Study Title: Phase 1/2a, Proof-of-Concept, Multicenter, Parallel, Vehicle-Controlled, Double-Masked, Randomized Study Evaluating the Safety, Tolerability, and Efficacy of IVW-1001 Ophthalmic Eyelid Wipe in Subjects With Dry Eye Disease

Study Number: IVW-1001-CS-101

CTG Number: NCT06400459

Document Date: 17 April 2024

PROTOCOL: IVW-1001-CS-101

Study Title:	Phase 1/2a, Proof-of-Concept, Multicenter, Parallel, Vehicle-Controlled, Double-Masked, Randomized Study Evaluating the Safety, Tolerability, and Efficacy of IVW-1001 Ophthalmic Eyelid Wipe in Subjects With Dry Eye Disease
Study Number:	IVW-1001-CS-101
Study Phase:	Phase 1/2a
IND:	164036
Product Name:	IVW-1001 Ophthalmic Eyelid Wipe
Sponsor:	IVIEW Therapeutics, Inc.
Sponsor Contact:	[redacted]
Sponsor Medical Monitor:	[redacted]

	Date
Original Protocol:	Version 1.0; 22 January 2024
Amended Protocol	Version 1.1; 17 April 2024

Confidentiality Statement

SUMMARY OF CHANGES

Version	**1.1**	**22 March 2024**
Affected Section(s)	**Summary of Revisions**	**Rationale**
1.2	Tweezers for removal of eyelid wipes from vial are not sterile.	Subjects will clean tweezers with alcohol wipes prior to use.
4.2 and 4.3	Inclusion criterion #9 and exclusion criterion #4 added.	Subjects to refrain from contact or scleral lens use during participation to assure safety.
5.3.2	Clarification regarding IP storage conditions	Refrigerated storage conditions apply to pharmacy storage prior to dispensation; after dispensation IP storage is at room temperature for up to 30 days.
6.1.2	Clarification regarding selection of study eye.	Secondary corneal fluorescein staining grades must meet all qualification criteria.
7.4, 7.5 and Appendices	Various explanatory clarifications added throughout	Assurance of testing uniformity and order of procedures across all sites.
8.6	Medical Monitor updated	Assure correct reporting procedures to Medical Monitor.
8.7	Drug Safety Specialist updated	Assure correct reporting procedures to pharmacovigilance.

SYNOPSIS

Sponsor	IVIEW Therapeutics, Inc.
Study Title	Phase 1/2a, Proof-of-Concept, Multicenter, Parallel, Vehicle-Controlled, Double-Masked, Randomized Study Evaluating the Safety, Tolerability, and Efficacy of IVW-1001 Ophthalmic Eyelid Wipe in Subjects With Dry Eye Disease
Protocol Number	IVW-1001-CS-101
Indication	Dry eye disease (DED)
Sites	Up to approximately 10 sites throughout the United States (US)
Phase of Development	Phase 1/2a
Objectives	The objectives of this study are to assess the safety and efficacy of IVW-1001 Ophthalmic Eyelid Wipe in subjects with DED.

Primary Safety Outcome Measures	The primary safety measures are:
	• Mean change from baseline in:
	  ○ Best-corrected visual acuity (BCVA)
	  ○ Slit lamp biomicroscopy
	  ○ Intraocular pressure (IOP)
	  ○ Dilated ophthalmoscopy
	• Visual analog scale (VAS) of investigational product (IP) tolerability
	• Adverse events (AEs)

Primary Efficacy Outcome Measures	The primary efficacy endpoint is: • Mean change from baseline at Day 29 (Week 4/End of Study) in the study eye in unanesthetized Schirmer's test

Exploratory Efficacy Outcome Measures	The exploratory efficacy endpoints are:
	• Mean change from baseline in:
	  ○ Unanesthetized Schirmer's test (Weeks 1, 2, and 3)
	  ○ VAS of IP comfort (ASHRAE 7-Point Scale)
	  ○ VAS of Eye Dryness Score (EDS)
	  ○ VAS of Ocular Discomfort Score (ODS)
	  ○ Symptom Assessment in Dry Eye (SANDE) questionnaire
	  ○ Corneal fluorescein staining (inferior zone)
	  ○ Corneal fluorescein staining (total of all zones)
	  ○ Anesthetized Schirmer's test
	• Proportion of subjects ≥10 mm increase in unanesthetized Schirmer's test score

	• Proportion of subjects ≥10 mm increase in anesthetized Schirmer's test score
Study Design	This is a randomized (1:1:1), multicenter, parallel, vehicle-controlled, double-masked study to evaluate the safety, tolerability, and efficacy of IVW-1001 Ophthalmic Eyelid Wipes in subjects with DED. Treatments will be IVW-1001 Ophthalmic Eyelid Wipe 0.2% (high dose), IVW-1001 0.1% (low dose), or IVW-1001 Ophthalmic Eyelid Wipe Placebo (vehicle). Subjects will participate in a 7-day, single-masked vehicle run-in period followed by a 28-day, double-masked treatment period.
Inclusion Criteria	Each subject must meet the following criteria to be randomized in this study. 1. Subjects of any gender at least 18 years of age at the Screening Visit 2. Able to voluntarily provide written informed consent to participate in the study 3. Able and willing to comply with all study procedures and restrictions, follow study instructions, and complete required study visits 4. Self-reported diagnosis of DED in one or both eyes 5. BCVA +0.70 logMAR (Snellen equivalent 20/100) or better in each eye at the Screening Visit 6. For women of childbearing potential, confirmed negative pregnancy test at the Screening Visit and the Baseline Visit, not nursing a child, and willing to comply with one of the acceptable methods of birth control described in the protocol 7. History (by subject recollection) of artificial tear use within 30 days prior to the Screening Visit 8. Willingness to suspend use of artificial tears during study participation 9. Willingness to suspend use of contact lenses during study participation 10. Able to demonstrate adequate self-administration of the run-in eyelid wipe to upper eyelid at the Screening Visit 11. Unanesthetized Schirmer's test score between 5 and 10 mm (inclusive) in at least 1 eye (same eye) at the Screening Visit and the Baseline Visit 12. Total corneal fluorescein staining score between 5 and 13, representing the sum of scores of all 5 regions (inferior, superior, nasal, temporal, and central) using the National Eye Institute (NEI) grading system (0-4 scale) in at least one eye at the Screening Visit and the Baseline Visit 13. EDS VAS ≥40 at the Screening Visit and the Baseline Visit, with ≤20 units of improvement from the Screening Visit to the Baseline Visit

Exclusion Criteria	Subjects who meet any of the following criteria will be excluded from randomization. *Ocular history – medical* 1. Corneal fluorescein staining score of 4 in either eye in any zone using the NEI grading system at either the Screening Visit or the Baseline Visit 2. IOP ≥23 mmHg in either eye at either the Screening Visit or the Baseline Visit 3. History of glaucoma or ocular hypertension in either eye requiring past or current medical or surgical intervention 4. History of contact or scleral lens use in either eye within 30 days prior to the Screening Visit or anticipated use during the study 5. Subjects with ocular inflammatory conditions (eg, conjunctivitis, keratitis, severe anterior blepharitis, etc.) not related to DED at the Screening Visit or the Baseline Visit 6. Suspected ocular fungal, viral, or bacterial infection at the Screening Visit or the Baseline Visit. Note: Mild blepharitis is permitted 7. Presence of trigger factors that, in the opinion of the Investigator, may confound the study data, including but not limited to conjunctivochalasis, allergic conjunctivitis, trichiasis, epithelial basement membrane dystrophy, infectious keratitis, or conjunctivitis *Ocular history – surgical/procedural* 8. Routine use (as defined by the Investigator) of lid hygiene products (warm compresses, medicinal eyelid wipes, eyelid scrubs, mechanical eyelid cleaning therapy) within 30 days prior to the Screening Visit or inability or unwillingness to withhold use during study participation. Note: Makeup removal products are permitted 9. Treatments for meibomian gland dysfunction (MGD) within 30 days prior to the Screening Visit or anticipated use during the study, including but not limited to thermal pulsation (Lipiflow®, iLux2®), debridement of lid margin (BlephEx®), moisture chamber goggles, or thermal application (MiBoFlo Thermoflo®, TearCare®) 10. Cauterization of the punctum within 90 days prior to the Screening Visit or anticipated during study participation 11. Non-dissolvable punctal plugs inserted within 90 days prior to the Screening Visit or, in the opinion of the Investigator, considered unstable and likely to become displaced 12. Long-term dissolvable punctal plugs inserted within 90 days prior to the Screening Visit *Prior medications and therapies in either eye*

	13. Use of artificial tears within 2 hours prior to the Screening Visit or anticipated use during study participation 14. Use of the following therapies within 30 days prior to the Screening Visit or anticipated use during study participation: a. Topical cyclosporine (Restasis®, Cequa®, or Vevye™ [previously known as CyclASol®]) b. Topical brimonidine (prescription or over-the-counter [OTC]) c. Topical lifitegrast (Xiidra®) d. Topical perfluorohexyloctane (Miebo™) e. Topical ocular corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) f. Any other prescription or OTC topical eye lid (including wipes) or ocular medications for DED and/or MGD or any other indication that, in the opinion of the Investigator, might interfere with study assessments *Prior non-ocular medications* 15. Use of medications for the treatment of DED and/or MGD such as oral tetracyclines, oral tetracycline derivatives, oral or topical macrolides (such as azithromycin), and oral retinoids (Note: Current or past isotretinoin use is exclusionary) within 30 days prior to the Screening Visit or anticipated use during the study 16. Initiation, discontinuation, or change in dosing of any systemic corticosteroid within 30 days prior to the Screening Visit or an anticipated change in dosage during the study a. Topical non-ocular dermal corticosteroids may be used up to 3 times per week in no more than 3 locations simultaneously. No periocular use is permitted b. Intranasal corticosteroids are permitted with a stable dosing history during the 30 days prior to the Screening Visit and without an anticipated change in dosage during the study 17. Use of NSAIDs, including aspirin, unless: a. Used with a stable dosing history during the 30 days prior to the Screening Visit without an anticipated change in dosage during the study b. Used as needed (PRN) no more than 3 times weekly c. Note: Acetaminophen has no restrictions on its use 18. Initiation, discontinuation, or change in dose of a systemic medication (oral or topical) known to cause ocular drying (eg, antihistamines or tricyclic antidepressants) within 30 days prior to the Screening Visit or an anticipated change in dosage during the study. Note: These agents are permitted when used PRN to treat insomnia 19. Initiation, discontinuation, or change in dose of any systemic immunomodulator (eg, hydroxychloroquine, methotrexate,

	cyclosporine) within 30 days prior to the Screening Visit or an anticipated change during the study. Note: Treatment with vaccines is allowed during study participation 20. Use of Tyrvaya® (varenicline solution, nasal spray) within 30 days prior to the Screening Visit or anticipated use during the study 21. Any prior use of isotretinoin (Accutane®) or anticipated use during the study *Systemic conditions or procedures* 22. History of allergic conjunctivitis requiring use of prescription or OTC topical antihistamine therapy within the last 14 days 23. History or presence of significant (in the opinion of the Investigator) systemic (eg, cardiovascular, pulmonary, hepatic, renal, hematologic, immunologic) conditions 24. Any significant physical or mental condition that, in the opinion of the Investigator, could interfere with study participation 25. Any planned surgical procedure that could interfere with study participation *Lifestyle related* 26. Participation in any interventional investigational drug or device trial within 30 days prior to the Screening Visit 27. Employed by study site, or an immediate family member of site staff, and directly involved in clinical activities related to this study
Study Population	The subject population to be studied is comprised of subjects with DED confirmed at the Screening Visit who, after a 7-day, single (subject)-masked vehicle run-in period, continue to meet eligibility requirements at the Baseline Visit.
Investigational Product, Dose, and Mode of Administration	The IPs to be administered in this study are IVW-1001 Ophthalmic Eyelid Wipe 0.1%, IVW-1001 Ophthalmic Eyelid Wipe 0.2%, and IVW-1001 Ophthalmic Eyelid Wipe Placebo (vehicle) for eyelid application. Each unit dose will contain 2 polyester wipes saturated with a solution containing active ingredient (except vehicle, which contains no active ingredient), sodium hyaluronate, mannitol, and water for injection in a clear glass bottle. One unique wipe will be used for the application to the upper eyelid of each eye, moving in a nasal to temporal direction while applying modest pressure.
Duration of Study	This study has a duration of approximately 5 weeks, with a 7-day run-in period and a 28-day treatment period.
Number of Subjects	Approximately 150 subjects are targeted for enrollment.
Safety Assessments	The safety assessments to be used in this study are: • BCVA

	• Slit lamp biomicroscopy • IOP • Dilated ophthalmoscopy • VAS of IP tolerability • AEs
Efficacy Assessments	The efficacy assessments to be used in this study are: • Unanesthetized Schirmer's test • VAS of IP comfort (ASHRAE 7-Point Scale) • VAS of EDS • VAS of ODS • SANDE questionnaire • Corneal fluorescein staining (inferior zone) • Corneal fluorescein staining (total of all zones) • Anesthetized Schirmer's test
Statistical Methods	The analysis of safety and efficacy will be performed after all subjects have completed the Day 29 Visit or been discontinued prior to Day 29, and after the study database has been cleaned, verified, and locked. It is planned that the data from all clinical sites participating in this study will be combined so that the target sample size will be available for analysis. For each efficacy parameter measured on a per-eye basis, the primary analysis will be done using data from the study eye (ie, the eye that satisfies all of the enrollment criteria). If both eyes satisfy all enrollment criteria, then a predefined method will be used to select the study eye. Analyses will be implemented using SAS® version 9.4 or later. More details regarding the analysis of the safety and efficacy data will be described in the Statistical Analysis Plan. ***Sample size determination*** Approximately 150 subjects will be enrolled (50/group) in order to obtain approximately 138 subjects who complete the study (46/group). For the primary efficacy endpoint, this sample size of 46 subjects per group should provide at least 80% power to detect a difference between the placebo group and each of the IVW-1001 groups of 3.3 mm or greater, assuming a standard deviation of 5.0 mm and a 0.025 two-sided significance level.
Interim Analysis	None

Table of Contents

List of Appendices

LIST OF ABBREVIATIONS

Abbreviation	Definition or Explanation
AE	adverse event
ASHRAE	American Society of Heating, Refrigerating and Air-conditioning Engineers
BCVA	best-corrected visual acuity
C3	cryosim-3; IVW-1001
CFS	corneal fluorescein staining
DED	dry eye disease
eCRF	electronic case report form
EDS	Eye Dryness Score
EOS	End of Study
ET	Early Termination
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Information Portability and Accountability Act
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IOP	intraocular pressure
IP	investigational product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MGD	meibomian gland dysfunction
mITT	Modified Intention-to-Treat
NEI	National Eye Institute
NSAID	nonsteroidal anti-inflammatory drug
ODS	Ocular Discomfort Score
OTC	over-the-counter
OU	oculus uterque; both eyes
PP	Per Protocol
PRN	pro re nata; as needed
SAE	serious adverse event
SANDE	Symptom Assessment in Dry Eye
SD	standard deviation
US	United States
VA	visual acuity
VAS	visual analog scale
WOCBP	women of childbearing potential

1 INTRODUCTION

In 2017, the Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS-DEWS II) defined dry eye disease (DED) as "…a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles" (Craig 2017). TFOS-DEWS II goes on to state, "The management of DED is complicated, due to its multifactorial etiology…The ultimate aim of DED management is to restore the homeostasis of the ocular surface and tear film, through breaking the vicious cycle of the disease." A wide range of treatments are available based upon the nature and severity of the patient's DED. Management of DED generally begins with conventional, low-risk self-administered therapies, including over-the-counter (OTC) lubricant eye drops, and progresses to more advanced therapies as severity increases (Craig 2017). However, many patients are still not optimally treated despite the availability of numerous approved therapeutic products.

As recently reviewed, researchers have discovered that thermal changes at the ocular surface activate cool neurons and may affect surface wetness (Yang 2018). TRPM8 receptors, which are located on the cornea and eyelid at the base of eyelash follicles (Yang 2017), appear to be first activated after evaporation of the tear film (Belmonte 2017); these may be associated with the detection of "dryness" on the eye surface (Parra 2014; Quallo 2015). TRPM8 may also be a direct stimulator of tear secretion from the lacrimal gland (Parra 2010).

In order to test this hypothesis, a TRPM8 agonist was synthesized (IVW-1001; cryosim-3; C3; 1-diisopropyl-phosphinoyl-nonae; Yang 2017). In nonclinical models of mouse DED, single topical ocular doses of C3 0.2% showed activity (Yang 2017). IVW-1001 0.2% singly applied ocular topically increased tear secretion in healthy rabbits.

In clinical C3 studies conducted in Korea in subjects with DED, 60 subjects (n=30 per group) participated in a single-dose study, and 40 subjects (n=20 per group) completed a 2-week, repeat-dose study. Cryosim-3 or vehicle (water) was applied with a cotton gauze pad to upper eyelids of subjects with DED (n=30). Cooling sensation, tear film break-up time (TBUT), basal tear secretion, and corneal staining were evaluated. Cryosim-3 was then applied 4 times daily (QID) for 2 weeks to subjects using a pre-loaded single-unit applicator containing C3 2 mg/mL (0.2%) in water (n=20) or water only. After 2 weeks of QID dosing with C3 0.2% as an eyelid wipe, subjects experienced improved signs and symptoms relative to the control (water) group (Yang 2017). An open-label, non-comparative pilot study was also conducted in Korea in 20 subjects with neuropathic ocular pain (Yoon 2021). After 1 month of treatment with C3 0.2% eyelid wipes, subjects experienced improvement in ocular pain symptoms, quality of life, and Schirmer's test scores.

In this protocol, IVW-1001 Ophthalmic Eyelid Wipe is being evaluated for the treatment of subjects with DED. The final drug product is a single-use, preservative-free, sterile eyelid wipe that is saturated with either C3 0.1% ophthalmic solution, C3 0.2% ophthalmic solution, or a vehicle ophthalmic solution on a polyester cloth. Two wipes (1 for each eye) are sealed into a glass vial. Also provided are tweezers to extract the wipe from the vial. IVW-1001 is a new drug substance, and there is no previous human experience in the United States (US).

1.1 Indication

In this clinical trial, the population to be studied is subjects with DED confirmed by Screening Visit 1 assessments.

1.2 Investigational Products

IVW-1001 Ophthalmic Eyelid Wipe is a single-use, preservative-free, sterile eyelid wipe that is saturated with C3 0.1% ophthalmic solution, C3 0.2% ophthalmic solution, or a vehicle ophthalmic solution on a polyester cloth. Two wipes (1 for each eye) are sealed into a glass vial. Also provided are tweezers to extract the wipe from the vial.

1.3 Nonclinical Experience

Please see the Investigator's Brochure for this information.

1.4 Clinical Experience

IVW-1001 is a new drug substance, and there is no previous human experience in the US.

1.5 Risks and Benefits

Based upon previous human evaluation and this class of compounds, the primary potential risk of IVW-1001 is ocular discomfort. The potential benefits are improvements in signs and symptoms of ocular surface disease.

2 STUDY OBJECTIVES AND MEASURES

2.1 Objective

The objectives of this study are to assess the safety and efficacy of IVW-1001 Ophthalmic Eyelid Wipe in subjects with DED.

2.2 Measures

2.2.1 Safety

The primary safety measures are:

- Mean change from baseline in:
  - Best-corrected visual acuity (BCVA)
  - Slit lamp biomicroscopy
  - Intraocular pressure (IOP)
  - Dilated ophthalmoscopy
- Visual analog scale (VAS) of investigational product (IP) tolerability
- Adverse events (AEs)

2.2.2 Efficacy

The primary efficacy endpoint is

- Mean change from baseline at Day 29 (Week 4/End of Study [EOS]) in the study eye in unanesthetized Schirmer's test

The exploratory efficacy endpoints are:

- Mean change from baseline in:
  - Unanesthetized Schirmer's test (Weeks 1, 2, and 3)
  - Visual analog scale of IP comfort (ASHRAE 7-Point Scale)
  - Visual analog scale of Eye Dryness Score (EDS)
  - Visual analog scale of Ocular Discomfort Score (ODS)
  - Symptom Assessment in Dry Eye (SANDE) questionnaire
  - Corneal fluorescein staining (inferior zone)
  - Corneal fluorescein staining (total of all zones)
  - Anesthetized Schirmer's test
- Proportion of subjects ≥10 mm increase in unanesthetized Schirmer's test score
- Proportion of subjects ≥10 mm increase in anesthetized Schirmer's test score

3 INVESTIGATIONAL PLAN

This study will be conducted in strict accordance with the Council for International Organizations of Medical Sciences International Ethical Guidelines, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines, and all applicable laws and regulations.

3.1 Overall Study Design

This is a randomized (1:1:1), multicenter, parallel, vehicle-controlled, double-masked study to evaluate the safety, tolerability, and efficacy of IVW-1001 Ophthalmic Eyelid Wipes in subjects with DED. Treatments will be IVW-1001 Ophthalmic Eyelid Wipe 0.2% (high dose), IVW-1001 0.1% (low dose), or IVW-1001 Ophthalmic Eyelid Wipe Placebo (vehicle). Subjects will participate in a 7-day, single-masked vehicle run-in period followed by a 28-day, double-masked treatment period.

3.2 Number of Subjects

A total of approximately 150 subjects are planned to be randomized.

3.3 Study Duration

The study is divided into 2 periods:

- Seven-day, single (subject)-masked vehicle run-in period
- Twenty-eight–day, active, double-masked treatment period commencing on Day 1, when the assigned treatment will be administered

3.4 Rescue Treatment

Subjects will not be eligible to receive rescue treatment during the study.

3.5 Study Treatments

This study will evaluate IVW-1001 Ophthalmic Eyelid Wipe 0.2% and IVW-1001 Ophthalmic Eyelid Wipe 0.1% compared to IVW-1001 Ophthalmic Eyelid Wipe Placebo (vehicle) for the treatment of DED.

3.6 Rationale for Study Design and Control Group

This Phase 1/2a study, which utilizes a vehicle comparator design, will evaluate the safety, tolerability, and efficacy of 2 different concentrations of IVW-1001 in a population of subjects with active DED to inform the clinical development of IVW-1001 Ophthalmic Eyelid Wipes.

This study includes treatment-experienced subjects, particularly those with a prior suboptimal response to artificial tear therapy.

3.7 Dose and Dosing Regimen

This study assesses twice daily (BID) administration to the upper eyelid of both eyes of 2 different doses of the IVW-1001 Ophthalmic Eyelid Wipe compared to vehicle. Subjects are not to use wipes

the morning of Visits 3 (Day 8), 4 (Day 15), 5 (Day 22), or 6 (Day 29), as they will be used during the visit.

3.8 Study Oversight

Study oversight will be the responsibility of the Sponsor, in conjunction with the clinical trial contract research organization and the study medical monitor.

4 STUDY POPULATION SELECTION AND WITHDRAWAL

4.1 Study Population

The subject population to be studied is comprised of subjects with DED confirmed at the Screening Visit who, after a 7-day, single (subject)-masked vehicle run-in period, continue to meet eligibility requirements at the Baseline Visit.

Subjects will be recruited from among the population of individuals with DED within the clinical practices of study Investigators and from among treatment-experienced patients with DED referred to the clinical practices of study Investigators. Potential subjects will be identified by appropriate study site personnel and will be approached by care providers known to the patients to discuss study participation. Patients who are potentially eligible for the clinical study will be referred to the study for screening and formal determination of study eligibility.

4.2 Inclusion Criteria

Each subject must meet the following criteria to be randomized in this study.

1. Subjects of any gender at least 18 years of age at the Screening Visit
2. Able to voluntarily provide written informed consent to participate in the study
3. Able and willing to comply with all study procedures and restrictions, follow study instructions, and complete required study visits
4. Self-reported diagnosis of DED in one or both eyes
5. Best-corrected visual acuity (VA) +0.70 logMAR (Snellen equivalent 20/100) or better in each eye at the Screening Visit
6. For women of childbearing potential (WOCBP), confirmed negative pregnancy test at the Screening Visit and the Baseline Visit, not nursing a child, and willing to comply with one of the acceptable methods of birth control described in the protocol (see Section 7.2.1)
7. History (by subject recollection) of artificial tear use within 30 days prior to the Screening Visit
8. Willingness to suspend use of artificial tears during study participation
9. Willingness to suspend use of contact lenses during study participation
10. Able to demonstrate adequate self-administration of the run-in eyelid wipe to upper eyelid at the Screening Visit
11. Unanesthetized Schirmer's test score between 5 and 10 mm (inclusive) in at least 1 eye (same eye) at the Screening Visit and the Baseline Visit
12. Total corneal fluorescein staining score between 5 and 13, representing the sum of scores of all 5 regions (inferior, superior, nasal, temporal, and central) using the National Eye Institute (NEI) grading system (0-4 scale) at the Screening Visit and the Baseline Visit
13. Eye Dryness Score VAS ≥40 at the Screening Visit and the Baseline Visit, with ≤20 units of improvement from the Screening Visit to the Baseline Visit

4.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from randomization.

Ocular history – medical

1. Corneal fluorescein staining score of 4 in either eye in any zone using the NEI grading system at either the Screening Visit or the Baseline Visit
2. Intraocular pressure ≥23 mmHg in either eye at either the Screening Visit or the Baseline Visit
3. History of glaucoma or ocular hypertension in either eye requiring past or current medical or surgical intervention
4. History of contact or scleral lens use in either eye within 30 days prior to the Screening Visit or anticipated use during the study
5. Subjects with ocular inflammatory conditions (eg, conjunctivitis, keratitis, severe anterior blepharitis, etc.) not related to DED at the Screening Visit or the Baseline Visit
6. Suspected ocular fungal, viral, or bacterial infection at the Screening Visit or the Baseline Visit. Note: Mild blepharitis is permitted
7. Presence of trigger factors that, in the opinion of the Investigator, may confound the study data, including but not limited to conjunctivochalasis, allergic conjunctivitis, trichiasis, epithelial basement membrane dystrophy, infectious keratitis, or conjunctivitis

Ocular history – surgical/procedural

8. Routine use (as defined by the Investigator) of lid hygiene products (warm compresses, medicinal eyelid wipes, eyelid scrubs, mechanical eyelid cleaning therapy) within 30 days prior to the Screening Visit or inability or unwillingness to withhold use during study participation. Note: Makeup removal products are permitted
9. Treatments for meibomian gland dysfunction (MGD) within 30 days prior to the Screening Visit or anticipated use during the study, including but not limited to thermal pulsation (Lipiflow®, iLux2®), debridement of lid margin (BlephEx®), moisture chamber goggles, or thermal application (MiBoFlo Thermoflo®, TearCare®)
10. Cauterization of the punctum within 90 days prior to the Screening Visit or anticipated during study participation
11. Non-dissolvable punctal plugs inserted within 90 days prior to the Screening Visit or, in the opinion of the Investigator, considered unstable and likely to become displaced
12. Long-term dissolvable punctal plugs inserted within 90 days prior to the Screening Visit

Prior medications and therapies in either eye

13. Use of artificial tears within 2 hours prior to the Screening Visit or anticipated use during study participation
14. Use of the following therapies within 30 days prior to the Screening Visit or anticipated use during study participation:
    a. Topical cyclosporine (Restasis®, Cequa®, or Vevye™ [previously known as CyclASol®])
    b. Topical brimonidine (prescription or OTC)
    c. Topical lifitegrast (Xiidra®)
    d. Topical perfluorohexyloctane (Miebo™)
    e. Topical ocular corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs)

f. Any other prescription or OTC topical eye lid (including wipes) or ocular medications for DED and/or MGD or any other indication that, in the opinion of the Investigator, might interfere with study assessments

Prior non-ocular medications

15. Use of medications for the treatment of DED and/or MGD such as oral tetracyclines, oral tetracycline derivatives, oral or topical macrolides (such as azithromycin), and oral retinoids (Note: Current or past isotretinoin use is exclusionary) within 30 days prior to the Screening Visit or anticipated use during the study
16. Initiation, discontinuation, or change in dosing of any systemic corticosteroid within 30 days prior to the Screening Visit or an anticipated change in dosage during the study
    a. Topical non-ocular dermal corticosteroids may be used up to 3 times per week in no more than 3 locations simultaneously. No periocular use is permitted
    b. Intranasal corticosteroids are permitted with a stable dosing history during the 30 days prior to the Screening Visit and without an anticipated change in dosage during the study
17. Use of NSAIDs, including aspirin, unless:
    a. Used with a stable dosing history during the 30 days prior to the Screening Visit without an anticipated change in dosage during the study
    b. Used as needed (PRN) no more than 3 times weekly
    c. Note: Acetaminophen has no restrictions on its use
18. Initiation, discontinuation, or change in dose of a systemic medication (oral or topical) known to cause ocular drying (eg, antihistamines or tricyclic antidepressants) within 30 days prior to the Screening Visit or an anticipated change in dosage during the study. Note: These agents are permitted when used PRN to treat insomnia
19. Initiation, discontinuation, or change in dose of any systemic immunomodulator (eg, hydroxychloroquine, methotrexate, cyclosporine) within 30 days prior to the Screening Visit or an anticipated change during the study. Note: Treatment with vaccines is allowed during study participation
20. Use of Tyrvaya® (varenicline solution, nasal spray) within 30 days prior to the Screening Visit or anticipated use during the study
21. Any prior use of isotretinoin (Accutane®) or anticipated use during the study

Systemic conditions or procedures

22. History of allergic conjunctivitis requiring use of prescription or OTC topical antihistamine therapy within the last 14 days
23. History or presence of significant (in the opinion of the Investigator) systemic (eg, cardiovascular, pulmonary, hepatic, renal, hematologic, immunologic) conditions
24. Any significant physical or mental condition that, in the opinion of the Investigator, could interfere with study participation
25. Any planned surgical procedure that could interfere with study participation

Lifestyle related

26. Participation in any interventional investigational drug or device trial within 30 days prior to the Screening Visit
27. Employed by study site, or an immediate family member of site staff, and directly involved in clinical activities related to this study

4.4 Discontinuation of Treatment and Withdrawal of Subjects

The Investigator may withdraw a subject from the study for any of the following reasons:

- A serious or intolerable AE occurs
- A clinically significant change in systemic health
- The Sponsor or Investigator terminates the study
- The subject requests to be discontinued from the study

Withdrawal of subjects from the study will occur with completion of an Early Termination (ET) Visit to collect EOS data.

Subjects who use prohibited concomitant medications during the study will not be withdrawn from the trial. The data from subjects who use prohibited concomitant medications during the study will be included in the Modified Intention-to-Treat (mITT) analysis and excluded from the per-protocol analysis.

4.4.1 Early Termination Visit

Subjects who are withdrawn from the study should complete an ET Visit, with assessments completed in a comparable manner to an EOS Visit.

4.5 Subject Replacement

Subjects who are withdrawn from the study will not be replaced.

5 STUDY TREATMENTS

5.1 Investigational Products

The IPs to be administered in this study are IVW-1001 Ophthalmic Eyelid Wipe 0.1%, IVW-1001 Ophthalmic Eyelid Wipe 0.2%, and IVW-1001 Ophthalmic Eyelid Wipe Placebo (hereinafter vehicle) for eyelid application.

Each unit dose will contain 2 polyester wipes saturated with a solution containing active ingredient (except vehicle, which contains no active ingredient), sodium hyaluronate, mannitol, and water for injection in a clear glass bottle.

One unique wipe will be used for the application to the upper eyelid of each eye, moving in a nasal to temporal direction while applying modest pressure.

5.2 Packaging and Labeling

Two polyester IVW-1001 Ophthalmic Eyelid Wipes (0.1% or 0.2%) are contained within each 20 mL clear glass bottle. The sterile, packaged bottles are contained within secondary packaging—a white carton with a unique identifier for IP for tracking and dispensing purposes—that does not reveal the specific identity of the IP. The cartons are contained within a larger kit package—a white carton with a unique identifier for tracking and dispensing purposes.

Vehicle is packaged and labeled in the same manner as IVW-1001 Ophthalmic Eyelid Wipes 0.1% and 0.2%.

Collectively, this approach will avoid revealing the specific identity of the IP (IVW-1001 Ophthalmic Eyelid Wipe 0.1%, IVW-1001 Ophthalmic Eyelid Wipe 0.2%, or vehicle) by the external appearance or external labeling of the packaging, ensuring that study personnel are not unmasked in the handling of the packaged drug products.

Separately, subjects will be provided with tweezers to aid in removing the wipes from the vial and decapper pliers (or similar) to aid in removing the rubber stoppers and aluminum-plastic caps.

5.3 Supply, Storage, and Administration of Investigational Product

5.3.1 Supply

Investigational products will be supplied to study sites in the packaging described above by an IP distribution vendor. Study site personnel will be responsible for receiving and recording the identification numbers and dates received for all IPs, and the supply will be masked as described above using appropriate packaging without identifying names or attributes and by use of appropriate unique identifiers on the external packaging.

5.3.2 Storage

Investigational product and comparator control are to be stored within the refrigerated (between 2°C and 8°C inclusive) temperature range at all times prior to dispensation to subjects. After dispensation to the subject, store IP at room temperature for up to 30 days.

5.3.3 Administration

Upon qualification, study site personnel will dispense vehicle using the Interactive Web Response System (IWRS) to each subject for the run-in period. Upon randomization, study site personnel will dispense IP (IVW-1001 Ophthalmic Eyelid Wipe 0.1%, IVW-1001 Ophthalmic Eyelid Wipe 0.2%, or vehicle) using the IWRS to each subject for the treatment period.

Site personnel will instruct subjects verbally on the eyelid administration procedures and frequency of use and provide written instructions that will document use of 1 unique wipe for application to the upper eyelid of each eye, moving in a nasal to temporal direction while applying modest pressure. Subjects will be instructed about best practices, i.e., storing IP with bottle cap positioned upwards, and shaking the IP bottle approximately 10 times prior to use. Subjects will be instructed to wait at least 15 minutes after eye makeup removal before application of the IP. Site personnel will oversee the first IP use while the subject is at the site.

Subjects are not to use wipes the morning of Visits 3 (Day 8), 4 (Day 15), 5 (Day 22), or 6 (Day 29).

5.4 Accountability, Retention, and Destruction (or Return)

Investigational products will be tracked at the study site. Subjects will be instructed to replace used IP wipes into the clear glass bottles and to retain all used vials. Subjects will be instructed to return all used and unused vials to the investigational site at each visit. Each subject's returned used and unused vials will be counted as a surrogate measure of compliance. Subjects will be queried as to how many doses they recall missing since the prior visit.

Unused IP unit packaging will be maintained at the site until the conclusion of the study, when appropriate destruction and disposal instructions will be provided. Study site personnel will be required to maintain drug accountability records as per GCP requirements for study record maintenance.

6 ALLOCATION AND DOSING OF INVESTIGATIONAL PRODUCT

6.1 Allocation to Treatment Groups

After the vehicle run-in period, during which all subjects receive vehicle, qualified subjects will be randomized 1:1:1 to 1 of 3 treatment groups to receive one of the following: IVW-1001 Ophthalmic Eyelid Wipe 0.1%, IVW-1001 Ophthalmic Eyelid Wipe 0.2%, or vehicle.

6.1.1 Subject Assignment

All subjects will receive the same vehicle control run-in at the Screening Visit (single-masked), and at the Baseline Visit, subjects will receive and be dispensed IP according to the treatment group to which they are assigned.

6.1.2 Study Eye Selection

The study eye will be designated by Data Management at randomization at the Baseline Visit. If both eyes have an unanesthetized Schirmer's test score between 5 and 10 mm inclusive, the study eye will be the one with the lower score. If both eyes have the same an unanesthetized Schirmer's test score, the study eye will be the one with the highest qualifying total CFS score. However, if both eyes have the same total qualifying CFS score, the right eye will be designated as the study eye. Site personnel are not required to designate the study eye.

Note that dosing of study medication will be in both eyes (OU).

6.1.3 Randomization Procedures

Central randomization using the IWRS will be utilized to provide assignment of a specific anonymized code, corresponding to vehicle during the run-in period at the Screening Visit and separately to the IP to which the subject is randomized (IVW-1001 Ophthalmic Eyelid Wipe 0.1%, IVW-1001 Ophthalmic Eyelid Wipe 0.2%, or vehicle) at the Baseline Visit.

Trial treatment randomization codes and procedures for breaking codes will be maintained by the central randomization provider.

6.1.4 Masking

6.1.4.1 Masking Method

Specific procedures used for masking include anonymized codes and barcoding of IP without identifiable names, marking, or labels.

In rare cases, masking can be broken for an individual subject in the event of an unexpected serious adverse event (SAE) necessitating identification of the specific IP received.

6.1.4.2 Emergency Unmasking

Only in case of medical emergency or occurrence of SAEs will the code be unmasked via the central randomization service. The code may then be made available to the Investigator, the Sponsor, and/or other personnel involved in the monitoring or conduct of this study as applicable.

7 PERMITTED MEDICATIONS AND THERAPIES AND CONTRAINDICATIONS

7.1 Concomitant Therapy

Ongoing medications are concomitant from the Screening Visit until the final study visit.

7.1.1 Permitted Therapies

Subjects are permitted to take necessary prescription and OTC systemic medications for the management of ongoing medical conditions unless prohibited by specific exclusion criteria.

- Intranasal corticosteroids with a stable dosing history during the 30 days prior to the Screening Visit without an anticipated change in dosage during the study are permitted
- Nonsteroidal anti-inflammatory drugs, including aspirin, with a stable dosing history during the 30 days prior to Screening Visit 1 without an anticipated change in dosage during the study are permitted. As-needed use is permitted if no more than 3 doses weekly are used
- Acetaminophen has no restrictions on its use

7.1.2 Prohibited Ocular Medications and Therapies

Subjects are not permitted to the following **ocular** medications and/or therapies during study participation and for specified periods of time noted below prior to the Screening Visit since usage could confound the study assessments.

Within 30 days prior to the Screening Visit and during study participation:

- Lid hygiene products (warm compresses, medicinal eyelid wipes, eyelid scrubs, mechanical eyelid cleaning therapy). Note: Makeup removal products are permitted
- MGD treatments including but not limited to thermal pulsation (Lipiflow®, iLux$^{2®}$), debridement of lid margin (BlephEx®), moisture chamber goggles, or thermal application (MiBoFlo Thermoflo®, TearCare®)
- Cauterization of the punctum
- Topical cyclosporine (Restasis, Cequa, or Vevye)
- Topical brimonidine (prescription or OTC)
- Topical lifitegrast (Xiidra)
- Topical perfluorohexyloctane (Miebo)
- Topical ocular corticosteroids or NSAIDs
- Any other prescription or OTC topical eye lid (including wipes) or ocular medications for DED or MGD or any other indication that, in the opinion of the Investigator, might interfere with study assessments

7.1.3 Prohibited Non-ocular Therapies

Subjects are not permitted to take the following **non-ocular** medications during study participation and for specified periods of time noted below prior to the Screening Visit since usage could confound the study assessments.

Within 30 days prior to the Screening Visit and during study participation:

- Medications for the treatment of DED or MGD such as oral tetracyclines, oral tetracycline derivatives, oral or topical macrolides (such as azithromycin), and oral retinoids
- Medications (oral or topical) known to cause ocular drying (eg, antihistamines or tricyclic antidepressants). Note: These agents are permitted when used PRN to treat insomnia.
- Tyrvaya (varenicline solution, nasal spray)
- Isotretinoin (Accutane; any prior use)
    - Topical non-ocular dermal products may be used up to 3 times per week in no more than 3 locations simultaneously. No periocular use is permitted

7.1.4 Concomitant Medication Assessments

The study site clinical research coordinator will be responsible for recording the subject's concomitant prescription and OTC medication use under the supervision of the Investigator. Diagnostic eye drops do not need to be recorded.

7.1.5 Makeup and Eyelid Hygiene

Subjects meeting exclusion criterion #5 (ie, unable or unwilling to refrain from eyelid hygiene [mechanical cleaning of the lid/lash margin] during study participation) must be excluded from study participation. Makeup removal is allowed. Sites should remove any residual eye makeup 20 minutes or more prior to study examinations at the beginning of a study visit using the eye makeup remover provided by the Sponsor.

7.2 Lifestyle Restrictions

7.2.1 Reproductive Restrictions

All WOCBP must have a negative urine pregnancy test at the Screening Visit and the Baseline Visit prior to randomization in the study and must not intend to become pregnant during the study.

Women of childbearing potential must use an effective method of birth control during study participation. Acceptable methods include the use of at least one of the following: intrauterine device, hormonal (oral, injection, patch, implant, ring) contraception, barrier with spermicide (condom, diaphragm), a vasectomized partner, or abstinence.

Refer to Section 8.8 for more information on management of subjects who become pregnant during the study or up until 30 days after the last dose of the IP.

7.3 Informed Consent

The study will be introduced to potentially eligible treatment-experienced patients with DED by a care provider known to the patient. Prior to conducting any screening activities, a complete discussion of the purpose of the study, IPs to be tested, and study activities and assessments will be explained and reviewed with the patient. The patient will be given ample time to ask any questions and will undergo a formal informed consent process, to discuss potential benefits and risks of study participation. The patient will sign and receive a copy of an informed consent form (ICF) that was approved by the Institutional Review Board (IRB) before any study-specific procedure is performed.

An original signed ICF will be retained in the patient's source documentation at the site and a copy will be provided to the patient.

Written informed consent must be obtained from the patient before any study-related procedures are performed, and if there is a change in the study procedures during study participation.

7.4 Clinical Assessments

All clinical assessments will be collected as indicated in the Schedule of Events (Appendix 1).

7.4.1 Demographics

Demographic data including sex, age, race, and ethnicity will be collected.

7.4.2 Medical and Ophthalmic History

A complete medical history that includes all relevant medical and surgical history will be collected. A complete ophthalmic history will be collected.

7.4.3 Prior and Concomitant Medications

The name, dose, and frequency of all prescription and OTC medications that the subject is taking or has taken within 30 days prior to the Screening Visit must be recorded. All allowed and excluded medications should be recorded, including all prescription drugs, vitamins, supplements, and OTC medications. Generic drug names should be used preferentially.

7.4.4 Pregnancy Test

A urine pregnancy test will be performed at the Screening and Baseline Visits for WOCBP.

7.4.5 In-Office Investigational Product Administration

Refer to Section 5.3.3 for a description of IP administration procedures.

IP administration must be performed at least 20 minutes after completion of CFS.

7.4.6 Investigational Product Tolerability Visual Analog Scale

Investigational product tolerability will be measured on a scale ranging from 0 (no discomfort) to 100 (severe discomfort; Appendix 2). Study staff will measure and record the VAS scores. Score cards will be retained for measurement confirmation.

7.4.7 Investigational Product Comfort Visual Analog Scale

Investigational product comfort will be measured using the American Society of Heating, Refrigerating and Air-conditioning Engineers (ASHRAE) 7-point VAS (Beizaee 2012) ranging from -3 to +3 (Appendix 3). The assessment will be conducted before IP administration (pre-dose) and 5, 15, 30, and 60 minutes post-IP administration, unless the score at 5 and 15 minutes is 0, in which case

the 30- and 60-minute assessments can be omitted. Study staff will measure and record the VAS scores. Score cards will be retained for measurement confirmation.

7.4.8 Eye Dryness Score Visual Analog Scale

Eye dryness will be measured using the EDS VAS ranging from 0 to 100 (Appendix 4). Study staff will measure and record the VAS scores. Score cards will be retained for measurement confirmation.

7.4.9 Ocular Discomfort Score Visual Analog Scale

Ocular discomfort will be measured using the ODS VAS ranging from 0 to 100 (Appendix 5). Study staff will measure and record the VAS scores. Score cards will be retained for measurement confirmation.

7.4.10 Symptom Assessment in Dry Eye Questionnaire

A modified SANDE instrument (Schaumberg, 2007) will be used to evaluate dry eye symptoms (Appendix 6). Subjects will respond to separate questions assessing frequency and severity of symptoms over the past week. Study staff will measure and record the SANDE. Score cards will be retained for measurement confirmation.

7.4.11 Unanesthetized Schirmer's Test

At all visits an unanesthetized Schirmer's test will be initiated in each eye at least 15 minutes after CFS. At Visits 1, 2 and 6 it will be repeated at least 20 ± 5 minutes after IP administration. (Appendix 7)

Strips should be placed in each eye, right before left. After placement OU the 5-minute testing period will be initiated. Strips will be removed after 5 minutes, and the amount of wetting marked and the measurement recorded in mm by comparison to a ruler. Strips should be preserved to allow for measurement confirmation.

7.4.12 Best-Corrected Visual Acuity (and Refraction)

LogMAR VA must be assessed for each eye using a standard Early Treatment Diabetic Retinopathy Study (ETDRS) illuminated chart (on wall or stand) at 4 m. The procedure used will be consistent with the recommendations provided for using the ETDRS eye chart, which will be provided separately to the clinical site. Visual acuity should be evaluated at the beginning of each visit in the study (ie, prior to slit lamp examination). Visual acuity testing should be done with the most recent correction. Subjects will undergo manifest refraction at Screening according to the Investigator's standard of care. At any study visit if there is a 3-line or more reduction in VA since the prior BCVA was performed, a repeat refraction and BCVA should be performed.

7.4.13 Slit Lamp Biomicroscopy

The anterior-segment examination of each eye will be performed according to the Investigator's usual clinical technique. Magnification, lighting, and examiner should be consistent for each subject throughout the study. Biomicroscopy should be performed prior to pupil dilation. The examination should include an evaluation of the lids, conjunctiva, cornea, anterior chamber, iris/pupil (Screening

Visit only), and lens using a 4-point grading scale (0, none; 1, mild; 2, moderate; and 3, severe, as applicable).

7.4.14 Corneal Fluorescein Staining (CFS)

Sodium fluorescein will be delivered according to the instructions in into the conjunctival cul-de-sac of each eye followed by adequate blinking (Appendix 8). Staining will be measured 2 to 2½ minutes after instillation using the cobalt blue light of the slit lamp and a yellow Tiffen lens (Appendix 9). The modified NEI Grading Scale will be used to grade each of the 5 corneal zones using a 0 to 4 scale (Lemp 1995). The Investigator must review the grading scale at every examination when scoring the amount of staining.

7.4.15 Intraocular Pressure

All IOP assessments must be measured by Goldmann applanation tonometry. The tonometer calibration should be checked for accuracy within 1 month before screening the first subject for the study with measurements recorded and filed before the first subject is screened; calibration must be checked monthly thereafter throughout the study. Variation within ±2 mmHg is acceptable. The fluorescein and anesthetic agents should remain consistent throughout the study. Intraocular pressure will be measured following biomicroscopy and always prior to dilation.

Two consecutive IOP measurements should be taken, with the right eye measured first. The applanation probe should be withdrawn between measurements. If the first 2 measurements differ by >2 mmHg, a third measurement will be taken. Repeat for the left eye.

At the Screening Visit, Goldmann applanation tonometry must be performed after the completion of the unanesthetized Schirmer's test and prior to randomization to run-in IP.

At the Baseline Visit, Goldmann applanation tonometry must be performed after the completion of the unanesthetized Schirmer's test and prior to randomization to IP assignment.

At Visit 6, Goldmann applanation tonometry must be performed after the completion of the anesthetized Schirmer's test.

7.4.16 Anesthetized Schirmer's Test

Five minutes after the instillation of anesthetic drops strips should be placed in each eye, right before left. After placement OU the 5-minute testing period will be initiated. Strips will be removed after 5 minutes, and the amount of wetting marked and the measurement recorded in mm by comparison to a ruler. Strips should be preserved to allow for measurement confirmation.

7.4.17 Fundoscopy (Dilated Ophthalmoscopy)

Indirect dilated ophthalmoscopy will be performed on all subjects, UNLESS one of the below scenarios occur:

- Indirect dilated ophthalmoscopy was performed by a licensed eye professional within 6 months prior to Visit 1. In that case, it is not necessary to repeat ophthalmoscopy

- Indirect dilated ophthalmoscopy was performed by a licensed eye professional between 6 and 12 months prior to Visit 1. In that case, either direct undilated or indirect dilated ophthalmoscopy will be performed

Posterior segment examination of each eye will be performed according to the Investigator's preferred procedure. Magnification, lighting, and examiner should be consistent for each subject throughout the study. Ophthalmoscopy should be performed after pupil dilation. The examination should include evaluation and grading of the vitreous, macula, retinal vessels, peripheral retina, and optic disc using a normal/abnormal grading scale, as applicable.

7.4.18 Adverse Events

At each visit, the subject should be asked general questions such as, "How are you/your eyes feeling today? Have you had any changes since the last study visit?"

Any AE occurring after the first dose of IP will be recorded as an AE. Adverse events occurring during the Screening Visit prior to the first dose of IP will be noted in the medical history.

7.5 Study Activities

The Schedule of Events (Appendix 1) outlines the below events and procedures.

7.5.1 Screening Visit (Day -7 to 1 +2 days)

Procedures should be conducted in the following order:

- Informed consent
- Eligibility determination
- Demographics
- Medical/Ophthalmic history
- Concomitant medications
- Urine pregnancy test (WOCBP only)
- Eye Dryness Score VAS
- Ocular Discomfort Score VAS
- Investigational product ASHRAE 7-point comfort VAS (pre-dose)
- Best-corrected VA and refraction OU
- Slit lamp biomicroscopy OU
- Corneal fluorescein staining OU
- First unanesthetized Schirmer's test OU (⩾15 minutes post-CFS)
- Intraocular pressure OU

- Assign run-in IP (vehicle)
- In-office IP (vehicle) administration OU (⩾20 minutes post-CFS)
- Investigational product ASHRAE 7-point comfort VAS (5 ±2 minutes post-dose)
- Symptom Assessment in Dry Eye questionnaire (5 +10 minutes post-dose)
- Investigational product tolerability VAS (5 +10 minutes post-dose)
- Investigational product ASHRAE 7-point comfort VAS (15 ±2 minutes post-dose)
- Second unanesthetized Schirmer's test OU (⩾20 ±5 minutes post-dose)
- Investigational product ASHRAE 7-point comfort VAS (30 ±5 and 60 ±5 minutes post-dose)
- Fundoscopy (indirect dilated ophthalmoscopy) OU
- Dispense run-in vehicle
- Adverse event assessment

7.5.2 Baseline/Randomization Visit (Day 1)

Procedures should be conducted in the following order:

- Eligibility determination
- Medical/Ophthalmic history
- Concomitant medications
- Collect run-in vehicle/compliance assessment
- Urine pregnancy test (WOCBP only)
- Eye Dryness Score VAS
- Ocular Discomfort Score VAS
- Investigational product ASHRAE 7-point comfort VAS (pre-dose)
- Best-corrected VA OU
- Slit lamp biomicroscopy OU
- Corneal fluorescein staining OU
- First unanesthetized Schirmer's test OU (≥15 minutes post-CFS)
- Anesthetized Schirmer's test OU
- Intraocular pressure OU

- Randomization
- In-office IP administration OU (≥20 minutes post-CFS)
- Investigational product ASHRAE 7-point comfort VAS (5 ±2 minutes post-dose)
- Symptom Assessment in Dry Eye questionnaire (5 +10 minutes post-dose)
- Investigational product tolerability VAS (5 +10 minutes post-dose)
- Investigational product ASHRAE 7-point comfort VAS (15 ±2 minutes post-dose)
- Second unanesthetized Schirmer's test OU (≥20 ±5 minutes post-dose)Investigational product ASHRAE 7-point comfort VAS (30 ±5 and 60 ±5 minutes post-dose)
- Anesthetized Schirmer's test OU (post final Investigational Product ASHRAE 7-point comfort VAS)
- Dispense IP
- Adverse event assessment

7.5.3 Visit 3 (Day 8 ±1 day), Visit 4 (Day 15 ±2 days), and Visit 5 (Day 22 ±2 days)

Procedures should be conducted in the following order:

- Concomitant medications
- Collect IP/compliance assessment/dispense IP
- Eye Dryness Score VAS
- Ocular Discomfort Score VAS
- Investigational product ASHRAE 7-point comfort VAS (pre-dose)
- Best-corrected VA OU
- Slit lamp biomicroscopy OU
- Corneal fluorescein staining OU
- Unanesthetized Schirmer's test OU (≥15 minutes post-CFS)
- In-office IP administration OU (≥20 minutes post-CFS)
- Investigational product ASHRAE 7-point comfort VAS (5 ±2 minutes post-dose)
- Symptom Assessment in Dry Eye questionnaire (5 +10 minutes post-dose)
- Investigational product tolerability VAS (5 +10 minutes post-dose)
- Investigational product ASHRAE 7-point comfort VAS (15 ±2 minutes post-dose)

- Investigational product ASHRAE 7-point comfort VAS (30 ±5 and 60 ±5 minutes post-dose)
- Adverse event assessment

7.5.4 Visit 6/End of Study (Day 29 -3 to +1 days)

Procedures should be conducted in the following order:

- Concomitant medications
- Collect IP/compliance assessment/dispense IP
- Eye Dryness Score VAS
- Ocular Discomfort Score VAS
- Investigational product ASHRAE 7-point comfort VAS (pre-dose)
- Best-corrected VA OU
- Slit lamp biomicroscopy OU
- Corneal fluorescein staining OU
- First unanesthetized Schirmer's test OU (≥15 minutes post-CFS)
- In-office IP administration OU (⩾20 minutes post-CFS)
- Investigational product ASHRAE 7-point comfort VAS (5 ±2 minutes post-dose)
- Symptom Assessment in Dry Eye questionnaire (5 +10 minutes post-dose)
- Investigational product tolerability VAS (5 +10 minutes post-dose)
- Investigational product ASHRAE 7-point comfort VAS (15 ±2 minutes post-dose)
- Second unanesthetized Schirmer's test OU (⩾20 ±5 minutes post-dose)
- Investigational product ASHRAE 7-point comfort VAS (30 ±5 and 60 ±5 minutes post-dose)
- Anesthetized Schirmer's test OU (post final Investigational Product ASHRAE 7-point comfort VAS)
- Intraocular pressure OU to be performed post anesthetized Schirmer's
- Adverse event assessment

8 ADVERSE EVENTS

8.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a subject regardless of its causal relationship to the IP. An AE can be any unfavorable and unintended sign (including any clinically significant laboratory test result), symptom, or disease temporally associated with the use of the IP, whether or not it is considered related to IP administration. Included in this definition is any newly occurring event or previous condition that has increased in severity or frequency since the administration of the IP.

8.2 Definition of a Serious Adverse Event

An SAE is any AE occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or a substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly or birth defect in an offspring of a subject taking the IP
- Is an important medical event

The term ‘hospitalization’ refers to any surgery or treatment that requires a formal admission into the hospital regardless of length of stay. The term does not include an emergency room visit or admission to an outpatient facility.

The term ‘life-threatening’ refers to an event in which the subject was at immediate risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Important medical events are those that may not meet any of the criteria defined above; however, they may be considered serious when, based upon appropriate medical judgement, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the SAE definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3 Assessment of Relationship to Investigational Product or Procedure

The Investigator must determine the relationship (if any) between an AE and the IP or procedure, as applicable. The Investigator should decide whether, in their medical judgment, there is a reasonable possibility that the event may have been caused by the IP (IVW-1001 Ophthalmic Eyelid Wipe) or the administration procedure (execution of wiping the upper eyelid with the IP wipe). The Investigator should use the following classifications and criteria to characterize the relationship or association of the IP or procedure in causing or contributing to the AE:

- Unrelated – This relationship suggests that there is no association between the IP and the reported event

- Related – This relationship suggests that there is a reasonable possibility of association between the IP and the reported event

8.4 Assessment of Severity

The Investigator must use the following criteria to rate the intensity of the AE as mild, moderate, or severe. Adverse events will be reported at the highest intensity experienced.

- Mild: Symptoms causing no or minimal interference with usual social and functional activities
- Moderate: Symptoms causing greater than minimal interference with usual social and functional activities
- Severe: Symptoms causing inability to perform usual social and functional activities

8.5 Recording of Adverse Events

All AEs should be reported starting after the first IP dose is administered (during the run-in period) and through 30 days after last dose of IP. The Sponsor may request follow-up on any unresolved AEs within 30 days after the final study visit.

All conditions present prior to receiving the IP should be documented as medical history. Information to be collected includes type of event, date of onset, date of resolution, and Investigator-specified assessment of severity and relationship to the IP.

While an AE is ongoing, changes in the severity (eg, worsening and improving) should be noted in the source documents but, when documenting the AE, only the total duration and greatest severity should be recorded in the electronic case report form (eCRF). Adverse events characterized as intermittent require documentation of onset and duration.

Pre-existing conditions (present before the start of the AE collection period) are considered concurrent medical conditions and should NOT be recorded as AEs. If the subject, however, experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded as an AE. The Investigator should ensure that the AE term recorded captures the change in the condition (eg, 'worsening of ……').

Each AE should be recorded as a single diagnosis. Accompanying signs (including abnormal laboratory test values) or symptoms should NOT be recorded as additional AEs. Changes in laboratory test values are only considered to be AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the Investigator judges the change to be beyond the range of normal physiological fluctuation). If abnormal laboratory test values are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), only the diagnosis should be reported as an AE.

Pre-planned elective procedures (surgeries or therapies) known at the time of randomization that are performed to manage/treat conditions that existed prior to the subjects' enrolling in the study (eg, elective periodontal surgery, elective hernia repair) should not be recorded as AEs but should be documented in the subject's source documents. If a pre-planned procedure is performed early (eg, as an emergency) because the pre-existing condition worsens, the worsening condition should be captured as an AE.

8.6 Recording of Serious Adverse Events

The Investigator is responsible for reporting to the Sponsor or designee all SAEs that are observed or reported by the subject during the study regardless of their relationship to the IP or their clinical significance. All SAEs reported or observed during the study must be followed to resolution or until the Investigator deems the event to be chronic or the subject to be stable. The Sponsor or designee may contact the Investigator to obtain additional information on any SAE that has not resolved at the time the subject completes the study. The Investigator may wish to contact the medical monitor to discuss the details of an SAE.

Medical monitor contact information:

8.7 Reporting of Serious Adverse Events

Any AE that the Investigator considers serious according to the previously described criteria must be reported within 24 hours from the time when site personnel first learn about the event. Serious AEs occurring after the subject receives the first dose of the IP will be reported to the Sponsor or its representative. The SAE should be reported using the SAE Report Form within 24 hours of knowledge of the event. This can be done by emailing a completed SAE Report Form to:

Any additional information that becomes available later should be submitted through a follow-up report within 1 working day of receipt.

The Sponsor or designee will notify the regulatory agencies of any fatal or life-threatening unexpected events associated with the use of the IP as soon as possible but no later than 7 calendar days after the initial receipt of the information. Initial notification will be followed by a written report within the timeframe established by the appropriate regulatory agency. For SAEs that do not meet the fatal or life-threatening unexpected criteria but are reported to be associated with the use of the IP, the Sponsor or designee will notify the appropriate regulatory agencies in writing with the timeframe established by those regulatory agencies. The Sponsor or designee will provide copies of any reports to regulatory agencies regarding serious and unexpected SAEs to the Investigators for review and submission to their IRBs or Ethics Committees.

8.8 Pregnancy

If a subject becomes pregnant during the study or up until 30 days after the last dose of the IP, the Investigator must notify the Sponsor or its representative immediately. The Pregnancy Report Form should be completed within 24 hours of learning of the pregnancy and sent to the Sponsor or its representative. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Any complications during pregnancy

should be recorded as an AE and may constitute an SAE if they fulfill any of the specified criteria for an SAE. If upon outcome, the pregnancy meets one of the serious criteria (eg, spontaneous miscarriage, congenital anomaly, or birth defect), it will then be considered an SAE and full details will be requested.

8.9 Appropriateness of Measurements

The measures selected to assess signs and symptoms of DED as well as ocular and systemic safety are consistent with standard of care.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

The analysis of safety and efficacy will be performed after all subjects have completed the Day 29 Visit or been discontinued prior to Day 29, and after the study database has been cleaned, verified, and locked. It is planned that the data from all clinical sites participating in this study will be combined so that the target sample size will be available for analysis. For each efficacy parameter measured on a per-eye basis, the primary analysis will be done using data from the study eye (ie, the eye that satisfies all of the enrollment criteria). If both eyes satisfy all enrollment criteria, then a predefined method will be used to select the study eye (Section 6.1.2).

Analyses will be implemented using SAS® version 9.4 or later. More details regarding the analysis of the safety and efficacy data will be described in the Statistical Analysis Plan.

9.2 Determination of Sample Size

Approximately 150 subjects will be enrolled (50/group) in order to obtain approximately 138 subjects who complete the study (46/group). For the primary efficacy endpoint, this sample size of 46 subjects per group should provide at least 80% power to detect a difference between the placebo group and each of the IVW-1001 groups of 3.3 mm or greater, assuming a standard deviation (SD) of 5.0 mm and a 0.025 two-sided significance level.

9.3 Analysis Populations

The safety and tolerability endpoints will be analyzed using the Safety Set, and the primary and secondary efficacy endpoints will be analyzed using the mITT and Per Protocol (PP) Sets. The Safety and mITT Sets will include all randomized subjects who receive at least 1 dose of the IP. The PP Set will include all randomized subjects who meet all of the enrollment criteria and complete the efficacy evaluations at Day 29 without any significant protocol deviations that could impact the integrity of the data. As a sensitivity analysis, the primary and secondary efficacy endpoints will be analyzed using the PP Set.

For the Safety Set, subjects will be analyzed in the group according to the treatment received during the majority of the study, irrespective of the group to which they were randomized, and no subjects will be excluded from this study population because of protocol deviations. For the mITT Set, subjects will be analyzed in the group to which they were randomized, irrespective of what they actually received, and no subjects will be excluded from this study population because of protocol deviations. The analysis sets will be determined prior to unmasking the treatment assignments.

9.4 Demographics and Baseline Characteristics

Subject demographic and baseline disease characteristics will be summarized by treatment group for all subjects. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum), and categorical variables will be summarized using the count and percentage of subjects in each category.

9.5 Safety Analyses

The assessment of safety will be based on the summaries of ocular and non-ocular AEs and ophthalmic examination findings. Adverse events reported during the study will have their verbatim

terms mapped to the corresponding thesaurus terms from the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. All summaries of AEs will be based on the assigned MedDRA preferred term and system organ class, and summaries will be given for each of the randomized treatment groups.

Separate summaries of AEs related to treatment (as reported by the Investigator) and by severity will be prepared. The number of SAEs will also be presented, and events leading to discontinuation from the study will be listed and tabulated.

Other safety assessments will be presented descriptively (absolute values and changes from baseline). These will include BCVA, IOP, slit lamp biomicroscopy, dilated ophthalmoscopy, and tolerability assessment. Continuous variables will be summarized by descriptive statistics, and categorical variables will be summarized using the count and percentage of subjects in each category. Shift tables will be prepared by treatment group showing all categorical changes from baseline to each study visit.

9.6 Efficacy Analyses

In this exploratory study, several measures of efficacy are being evaluated at the study visits. The populations will include mITT and PP Sets. In general, the high dose (0.2%) will be compared to vehicle, then the low dose (0.1%) will be compared to vehicle. The final on-drug visit, Week 4/EOS, will be evaluated, and then the other visits. Missing data for the test score will be imputed using last observation carried forward. From a statistical perspective, evaluations include:

- Unanesthetized Schirmer's test (mean change from baseline at Week 4/EOS)
- Unanesthetized Schirmer's tests (mean change from baseline at Weeks 1, 2, and 3)
- Visual analog scale of IP ASHRAE 7-point comfort (mean change from baseline)
- Visual analog scale of EDS (mean change from baseline)
- Visual analog scale of ODS (mean change from baseline)
- Symptom Assessment in Dry Eye (mean change from baseline)
- Corneal fluorescein staining (inferior zone) (mean change from baseline)
- Corneal fluorescein staining (total of all zones) (mean change from baseline)
- Anesthetized Schirmer's test (mean change from baseline)
- Anesthetized Schirmer's test (proportion of subjects with ≥10 mm increase)
- Unanesthetized Schirmer's test (proportion of subjects with ≥10 mm increase)

Each endpoint will be presented descriptively by visit (absolute values and changes from baseline as appropriate). Variables will be summarized by descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum).

The efficacy parameters will be analyzed using appropriate statistical methods (eg, mixed-effects models for repeated measures, analysis of covariance, etc.) to compare IVW-1001 to vehicle. Appropriate methods will be used to control the Type I error rate for multiple comparisons of the 2 dose groups versus the control group.

10 QUALITY CONTROL AND ASSURANCE

Investigators will be trained by the Sponsor or designee prior to conducting study activities and are responsible for training site staff to whom they delegate authority to conduct any study-related procedures.

Routine study monitoring will be conducted at each site at appropriate intervals to assure accurate, consistent, complete, and reliable data.

The Sponsor or designee may conduct site quality assurance audits at their discretion.

11 REGULATORY AND ETHICAL CONSIDERATIONS

11.1 Institutional Review Board

This protocol, the informed consent document, and all subject recruitment or advertising must be submitted to the IRB for review and must be approved before clinical use. Any amendments to the protocol must also be approved by the IRB prior to implementing changes in study conduct. The Investigator is responsible for keeping the IRB apprised of the progress of the study, SAEs, and any changes made to the protocol according to the requirements of the site's IRB.

11.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and are consistent with ICH/GCP and applicable regulatory requirements.

11.3 Subject Information and Consent

The subject must sign the ICF before participation in the study; once the ICF is signed, the subject is enrolled in the study. A copy of the ICF must be provided to the subject or the subject's legal guardian. Each subject will receive oral and written information about the study in their functional language, given the opportunity to ask questions, and allowed time to consider the information provided.

11.4 Subject Confidentiality

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is strictly prohibited. Information obtained during the conduct of this study will be used by IVIEW Therapeutics, Inc. in connection with the development of the IP. The study Investigator is obliged to provide IVIEW Therapeutics, Inc. or designee with complete test results and all data developed in this study. This information may be disclosed to other physicians who are participating in this trial, and to the US Food and Drug Administration (FDA) as deemed necessary by IVIEW Therapeutics, Inc. Subject-specific information may be provided to other appropriate medical personnel only with the subject's permission.

Subjects will provide consent to the disclosure of protected health information as required under the Health Information Portability and Accountability Act (HIPAA).

12 ADMINISTRATIVE CONSIDERATIONS

12.1 Access to Source Documentation

Study monitoring visits will be conducted by an authorized Sponsor representative to inspect study data, participants' medical records, and eCRFs in accordance with current GCP and the respective local, national government, and international regulations and guidelines.

The Investigator will permit authorized representatives of the Sponsor or its representative, the FDA, and any appropriate health authorities to inspect facilities and records relevant to this study.

12.2 Retention of Data

The Principal Investigator must maintain all study records according to ICH guidelines and according to the record retention policies of the country in which the study is being conducted. The FDA requires that records be retained for at least 2 years after the last marketing application approval, or if not approved, 2 years after the FDA has been notified of the discontinuance of the investigational use of the IP (21 CFR 312.57).

12.3 Study Termination

This study may be terminated by the Sponsor if deemed appropriate.

12.4 Financial Disclosure

Investigators will comply with applicable financial disclosure requirements in the country in which the study is being conducted.

12.5 Publication and Disclosure Policy

The Sponsor has proprietary interest in this study. Any authorship and manuscript composition resulting from the study will reflect cooperation between the Sponsor and multiple Investigators. Authorship will be established prior to the writing of the manuscript. No individual publication will be allowed prior to completion of the final study report except as agreed with the Sponsor.

13 REFERENCE LIST

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14 APPENDICES

Appendix 1 Schedule of Events

Study Period	**Screening [a]**	**Baseline/ Randomization [b]**	**Week 1 [b]**	**Week 2 [b]**	**Week 3 [b]**	**Week 4/ EOS/ET [b]**
Visit	**1**	**2**	**3**	**4**	**5**	**6**
Procedures Visit Timing (Window)	**Day -7 to 1 (+2)**	**Day 1**	**Day 8 (±1)**	**Day 15 (±2)**	**Day 22 (±2)**	**Day 29 (-3 to +1)**
Informed consent	X					
Eligibility determination (inclusion/exclusion criteria)	X	X				
Demographics	X					
Medical/Ophthalmic history	X	X				
Concomitant medications	X	X	X	X	X	X
Urine pregnancy test (WOCBP only [c])	X	X				
EDS VAS	X	X	X	X	X	X
ODS VAS	X	X	X	X	X	X
IP ASHRAE 7-point comfort VAS [d]	X	X	X	X	X	X
BCVA (and refraction [e]) OU	X	X	X	X	X	X
Slit lamp biomicroscopy OU	X	X	X	X	X	X
Corneal fluorescein staining OU	X	X	X	X	X	X
Unanesthetized Schirmer's test OU [f, g]	X [f, g]	X [f, g]	X [f]	X [f]	X [f]	X [f, g]
Anesthetized Schirmer's test OU [h, i]		X [h, i]				X [i]
IOP OU	X	X				X [j]
Randomization/assignment	X[k]	X				
In-office IP administration OU [l]	X	X [l]	X [l]	X [l]	X [l]	X [l]
SANDE questionnaire [m]	X	X	X	X	X	X
IP tolerability VAS [m]	X	X	X	X	X	X
Fundoscopy (dilated ophthalmoscopy) OU	X					X
Dispense/Return IP with accountability/compliance	X	X	X	X	X	X

Study Period	**Screening [a]**	**Baseline/ Randomization [b]**	**Week 1 [b]**	**Week 2 [b]**	**Week 3 [b]**	**Week 4/ EOS/ET [b]**
Visit	**1**	**2**	**3**	**4**	**5**	**6**
Procedures **Visit Timing (Window)**	**Day -7 to 1 (+2)**	**Day 1**	**Day 8 (±1)**	**Day 15 (±2)**	**Day 22 (±2)**	**Day 29 (-3 to +1)**
AE assessment	X	X	X	X	X	X

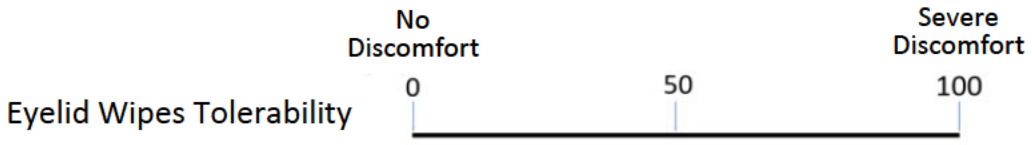
AE, adverse event; BCVA, best-corrected visual acuity; EDS, Eye Dryness Score; EOS, End of Study; ET, Early Termination; IOP, intraocular pressure; IP, investigational product; ODS, Ocular Discomfort Score; OU, both eyes; SANDE, Symptom Assessment in Dry Eye; VAS, visual analog scale; WOCBP, women of childbearing potential.
[a] The Screening Visit can occur any time of the day.
[b] The Baseline, Week 1, Week 2, Week 3, and EOS Visits should be conducted **between 7:00 am and 12:00 pm**.
[c] All WOCBP must have a negative pregnancy test result at Screening Visit 1 and Baseline Visit 2 prior to randomization in the study.
[d] IP ASHRAE 7-point comfort VAS to be performed pre-dose and 5 ±2, 15 ±2, 30 ±5, and 60 ±5 minutes post-dose, unless the score at 5 and 15 minutes is 0, in which case the 30- and 60-minute assessments can be omitted.
[e] Refraction at Visit 1 only unless ≥ 3 line reduction in VA.
[f] Unanesthetized Schirmer's to be performed at least 15 minutes post-CFS.
[g] Unanesthetized Schirmer's to be performed 20 ±5 minutes post-IP administration.
[h] Anesthetized Schirmer's to be performed after unanesthetized Schirmer's.
[i] Anesthetized Schirmer's to be performed post final IP ASHRAE 7-point comfort VAS. [j] IOP to be performed post anesthetized Schirmer's.
[k] Assignment of run-in IP (vehicle).
[l] IP administration must be performed at least 20 minutes after completion of CFS. Subjects should not dose IP at home the morning of Visits 2, 3, 4, 5, or 6.

[m] SANDE questionnaire and IP tolerability VAS to be performed between 5 and 15 minutes post-dose.

Appendix 2 Investigational Product Tolerability Visual Analog Scale

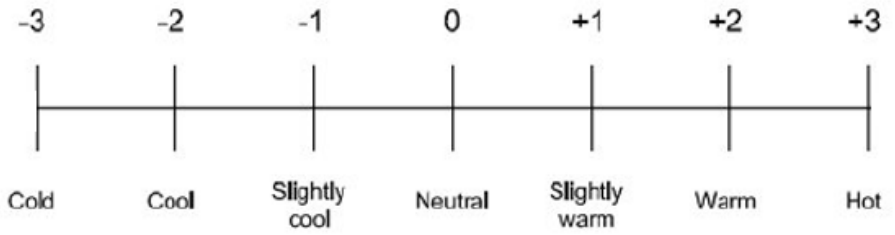
Representation of the IP Tolerability VAS. Subjects will grade the tolerability of IP after administration on a scale of 0 (no discomfort) to 100 (severe discomfort) by placing a vertical mark on the horizontal line. Study staff will measure and record the VAS.

Instructions: Please review the tolerability of the eyelid wipes. Rate how your eyes feel by drawing a single vertical mark through the horizontal line.



Appendix 3 Investigational Product ASHRAE 7-Point Comfort Visual Analog Scale

Representation of the IP ASHRAE 7-Point Comfort VAS. Subjects will rate the comfort of the eyelid wipes using the ASHRAE 7-point scale (-3 to +3) by placing a vertical mark on the horizontal line. Study staff will measure and record the VAS.



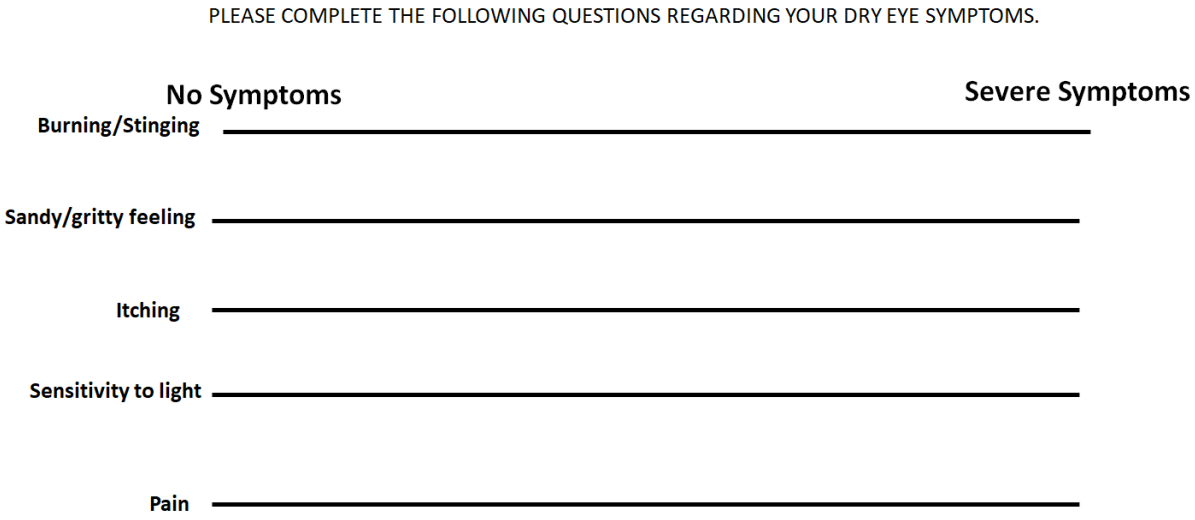
Appendix 4 Eye Dryness Score Visual Analog Scale

Representation of the EDS VAS. Subjects will grade their symptoms on a scale of 0 (no symptoms) to 100 (severe symptoms) by placing a vertical mark on the horizontal line. Study staff will measure and record the VAS score.

Instructions: Please review your eye dryness. Rate how your eyes feel at this **moment** by drawing a single vertical mark through the horizontal line that represents how your eyes feel.

Appendix 5 Ocular Discomfort Score Visual Analog Scale

Representation of the ODS VAS. Subjects will grade their symptoms at this moment on a scale of 0 (no symptoms) to 100 (severe symptoms) by placing a vertical mark on the horizontal line. Study staff will measure and record the VAS score.



Appendix 6 Symptom Assessment in Dry Eye Questionnaire

Subjects will grade their symptoms **over the past week** on a scale of 0 to 100 by placing a vertical mark on the horizontal line. Study staff will measure and record the VAS score.

SAnDE QUESTIONNAIRE

PLEASE COMPLETE THE FOLLOWING QUESTIONS REGARDING THE FREQUENCY AND SEVERITY OF YOUR DRY EYE SYMPTOMS.

Frequency of symptoms:

Place a vertical mark on the line to indicate how often, on average, your eyes feel **dry and/or irritated:**

Rarely ——— **All the time**

Severity of symptoms:

Place a vertical mark on the line to indicate how severe, on average, you feel your symptoms of **dryness and/or irritation:**

Very Mild ——— **Very Severe**

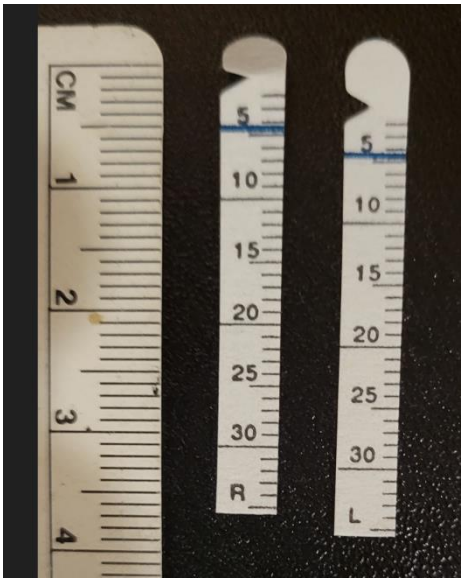
Appendix 7 Unanesthetized Schirmer's Test

Initiate unanesthetized Schirmer's Test in each eye at least 15 minutes after CFS at all visits.

At Visits 1, 2, and 6 initiate additional unanesthetized Schirmer's test OU at least 20 ±5 minutes after Investigational Product dose).

Unanesthetized Schirmer's test instructions:

- While still inside the plastic sheath, fold the rounded end of the Schirmer's test strip at the first line on the strip (closest to the rounded end).
- Remove the right eye strip from the sheath.
- Ask the subject to look up and gently draw the right lower lid of the unanesthetized eye in a downward and temporal direction.
- Place the rounded end of the strip toward the temporal one-third of the lower eyelid.
- Repeat this procedure in the left unanesthetized eye.
- Darken the room.
- Instruct the subject to focus on the 20/400 E letter on the eye chart.
- Start the timer.
- Remove strips after 5 minutes.
- After removing the strips, place each strip on a flat surface beside a ruler.
- Visualize the leading edge and the lowest point of moisture and, using the ruler, measure a point halfway between the 2 points. Record this value as the amount of wetting.
- Retain Schirmer's test strips in source documentation for confirmatory measurement purposes.



Appendix 8 Fluorescein Solution Administration Using Strips

Use Sponsor-supplied unpreserved sterile saline (if not available, unpreserved sterile water may be used) to moisten the dye on the fluorescein-impregnated strip supplied by the Sponsor.

Remove any excess fluid by shaking fluid from the strip to ensure a consistent amount of dye is dispensed at each assessment.

Instill the dye onto the inferior cul-de-sac of the first eye by touching the strip to the palpebral conjunctiva. Wait approximately 1 minute. Repeat the procedure for the second eye using the same strip. Ask the subject to blink several times to spread the dye.

For corneal fluorescein staining, assess the staining approximately 2 to 2½ minutes after the dye instillation.

The 1-minute waiting period between dye instillation into each eye will allow the evaluator to complete the assessment of the first eye before the 2- to 2½-minute waiting period has elapsed after dye instillation in the second eye.

Use a slit lamp with cobalt blue illumination (465–490 nm) and a Wratten #12 yellow filter to improve the ability to grade fluorescein staining. Grade the 5 areas of the cornea according to the scale for each zone (Appendix 9).

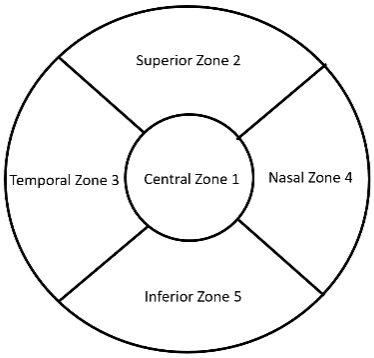
Appendix 9 Corneal Fluorescein Staining Grading

This scale is modified from the corneal grading scale presented in the Tear Film & Ocular Surface Society Dry Eye Workshop II report (Wolffsohn 2017).

Expanded NEI/Industry Workshop model (Lemp 1995):

- Cornea is divided into five (5) zones: inferior, nasal, central, temporal, superior; the central zone diameter should be 1/3 the cornea diameter with the 4 equally sized outer zones.

Example of right eye region, expanded NEI/Industry Workshop Model



- Score each zone using a scale of 0 to 4 based upon the PREDOMINANT finding within the zone. Note: The presence of an isolated small area of coalescent staining should be graded according to the predominant appearance in the entire zone.
    - 0= no staining
    - 1= few/rare punctate lesions
    - 2= discrete and countable lesions
    - 3= lesions too numerous to count, but not coalescent
    - 4= coalescent
- Total maximum score equals 20

Appendix 10 Anesthetized Schirmer's Test

Perform anesthetized Schirmer's Test after unanesthetized Schirmer's Test at Visit 2.

Perform anesthetized Schirmer's Test after the final IP ASHRAE 7-point comfort VAS (Visits 2 and 6).

Anesthetized Schirmer's test instructions:

- Instill proparacaine 0.5% drops bilaterally.
- Blot excess from ocular cul-de-sac and periorbital area; wait 5 minutes.
- While still inside the plastic sheath, fold the rounded end of the Schirmer's test strip at the first line on the strip (closest to the rounded end).
- Remove the right eye strip from the sheath.
- Ask the subject to look up and gently draw the right lower lid of the anesthetized eye in a downward and temporal direction.
- Place the rounded end of the strip toward the temporal one-third of the lower eyelid.
- Repeat this procedure in the left anesthetized eye.
- Darken the room.
- Instruct the subject to focus on the 20/400 E letter on the eye chart.
- Start the timer.
- Remove strips after 5 minutes.
- After removing the strips, place each strip on a flat surface beside a ruler.
- Visualize the leading edge and the lowest point of moisture and, using the ruler, measure a point halfway between the 2 points. Record this value as the amount of wetting.
- Retain Schirmer's test strips in source documentation for confirmatory measurement purposes.

Appendix 11 Sponsor Approval Signature

Study Title: Phase 1/2a, Proof-of-Concept, Multicenter, Parallel, Vehicle-Controlled, Double-Masked, Randomized Study Evaluating the Safety, Tolerability, and Efficacy of IVW-1001 Ophthalmic Eyelid Wipe in Subjects With Dry Eye Disease

Study Number: IVW-1001-CS-101

Version: 1.1

Final Date: 17 April 2024

This clinical study protocol has been approved by the Sponsor.

[redacted]

[redacted].

[redacted]

Appendix 12 Investigator's Signature

Study Title:	Phase 1/2a, Proof-of-Concept, Multicenter, Parallel, Vehicle-Controlled, Double-Masked, Randomized Study Evaluating the Safety, Tolerability, and Efficacy of IVW-1001 Ophthalmic Eyelid Wipe in Subjects With Dry Eye Disease
Study Number:	IVW-1001-CS-101
Version:	1.1
Final Date:	10 April 2024

By signing below, the Investigator agrees to adhere to the protocol as outlined and agrees that any changes to the protocol must be approved by IVIEW Therapeutics, Inc. prior to seeking approval from the Institutional Review Board.

The Investigator also agrees to conduct the study in accordance with current United States Food and Drug Administration regulations, International Council for Harmonisation guidelines, Good Clinical Practice standards, the Declaration of Helsinki, and local ethical and legal requirements.

Investigator Signature:_____

Date:_____

Printed Name:_____

Name of Institution:_____