1 (0, 2 and 12 hours), Days 2 through 7 (0 and 12 hours) Days 8, 15, 22, and 29 (0 hour)

Lissamine green staining (Baylor +Lid Margin [lid wiper epitheliopathy])	Screening, Day 1 (0 and 12 hours), Days 2 through 7 (0 and 12 hours) Days 8, 15, 22, and 29 (0 hour)

Please note: For Part A and B of this study all OSDI, DEQ-5 and VAS assessments will be completed prior to any laboratory or PK timepoints. TFBUT, Corneal fluorescein staining and Lissamine green staining will be scheduled to be completed following any laboratory or PK timepoints.

9.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

9.2.1. Ocular Safety

The following ocular safety assessments will be conducted during Part A at the time points listed:

Visual acuity (Snellen)	Screening, Day -1, Day 1 (12 and 24 hours)
Slit lamp biomicroscopy (w/out mydriatics)	Screening, Day 1 (0, 1, 2, 12, 24 hours)
Aesthesiometer	Screening
Schirmer I	Screening, Day -1, Day 1 (12 and 24 hours)
VAS with anesthesia	Screening
Intraocular pressure (iCare tonometer)	Screening, Day 1 (0, 2, 12, 24 hours)
Slit lamp biomicroscopy (w/ mydriatics; lens observation)	Screening, Day -1, Day 1(12 and 24 hours)
Ophthalmoscopy	Screening, Day -1, Day 1(12 and 24 hours)

The following ocular safety assessments will be conducted during Part B at the time points listed:

Visual acuity (Snellen)	Screening, Day -1, Day 1 (12 hours), Days 2 through 8, 15, 22, and 29 (0 hour)
Slit lamp biomicroscopy (w/out mydriatics)	Screening, Day 1 (0, 1, 2, 12 hours), Days 2 through 7 (0 and 12 hours), Days 8, 15, 22, and 29 (0 hour)
Aesthesiometer	Screening
Schirmer I	Screening, Day -1, Day 1 (12 hours), Days 2, 8 and 29 (0 hour)

VAS with anesthesia	Screening
Intraocular pressure (iCare tonometer)	Screening, Day 1 (0 and 12 hours), Days 2, 3, 8, 15, 22, and 29 (0 hour)
Slit lamp biomicroscopy (w/ mydriatics; lens observation)	Screening, Day -1, Day 1 (12 hours), Days 8 and 29 (0 hour)
Ophthalmoscopy	Screening, Day -1, Day 1 (12 hours), Days 8 and 29 (0 hour)

Please note: For Part A and B of this study, all ocular safety assessments will be scheduled to be performed following laboratory and PK time points.

9.2.2. Physical Examinations

A complete physical examination will include, at a minimum, assessments of HEENT, the Cardiovascular, Respiratory, Gastrointestinal, Dermatologic, and Neurologic systems. Height and weight will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.2.3. Vital Signs

Vital signs will be measured in a semi-supine position after 5 minutes rest and will include oral body temperature, systolic and diastolic blood pressure, heart rate, and respiratory rate. Vital signs will be measured before collection of blood samples for laboratory tests or PK.

9.2.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

9.3. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

AEs will be recorded from the beginning of the run-in phase. Any medical occurrence before run-in will be recorded as medical history. AE will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and/or designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the subject to discontinue the study (see Section 8).

9.3.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the beginning of the run-in phase to the follow-up visit.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

9.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.3.5. Pregnancy

- Details of all pregnancies in female subjects and, if indicated, female partners of male subjects will be collected after the start of study treatment and until termination or 8 weeks after birth.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

- Abnormal pregnancy outcomes (eg, spontaneous abortion, fatal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

9.4. Treatment of Overdose

An overdose occurring from topical administration of SJP-0132 ophthalmic [redacted] is unlikely but in the case of a suspected overdose, the subject will be instructed to contact the investigator or study coordinator immediately. General support measures should be used in the case of excessive pharmacological effects or overdose. No antidotes are available.

9.5. Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of SJP-0132 as specified in the SoA. Additional samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection and handling of biological samples will be detailed in a protocol specific lab manual. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the PK of SJP-0132. Samples collected for analyses of SJP-0132 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Drug concentration information that would unmask the study will not be reported to the Investigator or masked personnel until the study has been unmasked.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files,but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

The following PK parameters for SJP-0132 will be estimated using actual sample collection times:

C_{max}	maximum plasma concentration
$C_{max,norm}$	C_{max} divided by dose per body weight
C_{trough}	minimum (predose) plasma concentration during repeat dosing
t_{max}	time to reach the maximum plasma concentration
t_{last}	time to last quantifiable concentration
$AUC_{0\text{-}last}$	area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
$AUC_{0\text{-}\infty}$	area under the plasma concentration-time curve from time 0 to infinite time, calculated as the sum of $AUC_{0\text{-}last}$ and C_{last}/λ_z, in which C_{last} is the last observed quantifiable concentrations
$AUC_{0\text{-}last,norm}$	$AUC_{0\text{-}last}$ divided by dose per body weight
$AUC_{0\text{-}\infty,norm}$	$AUC_{0\text{-}\infty}$ divided by dose per body weight

$AUC_{\%extrap}$	percentage of $AUC_{0-\infty}$ that is due to extrapolation beyond t_{last}
$AUMC_{0-last}$	area under the moment curve from time 0 to time of the last quantifiable concentration
$AUMC_{0-\infty}$	area under the moment curve from time 0 to infinite time
MRT_{0-last}	mean residence time from time 0 to time of the last quantifiable concentration
$MRT_{0-\infty}$	mean residence time from time 0 to infinite time
$t_{1/2}$	elimination half-life associated with the terminal slope (λ_z) of the semilogarithmic drug concentration-time curve, calculated as $0.693/\lambda_z$
Vd/F	apparent volume of distribution
CL/F	apparent total body clearance
R_{ac}	accumulation ratios calculated as (C_{trough} on day 4) / (C_{trough} on day 2) and (C_{trough} on day 8) / (C_{trough} on day 2) (Part B)

9.6. Health Economics

No Health Economic information will be collected.

10. Statistical Considerations

10.1. General Considerations

The primary statistical analysis of the data will be descriptive in nature. For continuous variables this means calculation of the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by subject counts and related percentages. For ordinal-scaled variables, a combination of the above may be employed as appropriate: frequency and percentage of observations within a category and means and standard deviations of the scores of the categories. For categorical and ordinal variables, percentages will be calculated based on non-missing data.

10.2. Sample Size Determination

No formal sample size and/or power calculations were performed for the study, however a sample size was chosen based on feasibility to allow total of 92 randomized subjects for Part A (n=32) and Part B (n=60). Approximately 32 subjects are expected to complete Part A and 60 subjects are expected to complete Part B.

10.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	**Description**
Enrolled	Consist of all enrolled subjects. Subjects who signed the ICF. This population will be used in disposition outputs
Safety set	All subjects randomly assigned to study treatment and who take at least 1 dose of study treatment. Subjects will be analyzed according to the treatment they actually received. It will be the primary population for the safety and tolerability analysis.
Full analysis set	All subjects randomly assigned to study treatment and who take at least 1 dose of study treatment and have a post-baseline efficacy measurement. Subjects will be analyzed according to the treatment they actually received.
Per protocol set	All subjects who completes the study with at least 75% overall dosing compliance and without any other major protocol deviations/violations.
Pharmacokinetic set	All subjects who take at least 1 dose of active drug and have at least 1 quantifiable plasma concentration collected postdose without important protocol deviations/violations or events thought to significantly affect the PK.

10.4. Statistical Analyses

All the analysis will be carried out separately for Part A and Part B upon completion of the study visit (EOS). Data will be summarized by cohort and across all active dose levels. Complete details of the statistical analyses to be performed will be documented in a statistical analysis plan, which will be completed prior to database lock. This document will include more detail of analysis populations, summary strategies, and any amendments to the proposed analyses listed here, if necessary. Any changes to the statistical analysis plan will be outlined in the final study report.

10.4.1. Efficacy Analyses

This section is a summary of the planned statistical analyses of the primary and secondary endpoints. All analyses, summaries, and listings will be performed using SAS® software (Version 9.4 or higher version)

Endpoint	Statistical Analysis Methods
Primary	Change from baseline (predose on Day 1) in eye dryness symptom (visual analog scale [VAS]) at 4 hours on Day 29 Change from baseline (predose on Day 1) in corneal fluorescein staining (CFS) score at the central zone on Day 29
Secondary	Changes from baseline in dry eye signs: CFS scores at the central, superior, inferior, nasal, temporal and total zones, conjunctival lissamine green staining (CLGS) scores at each of 3 nasal and 3 temporal zone and total zone of bulbar conjunctiva, lid wiper epitheliopathy score, and tear film break-up time (TFBUT) at each time point tested Changes from baseline in dry eye symptoms (VAS [ie, severity of eye dryness, discomfort, burning/stinging, sticky feeling, foreign body sensation, itching, pain, blurred vision, and sensitivity to light], ocular surface disease index [OSDI©], Dry eye Questionnaire 5 [DEQ-5] scores) at each time point tested Biomarker (Matrix Metalloproteinase-9 (MMP-9), InflammaDry®)

The study eye will be the eye with the greater central zone corneal fluorescein staining score at predose on Day 1. If both eyes meet all of the inclusion and none of the exclusion criteria and the central zone corneal fluorescein staining scores are equal, the right eye (OD) will be designated as the study eye for the duration of this study.

The fellow eye (non-study eye) will be treated with the product as per the assigned dosing schedule.

Change in eye assessments will be summarized using descriptive statistics (mean, standard deviation, coefficient of variation (%CV), median, minimum, and maximum).

For this study co-primary endpoints will be as follows: the differences between SJP-0132 and placebo in changes from baseline in eye dryness symptom (visual analog scale [VAS]) and change from baseline (predose on Day 1) in corneal fluorescein staining (CFS) score at the central zone on Day 29.

Secondary endpoints are changes from baseline in dry eye signs: CFS scores at the superior, inferior, nasal, temporal and total zones, conjunctival lissamine green staining (CLGS) scores at each of 3 nasal and 3 temporal zone and total zone of bulbar conjunctiva, lid wiper epitheliopathy score, and tear film break-up time (TFBUT) at each time point tested. Changes from baseline in dry eye symptoms (VAS [ie, severity of eye dryness, discomfort, burning/stinging, sticky feeling, foreign body sensation, itching, pain, blurred vision, and sensitivity to light], ocular surface disease

index [OSDI©], Dry eye Questionnaire 5 [DEQ-5] scores) at each time point tested and Biomarker (Matrix Metalloproteinase-9 (MMP-9), InflammaDry®).

10.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Primary	The number and severity of AEs including abnormal changes from baseline in clinical laboratory results, vital signs, and physical and ophthalmologic examinations

Safety assessments and changes from baseline in vital signs, clinical laboratory results, adverse events (AEs), treatment-emergent AEs (TEAEs), will be summarized using descriptive statistics as outlined in the statistical analysis plan including but not limited to (mean, standard deviation, coefficient of variation (%CV), median, minimum, and maximum). Concomitant medications and physical examination findings will be listed.

10.4.3. Pharmacokinetic Analyses

Plasma samples will be analyzed to determine the concentration of SJP-0132. Pharmacokinetic variables will be calculated using non-compartmental analysis.

Individual PK concentrations and PK parameters will be listed. The PK data will be summarized descriptively by dose/cohort using appropriate statistics (eg, N, n, arithmetic mean, SD, minimum, median, maximum, geometric mean [PK parameters only, as appropriate], and coefficient of variance [CV%]). Graphical presentations will include by-subject and mean concentrations plots which will be presented on linear and semi-logarithmic scales. Scatterplots of individual and geometric mean exposure parameters [$AUC_{0-\infty}$, AUC_{0-last}, and C_{max}] will be presented by dose. Additional graphical presentations of PK data may be added at the discretion of the PK scientist

Part A: C_{max}, t_{max}, t_{last}, AUC_{0-last}, $AUC_{0-\infty}$, $AUC_{\%extrap}$, $t_{1/2}$, $AUMC_{0-last}$, $AUMC_{0-\infty}$, MRT_{0-last}, $MRT_{0-\infty}$, Vd/F, CL/F, $C_{max,norm}$, $AUC_{0-last,norm}$, $AUC_{0-\infty,norm}$.

Part B: Part B: C_{max}, t_{max}, t_{last}, AUC_{0-last}, $C_{max,norm}$, and $AUC_{0-last,norm}$ on Day 1, C_{trough} on Days 2, 4 and 8, and Rac.

11. References

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12. Appendices

Appendix 1: Abbreviations and Terms

Abbreviation	Definition
AE	Adverse event
AUC	Area under the plasma concentration-time curve
AUC_{0-16}	Area under the plasma concentration-time curve from time 0 to 16 hours
AUC_{0-last}	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time 0 to infinite time
$AUC_{0-last,norm}$	AUC_{0-last} divided by dose per body weight
$AUC_{0-\infty,norm}$	$AUC_{0-\infty}$ divided by dose per body weight
$AUC_{\%extrap}$,	Percentage of $AUC_{0-\infty}$ that is due to extrapolation beyond t_{last}
$AUMC_{0-last}$	Area under the moment curve from time 0 to time of the last quantifiable concentration
$AUMC_{0-\infty}$	Area under the moment curve from time 0 to infinite time
CFS	Corneal fluorescein staining
[redacted]	[redacted]
CLGS	conjunctival lissamine green staining
CL/F	Apparent total body clearance
CL_T	Total plasma clearance
C_{max}	Maximum plasma concentration
$C_{max,norm}$	C_{max} divided by dose per body weight
[redacted]	[redacted]
C_{trough}	Minimum (predose) plasma concentration during repeat dosing
%CV	Coefficient of variation, percent
CYP	Cytochrome P-450
DED	Dry Eye Disease
DEQ-5	5-item dry eye questionnaire
DEWS	International Dry Eye Workshop
[redacted]	[redacted]
F	Bioavailability
[redacted]	[redacted]
GLP	Gppd Laboratory Practice
[redacted]	[redacted]
IC_{50}	Concentration producing inhibition in 50% of population tested
IOP	Intraocular pressure
IV	Intravenous
JP	Japanese
MRT_{0-last}	Mean residence time from 0 to time of last quantifiable concentration

Abbreviation	Definition
$MRT_{0-\infty}$	Mean residence time from 0 to infinite time
[redacted]	[redacted]
OD	Oculus dexter (right eye)
OSDI	Ocular Surface Disease Index
[redacted]	[redacted]
PK	Pharmacokinetic(s)
[redacted]	[redacted]
Rac	Accumulation ratio
SAE	Serious adverse event
SoA	Schedule of Activities
[redacted]	[redacted]
SPK	Superficial punctate keratitis
[redacted]	[redacted]
$t_{1/2}$	Apparent elimination half-life
TEAE	Treatment-emergent adverse event
TFBUT	tear film break up time
[redacted]	[redacted]
t_{last}	Time to last quantifiable concentration
t_{max}	Time to reach the maximum plasma concentration
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
VAS	Visual analog scale
Vd_{ss}	Steady-state volume of distribution
Vd/F	Apparent volume of distribution
WOCBP	Woman of child-bearing potential

Appendix 2: Clinical Laboratory Tests

The tests detailed below will be performed by the local laboratory.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td>Hematology</td><td>Platelet Count
RBC Count
Hemoglobin
Hematocrit</td><td>RBC Indices:
MCV
MCH
%Reticulocytes</td><td>WBC Count with Differential:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td>Clinical Chemistry</td><td colspan="2">BUN
Potassium
Creatinine
Sodium
Glucose (fasting)
Calcium
Total Protein</td><td>Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)
Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)
Alkaline phosphatase
Total and direct bilirubin</td></tr>
<tr><td>Routine Urinalysis</td><td colspan="3">• Specific gravity
• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick
• Microscopic examination (if blood or protein is abnormal)</td></tr>
<tr><td>Other Screening Tests</td><td colspan="3">• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only)
• Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)]
• Alcohol urine test
• Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) at Screening and Day 29 (Part B). Urine pregnancy test at Day -1.
• Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)</td></tr>
</table>

Investigators must document their review of each laboratory safety report.

Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

Data Protection

- Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

This study and its results will be posted on the US National Institutes of Health's website www.ClinTrials.gov.

Data Quality Assurance

- All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.

- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period (ie, at least 2-years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2-years have elapsed since the formal discontinuation of clinical development of the investigational product). No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study treatment development

Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study subject, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • A treatment-emergent adverse event (TEAE) is any AE that occurs or worsens in either intensity or frequency after exposure to study drug in the treatment phase. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF (eg, event term, date and time of onset, date and time of resolution, anatomical site or system). If the AE/SAE is to an eye, the study eye or fellow eye must be identified.
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to Senju in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Senju. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to Senju.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Grade 1 (Mild): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Grade 2 (Moderate): minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL*.
- Grade 3 (Severe): medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4 (Life threatening): urgent intervention indicated
- Grade 5 (Death): death related to AE

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

* Activities of daily living

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Senju. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Senju.**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Senju to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • Drug related AEs or SAEs will be followed up until resolution, stabilization, or the event is otherwise explained, or the subject is lost to follow-up. • Non-drug-related AEs or SAEs will not be followed after the telephone follow-up call is complete. Any non-drug-related AEs or SAEs, that have not been resolved, stabilized, or otherwise explained by the follow-up telephone visit will be referred to the subjects Primary Care Physician for ongoing care. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Senju with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to Senju within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to Senju via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Senju will be the electronic data collection tool. • If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section). • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Senju by telephone. • Contacts for SAE reporting can be found in the Study Reference Manual.

SAE Reporting to Senju via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to Senju. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the Study Reference manual

Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's: review of the subject's medical records, medical examination, or medical history interview.

3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male subjects

- Male subjects with female partners of childbearing potential are eligible to participate if they agree to ONE of the following [during the protocol-defined time frame in Section 6.1]:

Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described below when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant

Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration [during the protocol-defined time frame]

Female subjects

Female subjects of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described below.

Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen only hormonal contraception associated with inhibition of ovulationIntrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) Bilateral tubal occlusion
Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, two highly effective methods of contraception should be utilized during the treatment period and for at least 30 days after the last dose of study treatment

Pregnancy Testing

WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive pregnancy test.

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected

Collection of Pregnancy Information

Male subjects with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive SJP-0132.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Subjects who become pregnant

- The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the study treatment by the investigator will be reported to the sponsor as described in Section 9.3. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will be withdrawn from the study.