Phase 1/2, Multicenter, Randomized, Double-Masked, Vehicle-Controlled, Multiple Ascending Dose (MAD) (Part 1) and Optional Dose Expansion (Part 2) Study of INV-102 Ophthalmic Solution in Adult Subjects With Moderate Symptomatic Dry Eye Disease

Study ID

INV-102-CS-001

Protocol v1.4

14 February 2023

NCT05586152

Phase 1/2, Multicenter, Randomized, Double-Masked, Vehicle-Controlled, Multiple Ascending Dose (MAD) (Part 1) and Optional Dose Expansion (Part 2) Study of INV-102 Ophthalmic Solution in Adult Subjects With Moderate Symptomatic Dry Eye Disease

Protocol Number: INV-102-CS-001

Investigational New Drug Sponsor: Invirsa, Inc.

Version Number: v.1.4

14 February 2023

SPONSOR APPROVAL AND SIGNATURE PAGE

Study Title:	Phase 1/2, Multicenter, Randomized, Double-Masked, Vehicle-Controlled, Multiple Ascending Dose (MAD) (Part 1) and Optional Dose Expansion (Part 2) Study of INV-102 Ophthalmic Solution in Adult Subjects With Moderate Symptomatic Dry Eye Disease
Study Number:	INV-102-CS-001
Original Protocol:	Version 1.4; 14 February 2023

Person authorized to sign the protocol and protocol amendment(s) for the Sponsor, Invirsa, Inc.

INVESTIGATOR'S AGREEMENT

Protocol INV-102-CS-001

Phase 1/2, Multicenter, Randomized, Double-Masked, Vehicle-Controlled, Multiple Ascending Dose (MAD) (Part 1) and Optional Dose Expansion (Part 2) Study of INV-102 Ophthalmic Solution in Adult Subjects With Moderate Symptomatic Dry Eye Disease

Investigator Agreement:

I, the undersigned, have reviewed this protocol and I agree to conduct this protocol in accordance with Good Clinical Practice, the ethical principles set forth in the Declaration of Helsinki and with the U.S. Code of Federal Regulations governing the protection of human subjects (21 CFR 50), Institutional Review Boards (21 CFR 56), and the obligations of clinical investigators (21 CFR 312).

Signature: _____ Date: _____

Printed Name: _____

PROCEDURES IN CASE OF EMERGENCY

Emergency Contact Information

Role in Study	Name	Contact Information
Clinical Study Leader	[redacted]	[redacted]
Medical Monitor	[redacted]	[redacted]

TABLE OF CONTENTS

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP), and applicable United States Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug Sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made by the IRB regarding whether reconsent of previously consented participants will be required.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Phase 1/2, Multicenter, Randomized, Double-Masked, Vehicle-Controlled, Multiple Ascending Dose (MAD) (Part 1) and Optional Dose Expansion (Part 2) Study of INV-102 Ophthalmic Solution in Adult Subjects With Moderate Symptomatic Dry Eye Disease
Study Number:	INV-102-CS-001
Study Description:	Phase 1/2, first-in-human (FIH), randomized, double-masked, vehicle-controlled, 2-part study to assess topically administered eyedrops of INV-102 during 2-week repeat dosing in subjects with moderate symptomatic dry eye disease (DED); also called keratoconjunctivitis sicca. Part 1 will be a Dose Escalation phase across 4 cohorts of subjects to assess safety, tolerability, and systemic pharmacokinetics (PK) of INV-102, and Part 2 will be an Optional Dose Expansion phase in a fifth cohort of subjects conducted pending the outcome of Part 1, to assess efficacy of INV-102 in the treatment of moderate symptomatic DED.
Objectives:	**Part 1 (Dose Escalation):** Primary Objective: To characterize the safety profile of INV-102 in subjects with moderate symptomatic DED using multiple concentrations and dosing regimens Other Objectives: [redacted] **Part 2 (Optional Dose Expansion):** Primary Objective: To evaluate the efficacy of INV-102 in subjects with moderate symptomatic DED in an expanded cohort Secondary Objective: To evaluate the efficacy of INV-102 using signs and symptoms in a combined outcome score in subjects with moderate symptomatic DED

	Other Objectives: [redacted]
Endpoints:	**Part 1 (Dose Escalation):** Primary Endpoint: Treatment-emergent adverse events (TEAEs) Other Endpoints: • Safety endpoints: [redacted] • Plasma PK endpoints: [redacted]

	[redacted] **Part 2 (Optional Dose Expansion):** <u>Primary Endpoint:</u> • Efficacy endpoint of change from Baseline to Day 15 in either the eye dryness score or eye discomfort score from the [redacted] DED symptom VAS (the specific endpoint for Part 2 will be chosen based on results from Part 1 [Dose Escalation] Cohorts 1 to 4 [redacted] <u>Secondary Endpoint:</u> • Chosen as per primary endpoint (change from Baseline to Day 15): – Eye Dryness Composite Score, or – Eye Discomfort Composite Score <u>Other Endpoints:</u> [redacted]
Study Design:	This FIH, multicenter, Phase 1/2 study has a randomized, double-masked, vehicle-controlled MAD part (Part 1) and an optional randomized, double-masked, vehicle-controlled dose-expansion part (Part 2) to evaluate INV-102 in subjects with moderate symptomatic DED.

	Prescription eyedrops/medications for DED must be washed out and contact lens wear must be discontinued [redacted] and both are prohibited throughout the dosing and follow-up phases of the study. OTC eyedrops, [redacted] are also prohibited throughout the dosing and follow-up phases of the study. [redacted] In Part 1 (Dose Escalation), subjects will be enrolled in a sequential manner into 1 of 4 cohorts, where they will be randomized 2:1 to receive either INV-102 or vehicle, respectively. Enrollment of the next cohort can begin once the current cohort is fully enrolled [redacted]. In Part 1, subjects will instill topical ocular study drug (INV-102 or vehicle) in both eyes (OU) for 2 weeks (***Note:*** study drug will be dosed in both eyes in Part 1 regardless of whether both eyes meet the criteria as a Qualifying Eye). The formulation concentration and frequency of dosing will be determined by cohort, with Cohorts 1 to 3 receiving twice daily (BID) dosing (approximately every 12 hours with at least 6 hours between doses) and Cohort 4 receiving 3 times daily (TID) dosing (approximately every 8 hours with at least 6 hours between doses). Subjects who fail to take a dose of study drug within the dosing window should skip that dose and not attempt to make it up. • Cohort 1 (0.1% INV-102 vs vehicle): 1 drop OU on Day 1, then BID OU for 13 days (Days 2-14), then 1 drop OU on Day 15 • Cohort 2 (0.25% INV-102 vs vehicle): 1 drop OU on Day 1, then BID OU for 13 days (Days 2-14), then 1 drop OU on Day 15 • Cohort 3 (0.7% INV-102 vs vehicle): 1 drop OU on Day 1, then BID OU for 13 days (Days 2-14), then 1 drop OU on Day 15 • Cohort 4 (0.7% INV-102 vs vehicle): 1 drop OU on Day 1, then TID OU for 13 days (Days 2-14), then 1 drop OU on Day 15 [redacted] After Part 1 (Dose Escalation) Cohorts 1 to 4 have been completed the study may advance to the optional Part 2 based on review of available [redacted] data [redacted]. In Part 2 (Optional Dose Expansion) Cohort 5, subjects will be randomized 2:1 to INV-102 or vehicle, respectively, and will instill topical ocular study

	drug in eligible eye(s) (ie, Qualifying Eyes) for 2 weeks either BID (1 drop on Day 1, then BID for 13 days, then 1 drop on Day 15) or TID (1 drop on Day 1, then TID for 13 days, then 1 drop on Day 15). Frequency and dose will be chosen [redacted] based on the results from Part 1 (Dose Escalation) Cohorts 1 to 4 (***Note:*** study drug may be dosed in a single eye or in both eyes in Part 2, depending on whether each eye individually meets the criteria as a Qualifying Eye. For subjects dosing only one eye in Part 2 [ie, having only one Qualifying Eye], assessments will only be performed on the eye being dosed).
Estimated Number of Subjects:	Part 1 (Dose Escalation) Cohorts 1 to 4: Approximately 9 subjects in each cohort (6 active: 3 vehicle; total of approximately 36 subjects) Part 2 (Optional Dose Expansion) Cohort 5: Approximately 48 subjects (32 active: 16 vehicle)
Study Population:	Inclusion criteria: 1. Healthy male or female subject ≥18 years of age 2. Presence of moderate DED in at least one eye [redacted] as defined by the following criteria (for an eye to qualify, all criteria must be present in the same eye): [redacted] 3. Ability to comply with all protocol-mandated procedures and to attend all scheduled office visits 4. Able to self-administer study drug or to have the study drug administered by a caregiver throughout the study period Exclusion criteria: 1. BCVA [redacted] as assessed using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart 2. IOP [redacted] 3. Presently using prescription eyedrops, [redacted] 4. Use of OTC eyedrops [redacted]

5. [redacted]
6. [redacted]
7. External eye disease [redacted] except primary DED
8. [redacted]
9. Systemic disease associated with DED [redacted]
10. [redacted]
11. [redacted]
12. History or evidence of ocular infection within 30 days prior to initiation of study drug dosing
13. History or evidence of ocular herpes simplex or ocular herpes zoster
14. Blepharitis or meibomian gland disease requiring the use of either topical or systemic antibiotics within 2 months prior to initiation of study drug dosing
15. [redacted]
16. [redacted]
17. [redacted]
18. [redacted]
19. [redacted]

	20. [redacted] 21. Any significant chronic illness or ocular anatomical abnormality [redacted] that, in the opinion of the investigator, could interfere with the study parameters 22. Females who are pregnant or nursing. Females of childbearing potential or non-vasectomized males who are unwilling or not using a medically acceptable form of birth control. [redacted]
Clinical Phase:	1/2
Number and Location of Investigational Sites:	[redacted] sites in the United States
Description of Study Intervention:	INV-102 Ophthalmic Solution in concentrations of 0.1%, 0.25%, and 0.7%. Vehicle Ophthalmic Solution is identical to the formulation of INV-102 Ophthalmic Solution but does not contain the active ingredient.
Study Duration:	[redacted] months from first subject first visit to last subject last visit
Subject Duration:	Up to 28 days of Screening [redacted] 2 weeks of dosing, and 1 week of follow-up.
Statistical Considerations:	Eyes meeting the study-defined DED eligibility criteria will be deemed Qualifying Eyes and each subject may have either 1 or 2 Qualifying Eyes. All subjects, regardless of whether they receive study drug in one or both eyes, will have only one eye designated as the Study Eye. The Study Eye is defined as the eye with more severe disease based on corneal fluorescein staining. The other eye is designated as the Fellow Eye. If both eyes have the same corneal fluorescein staining score, the eye with the more severe eye dryness score from the [redacted] DED symptom VAS will be the Study Eye. If both eyes have the same eye dryness score, the right eye will be the Study Eye. In Part 1 (Dose Escalation) Cohorts 1 to 4, both eyes will receive study drug regardless of whether both eyes meet the criteria as Qualifying Eyes, and study assessments will be performed for both eyes (unless noted

	otherwise). Safety data from each eye will be analyzed. Non–eye-specific safety data (adverse event [AE] data) will be collected and analyzed at the subject level, and eye-specific safety data and efficacy data will be collected and analyzed at the eye level (Study Eye and Fellow Eye). In Part 2 (Optional Dose Expansion) Cohort 5, only eyes meeting DED eligibility (Qualifying Eyes) will receive study drug and be assessed. Safety data from only those eyes will be analyzed. Non–eye-specific safety data (AE data) will be collected and analyzed at the subject level, and eye-specific safety data and efficacy data will be collected and analyzed at the eye level (Study Eye and, if applicable, Fellow Eye). All continuous variables will be summarized by study drug and time point (as applicable) using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). All categorical variables will be summarized by study drug and time point (as applicable) using frequency counts and percentages. All study data will be presented by study drug and time point (as applicable). All statistical tests will be performed using a significance level of 5% (2-tailed). The p-values for the analysis of efficacy endpoints will be considered descriptive.
Sample Size Justification:	Part 1 (Dose Escalation): The sample size of approximately 9 subjects each in Cohorts 1 to 4 (6 active: 3 vehicle) is considered sufficient for evaluation of safety, tolerability, and PK of each cohort. The sample size was not based on statistical power considerations. Part 2 (Optional Dose Expansion): The sample size of approximately 48 subjects in Cohort 5 (32 active: 16 vehicle) is considered sufficient for evaluation of preliminary efficacy of INV-102. The sample size was not based on statistical power considerations.
[redacted]	[redacted]

1.2 STUDY ACTIVITIES SCHEMA

Note: **Refer to Section 9 (Study Assessments and Procedures) for additional details regarding the protocol activities.**

[redacted]

All ocular assessments will be conducted on both eyes individually in Part 1 (Dose Escalation) and on all Qualifying Eyes in Part 2 (Optional Dose Expansion), unless noted otherwise.

1.2.1 PART 1 (DOSE ESCALATION)

Screening Visit: Day -28 to Day -1

[redacted]

Total n=approximately 36 subjects

Procedures:

- Informed consent
- Inclusion/Exclusion criteria
- Demographics
- Ophthalmic medical and surgical history
- General medical and surgical history
- Concomitant medication review
- Urine pregnancy test (for women of childbearing potential)
- [redacted] DED symptom VAS
- Ophthalmologic assessments: visual acuity, [redacted] slit lamp exam [redacted] corneal fluorescein staining [redacted], and IOP
- AE assessment

Baseline/Initiation of Dosing Visit: Day 1

Cohorts (study drug will be dosed in both eyes in Part 1 regardless of whether they both meet the criteria as a Qualifying Eye):

- BID 0.1% Cohort: INV-102 (n=approximately 6) vs vehicle (n=approximately 3)
- BID 0.25% Cohort: INV-102 (n=approximately 6) vs vehicle (n=approximately 3)
- BID 0.7% Cohort: INV-102 (n=approximately 6) vs vehicle (n=approximately 3)
- TID 0.7% Cohort: INV-102 (n=approximately 6) vs vehicle (n=approximately 3)

Procedures:

- Inclusion/Exclusion criteria
- Concomitant medication review
- Vital signs (including height and weight)
- Urine pregnancy test (for women of childbearing potential)
- [redacted] DED symptom VAS
- [redacted]

- [redacted]
- [redacted]
- Ophthalmologic assessments: noncontact pachymetry, endothelial cell count, visual acuity, [redacted], slit lamp exam [redacted], corneal fluorescein staining [redacted] IOP, and dilated fundus exam
- [redacted]
- Randomization
- Study drug dispensing
- [redacted]
- Study drug administration by site staff
- [redacted]
- PK blood sample collection (pre-dose and at 5, 15, 30, 60, and 120 minutes post-dose)
- AE assessment

AE Assessment Telephone Visit: Day 2

- AE assessment

Mid-dosing Visit: Day 8 (±1 day)

Procedures:

- Concomitant medication review
- Vital signs
- [redacted] DED symptom VAS
- [redacted]
- [redacted]
- Study drug administration by site staff
- [redacted]
- [redacted]
- PK blood sample collection (pre-dose and at 5, 15, 30, 60, and 120 minutes post-dose)
- Ophthalmologic assessments (≥15 minutes AFTER administration of study drug): noncontact pachymetry, visual acuity, [redacted] slit lamp exam [redacted] corneal fluorescein staining [redacted] IOP, and dilated fundus exam
- [redacted]
- AE assessment

Completion of Dosing Visit: Day 15 (+1 day)

Procedures:

- Concomitant medication review

- Vital signs
- [redacted] DED symptom VAS
- [redacted]
- [redacted]
- Study drug administration by site staff
- [redacted]
- Bottle of remaining unused study drug will be collected and retained by site staff
- [redacted]
- Ophthalmologic assessments (≥15 minutes AFTER administration of study drug): noncontact pachymetry, endothelial cell count, visual acuity, [redacted] slit lamp exam [redacted] corneal fluorescein staining [redacted], IOP, and dilated fundus exam
- [redacted]
- AE assessment

Follow-Up Visit: Day 22 (±2 days)

- Concomitant medication review
- Vital signs
- Urine pregnancy test (for women of childbearing potential)
- [redacted] DED symptom VAS
- [redacted]
- [redacted]
- Ophthalmologic assessments: noncontact pachymetry, visual acuity, [redacted] slit lamp exam [redacted] corneal fluorescein staining [redacted] IOP, and dilated fundus exam
- [redacted]
- AE assessment

1.2.2 PART 2 (OPTIONAL DOSE EXPANSION)

Screening Visit: Day -28 to Day -1

[redacted]

Total n=approximately 48 subjects

Procedures:

- Informed consent
- Inclusion/Exclusion criteria
- Demographics
- Ophthalmic medical and surgical history
- General medical and surgical history

- Concomitant medication review
- Urine pregnancy test (for women of childbearing potential)
- [redacted] DED symptom VAS
- Ophthalmologic assessments: visual acuity, [redacted] slit lamp exam [redacted] corneal fluorescein staining [redacted] and IOP
- AE assessment

Baseline/Initiation of Dosing Visit: Day 1

One (1) BID or TID cohort (dose and frequency to be determined by Part 1 results): INV-102 (n=approximately 32) vs vehicle (n=approximately 16)

Study drug will be dosed in either a single eye or in both eyes in Part 2 depending on whether each eye individually meets the criteria as a Qualifying Eye. For subjects dosing only one eye in Part 2 (ie, having only one Qualifying Eye), assessments will only be performed on the eye being dosed.

Procedures:

- Inclusion/Exclusion criteria
- Concomitant medication review
- Vital signs (including height and weight)
- Urine pregnancy test (for women of childbearing potential)
- [redacted] DED symptom VAS
- [redacted]
- [redacted]
- [redacted]
- Ophthalmologic assessments: visual acuity, [redacted] slit lamp exam [redacted] corneal fluorescein staining [redacted]
- [redacted]
- Randomization
- Study drug dispensing
- [redacted]
- Study drug administration by site staff
- [redacted]
- AE assessment

AE Assessment Telephone Visit: Day 2

- AE assessment

Mid-dosing Visit: Day 8 (±1 day)

Procedures:

- Concomitant medication review
- Vital signs
- [redacted] DED symptom VAS
- [redacted]

- [redacted]
- Study drug administration by site staff
- [redacted]
- [redacted]
- Ophthalmologic assessments (≥15 minutes AFTER administration of study drug): visual acuity, [redacted] slit lamp exam [redacted] corneal fluorescein staining [redacted]
- [redacted]
- AE assessment

Completion of Dosing Visit: Day 15 (+1 day)

Procedures:

- Concomitant medication review
- Vital signs
- [redacted] DED symptom VAS
- [redacted]
- [redacted]
- Study drug administration by site staff
- [redacted]
- Bottle of remaining unused study drug will be collected and retained by site staff
- [redacted]
- Ophthalmologic assessments (≥15 minutes AFTER administration of study drug): visual acuity, [redacted] slit lamp exam [redacted] corneal fluorescein staining [redacted]
- [redacted]
- AE assessment

Follow-Up Visit: Day 22 (±2 days)

- Concomitant medication review
- Vital signs
- Urine pregnancy test (for women of childbearing potential)
- [redacted] DED symptom VAS
- [redacted]
- [redacted]
- Ophthalmologic assessments: visual acuity, [redacted] slit lamp exam [redacted] corneal fluorescein staining [redacted]
- [redacted]
- AE assessment

1.3 SCHEDULES OF ACTIVITIES

***Note*: Refer to Section 1.2 (Study Activities Schema) and Section 9 (Study Assessments and Procedures) for additional details regarding the protocol activities.**

Part 1 (Dose Escalation)

Protocol Activities	Screening (Day -28 to Day -1) [1]	Day 1 (Baseline/Initiation of Dosing) [1]	Day 2 (Phone Contact) AE Assessment	Day 8 (Mid-dosing Visit) (±1 day)	Day 15 (Completion of Dosing Visit) (+1 day)	Day 22 (Follow-Up Visit) (±2 days)
Informed consent	X					
Inclusion/Exclusion criteria	X	X				
Demographics	X					
Ophthalmic medical & surgical history	X					
General medical & surgical history	X					
Concomitant medication review [2]	X	X		X	X	X
Vital signs (BP, HR; including height and weight at Baseline) [3]		X		X	X	X
Urine pregnancy test [4]	X	X				X
Randomization		X				
Study drug dispensing		X				
Study drug [redacted]		X (pre-dose)		X (post-dose)	X (post-dose)	
Study drug administration by site staff [6]		X		X	X	
Subject-reported assessments [7]						
[redacted] DED symptom VAS	X	X		X	X	X
[redacted]		X		X	X	X
[redacted]		X		X	X	
[redacted]		---------- X ----------				
Ophthalmologic assessments [10]						
Noncontact pachymetry		X		X	X	X
Endothelial cell count		X			X	
Visual acuity	X	X		X	X	X
[redacted]	X	X		X	X	X
Slit lamp exam [redacted]	X	X		X	X	X
[redacted]		X		X	X	X
Corneal fluorescein staining [redacted]	X	X		X	X	X
[redacted]		X		X	X	X
IOP [13]	X	X		X	X	X
Dilated fundus exam [14]		X		X	X	X
PK blood sample collection [15]		X		X		
[redacted]		X		X	X	X
AE assessment	X	X	X	X	X	X

AE, adverse event; BP, blood pressure; CCLRU, Cornea and Contact Lens Research Unit; DED, dry eye disease; eCRF, electronic case report form; HR, heart rate; IOP, intraocular pressure; [redacted] PK, pharmacokinetic; [redacted] SRM, Study Reference Manual; VAS, visual analog scale.

Part 2 (Optional Dose Expansion)

Protocol Activities	Screening (Day -28 to Day -1) [1]	Day 1 (Baseline/Initiation of Dosing) [1]	Day 2 (Phone Contact) AE Assessment	Day 8 (Mid-dosing Visit) (±1 day)	Day 15 (Completion of Dosing Visit) (+1 day)	Day 22 (Follow-Up Visit) (±2 days)
Informed consent	X					
Inclusion/Exclusion criteria	X	X				
Demographics	X					
Ophthalmic medical & surgical history	X					
General medical & surgical history	X					
Concomitant medication review [2]	X	X		X	X	X
Vital signs (BP, HR; including height and weight at Baseline) [3]		X		X	X	X
Urine pregnancy test [4]	X	X				X
Randomization		X				
Study drug dispensing		X				
Study drug [redacted]		X (pre-dose)		X (post-dose)	X (post-dose)	
Study drug administration by site staff [6]		X		X	X	
Subject-reported assessments [7]						
[redacted] DED symptom VAS	X	X		X	X	X
[redacted]		X		X	X	X
[redacted]		X		X	X	
[redacted]		X				
Ophthalmologic assessments [10]						
Visual acuity	X	X		X	X	X
[redacted]	X	X		X	X	X
Slit lamp exam [redacted]	X	X		X	X	X
[redacted]		X		X	X	X
Corneal fluorescein staining [redacted]	X	X		X	X	X
[redacted]		X		X	X	X
IOP [13]	X					
[redacted]		X		X	X	X
AE assessment	X	X	X	X	X	X

AE, adverse event; BP, blood pressure; CCLRU, Cornea and Contact Lens Research Unit; DED, dry eye disease; eCRF, electronic case report form; HR, heart rate; IOP, intraocular pressure; [redacted] VAS, visual analog scale.

[redacted]

2 ABBREVIATIONS

ADPr	adenosine 5'-diphosphoribose
AE	adverse event
AUC	area under the concentration-time curve
BCVA	best-corrected visual acuity
BID	twice daily
BP	blood pressure
CCLRU	Cornea and Contact Lens Research Unit
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum drug concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
DED	dry eye disease
eCRF	electronic case report form
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
FIH	first-in-human
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonisation
IND	Investigational New Drug
IOP	intraocular pressure
IRB	Institutional Review Board
LS	least squares
MAD	multiple ascending dose
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
[redacted]	[redacted]
MMRM	mixed model for repeated measures
[redacted]	[redacted]
NEI	National Eye Institute
NF	National Formulary
NOAEL	no-observed-adverse-effect level
OTC	over-the-counter
OU	both eyes
PHI	Personal Health Information
PK	pharmacokinetic(s)
PP	per protocol
PRK	photorefractive keratectomy
SAE	serious adverse event
[redacted]	[redacted]

SAP	Statistical Analysis Plan
SoA	Schedule of Activities
[redacted]	[redacted]
SRM	Study Reference Manual
SUSAR	suspected unexpected serious adverse reaction
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
TID	3 times daily
T_{max}	time to reach maximum drug concentration
USP	United States Pharmacopeia
UV	ultraviolet
VAS	visual analog scale

3 INTRODUCTION

3.1 STUDY RATIONALE

Invirsa intends to conduct this initial Phase 1/2 multiple ascending dose (MAD) study of INV-102 in subjects with dry eye disease (DED; also called keratoconjunctivitis sicca). Subjects with DED were chosen for this study to evaluate the safety of INV-102 in eyes that are at least partially compromised. Previous research has shown that compounds that demonstrate safety in healthy subjects do not necessarily demonstrate the same safety or tolerability in compromised eyes. Invirsa looks to ensure the tolerability of INV-102 in compromised eyes by enrolling and evaluating subjects with moderate symptomatic DED in this Phase 1/2 clinical trial.

3.2 BACKGROUND

[redacted]

3.3 RISK/BENEFIT ASSESSMENT

3.3.1 KNOWN POTENTIAL RISKS

Since this is the first-in-human (FIH) clinical study with INV-102 topical ocular solution, the risk profile for the compound in humans has not been determined. [redacted]

3.3.2 KNOWN POTENTIAL BENEFITS

This is the first study of INV-102 topical ocular solution in humans and, therefore, benefits from its use have not been established. [redacted]

[redacted]

3.3.3 POTENTIAL IMPACT OF THE COVID-19 PANDEMIC

In acknowledgement of hospital, local, state, or national government Coronavirus Disease 2019 (COVID-19) restrictions or other site- or subject-related factors, which may prevent investigators from conducting certain assessments or procedures according to the Schedules of Activities (SoAs), investigators may seek approval from Invirsa to modify when or if certain assessments or procedures are conducted according to the SoAs. While sites must employ all efforts to see subjects in the clinic for assessments, exceptions may be granted for alternative methods for conducting subject visits with approval by Invirsa and notification to the Institutional Review Board (IRB). In evaluating such requests, the Invirsa team will give the highest priority to the safety and welfare of the subjects. Investigators are expected to evaluate the impact to the safety of the subjects and site personnel for subjects to continue. Subjects must be willing and able to continue receiving study drug and remain compliant with the protocol. For subjects who are impacted, any procedures not conducted per the original study plan will be documented in the study records.

When approval is given for a subject to miss an in-person visit, site staff will speak directly with the subject by telephone or other medium (eg, a computer-based video communication) during each visit window to assess subject safety and overall clinical status. During this contact with the subject, the investigator or other qualified site staff should also, at a minimum, conduct the following assessments: adverse event (AE) collection and concomitant medication documentation. Other study assessments may be collected remotely as feasible. Sites may also seek approval to extend a visit window in order to conduct an onsite visit.

Data collected with alternative methods may be handled differently in the final data analyses. This will be documented in the Statistical Analysis Plan (SAP).

4 OBJECTIVES AND ENDPOINTS

Part 1 (Dose Escalation)

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To characterize the safety profile of INV-102 in subjects with moderate symptomatic DED using multiple concentrations and dosing regimens	***Safety endpoint:*** treatment-emergent adverse events (TEAEs)	***Safety endpoint*** assessing the ocular and systemic safety of INV-102 is necessary in this FIH study
Other		

[redacted]

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
[redacted]		

Part 2 (Optional Dose Expansion)

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To evaluate the efficacy of INV-102 in subjects with moderate symptomatic DED in an expanded cohort	***Efficacy endpoint*** using change from Baseline to Day 15 in either the eye dryness score or eye discomfort score from the [redacted]DED symptom VAS (the specific endpoint for Part 2 will be chosen based on results from Part 1 [Dose Escalation] Cohorts 1 to 4[redacted]	***An efficacy endpoint*** using a subject-reported outcome of DED symptoms is useful to provide preliminary information regarding the efficacy of INV-102 in the treatment of DED
Secondary		
To evaluate the efficacy of INV-102 using signs and symptoms in a combined outcome score in subjects with moderate symptomatic DED	***Efficacy endpoint*** *chosen as per primary endpoint (change from Baseline to Day 15):* Eye Dryness Composite Score or Eye Discomfort Composite Score	***Efficacy endpoint*** using 2 subject-reported outcomes (assessing DED symptoms) and 1 objective measure of DED signs (corneal fluorescein staining) is useful to provide preliminary information regarding the efficacy of INV-102 in the treatment of DED. A composite score combining symptoms (VAS individual item score) and signs (corneal fluorescein staining) will provide a more robust measure of efficacy
Other		
[redacted]		

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS

5 STUDY DESIGN

5.1 OVERALL DESIGN

This FIH, multicenter, Phase 1/2 study has a randomized, double-masked, vehicle-controlled MAD part (Part 1) and an optional randomized, double-masked, vehicle-controlled dose-expansion part (Part 2) to evaluate INV-102 in subjects with moderate symptomatic DED. Part 1 will be a Dose Escalation phase across 4 cohorts of subjects to assess safety, tolerability, and systemic PK of INV-102, and Part 2 will be an Optional Dose Expansion phase in a fifth cohort of subjects conducted pending the outcome of Part 1, to assess efficacy of INV-102 in the treatment of moderate symptomatic DED.

Prescription eyedrops/medications for DED must be washed out and contact lens wear must be discontinued [redacted] and both are prohibited throughout the dosing and follow-up phases of the study. Over-the-counter eyedrops, [redacted] are also prohibited throughout the dosing and follow-up phases of the study. [redacted]

In Part 1 (Dose Escalation) Cohorts 1 to 4, both eyes (OU) will receive study drug and data from each eye will be analyzed. In Part 2 (Optional Dose Expansion) Cohort 5, only eyes meeting DED eligibility (ie, Qualifying Eyes) will receive study drug and data only from those eyes will be analyzed. However, regardless of whether subjects receive study drug in one or both eyes, all subjects in both parts of the study will have only one eye designated as the Study Eye. The Study Eye is the eye with more severe DED based on corneal fluorescein staining. The other eye is designated as the Fellow Eye. If both eyes have the same corneal fluorescein staining score, the eye with the more severe eye dryness score from the [redacted] DED symptom VAS will be the Study Eye. If both eyes also have the same eye dryness score, the right eye will be the Study Eye.

In Part 1 (Dose Escalation), subjects will be enrolled in a sequential manner into 1 of 4 cohorts, where they will be randomized 2:1 to receive either INV-102 or vehicle, respectively. Enrollment of the next cohort can begin once the current cohort is fully enrolled [redacted]

In Part 1, subjects will instill topical ocular study drug (INV-102 or vehicle) in both eyes for 2 weeks. (***Note:*** study drug will be dosed in both eyes in Part 1 regardless of whether both eyes meet the criteria as a Qualifying Eye). The formulation concentration and frequency of dosing will be determined by cohort, with Cohorts 1 to 3 receiving BID dosing (approximately every 12 hours with at least 6 hours between doses) and Cohort 4 receiving TID dosing (approximately every 8 hours with at least 6 hours between doses). Subjects who fail to take a dose of study drug within the dosing window should skip that dose and not attempt to make it up.

- Cohort 1 (0.1% INV-102 vs vehicle): 1 drop OU on Day 1, then BID OU for 13 days (Days 2-14), then 1 drop OU on Day 15
- Cohort 2 (0.25% INV-102 vs vehicle): 1 drop OU on Day 1, then BID OU for 13 days (Days 2-14), then 1 drop OU on Day 15

- Cohort 3 (0.7% INV-102 vs vehicle): 1 drop OU on Day 1, then BID OU for 13 days (Days 2-14), then 1 drop OU on Day 15
- Cohort 4 (0.7% INV-102 vs vehicle): 1 drop OU on Day 1, then TID OU for 13 days (Days 2-14), then 1 drop OU on Day 15

[redacted]

After Part 1 (Dose Escalation) Cohorts 1 to 4 have been completed and Cohort 4 has been fully enrolled [redacted] the study may advance to the optional Part 2 based on review of available [redacted] data [redacted].

In Part 2 (Optional Dose Expansion) Cohort 5, subjects will be randomized 2:1 to INV-102 or vehicle, respectively, and will instill topical ocular study drug in eligible eye(s) (ie, Qualifying Eyes) for 2 weeks either BID (1 drop on Day 1, then BID for 13 days, then 1 drop on Day 15) or TID (1 drop on Day 1, then TID for 13 days, then 1 drop on Day 15). Frequency and dose will be chosen [redacted] based on the results from Part 1 (Dose Escalation) Cohorts 1 to 4 (***Note:*** study drug may be dosed in a single eye or in both eyes in Part 2, depending on whether each eye individually meets the criteria as a Qualifying Eye. For subjects dosing only one eye in Part 2 [ie, having only one Qualifying Eye], assessments will only be performed on the eye being dosed).

5.2 MASKING OF SUBJECTS, SITE PERSONNEL, AND STUDY PERSONNEL

Masking of individual subject study drug assignments will be maintained throughout the study for all subjects and all site and study personnel, aside from designated personnel assigned to review the data from Cohorts 1 to 4 for purposes of selecting the dose for Part 2 (Optional Dose Expansion) as defined in the Unmasked Data Review Plan, until the database is locked for the final analysis. If it is necessary for the safety and appropriate treatment of a subject, the study drug assignment can be unmasked. When possible, the medical monitor should be notified prior to the unmasking, and the reason for breaking the mask will be documented. The investigator should inform the medical monitor of the unmasking if there is no notification prior to the unmasking.

5.3 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The first part of the study is designed as a dose-escalation, FIH Phase 1 study. Part 1 (Dose Escalation) will assess safety at various INV-102 dose levels and aid in the determination of the dose for Part 2 [redacted] Part 2 (Optional Dose Expansion) is the optional Phase 2 portion of the study and is intended to assess both safety and gather expanded efficacy [redacted] for INV-102 in subjects with DED.

Both parts of the study are randomized to INV-102 or vehicle. Vehicle is useful in this Phase 1/2 study because some of the endpoints are subjective. Therefore, it is important to assess responses of subjects receiving vehicle to account for any placebo effect, in which subjects may believe their disease is improving simply because they are receiving study drug. The 2:1 (INV-102:vehicle) ratio of subject assignment was chosen so that the majority of subjects will receive INV-102.

5.4 JUSTIFICATION FOR DOSE

Topical INV-102 has been shown to be efficacious in rabbit models [redacted]

Therefore, INV-102 is anticipated to be safe and effective when dosed in the concentration range from 0.1% to 0.7%, administered as 30 µL drops, BID or TID OU for 14 days. In Part 1 (Dose Escalation) of this study, the first 4 cohorts will receive study drug as follows:

- Cohort 1 (0.1% INV-102 vs vehicle): 1 drop OU on Day 1, then BID OU for 13 days (Days 2-14), then 1 drop OU on Day 15
- Cohort 2 (0.25% INV-102 vs vehicle): 1 drop OU on Day 1, then BID OU for 13 days (Days 2-14), then 1 drop OU on Day 15
- Cohort 3 (0.7% INV-102 vs vehicle): 1 drop OU on Day 1, then BID OU for 13 days (Days 2-14), then 1 drop OU on Day 15
- Cohort 4 (0.7% INV-102 vs vehicle): 1 drop OU on Day 1, then TID OU for 13 days (Days 2-14), then 1 drop OU on Day 15

The dose and frequency for Part 2 (Optional Dose Expansion) will be determined by the results of the 4 cohorts in Part 1. Subjects will instill study drug in eligible eye(s) only [ie, Qualifying Eye(s)] using the regimen of either BID (1 drop on Day 1, then BID for 13 days (Days 2-14), then 1 drop on Day 15) or TID (1 drop on Day 1, then TID for 13 days (Days 2-14), then 1 drop on Day 15).

5.5 END OF STUDY DEFINITION

A subject is considered to have completed the study if he or she has completed the dosing and follow-up phases of the study, including the last visit or the last scheduled procedure shown in the SoA (Section 1.3).

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

6 STUDY POPULATION

6.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Healthy male or female subject ≥18 years of age
2. Presence of moderate DED in at least one eye [redacted] as defined by the following criteria (for an eye to qualify, all criteria must be present in the same eye):
   - [redacted]
   - [redacted]
   - [redacted]
3. Ability to comply with all protocol-mandated procedures and to attend all scheduled office visits
4. Able to self-administer study drug or to have the study drug administered by a caregiver throughout the study period

6.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Best-corrected visual acuity [redacted] as assessed using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart
2. Intraocular pressure [redacted]
3. Presently using prescription eyedrops, [redacted]
4. Use of OTC eyedrops [redacted]
5. [redacted]
6. [redacted]
7. External eye disease [redacted]
8. [redacted]

9. Systemic disease associated with DED [redacted]
10. [redacted]
11. [redacted]
12. History or evidence of ocular infection within 30 days prior to initiation of study drug dosing
13. History or evidence of ocular herpes simplex or ocular herpes zoster
14. Blepharitis or meibomian gland disease requiring the use of either topical or systemic antibiotics within 2 months prior to initiation of study drug dosing
15. [redacted]
16. [redacted]
17. [redacted]
18. [redacted]
19. [redacted]
20. [redacted]
21. Any significant chronic illness or ocular anatomical abnormality [redacted] that, in the opinion of the investigator, could interfere with the study parameters
22. Females who are pregnant or nursing. Females of childbearing potential or non-vasectomized males who are unwilling or not using a medically acceptable form of birth control. [redacted]

6.3 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes [redacted]

6.4 STRATEGIES FOR RECRUITMENT AND RETENTION

[redacted]

7 STUDY INTERVENTION

7.1 STUDY INTERVENTIONS ADMINISTRATION

7.1.1 STUDY INTERVENTION DESCRIPTION

INV-102 Ophthalmic Solution is a topical eyedrop containing the active ingredient INV-102. INV-102 is [redacted]

Vehicle Ophthalmic Solution is identical to the formulation of INV-102 Ophthalmic Solution but does not contain the active ingredient.

7.1.2 DOSING AND ADMINISTRATION

INV-102 is provided in concentrations of 0.1%, 0.25%, and 0.7%.

In Part 1 (Dose Escalation), subjects will be enrolled in a sequential manner into 1 of 4 cohorts as shown below, where they will be randomized 2:1 to receive either INV-102 or vehicle, respectively. Enrollment of the next cohort can begin once the current cohort is fully enrolled [redacted]. Subjects will instill topical ocular study drug (INV-102 or vehicle) in both eyes for 2 weeks. Study drug will be dosed in both eyes in Part 1 regardless of whether they meet the criteria as a Qualifying Eye. The formulation concentration and frequency of dosing will be determined by cohort, with Cohorts 1 to 3 receiving BID dosing (approximately every 12 hours with at least 6 hours between doses) and Cohort 4 receiving TID dosing (approximately every 8 hours with at least 6 hours between doses). Subjects who fail to take a dose of study drug within the dosing window should skip that dose and not attempt to make it up.

- Cohort 1 (0.1% INV-102 vs vehicle): 1 drop OU on Day 1, then BID OU for 13 days (Days 2-14), then 1 drop OU on Day 15
- Cohort 2 (0.25% INV-102 vs vehicle): 1 drop OU on Day 1, then BID OU for 13 days (Days 2-14), then 1 drop OU on Day 15
- Cohort 3 (0.7% INV-102 vs vehicle): 1 drop OU on Day 1, then BID OU for 13 days (Days 2-14), then 1 drop OU on Day 15
- Cohort 4 (0.7% INV-102 vs vehicle): 1 drop OU on Day 1, then TID OU for 13 days (Days 2-14), then 1 drop OU on Day 15

In Part 2 (Optional Dose Expansion), subjects in Cohort 5 will be randomized 2:1 to INV-102 or vehicle, respectively, and will instill topical ocular study drug in eligible eye(s) (ie, Qualifying Eyes) for 2 weeks either BID (1 drop on Day 1, then BID for 13 days, then 1 drop on Day 15) or TID (1 drop on Day 1, then TID for 13 days, then 1 drop on Day 15). Frequency and dose chosen [redacted] based on the results from Part 1 (Dose Escalation) Cohorts 1 to 4. Study drug may be dosed in a single eye or in both eyes in Part 2 depending on whether each eye individually meets the criteria as a Qualifying Eye.

7.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

7.2.1 ACQUISITION AND ACCOUNTABILITY

The investigator or designee (eg, study coordinator or pharmacist) will maintain a full accountability record for the study drug and will be responsible for recording the receipt, dispensing, and return of all supplies of the study drug using the inventories supplied for the study. The investigator or designee will account for all study drug. The monitor will review dispensing and study drug accountability records during study visits, or remotely, if applicable, and at the completion of the study and note any discrepancies.

When the study is completed or is terminated by Invirsa, all study material, including used and unused study drug, will be returned to Invirsa (or its designee) or destroyed under the specific direction of same. All study drug accounting procedures must be completed before the study is considered completed. A final study drug disposition will be completed by the study coordinator.

7.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

INV-102 Ophthalmic Solution is [redacted]

Vehicle Ophthalmic Solution is identical to the formulation of INV-102 Ophthalmic Solution but does not contain the active ingredient.

Both study drug and vehicle are provided in a multi-use eyedrop sterile container closure system [redacted] The bottle will be labeled with an investigational label showing the study protocol number and other relevant information, including a statement "Caution – New Drug – Limited by Federal (US) Law to Investigational Use".

7.2.3 PRODUCT STORAGE

Prior to dispensing, all study drug must be stored in a secure locked location with access limited to authorized persons who may dispense investigational materials. [redacted]

7.3 RANDOMIZATION

Prior to initiation of study drug dosing, 2:1 randomization (INV-102:vehicle) will occur by site personnel [redacted] once it is confirmed that the subject meets the study entry criteria. [redacted] provide the subject identification number listed on all study documents and used to manage the randomization and study drug assignment based on a central randomization

scheme [redacted] Study drug will be labeled with medication kit (bottle) numbers, and [redacted] provide each site with the specific medication kit number for each randomized subject at the time of randomization. Sites will dispense study drug according [redacted] instructions and will [redacted] confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

7.4 STUDY INTERVENTION COMPLIANCE

Dosing compliance will be assessed by [redacted]

[redacted]

Noncompliance at Day 8 will result in re-education of the subject, and noncompliance at either Day 8 or Day 15 will be recorded as a protocol deviation.

7.5 CONCOMITANT THERAPY

All medications taken within 30 days prior to the start of study drug and during the trial (through the Follow-Up Visit) should be recorded on the appropriate electronic case report form (eCRF).

[redacted]

[redacted]

7.5.1 RESCUE MEDICINE

Not applicable.

8 STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

8.1 DISCONTINUATION OF STUDY INTERVENTION

Study drug may be discontinued for the following reasons:

- **Adverse events:** Adverse events include clinically significant laboratory abnormalities and intercurrent diseases reported by the subject or observed by the investigator or designee with documentation on the eCRF
- **Death:** If a subject dies, the AE that caused the death should be documented on the eCRF and be noted as serious and fatal
- **Investigator decision:** A subject may be discontinued for reasons other than those bulleted previously if the investigator thinks it is not in the best interest of the subject to continue
- **Other:** Any other reason for subject discontinuation should be noted on the eCRF

The reason for premature study drug discontinuation should be recorded on the eCRF.

[redacted]

8.2 SUBJECT WITHDRAWAL FROM THE STUDY

Subjects are free to withdraw from participation in the study at any time, for any reason, and without prejudice. An investigator may withdraw a subject from the study for the following reasons:

- Pregnancy
- Noncompliance with study drug
- Lost to follow-up
- Any clinical AE or other medical condition or situation such that, in the opinion of the investigator, continued participation in the study would not be in the best interest of the subject
- Safety concern by the investigator or Sponsor

[redacted]

The reason for subject withdrawal from the study should be recorded on the eCRF. [redacted]

8.3 LOST TO FOLLOW-UP

At any point during the trial, if a subject fails to return for a scheduled visit and is unable to be contacted by the site staff as outlined below, he or she will be considered lost to follow-up. This does not include a single missed visit of which the site was notified or a missed visit with subsequent contact from the subject, indicating an intention to continue on the study.

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

- The site will attempt to contact the subject and reschedule the missed visit within the visit window and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls). These contact attempts should be documented in the subject's medical record or study file
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up

9 STUDY ASSESSMENTS AND PROCEDURES

9.1 CLINICAL ASSESSMENTS

[redacted]

All ocular assessments will be conducted individually on both eyes in Part 1 (Dose Escalation) and on all Qualifying Eyes in Part 2 (Optional Dose Expansion), unless noted otherwise. Refer to the SoA (Section 1.3) to determine at which visits these assessments will be performed.

- **Vital sign measurements.** Vital signs (heart rate and blood pressure) will be taken after the subject has been in a seated position for at least 5 minutes. Height and weight will also be collected at the Baseline visit.
- [redacted] **dry eye disease symptom visual analog scale**. A VAS [redacted] will be completed by the subject for each eye individually, if applicable. The subject will rate each [redacted] symptoms by placing a single vertical mark on a horizontal line based on the extent of their symptoms. For each parameter, subjects will be asked to rate their discomfort from 0 (no discomfort) to 100 (maximal discomfort)
- [redacted]
- [redacted]
- [redacted]

- **Noncontact pachymetry**. Central corneal thickness in both eyes of a subject will be measured using a noncontact corneal pachymeter
- **Endothelial cell count.** Endothelial cell density will be assessed using noncontact specular microscopy
- **Visual acuity.** Best-corrected visual acuity will be measured for each eye using an ETDRS chart as per the investigator's standard clinical practice and performed with best correction. Best-corrected visual acuity refraction must be used for all visual acuity assessments for the duration of the study. Subject must wear the same glasses/trial frame (if applicable) at each visit
- [redacted]
- **Slit lamp examination** [redacted] Biomicroscopy will be performed for each eye. Eye structures/surfaces to be assessed include, but are not limited to, eyelid, lashes, bulbar conjunctiva, cornea, anterior chamber, iris, and lens. All observations will be recorded. [redacted]
- [redacted]
- **Corneal fluorescein staining** [redacted] corneal fluorescein staining assessment will be performed using the NEI grading system to score each of 5 corneal zones on a 0 to 3 scale (Appendix 13.2). The cornea will be assessed under the slit lamp using a cobalt blue light source and a Wratten #12 filter as per the investigator's standard clinical practice. [redacted]
- [redacted]
- **Intraocular pressure**. All IOP measurements must be measured by Goldmann applanation or Tono-Pen tonometry as per the investigator's standard clinical practice. To minimize

confounding variables, every effort should be made to measure all IOP measurements for each subject by the same examiner using the same tonometer and approximately at the same time at all visits

- **Fundus examination**. A dilated fundus exam (using 1 drop of tropicamide 1%) consisting of the vitreous, optic nerve, macula, and peripheral retina will be conducted, and the structures will be graded as normal or abnormal
- [redacted]
- **Pharmacokinetic assessment**. Blood will be collected and sent for analysis (C_{max}, T_{max}, AUC) of single-dose and repeated-dose INV-102. A blood sample will be collected pre-dose and 5, 15, 30, 60, and 120 minutes post-dose. [redacted] Refer to the SRM for details on collecting and processing blood samples
- **Adverse events.** The subject will be queried for AEs at each study visit and all AEs will be recorded in the eCRFs, including severity, action taken, and relationship to the study drug

9.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

9.2.1 DEFINITION OF ADVERSE EVENTS

An AE is any untoward medical occurrence in a subject or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this study drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to that product.

All AEs that occur following consent and through the final study visit will be collected on the appropriate AE eCRF. All AEs recorded after starting study drug with the investigational product are considered TEAEs.

9.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS

An AE or suspected adverse reaction is considered “serious” if, in the view of either the investigator or Sponsor, it meets one or more of the following criteria/outcomes:

- Death
- Life-threatening

- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The following events are not considered SAEs:

- Outpatient treatment that does not result in hospital admission
- Hospitalization that is elective or preplanned for a pre-existing condition unrelated to the study drug and has not worsened since the start of the study

9.2.3 CLASSIFICATION OF AN ADVERSE EVENT

9.2.3.1 SEVERITY OF EVENT

The following guidelines will be used to describe severity.

- **Mild:** Require minimal or no treatment and do not interfere with the subject's daily activities
- **Moderate:** Result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning
- **Severe:** Interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious"

9.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the subject based on temporal relationship and the clinician's clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Probably related:** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal
- **Possibly related:** There is some evidence to suggest a causal relationship (eg, the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (eg, the subject's clinical condition, other concomitant events)
- **Not related:** The AE is considered to be completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology

9.2.3.3 EXPECTEDNESS

The medical monitor, in conjunction with the Sponsor, will be responsible for determining whether an AE is expected or unexpected in accordance with the Investigator's Brochure. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

9.2.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a subject presenting for medical care or upon review by a study monitor.

All AEs, including local and systemic reactions not meeting the criteria for SAEs, will be captured on the appropriate eCRF. Information to be collected includes event description, date of onset, clinician's assessment of severity, relationship to study drug (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the subject's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

Site staff will record all reportable events with start dates occurring any time after informed consent is obtained through the Follow-Up Visit. At each study visit, the investigator or designee will inquire about the occurrence of AE/SAEs since the last visit. All AEs will be followed for outcome information until resolution or stabilization or the subject's participation in the trial ends. All SAEs and those nonserious events assessed by the investigator as possibly or probably related to the study drug should continue to be followed even after the subject's participation in the trial is over. Such events should be followed until they resolve or until the investigator assesses them as "chronic" or "stable."

9.2.5 ADVERSE EVENT REPORTING

Any AE should be recorded on the appropriate eCRF. All SAEs that are drug-related and unexpected are to be reported to the governing IRB as required by the IRB, local regulations, and the governing health authorities.

9.2.6 SERIOUS ADVERSE EVENT REPORTING

The investigator will report any SAE, whether or not considered related to the study drug, to the Sponsor within 24 hours of its occurrence or of learning of its occurrence. Recurrent episodes or progression of the initial SAE must be reported to the Sponsor within 24 hours of the investigator receiving the information. The investigator must include an assessment of whether there is a reasonable possibility that the study drug caused the event. The investigator must promptly inform the IRB of the SAE if it is deemed related to study drug and unexpected. All SAEs will be followed until satisfactory

resolution or until the investigator deems the event to be chronic or the subject is stable. The investigator should supply the Sponsor and the IRB with any additional requested information (eg, autopsy reports and terminal medical reports).

Adverse drug reactions that are both serious and unexpected (suspected unexpected serious adverse reactions [SUSARs]) will be subject to expedited reporting by the Sponsor to the United States Food and Drug Administration (FDA), as described in the Safety Plan. In addition, the Sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the Sponsor determines that the information qualifies for reporting.

9.2.7 REPORTING OF PREGNANCY

If a female subject becomes pregnant during the study, the investigator will notify the Sponsor (or its designee) and the medical monitor immediately after the pregnancy is confirmed and the female subject will be exited from the study. The investigator will (1) notify the subject's physician that the subject was being treated with INV-102 (or vehicle, as appropriate), and (2) follow the progress of the pregnancy to term and the health of the child to 12 months of age, providing written informed consent for release of this information. The investigator should document the outcome of the pregnancy and provide a copy of the documentation to the Sponsor.

10 STATISTICAL CONSIDERATIONS

10.1 SAMPLE SIZE DETERMINATION

Part 1 (Dose Escalation): The sample size of approximately 9 subjects each in Cohorts 1 to 4 (6 active: 3 vehicle) is considered sufficient for evaluation of safety, tolerability, and PK of each cohort. The sample size is not based on statistical power considerations.

Part 2 (Optional Dose Expansion): The sample size of approximately 48 subjects in Cohort 5 (32 active: 16 vehicle) is considered sufficient for evaluation of preliminary efficacy of INV-102. The sample size is not based on statistical power considerations.

10.2 POPULATIONS FOR ANALYSES

Three analysis populations will be defined and used in the statistical analyses: (1) a safety population, (2) a modified intent-to-treat (mITT) population, and (3) a per protocol (PP) population. Separate analysis populations will be defined in each part of the study.

Safety population: The safety population will include all randomized subjects who received at least 1 drop of study drug. The safety population will be used to summarize safety variables, using the study drug they actually received.

Modified intent-to-treat population: The mITT population will include all randomized subjects who received at least 1 drop of study drug in the Study Eye and completed at least 1 scheduled post-dosing assessment in the Study Eye. The mITT population will be used to analyze all efficacy endpoints, with subjects included in their randomized study drug regardless of the study drug they actually received. The Study Eye is defined as the eye with more severe disease based on corneal fluorescein staining. The other eye is designated as the Fellow Eye. If both eyes have the same corneal fluorescein staining score, the eye with the more severe eye dryness score from the [redacted] DED symptom VAS will be the Study Eye. If both eyes have the same eye dryness score, the right eye will be the Study Eye.

Per protocol population: The PP population includes all subjects in the mITT population who have study drug compliance of ≥80% as defined by [redacted] and have no major protocol deviations considered to have significant impact on study drug outcome. The PP population will be used to analyze selected efficacy endpoints.

10.3 STATISTICAL ANALYSES

10.3.1 GENERAL APPROACH

Eyes meeting the study-defined DED eligibility criteria will be deemed Qualifying Eyes and each subject may have either 1 or 2 Qualifying Eyes. All subjects, regardless of whether they receive study drug in one or both eyes, will have only one eye designated as the Study Eye. The Study Eye is defined as the eye with more severe disease based on corneal fluorescein staining. The other eye is designated as the Fellow Eye. If both eyes have the same corneal fluorescein staining score, the eye with the more severe eye dryness score from the [redacted] DED symptom VAS will be the Study Eye. If both eyes have the same eye dryness score, the right eye will be the Study Eye.

In Part 1 (Dose Escalation) Cohorts 1 to 4, both eyes will receive study drug regardless of whether both eyes meet the criteria as Qualifying Eyes, and study assessments will be performed for both eyes (unless noted otherwise). Safety data from each eye will be analyzed. Non–eye-specific safety data (AE data) will be collected and analyzed at the subject level, and eye-specific safety data and efficacy data will be collected and analyzed at the eye level (Study Eye and Fellow Eye).

In Part 2 (Optional Dose Expansion) Cohort 5, only eyes meeting DED eligibility (Qualifying Eyes) will receive study drug and be assessed. Safety data from only those eyes will be analyzed. Non–eye-specific safety data (AE data) will be collected and analyzed at the subject level, and eye-specific safety data and efficacy data will be collected and analyzed at the eye level (Study Eye and, if applicable, Fellow Eye).

The database will be locked after all subjects exit the study and all data clarification forms or queries have been resolved. Prior to database lock, a detailed SAP will be finalized and approved.

All continuous variables will be summarized by study drug and time point (as applicable) using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). All categorical variables will be summarized by study drug and time point (as applicable) using frequency counts and percentages. Analysis of the efficacy endpoints will be based on the mITT population and safety endpoints will be based on the safety population unless otherwise specified.

Safety and efficacy endpoint results will be presented separately for Part 1 (Dose Escalation) and Part 2 (Optional Dose Expansion). [redacted]

All study data will be presented by study drug and time point (as applicable).

All statistical tests will be performed using a significance level of 5% (2-tailed). The p-values for the analysis of efficacy endpoints will be considered descriptive.

10.3.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

For Part 2 (Optional Dose Expansion), the primary efficacy endpoint is the change from Baseline to Day 15 in either eye dryness VAS score OR eye discomfort VAS score from the [redacted] DED symptom VAS, [redacted] based on results from Part 1 (Dose Escalation) Cohorts 1 to 4.

The change in VAS score will be analyzed using a mixed model for repeated measures (MMRM) that includes treatment (INV-102 or vehicle), visit (Days 8 and 15), and treatment-by-visit interaction terms and Baseline as a covariate. The least squares (LS) mean and 95% confidence interval (CI) for each study drug group, the LS mean difference between study drug groups, and the associated p-value and 95% CI for the mean difference will be presented at each visit. Sensitivity analyses may be performed imputing missing data. Full details will be provided in the SAP.

The primary efficacy analyses will be conducted on the mITT and PP populations.

10.3.3 ANALYSIS OF THE SECONDARY AND OTHER EFFICACY ENDPOINTS

All secondary and other efficacy analyses will be conducted on the mITT population, and select analyses on the PP population, using the following efficacy variables [redacted]

- Eye Dryness Composite Score (combines the change in eye dryness score from the [redacted] DED symptom VAS plus the change in corneal fluorescein staining)

- Eye Discomfort Composite Score (combines the change in eye discomfort score from the [redacted] DED symptom VAS plus the change in corneal fluorescein staining)
- Changes in VAS (individual item scores and overall score [sum [redacted]
- [redacted]
- Changes in corneal fluorescein staining [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

The Eye Dryness Composite Score and the Eye Discomfort Composite Score will each be a combination score of the VAS (either the "eye dryness score" or the "eye discomfort score") change from Baseline and corneal fluorescein staining change from Baseline using the following equation:

[redacted]

Endpoints in Part 1 (Dose Escalation) will be summarized descriptively at each visit, showing actual values and change from Baseline values.

For Part 2 (Optional Dose Expansion), continuous endpoints measured over multiple visits will be analyzed using MMRM that include treatment, visit, and treatment-by-visit interaction terms and Baseline as a covariate.

10.3.4 SAFETY ANALYSES

All safety analyses will be conducted on the safety population using the following safety variables in Parts 1 and 2, unless as described below:

- Treatment-emergent AEs
- Vital signs
- Best-corrected visual acuity
- Slit lamp examination findings
- [redacted]
- Intraocular pressure (Part 1 only)
- Fundus examination (Part 1 only)
- Pachymetry (Part 1 only)
- Endothelial cell count (Part 1 only)
- Corneal fluorescein staining (Part 1 only)
- [redacted]

- [redacted]
- [redacted]
- [redacted]

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; version 24.1). For each TEAE reported, the number and percent of subjects will be tabulated based on the preferred term. The tables will be generated by relationship to study drug as well as by system organ class and severity. Serious TEAEs and TEAEs leading to discontinuation of study drug and of study will also be summarized. Treatment-emergent AEs will be summarized; any AEs occurring after ICF signing but before initiation of study drug dosing will be presented in the listings but will not be summarized in tables.

Other safety endpoints will be summarized descriptively at each visit, showing actual values and change from Baseline values, where appropriate.

10.3.5 BASELINE DESCRIPTIVE STATISTICS

Baseline and demographic assessments will be presented descriptively.

10.3.6 PLANNED INTERIM ANALYSES

No formal interim analysis is planned. However, unmasked designated personnel will review the data from Cohorts 1 to 4 for purposes of selecting the dose for Part 2 (Optional Dose Expansion). See Section 5.2 for more details.

10.3.7 TABULATION OF INDIVIDUAL SUBJECT DATA

Line listings will be provided for each subject.

11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

11.1.1 INFORMED CONSENT PROCESS

11.1.1.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO SUBJECTS

Consent forms describing in detail the study drug, study procedures, and risks, that have been reviewed and approved by the relevant IRB, will be given to the subject and written documentation of informed consent is required prior to performing any study assessments or starting study drug.

11.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Subjects will be asked to read and review the ICF. The investigator or designee will explain the research study to the subjects and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subjects' comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The subjects will sign the ICF prior to any study-specific procedures.

Each subject who provides informed consent will be assigned a subject number [redacted] that will be used on subject documentation throughout the study.

11.1.2 STUDY DISCONTINUATION AND CLOSURE

The study may be stopped at the subject's study site at any time by the site investigator. Invirsa may stop the study (and/or the study site) for any reason with appropriate notification.

11.1.3 CONFIDENTIALITY AND PRIVACY

Subject confidentiality and privacy are strictly held in trust by the participating investigators, their staff, and the Sponsor and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

In accordance with Health Insurance Portability and Accountability Act (HIPAA) Standards for Privacy of Individually Identifiable Personal Health Information (PHI) requirements, additional purposes of this study include (1) the publishing of anonymous subject data from the study, and (2) the creation and maintenance of a data repository.

All relevant study-related correspondence, subject records, ICFs, subject privacy documentation, records of the distribution and use of study drugs, and subject questionnaires, correspondence with IRB, and other essential documents should be maintained on file.

Invirsa requires notification in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

11.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

[redacted]

11.1.5 SAFETY OVERSIGHT

[redacted]

11.1.6 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the contract research organization
- A representative of Invirsa may monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations, such as the objective, purpose, design, complexity, masking, size, and endpoints of the study
- Representatives of Invirsa or regulatory authority representatives may conduct onsite visits to review, audit, and copy study-related documents. These representatives may meet with the investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions

11.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion.

Quality control procedures will be implemented, beginning with the data entry system, and data quality control checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

The progress of the study will be monitored by onsite, written, and telephone communications between personnel at the investigator's site and the study monitor. Should the COVID-19 pandemic restrict monitors from traveling to a site, remote review will be conducted to the extent possible, while still ensuring the study is monitored appropriately per applicable regulations and guidelines. The investigator will allow Invirsa, the study monitor, and the medical monitor to inspect all eCRFs, subject records (source documents), signed ICFs, records of study drug receipt, storage, preparation, and disposition, and regulatory files related to this study.

11.1.8 DATA HANDLING AND RECORD KEEPING

11.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Source documents are the first place data is recorded. All source documents, paper or electronic, should be completed in a neat, legible manner to ensure accurate interpretation of data.

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Source documents may include the eCRF, a subject's medical records, diaries, hospital charts, clinic charts, the investigator's subject study files, as well as the results of diagnostic tests. The investigator's copy of the eCRFs serves as part of the investigator's record of a subject's study-related data.

11.1.8.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 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 until at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is

the responsibility of the Sponsor to inform the investigator when these documents no longer need to be retained.

11.1.9 PROTOCOL DEVIATIONS

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the Sponsor or designee (and IRB, as required) to determine the appropriate course of action.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the Sponsor or its designee (and IRB, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health or privacy risk to the subject, or confound interpretation of primary study assessments.

11.1.10 PUBLICATION AND DATA SHARING POLICY

[redacted]

This study will be registered on the ClinicalTrials.gov registry.

11.1.11 CONFLICT OF INTEREST POLICY

[redacted]

12 REFERENCES

[redacted]

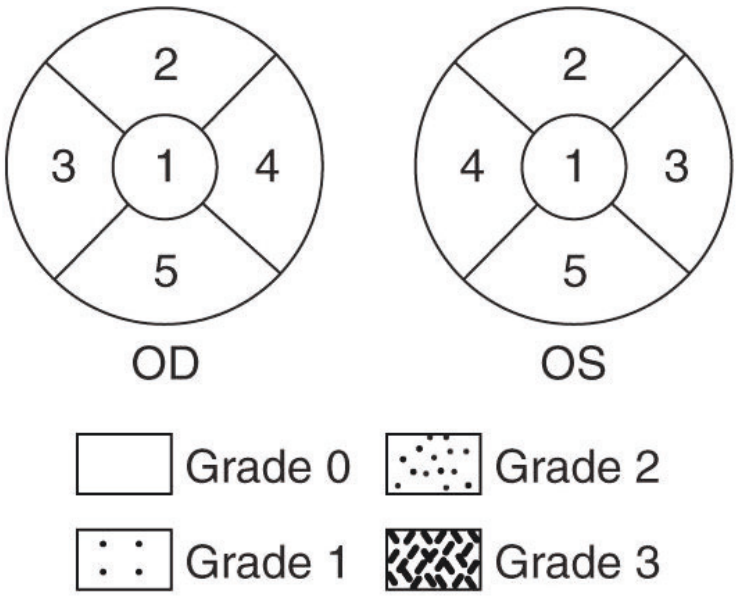
13 APPENDICES

13.1 [redacted]

[redacted]

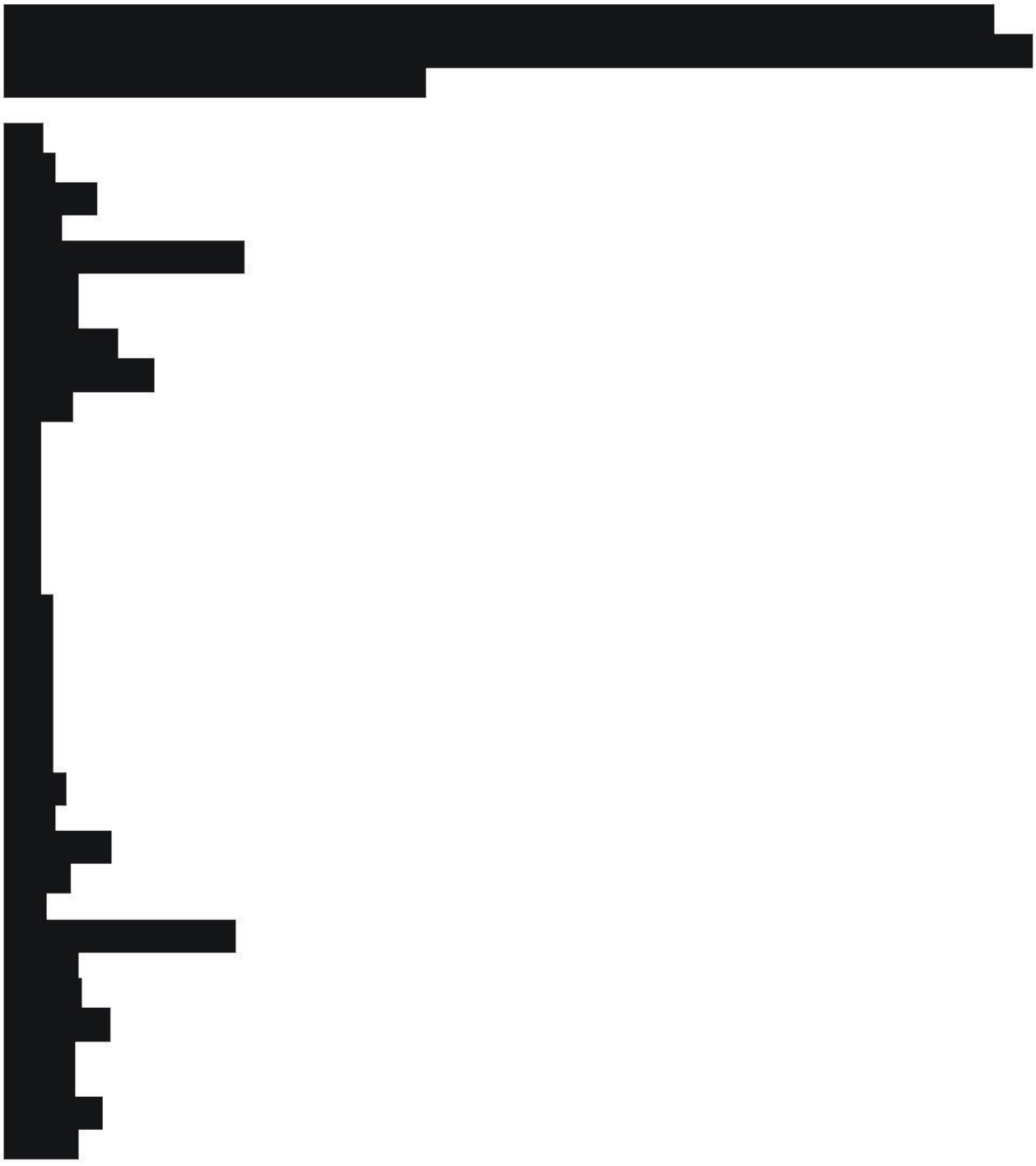
13.2 NATIONAL EYE INSTITUTE CORNEAL STAINING GRADING SCALE

Corneal fluorescein staining assessment will be performed using the National Eye Institute/Industry grading scale (Lemp, 1995) to score each of 5 corneal zones on a 0 to 3 scale (with a total score of 0 to 15).



13.3 [redacted]

13.4 [redacted]



13.5 DOCUMENT HISTORY

Version #	Effective Date	Summary of Changes
1.0	01 March 2022	Original version
1.1	01 June 2022	[redacted]
1.2	21 October 2022	[redacted]
1.3	11 December 2022	[redacted]
1.4	14 February 2023	[redacted]

Protocol Version 1.1 Changes:

[redacted]

- [redacted]
- [redacted]

Protocol Version 1.2 Changes:

- [redacted]
- [redacted]

Protocol Version 1.3 Changes:

- [redacted]
- [redacted]
- [redacted]

Protocol Version 1.4 Changes:

- [redacted]
- [redacted]
- [redacted]