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

Statistical Analysis Plan v1.0

13 June 2023

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[redacted] | CONFIDENTIAL

Invirsa, Inc.

STATISTICAL ANALYSIS PLAN

Protocol 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
Phase:	Phase 1/2
Sponsor:	Invirsa, Inc. 1275 Kinnear Rd. Columbus, Ohio 43212 USA
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2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Only abbreviations and terms relevant to the analysis plan are repeated herein. The reader is referred to the protocol for the complete and comprehensive list of abbreviations and definitions of terms for the study.

Abbreviation/Term	Definition
ADaM	analysis data model
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
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
C_{max}	maximum drug concentration
DED	dry eye disease
eCRF	electronic case report form
EDC	electronic data capture
FIH	first-in-human
HR	heart rate
ICF	informed consent form
IOP	intraocular pressure
LOCF	least observation carried forward
LS	least squares
MAD	multiple ascending dose
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed model for repeated measures
OTC	over-the-counter
OU	both eyes
PK	pharmacokinetic(s)
PP	per protocol
PT	preferred term
[redacted]	[redacted]

Abbreviation/Term	Definition
SAP	statistical analysis plan
SDTM	study data tabulation model
SOC	system organ class
[redacted]	[redacted]
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
TFL	tables, figures, and listings
T_{max}	time to reach maximum drug concentration
VAS	visual analog scale
WHO-DD	World Health Organization Drug Dictionary

3. INTRODUCTION

3.1. Preface

This document presents an analysis plan for the Invirsa, Inc. 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*).

Reference materials for this plan include the protocol INV-102-CS-001 Version 1.4 (14 February 2023) and Case Report Forms (CRFs) Final Version (08 August 2022).

3.2. Purpose of Analyses

INV-102-CS-001 is a 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). Part 1 is a Dose Escalation phase across 4 cohorts of subjects to assess safety, tolerability, and systemic pharmacokinetics (PK) of INV-102, and Part 2 is 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.

3.3. Deviations from Study Protocol

A PK population was added to the set of analysis populations. [redacted] Otherwise, the SAP is consistent with the methods described in the study protocol.

4. STUDY OBJECTIVES

The objectives of this study are as follows:

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]

4.1. Study Endpoints

Part 1 (Dose Escalation):

Primary endpoint

- Treatment-emergent adverse events (TEAEs)

Safety endpoints

[redacted]

Plasma PK endpoints

[redacted]

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

Part 2 (Optional Dose Expansion):

The primary and secondary endpoints for Part 2 were chosen based on results from Part 1 (Dose Escalation) Cohorts 1 to 4 [redacted].

Primary endpoint

- Change from Baseline to Day 15 in the Eye Dryness Score from the [redacted] DED symptom VAS

Secondary endpoint

- Eye Dryness Composite Score at Day 15

Additional efficacy endpoints

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

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

[redacted]

- [redacted]

Safety endpoints

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

5. STUDY METHODS

5.1. General Study Design and Plan

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.

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 twice daily (BID) dosing (approximately every 12 hours with at least 6 hours between doses) and Cohort 4 receiving three 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 and Cohort 4 has been fully enrolled [redacted], the study may advance to the optional Part 2 based on review of available efficacy and safety 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) (i.e., 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 [i.e., having only one Qualifying Eye], assessments will only be performed on the eye being dosed).

The schedule for assessments and timing of events is presented in Table 1.

Table 1 Screening, Qualification/Baseline, Treatments, and Follow-up Visits and Procedures

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.

[redacted]

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.

5.2. Inclusion – Exclusion Criteria and General Study Population

The study population will consist of healthy male or female subjects ≥18 years of age with presence of moderate DED in at least one eye [redacted]. Approximately 84 subjects will be enrolled in total between Parts 1 and 2. Written informed consent will be obtained from each subject.

The full inclusion and exclusion criteria defined in the protocol apply to all subjects and are not repeated herein. Reference is made to the final protocol for the specific inclusion and exclusion criteria for study subjects.

5.3. Randomization and Blinding

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] will 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] will provide each site with the specific medication kit number for each randomized subject at the time of randomization.

Study drug will be masked to both Investigator and study subjects, as well as Invirsa. The individual treatment assignments will be masked to the Investigator, Invirsa, and the subjects.

5.4. Analysis Variables

The following efficacy variables will be collected [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]
- [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]

The following safety variables will be collected in Parts 1 and 2, unless as described below:

- TEAEs
- 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]

6. SAMPLE SIZE

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.

7. GENERAL CONSIDERATIONS

7.1. Analysis Populations

The following analysis populations will be defined for this study.

7.1.1. Modified Intention-to-Treat (mITT)

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.

7.1.2. Per Protocol Population (PP)

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 primary and secondary efficacy endpoints.

7.1.3. Safety Population (SP)

The safety population (SP) 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 actually received.

7.1.4. Pharmacokinetic Population (PK)

The PK population will include all subjects in the SP who had at least one valid PK sample taken at any post-treatment timepoint. The PK population will be used to summarize PK variables, using the actual treatment a subject received.

7.2. Covariates and Subgroups

7.2.1. Planned Covariates

Planned covariates include baseline values for the given assessment.

7.2.2. Planned Subgroups

Efficacy and safety variables related to eye assessments will be analyzed separately for the study eye and fellow eye, as appropriate. Other possible subgroups include age, sex, and race.

7.3. Management of Analysis Data

7.3.1. Data Handling

For assessments collected at specific visits, the data from unscheduled visits will be included in the analysis of efficacy or safety if the data at the nearest scheduled visit is missing; all unscheduled visit data will be listed. All data from log pages (e.g., concomitant medications and AEs) will be included in the analysis tables.

7.3.2. Missing Data

For the analysis of the efficacy endpoints, observed values will be used; no imputation will be performed for missing efficacy data. Missing safety data will be imputed in limited cases, as described below.

7.3.2.1. Handling of Missing Date Values

Partial or Missing Dates

Missing portions of dates for AEs or concomitant medications will not be formally imputed. Instead, an AE will be classified as treatment-emergent or a medication as concomitant using the most conservative date that can be derived from the non-missing portion of the date.

7.3.2.2. Missing Baseline Data

Every effort will be made to ensure that accurate baseline information on the subjects is collected. In the event that a subject is missing baseline information, the subject will be included in the SP for assessment of safety and excluded from the primary analyses. Each case of missing baseline data will be evaluated for potential inclusion in the exploratory endpoints. All baseline data will be observed cases, without imputation.

7.3.3. Handling of Early Termination Visit Information

In the event that a subject is terminated early from this study, the early termination data will be assigned to the closest visit. If the closest visit has valid data, the early termination data will be assigned to the next available visit, and treated as observed data for that visit. For subjects who had efficacy measurements taken after the last dose, all observed measurements will be used for analyses.

7.3.4. Coding Conventions for Events and Medications

All AEs, medical and ophthalmic history, and concomitant procedures/therapies will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA Version 25.0) system for reporting.

Prior and concomitant medications will be coded using WHO-DD (World Health Organization Drug Dictionary) (Version Global C3 2022-03-01).

7.3.5. Analysis Software

Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed using SAS (release 9.4 or higher) for Windows.

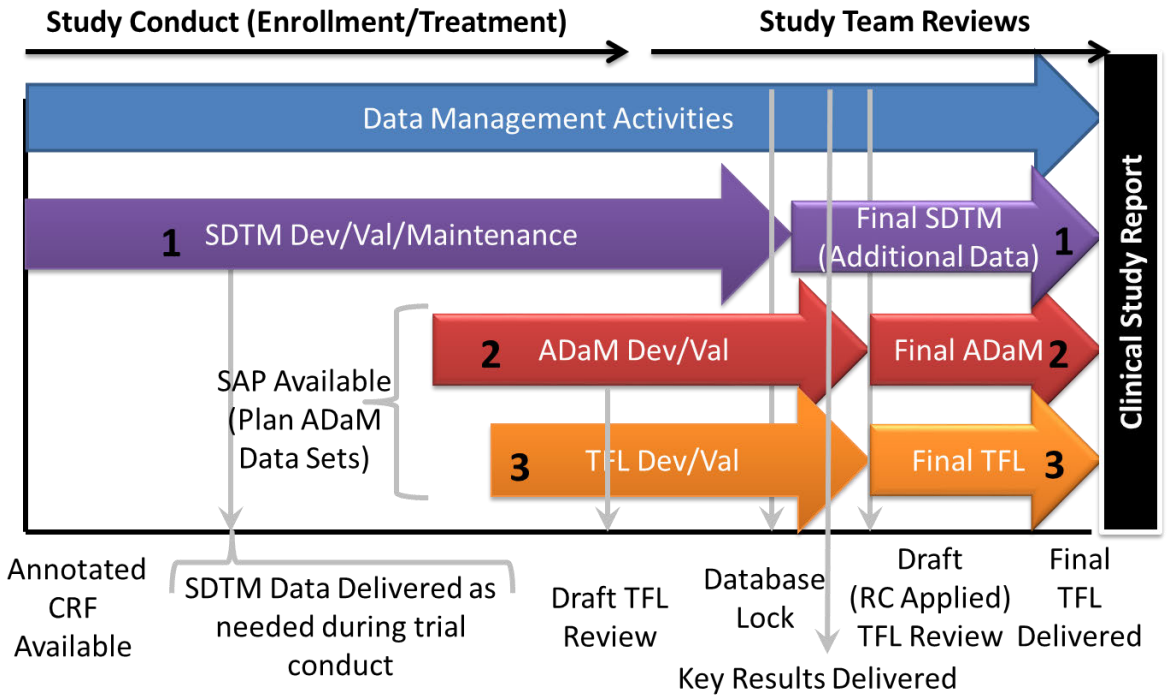
7.3.6. Study Data

Study data identified in the schedule for time and events (Table 1) are collected, and source verified, on the electronic data capture (EDC) [redacted] PK concentration data will be provided by [redacted].

All study data will be formulated into regulatory-compliant data sets to provide transparency, traceability, and integrity of trial analysis results from the collection source. Observed study data will be mapped to the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) and serve as the source data from the trial. All study analyses will be completed using analysis data sets that are derived from the SDTM and follow the CDISC Analysis Data Model (ADaM) architecture.

The methods for programming the CDISC SDTM and ADaM data sets are described in Figure 1.

Figure 1 SDTM, ADaM, and TFL Development and Validation



Where:

1. Development, validation, and maintenance of SDTM domains
2. Development and validation of ADaM data sets, with input source the appropriate SDTM domains.
3. Development and validation of tables, figures, and listings (TFL), with input data source the SDTM domains and analysis specific ADaM data sets.

7.4. Planned Study Analyses

7.4.1. Statistical Summaries: Descriptive and Inferential

Safety and efficacy endpoint results will be presented separately for Part 1 (Dose Escalation) and Part 2 (Optional Dose Expansion). For Part 1, [redacted] presented separately by treatment group (0.1% INV-102 BID, 0.25% INV-102 BID, 0.7% INV-102 BID, and 0.7% INV-102 TID), but vehicle subjects will be pooled across cohorts in the summaries. Categories for data presentation and analysis will consist of each treatment (INV-102 or Vehicle) and INV-102 dose level.

All p-values will be rounded to and displayed in four decimals. If a p-value less than 0.0001 occurs, it will be shown in tables as <0.0001. 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.

Descriptive summaries of variables will be provided where appropriate. For continuous variables, the number of non-missing values (n), mean, standard deviation, median, minimum, and maximum will be tabulated by treatment group. For categorical variables, the counts and proportions of each value will be tabulated by treatment group. Expansion of descriptive table categories within each treatment may occur if such elaborations are thought to be useful.

All study-related data collected will be presented in listings. Study-related data not subject to analysis according to this plan will not appear in any tables or graphs but will be included in the data listings.

7.4.2. Interim Analyses and Data Monitoring

[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] [redacted].

7.4.3. Final Analysis and Publication of Study Results

The final analysis will be completed after all subjects have completed the study.

7.5. Multiple Testing Procedures

There will be no adjustments for multiplicity and no formal multiple testing procedures are to be implemented with this analysis plan.

7.6. Baseline Values

Baseline values are the values obtained prior to any drug administration at the Baseline Visit (Day 1). If the Day 1 value is missing or is not scheduled to be collected, any value collected prior to treatment administration (e.g., from the Screening visit) will be used as the baseline.

8. SUMMARY OF STUDY DATA

8.1. Subject Disposition

A summary of the analysis sets includes the number and percentage of subjects by treatment group and overall for the following categories: subjects in the SP, the mITT Population, the PP Population, and the PK Population. All percentages will be based on the number of randomized subjects.

End of trial information will also be summarized in this table, including the number of subjects completing the study, the number of subjects who prematurely discontinued the study with reasons for withdrawal, the number of subjects completing the study drug dosing, and the number of subjects who prematurely discontinued the study drug with reasons for study drug discontinuation.

A by-subject data listing of study completion information including the reason for premature study withdrawal or study drug discontinuation, if applicable, will be presented.

8.2. Protocol Deviations

Major protocol deviations considered to have significant impact on treatment outcome will be determined by a Sponsor blinded review of the data. The Sponsor or designee will be responsible for producing the final deviation file; this file will include a description of the protocol deviation and clearly identify whether this violation warrants exclusion from the PP Population. This file will be finalized prior to database lock.

Protocol deviations will be presented in a by-subject data listing.

8.3. Demographics and Baseline Characteristics

Subject demographic data and baseline characteristics will be tabulated and summarized descriptively by treatment group and overall. The demographic data and baseline characteristics will be summarized for the mITT, Safety, PP, and PK Populations.

The demographics consist of age (year), sex, race, ethnicity, and study eye. Age will be summarized using descriptive statistics. The number and percentage of subjects by sex, race, ethnicity, study eye will be presented. Percentages will be based on the total number of subjects in the study population presentation.

The following baseline characteristics will be summarized using descriptive statistics:

- Height
- Weight

8.4. Medical History

The number and percent of subjects with individual ophthalmic and general (non-ophthalmic) medical and surgical histories will be summarized for all subjects by treatment group and overall. Ophthalmic and general histories will be summarized separately.

Ophthalmic and general medical and surgical history will be coded using the MedDRA Version 25.0. The number and percentage of subjects with any ophthalmic and general medical history will be summarized and for each system organ class (SOC) and preferred term (PT). Percentages will be calculated based on number of subjects in the SP.

Ophthalmic and general medical history data including specific details will be presented in by-subject listings.

8.5. Prior and Concomitant Medications

A concomitant medication is defined as any medication taken on or after the day of first exposure to study drug. The number and percentages of all concomitant medications will be summarized by treatment group, Anatomical Therapeutic Chemical (ATC) level 2, and PT. The total number of concomitant medications and the number and percentages of subjects with at least 1 concomitant medication will be summarized by treatment group.

Prior medications are defined as any medication that has a start and stop date prior to the day of first exposure to study drug. Prior medications will be summarized the same way as for concomitant medications.

Prior and concomitant medication summaries will be performed using the SP.

8.6. Treatment Exposure and Compliance

The number of study drug exposure days will be calculated for each subject in the SP as the last date of study drug administration – first date of study drug administration. [redacted]

Minimum study drug compliance (yes/no) for each subject in the SP will be determined as follows, depending on the study cohort:

- [redacted]
- [redacted]

[redacted]

[redacted]

The number of study drug exposure days, exposure to study drug, and study drug compliance will be tabulated and summarized descriptively by treatment group and overall.

Treatment exposure and compliance will be presented in by-subject listings.

9. EFFICACY ANALYSES

Efficacy will be assessed using the mITT Population with subjects included in the treatment arm in which they were randomized. Primary and secondary efficacy endpoints will also be assessed using the PP Population. Efficacy results will be presented separately by cohort (Cohorts 1–5 as applicable). Data will be presented and analyzed by treatment group (INV-102 or Vehicle) and INV-102 dose level. Subjects assigned to vehicle in Cohorts 1–4 will be pooled across cohorts in the summaries.

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. Observed cases will be used for all efficacy analyses—no imputation for missing values will be applied.

9.1. Primary Efficacy

The primary efficacy endpoint to be used in Part 2 was [redacted] the Change from Baseline to Day 15 in the Eye Dryness Score from the [redacted] DED symptom VAS.

[redacted]

For Part 2 (Cohort 5), the primary efficacy endpoint, which is measured over multiple visits, will be summarized [redacted]. In addition, the Part 2 data will be analyzed using a mixed model for repeated measures (MMRM) that include treatment, visit, and treatment-by-visit interaction terms, and baseline eye dryness or eye discomfort VAS score as a covariate. The output from the MMRM will include the least-squares mean (LSM) and standard error for both treatment groups, along with the vehicle-corrected LSM, its 95% CI, and associated p-value. Include the average of study eye and fellow eye. LS mean values will also be displayed by visit and treatment group using line graphs.

[redacted]

9.2. Secondary and Other Efficacy

Secondary and other efficacy endpoints are indicated in Section 4.1. [redacted]

[redacted]

Secondary and other efficacy data in Part 2 will be summarized [redacted]. In addition, Part 2 data will be analyzed using a similar MMRM as for the primary endpoint, with change from baseline as the dependent variable, treatment as factor, and the respective baseline value included as the covariate. The output from each MMRM will include the LSM and standard error for both treatment groups, along with the vehicle-corrected LSM, its 95% CI, and associated p-value.

[redacted]

If there are sufficient missing data, appropriate MI methods will be applied as described in Section 7.3.2.3.

10. SAFETY ANALYSES

All safety analyses will be conducted using the SP. All safety analyses will be completed using the actual treatment a subject received. Observed case data will be used; no imputation will be performed for missing safety data except for the limited situations described in Section 7.3.2. Safety data will be tabulated and summarized descriptively by treatment group and for all subjects who took INV-102.

All safety data will be presented in by-subject listings.

10.1. Adverse Events

AEs will be coded using MedDRA, Version 25.0.

Treatment-emergent adverse events (TEAEs) are defined as any AE that begins or worsens after initiation of the study drug. If the onset of an AE is on or after the date of first dose of study drug or is increasing in severity after first dose of study drug, then the AE will be considered treatment-emergent. Only TEAEs will be summarized in the tables.

The number and percent of subjects with any TEAEs will be summarized by SOC and PT by treatment group. At each level of tabulation (e.g., at the PT level), subjects will be counted only once if they had more than one such event reported during the AE collection period.

The following summary tables will be presented for TEAE data, by SOC and PT:

- TEAEs
- Serious TEAEs
- TEAEs leading to withdrawal from the study
- TEAEs leading to study drug discontinuation
- TEAEs by maximum severity (mild, moderate, severe)
- TEAEs by greatest relationship (not related, possibly related, or probably related).

All TEAEs and non-TEAEs will be presented in a by-subject listing.

10.2. Deaths, Serious Adverse Events and Other Significant Adverse Events

10.2.1. Deaths

Fatal TEAEs, regardless of causality, will be presented in a by-subject listing.

10.2.2. Serious Adverse Events

Treatment-emergent serious AEs will be presented in a by-subject listing.

10.2.3. Adverse Events Leading to Withdrawal from the Study

Treatment-emergent AEs leading to withdrawal will be presented in a by-subject listing.

10.2.4. Adverse Events Leading to Discontinuation of Study Drug

Treatment-emergent AEs leading to discontinuation of study drug will be presented in a by-subject listing.

10.3. Other Safety Variables

All safety variables are listed in Section 5.4. [redacted]

Categorical safety variables will be summarized descriptively using counts and percentages for each treatment group at each visit.

For continuous safety variables, observed values and change from baseline will be summarized descriptively for each parameter (as appropriate) by treatment group at each visit.

For safety endpoints that assess each eye separately, summaries will be created for the study eye and the fellow eye.

[redacted]

12. PK ANALYSES

All PK analyses will be conducted using the PK population. All PK analyses will be completed using the actual treatment a subject received. Observed case data will be used; no imputation will be performed for missing PK data.

Analysis of plasma samples for INV-102 concentration determinations will be performed by a central PK laboratory. Plasma concentrations will be summarized by visit and time point using descriptive statistics. For concentrations that are below the LLOQ, the summary will use one-half the LLOQ as the analysis value. Plots of mean INV-102 concentrations by visit and time point will also be presented.

If appropriate, PK assessments (C_{max}, T_{max}, AUC) after a single dose and after repeated INV-102 administration will be summarized by visit using descriptive statistics.

All PK data will be presented in by-subject listings. Unscheduled assessments will not be summarized but will be included in the listings.

13. REFERENCES

[1] ICH E9 Expert Working Group. Statistical Principles for Clinical Trials: ICH Harmonized Tripartite Guideline, September 1998

14. APPENDICES

14.1. List of Planned Tables

The list of planned tables includes all of the *main* tables to be presented

Table	Description of Table	All	Safety	mITT	PP	PK
14.1.1.1	Subject Disposition – Part 1	X				
14.1.1.2	Subject Disposition – Part 2	X				
14.1.2.x.1	Demographics and Baseline Characteristics – Part 1		X	X	X	X
14.1.2.x.2	Demographics and Baseline Characteristics – Part 2		X	X	X	X
14.1.3.1.1	Ophthalmic Medical and Surgical History – Part 1		X			
14.1.3.1.2	Ophthalmic Medical and Surgical History – Part 2		X			
14.1.3.2.1	General Medical and Surgical History – Part 1		X			
14.1.3.2.2	General Medical and Surgical History – Part 2		X			
14.1.4.1.1	Prior Medications – Part 1		X			
14.1.4.1.2	Prior Medications – Part 2		X			
14.1.4.2.1	Concomitant Medications – Part 1		X			
14.1.4.2.2	Concomitant Medications – Part 2		X			
14.1.5.1	Study Drug Exposure and Compliance – Part 1		X			
14.1.5.2	Study Drug Exposure and Compliance – Part 2		X			
[redacted]						

Table	Description of Table	All	Safety	mITT	PP	PK
[redacted]				X	X	
				X	X	
				X		
				X		
				X		
				X		
				X		
				X		
				X		
				X		
				X		
				X		
				X		
				X		
				X		
				X		
				X		

Table	Description of Table	All	Safety	mITT	PP	PK
14.3.1.1.1	Treatment-Emergent Adverse Events (TEAE) by System Organ Class and Preferred Term – Part 1		X			
14.3.1.1.2	Treatment-Emergent Adverse Events (TEAE) by System Organ Class and Preferred Term – Part 2		X			
14.3.1.2.1	Serious Treatment-Emergent Adverse Events (TEAE) by System Organ Class and Preferred Term – Part 1		X			
14.3.1.2.2	Serious Treatment-Emergent Adverse Events (TEAE) by System Organ Class and Preferred Term – Part 2		X			
14.3.1.3.1	Treatment-Emergent Adverse Events (TEAE) Leading to Withdrawal From the Study by System Organ Class and Preferred Term – Part 1		X			
14.3.1.3.2	Treatment-Emergent Adverse Events (TEAE) Leading to Withdrawal From the Study by System Organ Class and Preferred Term – Part 2		X			
14.3.1.4.1	Treatment-Emergent Adverse Events (TEAE) Leading to Study Drug Discontinuation by System Organ Class and Preferred Term – Part 1		X			
14.3.1.4.2	Treatment-Emergent Adverse Events (TEAE) Leading to Study Drug Discontinuation by System Organ Class and Preferred Term – Part 2		X			
14.3.1.5.1	Treatment-Emergent Adverse Events (TEAE) by System Organ Class, Preferred Term, and Severity – Part 1		X			
14.3.1.5.2	Treatment-Emergent Adverse Events (TEAE) by System Organ Class, Preferred Term, and Severity – Part 2		X			
14.3.1.6.1	Treatment-Emergent Adverse Events (TEAE) by System Organ Class, Preferred Term, and Relationship to Study Treatment – Part 1		X			
14.3.1.6.2	Treatment-Emergent Adverse Events (TEAE) by System Organ Class,		X			

Table	Description of Table	All	Safety	mITT	PP	PK
	Preferred Term, and Relationship to Study Treatment – Part 2					
14.3.2.1	Listing of Fatal Treatment-Emergent Adverse Events (TEAE)		X			
14.3.2.2	Listing of Serious Treatment-Emergent Adverse Events (TEAE)		X			
14.3.2.3	Listing of Treatment-Emergent Adverse Events (TEAE) Leading to Withdrawal From the Study		X			
14.3.2.4	Listing of Treatment-Emergent Adverse Events (TEAE) Leading to Study Drug Discontinuation		X			
14.3.3.1	Vital Signs by Visit – Part 1		X			
14.3.3.2	Vital Signs by Visit – Part 2		X			
14.3.4.1	Best Corrected Visual Acuity (logMAR) by Visit – Part 1		X			
14.3.4.2	Best Corrected Visual Acuity (logMAR) by Visit – Part 2		X			
14.3.5.1	Slit Lamp Examination by Visit – Part 1		X			
14.3.5.2	Slit Lamp Examination by Visit – Part 2		X			
[redacted]						
14.3.7.1	Intraocular Pressure (mmHg) by Visit – Part 1		X			
14.3.8.1	Fundus Examination by Visit – Part 1		X			
14.3.9.1	Pachymetry (um) by Visit – Part 1		X			
14.3.10.1	Endothelial Cell Count (cells/mm^2) by Visit – Part 1		X			
[redacted]						
14.4.2.1	INV-102 Plasma Concentrations (ng/mL) by Visit and Time Point – Part 1					X

14.2. List of Planned Listings

Listing	Description of Listing
16.2.1.1	Subject Disposition
16.2.1.2	Eligibility and Randomization
16.2.1.3	Screen Failures
16.2.2	Protocol Deviations
16.2.3	Treatment Assignment and Analysis Populations
16.2.4.1	Demographics
16.2.4.2	General Medical and Surgical History
16.2.4.3	Ophthalmic Medical and Surgical History
16.2.4.4	Prior and Concomitant Medications
16.2.5.1	Study Drug Dispensing
16.2.5.2	Study Drug Administration
16.2.5.3	Study Drug Return
16.2.5.4	Study Drug Exposure and Compliance
16.2.5.5	INV-102 Plasma Concentrations
[redacted]	
16.2.6.1	[redacted]Dry Eye Disease Symptom VAS
16.2.6.2	Eye Dryness and Eye Discomfort Composite Scores
[redacted]	
16.2.6.4	Corneal Fluorescein Staining
[redacted]	
16.2.7	Adverse Events
16.2.8	Vital Signs
16.2.9	Best Corrected Visual Acuity
16.2.10	Slit Lamp Examination
[redacted]	
16.2.12	Intraocular Pressure (IOP)
16.2.13	Fundus Examination
16.2.14	Noncontact Pachymetry
16.2.15	Endothelial Cell Count

Listing	Description of Listing
16.2.16	Urine Pregnancy Test
16.2.17	General Comments

14.3. List of Planned Figures

Figure	Description of Figure	All	Safety	mITT	PP	PK
[redacted]						