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: 6 November 2024

STATISTICAL ANALYSIS PLAN

Protocol 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 (Version 1.1, 17 April 2024)
Compound Number:	IVW-1001
Short Title:	IVW-1001 Ophthalmic Eyelid Wipes in Subjects With Dry Eye Disease
Sponsor Name:	IVIEW Therapeutics, Inc.
Legal Registered Address:	[redacted]
[redacted]	[redacted]
Registry ID:	NCT06400459

SIGNATURE PAGE

Protocol 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 (Version 1.1, 17 April 2024)
Date of Plan:	06 November 2024
Version:	1.1 (Final)

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VERSION HISTORY

This statistical analysis plan (SAP) for IVW-1001-CS-101 is based on the protocol dated 17 April 2024.

SAP Version	***Date***	***Change***	***Rationale***
1.1	*06 Nov 2024*	*Not applicable*	*Original version*

ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AE	Adverse Event
AIC	Akaike's Information Criterion
AR(1)	First-Order Autoregressive
ASHRAE	American Society of Heating, Refrigerating and Air-Conditioning Engineers
ATC	Anatomical-Therapeutic-Chemical
BCVA	Best-Correct Visual Acuity
CFB	Change from Baseline
CFS	Corneal Fluorescein Staining
CS	Compound Symmetry
DED	Dry Eye Disease
eCRF	Electronic Case Report Form
EDS	Eye Dryness Score
EOS	End of Study
FE	Fellow Eye
ICH	International Council for Harmonisation
IOP	Intraocular Pressure
IP	Investigational Product
IWRS	Interactive Web Response System
LogMAR	Logarithm of the Minimum Angle of Resolution
MedDRA®	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-To-Treat (Population)
MMRM	Mixed Model for Repeated Measures
N or n	Number of observations
NEI	National Eye Institute
OD	Oculus Dexter (Right eye)
ODS	Ocular Discomfort Score
OS	Oculus Sinister (Left eye)
OTC	Over-the-Counter
OU	Oculus Uterque (Both eyes)
PP	Per-Protocol (Population)

Abbreviation	Definition
PT	Preferred Term
QID	4 times daily
SAE	Serious Adverse Event
SAF	Safety (Population)
SAnDE	Symptom Assessment in Dry Eye
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Study Eye
SOC	System Organ Class
TBUT	Tear Film Break-up Time
TEAE	Treatment-Emergent Adverse Event
US	United States
VAS	Visual Analog Scale
VC	Variance Components
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential

1. INTRODUCTION

This statistical analysis plan (SAP) for study IVW-1001-CS-101 describes the endpoints, datasets, and analyses planned for the safety and efficacy data of this study. The variables and methods described in this plan supersede those described in the protocol. If revisions are needed after finalizing, then this document will be amended. All SAP amendments will be finalized prior to locking the database and unmasking of the treatment codes to the sponsor. All deviations from the analyses described in the final SAP will be noted in the clinical study report.

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).

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 topical doses 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 Phase 1/2a study, IVW-1001 Ophthalmic Eyelid Wipes are 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. Tweezers are also provided 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).

2. STUDY DESCRIPTION

2.1. Objectives, Endpoints, and Estimands

Objectives and Endpoints

Objectives	Measures
Primary Safety	
To assess the safety of IVW-1001 Ophthalmic Eyelid Wipes in subjects with DED	• Mean change from baseline in: o Best-corrected visual acuity (BCVA) o Slit lamp biomicroscopy o Intraocular pressure (IOP) o Dilated ophthalmoscopy • Visual analog scale (VAS) of investigational product (IP) tolerability • Adverse Events (AEs)
Primary Efficacy	
To assess the efficacy of IVW-1001 Ophthalmic Eyelid Wipes in subjects with DED	• Mean change from baseline at Day 29 (Week 4/EOS) in the study eye in the unanesthetized Schirmer's test
Exploratory Efficacy	
To further assess the efficacy of IVW-1001 Ophthalmic Eyelid Wipes with respect to other exploratory efficacy endpoints	• Mean change from baseline in the study eye at each visit assessed in: o Unanesthetized Schirmer's test (Weeks 1, 2, and 3) o VAS of IP comfort (ASHRAE 7-point scale) o VAS of Eye Dryness Score (EDS) o VAS of Ocular Discomfort Score (ODS) o Symptom Assessment in Dry Eye (SAnDE) questionnaire o Corneal fluorescein staining (inferior zone) o Corneal fluorescein staining (total of all zones)

	○ Anesthetized Schirmer's test • Proportion of subjects with a ≥10 mm increase in unanesthetized Schirmer's test score • Proportion of subjects with a ≥10 mm increase in anesthetized Schirmer's test score

Primary Estimand:

The estimand for the primary efficacy endpoint in this study is:

- The difference between IVW-1001 and Vehicle in the mean change from baseline at Day 29 (Week 4) in the study eye in the unanesthetized Schirmer's test score estimated using all data collected from the mITT population.

2.2. Study Design

Protocol IVW-1001-CS-101 is a Phase 1/2a study designed to evaluate the safety, efficacy and tolerability of IVW-1001 Ophthalmic Eyelid Wipe in subjects with DED. It is a randomized (1:1:1), multicenter, parallel, vehicle-controlled, double-masked study. The study includes treatment-experienced subjects, with a focus on those with a prior suboptimal response to artificial tear therapy. A total of 150 subjects will be randomized to one of the following treatments:

- IVW-1001 Ophthalmic Eyelid Wipe 0.2% (High Dose)
- IVW-1001 Ophthalmic Eyelid Wipe 0.1% (Low Dose)
- IVW-1001 Ophthalmic Eyelid Wipe Placebo (Vehicle)

The study is divided into 2 sections:

1. A 7-day single, subject-masked vehicle run-in period
2. A 28-day, active, double-masked treatment period, commencing on Day 1, the date of treatment assignment and initial treatment administration

Subjects will self-administer the treatment twice daily to the upper eyelid of both eyes for the 28-day section of the study, excluding the mornings of Visits 3, 4, 5 and 6 (Days 8, 15, 22 and 29) when the dose will be self-administered with study staff oversight. Subjects will not be eligible for rescue treatment during the study.

2.3. Schedule of Activities and Visit Windows

The structure and exam schedule of each phase of the study is outlined below in Table 1.

Visit windows indicated are intended to provide structure for the study. Any data collected during out-of-window visits will not be excluded, but will be evaluated as a part of the analysis, when appropriate, and will be included in the subject data listings.

Table 1. Schedule of Activities

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
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.

2.3.1. Study Day Definition

In addition to visit date, study day will be calculated for each visit date as a continuous representation of visit timing. The study day of an event is defined as the relative day of the event, starting with the date of the first study drug administration (reference date) as Day 1 (there will be no Day 0).

The study day of events occurring before the first study drug administration will be calculated as:

Study Day = (Date of Event – Date of First Study Drug Administration)

For events occurring on or after Day 1, study day will be calculated as:

Study Day = (Date of Event – Date of First Study Drug Administration) + 1

Note: Study days will only be calculated for events with complete dates and will be undefined for events that are 'Ongoing' at the end of the study.

2.4. Study Treatments, Randomization and Masking

Central randomization using an Interactive Web Response System (IWRS) will be utilized to provide assignment of a specific anonymized code, corresponding to the IP to which the subject is randomized at the baseline visit.

A total of 150 subjects will be randomized to one of the following treatments:

- IVW-1001 Ophthalmic Eyelid Wipe 0.2% (High Dose)
- IVW-1001 Ophthalmic Eyelid Wipe 0.1% (Low Dose)
- IVW-1001 Ophthalmic Eyelid Wipe Placebo (Vehicle)

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

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.

2.4.1. 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 appropriate.

2.5. Study Eye Selection

While both eyes (OU) will be dosed with the IP, a study eye (SE) will be designated by the Data Management team at the baseline visit, following the process below:

- If both eyes have an unanesthetized Schirmer's score between 5-10 mm inclusive, the SE will be the eye with the lower score.

- If both eyes have the same unanesthetized Schirmer's score, the SE will be the eye with the highest qualifying total corneal fluorescein staining (CFS) score.
- If both eyes have the same total CFS score, the right eye (OD) will be designated as the SE.

3. HYPOTHESIS, SAMPLE SIZE AND POWER

3.1. Statistical Hypothesis

The primary efficacy endpoint is the mean change from baseline (CFB) at Day 29 (Week 4/EOS) in the SE in the unanesthetized Schirmer's test.

The clinical hypothesis is that IVW-1001 Ophthalmic Eyelid Wipe administered BID bilaterally for 29 days is more effective than Vehicle when evaluating tear production in subjects with DED.

The following 2-sided hypothesis will be tested:

H_0: $\Delta = 0$

H_a: $\Delta \neq 0$

Where Δ is the difference in mean CFB in the unanesthetized Schirmer's score as measured at Day 29 (Week 4) between the IVW-1001 Ophthalmic Eyelid Wipe and Vehicle treated groups.

In brief, the null hypothesis indicates that the mean CFB in the unanesthetized Schirmer's score as measured at Day 29 for subjects treated with IVW-1001 Ophthalmic Eyelid Wipe 0.2% or IVW-1001 Ophthalmic Eyelid Wipe 0.1% will not differ from the mean CFB in the unanesthetized Schirmer's score for subjects treated with Vehicle. The alternative hypothesis indicates that there is a significant difference at Day 29 between subjects treated with IVW-1001 Ophthalmic Eyelid Wipe and subjects treated with Vehicle.

3.2. Sample Size and Power

Approximately 150 subjects will be enrolled (50/group) 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 vehicle group and each of the IVW-1001 groups of 3.0 mm or greater in the unanesthetized Schirmer's test, assuming a standard deviation (SD) of 5.0 mm and a 0.05 two-sided significance level.

3.3. Multiplicity Adjustment

Due to the early phase of the study and because the primary objective is the assessment of safety, there will be no adjustments for multiplicity in the testing of the efficacy endpoints.

4. ANALYSIS POPULATIONS

Three analysis populations will be defined for this study: Safety (SAF), modified Intent-to-Treat (mITT) and Per-Protocol (PP). The determination of which subjects will be included in each population will be determined prior to the final database lock and unmasking of treatment codes. The analysis populations in this study will be defined as follows:

4.1. Safety (SAF)

All subjects who receive at least one (1) dose of the IP will be included in the SAF population. This is the population that will be used for all safety and AE analyses. Subjects will be analyzed in the treatment arm according to the IP they received, regardless of the group they were randomized to, and no subjects (or data) will be excluded due to protocol deviations that occur during the study.

4.2. Modified Intent-to-Treat (mITT)

All randomized subjects who receive at least one (1) dose of the IP will be included in the mITT population. The mITT will be the population used for the efficacy analyses. Subjects will be analyzed according to the treatment arm assigned at randomization, irrespective of compliance or any deviations in the study drug received. In addition, no subjects (or data) will be excluded due to protocol deviations that occur during the study.

4.3. Per-Protocol (PP)

The PP population will include all mITT subjects who meet all of the enrollment criteria and complete the efficacy evaluations at Day 29 without any major protocol deviations that have been deemed to affect the efficacy assessments. Significant deviations may include poor compliance, use of a prohibited concomitant drug, etc. The determination of all protocol deviations and any subjects excluded from the PP population will be made prior to locking the final database.

The PP population will be evaluated as a sensitivity analysis for the primary efficacy endpoint.

5. MISSING DATA

If a baseline value is missing, then the screening value will be carried forward and imputed to baseline if a screening value exists. If a baseline value is missing and there is more than one screening value, then the value taken on the date closest to the baseline date will be used.

For the SAF, mITT and PP populations, only observed data will be included and no outcome data will be imputed for missing values. This includes the primary and exploratory efficacy endpoints.

5.1. Conversion of Categorical Values

In some instances, continuous variables are expressed as a range (i.e., <10). In such cases, values may be converted to the range boundary (upper or lower limit as applicable). For example, a value of <10 may be converted to 10. Any adjustments made in this scenario will be clearly documented in the footnotes of relevant outputs.

6. GENERAL STUDY ASSESSMENTS

Study assessments and their schedules are presented in Section 2.3, Table 1. For more details on the assessments and procedures, please refer to the study protocol.

6.1. Disposition

Population: All Subjects

Subject disposition will include the following information, tabulated by treatment arm:

- Number and percentage of subjects who were:
    - Screened
    - Screen failed at Visit 1
    - Screen failed at Visit 2
    - Randomized
    - Treated
    - Withdrawn
    - Completed the study and completed each visit

  Note: For the subjects treated with study drug, withdrawn, completing the study, and completing each visit, percentages will be calculated based on total number of subjects randomized.
- Populations outlined in Section 4 will be described by treatment arm, with percentages based on the total number randomized.
- Subjects who are withdrawn from the study and the reason for withdrawal will be tabulated and listed for all randomized subjects. Summaries will include the number and percentage of subjects within each treatment arm. Reasons will include the following:
    - A serious or intolerable AE
    - A clinically significant change in systemic health
    - Sponsor or Investigator terminated the study
    - Subject requested to be discontinued from the study
    - Other

6.2. Protocol Deviations

Population: All Randomized Subjects

Protocol deviations will be summarized and listed by treatment arm and deviation type (study visit window, study drug, etc.) for all randomized subjects. Out-of-window protocol deviations will be evaluated on a case-by-case basis.

6.3. Demographic and Baseline Information

Population: All Randomized Subjects

Demographic and baseline characteristics will be summarized by treatment arm. Demographic variables will include age, sex, race, ethnicity, and iris color.

Disease-specific baseline variables will include summaries at Day 1 of the SE for the following parameters:

- Unanesthetized Schirmer's Test
- Anesthetized Schirmer's Test
- VAS of IP Comfort (ASHRAE 7-Point Scale)
- VAS of Eye Dryness Score
- VAS of Ocular Discomfort Score
- SAnDE Scores (assessed OU)
- Inferior CFS Score
- Total CFS Score
- BCVA (LogMAR Score)
- IOP (mmHg)

Continuous variables will be summarized using descriptive statistics, including the n, mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized using counts and percentages of subjects.

It is assumed that the randomization plan used in this study will minimize differences between treatment arms with respect to the demographic and baseline characteristics. Baseline comparability between treatment arms will be assessed via descriptive statistics.

6.4. Medical and Ocular History

Population: SAF

Significant, relevant medical history will be recorded at Screening.

All medical and ophthalmic histories reported at Screening will have their verbatim term mapped to their corresponding thesaurus terms using version 27.1 of the Medical Dictionary for Regulatory Activities (MedDRA®) coding dictionary. All summaries will be based on the assigned MedDRA Preferred Term (PT) and System Organ Class (SOC), and summaries will be provided by treatment arm. Separate summaries will be created for the medical (non-ocular) and ophthalmic histories. For ophthalmic histories, separate summaries will be created for the SEs and fellow eyes (FEs).

Results will be reported as subject incidence counts (number and percentage of subjects) within each PT and SOC. If a subject has more than one history that was coded to the same PT and SOC, then the subject will only be counted once for that PT and SOC.

6.5. Concomitant Medications

Population: SAF

All concomitant medications and procedures listed on the electronic case report form (eCRF)

will be provided in data listings.

Each medication will be mapped to its corresponding thesaurus terms (Anatomical-Therapeutic-Chemical [ATC] Class and Standardized Medication Name) from the January 2024 version of the World Health Organization (WHO) Drug Dictionary. A subject incidence count summary table (i.e., number and percentage of subjects) of all concomitant medications used during the study, sorted by ATC Class and Standardized Name, will be provided by treatment arm. For incidence count reporting, if a subject has more than one medication that is coded to the same Standardized Name and ATC Class, then the subject will only be counted once for that Standardized Name and ATC Class.

7. ANALYSIS OF ENDPOINTS

7.1. General Considerations

Summary statistics for the data collected during this study will be presented to give a general description of the subjects studied. Data from all sites will be combined in the computation of these descriptive summaries. Categorical variables will be summarized by the frequency and percentage of subjects in each category. Unless otherwise noted, the denominator to determine the percentage of subjects in each category will be based on the number of subjects with available data. When appropriate, comparisons on categorical data will be analyzed using the Cochran-Mantel-Haenszel or Fisher's exact test. Continuous variables will be summarized using N, mean, standard deviation (SD), median, minimum, and maximum values, and will be analyzed comparatively using the methodologies outlined under the primary and exploratory efficacy considerations (Sections 7.3 and 7.4) when appropriate.

For the descriptive statistics, minimum and maximum values will be calculated to the same number of decimal places as the source data. Means, medians and confidence limits will be calculated to one more decimal place than the source data. Standard deviations will be calculated to two more decimal places than the source data. Percentages will be calculated to the nearest one decimal place.

Unless otherwise specified or the parameter is evaluated OU, efficacy analyses will be performed on the SE only. Ocular safety summaries will be presented separately for the SE and the fellow eye (FE).

Efficacy variables will be summarized descriptively at each visit (where assessed) for both the SE and FE, and analyzed using appropriate statistical methods. The exam performed at Visit 2 (Day 1) will be used as baseline. If the assessment is missing or not evaluated on Day 1, the screening exam will be used, if available. Data from all clinical sites will be pooled so that the target sample size is available for analysis.

Treatment-group comparisons will include IVW-1001 Ophthalmic Wipe 0.2% vs. Vehicle and IVW-1001 Ophthalmic Wipe 0.1% vs. Vehicle for the primary and exploratory efficacy endpoints. Statistical tests will be presented as two-sided p-values rounded to four decimal places; p-values less than 0.0001 will be presented as '<0.0001' and p-values = 1 will be presented as '>0.999' in all tables. Efficacy analyses will be carried out using a two-sided, $\alpha = 0.05$ significance level without adjustments for multiplicity, as this is a Phase 1/2a study.

All data collected in this study will be presented in individual data listings for all subjects.

7.1.1. Efficacy Analyses Specific Considerations

For all efficacy parameters, descriptive statistics will be presented as outlined in Section 7.1. A basic statistical model assessment will be done for all parameters, where appropriate, including but not limited to, the Shapiro-Wilk test to confirm normality of the data, and residual assessment for independence, lack of fit, and equality of variance.

Departures from normality will be addressed by first assessing for multiple distributions in the data through the generation of histograms, and for potential outliers by boxplot creation. Outliers will be discarded if the values are deemed impossible for the assessment, or there is independent

evidence that the observation is incorrect and there is no information to correct the error. Other apparent outliers will be noted but not discarded. One of the following transformations, applied as appropriate, may be employed:

- If data are skewed, it will be transformed by a log or square root transformation
- If data is relatively normal with a few unexplained outliers, it will be analyzed with and without identified outliers as an ad-hoc sensitivity analysis
- If normalization cannot be achieved via transformation methods, non-parametric analysis methodology will be used

7.2. Primary Safety Endpoint Assessments and Analysis

The primary objectives for this study are to investigate the safety and tolerability of the IVW-1001 Ophthalmic Wipe based on the following safety endpoints:

- CFB in BCVA, slit lamp biomicroscopy, IOP and dilated ophthalmoscopy
- VAS of IP tolerability
- Adverse Events

Safety analyses will be performed on all subjects who received at least 1 dose of IP (SAF Population). The assessment of safety will be based on the summary of ocular and non-ocular AEs and ophthalmic/medical exams (BCVA, slit lamp biomicroscopy, IOP, dilated ophthalmoscopy and tolerability assessment). Summaries will be provided for each treatment arm, and for the ophthalmic exams, separately for SE and FE.

Safety variables will be presented descriptively. Continuous variables will be summarized by descriptive statistics (absolute values and changes from baseline), and categorical variables will be summarized using the count and percentage of subjects in each category. For the biomicroscopy and ophthalmoscopy variables, shift tables will be prepared by treatment arm showing all categorical changes (e.g., normal to abnormal) from baseline to each study visit.

All data will be presented in data listings.

7.2.1. Adverse Events

Population: SAF

An AE is the development of an undesirable medical condition or the deterioration of a preexisting medical condition during the study, whether considered causally related to the product or not. An AE can therefore be any unfavorable or unintended sign (including a clinically significant change in laboratory values or other clinical tests), symptom, or medical condition occurring at any time during or after IP administration.

Note: Any clinically significant findings (including a clinically significant change in laboratory values or other clinical tests) prior to study drug administration or at Screening (after informed consent) will be recorded in medical/ocular history.

Ongoing AEs at study completion or the subject's final study visit will be followed until the event resolves, stabilizes, or for 30 days, whichever comes first.

AEs 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, version 27.1. All summaries will be based on the assigned MedDRA Preferred Term and System Organ Class, and summaries will be given for each treatment arm. If a subject has more than one AE that is coded to the same PT and SOC, then the subject will only be counted once for that PT and SOC.

The following AE summaries will be prepared:

- Overall Summary of AEs
- Treatment-Emergent Adverse Events (TEAEs) by SOC and PT
- TEAEs by SOC, PT and Maximum Severity (mild, moderate, severe)
- Study Drug Related TEAEs by SOC and PT
- TEAEs Causing the IP to be Discontinued (listing only)
- All Serious Adverse Events (SAEs) (listing only)

7.2.1.1. Adverse Events Occurring During the Run-In Period

Adverse events will be collected throughout the entirety of the study, including during the run-in period. If an AE begins during the run-in period and continues into the treatment period, then the AE will also be counted as a treatment-period event.

7.2.2. Treatment Exposure and Compliance

Population: SAF

Study drug exposure will be calculated for each subject as the total number of days on the treatment, from the date of the first wipe used to the date of the last wipe used. The number and percentage of subjects by treatment arm will be summarized according to the following duration-of-exposure categories: ‘1 - 7 days’, ‘8 - 14 days’, ‘15 - 21 days’, ’22 - 28 days’ and ‘≥29 days’. In addition, these data will be summarized using descriptive statistics.

The number of missed days of dosing will also be determined as the number of days on study minus the total days of dosing, i.e., the (number of opened glass vials of wipes)/2. These results will be summarized using frequency distributions and descriptive statistics, as appropriate.

Dosing compliance will be computed as the proportion of doses taken over the dose-administration period (the time between the first dose of IP and the Day 29/EOS visit). The compliance percentage will be computed as the (number of opened glass vials of wipes)/2 divided by the number of days on study, times 100. These data will be provided as a listing giving the beginning and end dates for the dosing interval with the calculated compliance. The number and percentage of subjects by treatment arm will be summarized according to the following drug compliance categories: ‘≤50%’, ‘>50% - 60%’, ‘>60% - 70%’, ‘>70% - 80%’, ‘>80% - 90%’, ‘>90% - 100%’, and ‘>100%’. The overall compliance by treatment arm will be summarized using descriptive statistics.

7.2.3. Ocular Safety Assessments

Population: SAF

7.2.3.1. BCVA

BCVA will be measured at all visits and the Day 1 value will be used as the baseline value. The observed value and change from baseline will be summarized descriptively by visit and treatment arm for both eyes (SE and FE) in logarithm of the minimum angle of resolution (logMAR) units.

7.2.3.2. IOP

IOP (mmHg) will be measured at Screening, Baseline and Day 29 (Week 4). The observed values and changes from baseline will be summarized descriptively by visit and treatment arm for both eyes (SE and FE).

7.2.3.3. Slit Lamp Biomicroscopy

Slit lamp biomicroscopy will be performed at every visit during the study. The following anterior ocular structures will be evaluated at each exam:

- Lids (overall, erythema, edema)
- Conjunctiva (overall, hyperemia, edema)
- Cornea (overall)
- Anterior chamber (overall, cells, flare)
- Iris/Pupil (screening visit only)
- Lens (status, severity and opacity)

The number and percentage of subjects within each category will be summarized by visit and treatment arm for both eyes (SE and FE). Any open text field information will be presented in the data listings. In addition, shift tables will be prepared showing any categorical changes from baseline to each follow-up exam.

7.2.3.4. Dilated Ophthalmoscopy

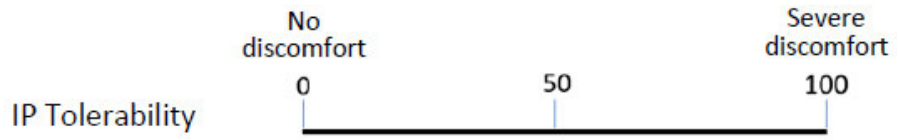
A dilated ophthalmoscopy exam will be performed at Screening and Day 29 (Week 4), and the screening value will be used as the baseline value. Assessments on the following structures will be made during each exam:

- Vitreous
- Macula
- Retinal Vessels
- Peripheral Retina
- Optic Disc

The number and percentage of subjects within each category will be summarized by visit, treatment arm, and eye (SE and FE). In addition, shift tables will be prepared showing any categorical changes from baseline to the Week 4 exam.

7.2.3.5. VAS of IP Tolerability

A VAS evaluation of the IP tolerability will be performed at all visits and the Day 1 value will be used as the baseline value. Subjects will grade the tolerability of the IP after administration on a scale of 0 (no discomfort) to 100 (severe discomfort) by placing a vertical mark on the horizontal line shown below. The mark will be measured and recorded.



The VAS will be measured at all visits and the Day 1 value will be used as the baseline value. The observed value and change from baseline for each subsequent post-baseline visit will be summarized descriptively by visit and treatment arm.

7.2.4. Non-Ocular Safety Assessments

Additional non-ocular safety assessments will be presented as follows:

- Urine Pregnancy Test (listing only)

7.3. Primary Efficacy Endpoint and Estimand

7.3.1. Primary Efficacy Endpoint and Considerations

The primary efficacy endpoint of the study is defined as:

- The mean change from baseline at Day 29 (Week 4/EOS) in the study eye of the unanesthetized Schirmer's test in the mITT population.

7.3.1.1. Unanesthetized Schirmer's Test

The unanesthetized Schirmer's test will be performed at least 15 minutes after CFS at each visit in each eye. In brief, a standardized Schirmer's test strip will be placed towards the temporal third of the lower eyelid of both eyes. The subject is left in a darkened room for 5 minutes, and the strips are then removed. The amount of wetting for each eye is recorded in mm by comparison to a ruler. The value recorded at Visit 2 will be used as the baseline value.

For the exploratory efficacy analysis, an evaluation of the proportion of subjects with a ≥10 mm increase in the unanesthetized Schirmer's test score at Day 29 (Week 4) will be summarized by the frequency and percentage of subjects in each category. Categorical comparisons will be evaluated using the methodology outlined in Section 7.4.3.

7.3.2. Primary Efficacy Estimand

The primary estimand includes the 4 attributes as described in the International Council for Harmonisation (ICH) E9 (R1) addendum on estimands and sensitivity analysis in clinical trials (population of interest, endpoint of interest, specification of how intercurrent events are reflected, and population-level summary), and is described for this study as follows:

Primary Estimand: The difference between IVW-1001 and Vehicle in the mean change from baseline at Day 29 (Week 4) in the study eye in the unanesthetized Schirmer's test score estimated using all data collected from the mITT population.

7.3.3. Primary Efficacy Analytical Approach

For the analysis of the primary efficacy endpoint (mean change from baseline at Week 4/EOS in the study eye of the unanesthetized Schirmer's test in the mITT population), the mean changes from baseline will be analyzed using a mixed model for repeated measures (MMRM), with a restricted maximum likelihood approach for model fitting. This MMRM model will include the fixed effects of Treatment (IVW-1001 Ophthalmic Wipe 0.2%, IVW-1001 Ophthalmic Wipe 0.2%, or Vehicle), Visit, and Treatment*Visit interaction, with the baseline value of the outcome parameter included as a covariate, and with Subject included as a subject effect. Additional baseline and other covariate parameters will be assessed for possible inclusion into the model. An unstructured correlation structure will be used to model the within-subject errors. If there is a failure of the model to converge, then variance components (vc), first-order autoregressive [ar(1)], and compound symmetry (cs) correlation structures will be tested. The correlation structure indicating the best fit based on Akaike's Information Criterion (AIC) will be used for the analysis. Significance assessments will be 2-sided and based on least-squares means with a significance of 0.05 for each endpoint. The results from the model will describe the least-squares adjusted mean differences from baseline with standard errors and their associated confidence intervals.

Sample code for the change from baseline outcome parameter will be analyzed using SAS as follows (please note that the code is approximate and may be adjusted as needed at the discretion of the statistician upon review of the data structure and model convergence):

```
proc mixed data=IVIEW_Data;
      class Visit Treatment SubjectID;
      model Parameter_CFB = Parameter_Baseline Treatment Visit
      Treatment*Visit / solution;
      repeated Visit / type=un subject=SubjectID;
      lsmeans Visit*Treatment / pdiff cl alpha=0.05;
      estimate "X Dose vs. Vehicle Comparison" Visit*Treatment
               1 -1/ cl;

run;
quit;
```

The variables in the model statement are defined as follows:

- Parameter_CFB: The dependent variable representing the mean CFB of the outcome variable in question
- Parameter_Baseline: The value of the outcome variable at baseline
- Treatment: The treatment group designated at baseline
- Visit: The study visit timepoint
- Treatment*Visit: The interaction between treatment group and visit

7.4. Exploratory Efficacy Endpoints and Estimands

7.4.1. Exploratory Endpoints and Considerations

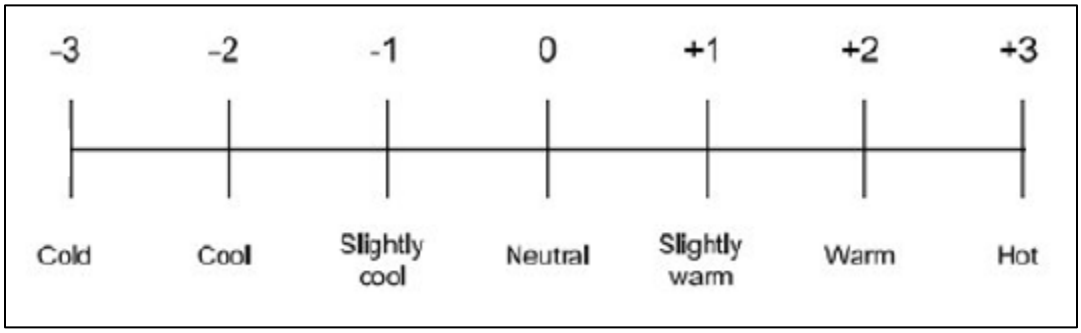
The analysis of the exploratory efficacy endpoints in the SE will be assessed by evaluating the following parameters. Descriptive statistics and comparisons between treatment arms will be provided for all visits assessed:

- Mean change from baseline at Weeks 1, 2, and 3 in the study eye of the unanesthetized Schirmer's test
- Mean change from baseline in VAS of IP comfort (ASHRAE 7-point Scale)
- Mean change from baseline in VAS of EDS
- Mean change from baseline in VAS of ODS
- Mean change from baseline in SAnDE questionnaire (assessed for OU)
- Mean change from baseline in inferior CFS
- Mean change from baseline in total CFS
- Mean change from baseline in anesthetized Schirmer's test (assessed at Week 4 only)
- The proportion of subjects with a ≥10 mm increase in the unanesthetized Schirmer's test score
- The proportion of subjects with a ≥10 mm increase in the anesthetized Schirmer's test score

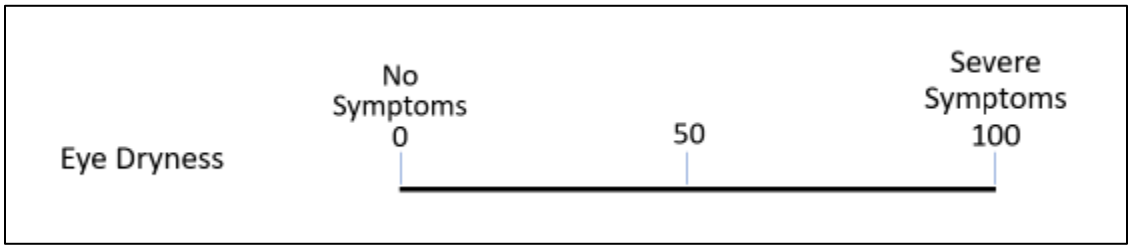
7.4.1.1. VAS of IP Comfort, EDS and ODS

As described in Section 7.2.3.5, a similar methodology will be used to evaluate IP comfort, eye dryness and ocular discomfort. The following scales will be presented to the subject for each of the respective evaluations:

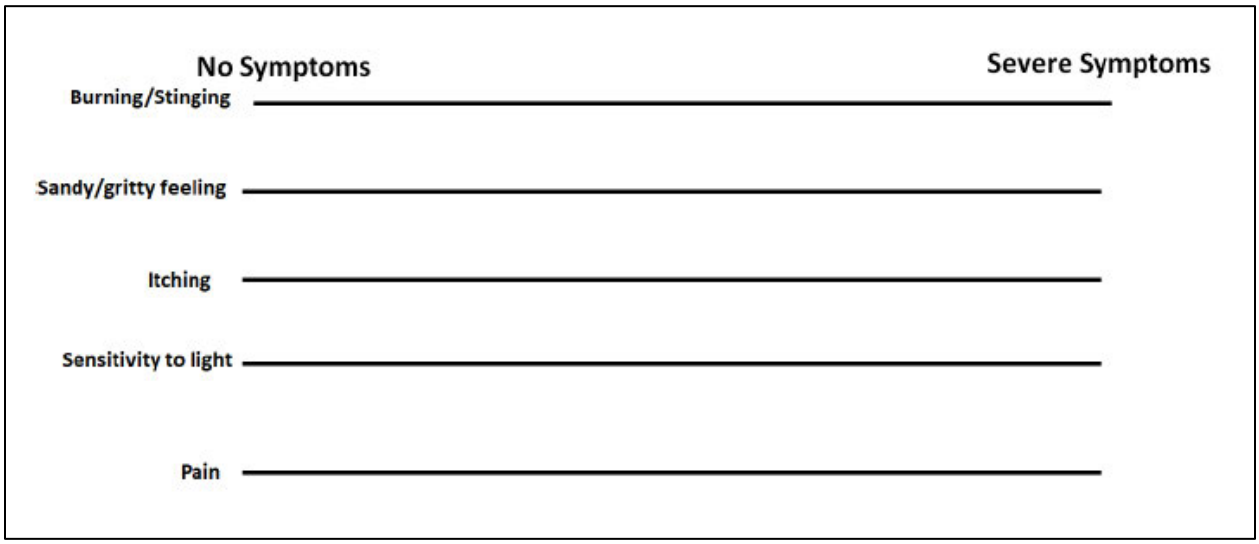
VAS of IP Comfort (ASHRAE 7-point Scale)



VAS of EDS



VAS of ODS



The VAS will be measured at all visits and the Day 1 value will be used as the baseline value. The observed value and change from baseline for each subsequent post-baseline visit will be summarized descriptively by visit and treatment arm. Comparative analyses will be evaluated using the methodology outlined in Section 7.3.3.

7.4.1.2. Corneal Fluorescein Staining

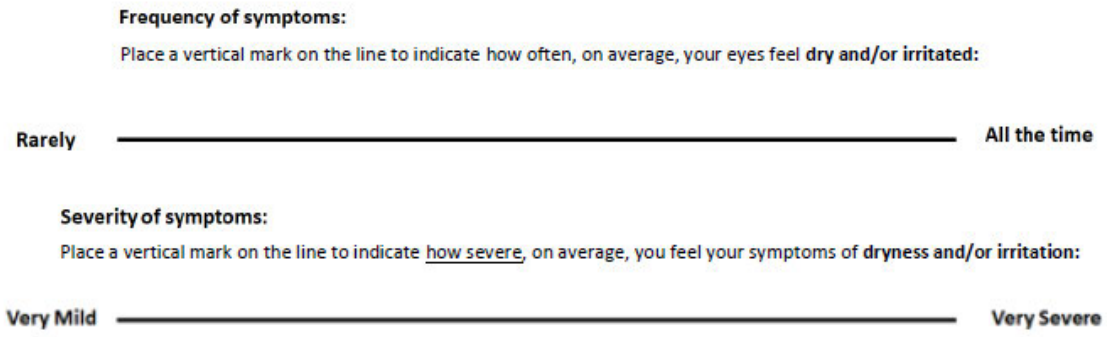
Corneal fluorescein staining will be performed at every visit during the study. Scores will be reported using the National Eye Institute (NEI) Grading Scale, to grade each of the 5 corneal zones on a 0 to 4 scale. CFS will be measured at all visits and the Day 1 value will be used as the baseline value. The observed value and change from baseline for each subsequent post-baseline visit will be summarized descriptively by eye, visit and treatment arm. Comparative analyses will be evaluated using the methodology outlined in Section 7.3.3.

7.4.1.3. Anesthetized Schirmer's Test

The anesthetized Schirmer's test will follow the same procedures as the unanesthetized Schirmer's test with proparacaine 0.5% drops administered bilaterally prior to the exam. The observed value and change from baseline at Week 4 will be summarized descriptively by eye, visit and treatment arm. Comparative analyses will be evaluated using the methodology outlined in Section 7.3.3. For the analysis evaluating the proportion of subjects with a ≥10 mm increase at Visit 4, data will be summarized by the frequency and percentage of subjects in each category. Categorical comparisons will be evaluated using the methodology outlined in Section 7.4.3.

7.4.1.4. SAnDE

A SAnDE evaluation will be conducted at each visit to measure dry eye symptoms from the week prior to the visit using the following scales, and measured using a similar methodology as identified in Section 7.2.3.5:



The observed value and change from baseline for each subsequent post-baseline visit will be summarized descriptively by visit and treatment arm. Comparative analyses will be evaluated using the methodology outlined in Section 7.3.3.

7.4.2. Exploratory Endpoint Estimands

The exploratory estimands include the 4 attributes as described in the International Council for Harmonisation (ICH) E9 (R1) addendum on estimands and sensitivity analysis in clinical trials (population of interest, endpoint of interest, specification of how intercurrent events are reflected, and population-level summary). The exploratory estimands are as follows:

- The difference between IVW-1001 and Vehicle in the mean change from baseline at Weeks 1, 2, and 3 in the study eye in the unanesthetized Schirmer's test score estimated using all data collected from the mITT population.

- The difference between IVW-1001 and Vehicle in the mean change from baseline at Weeks 1, 2, 3, and 4 in the VAS of IP comfort (ASHRAE 7-point Scale) estimated using all data collected from the mITT population.
- The difference between IVW-1001 and Vehicle in the mean change from baseline at Weeks 1, 2, 3, and 4 in the VAS of EDS estimated using all data collected from the mITT population.
- The difference between IVW-1001 and Vehicle in the mean change from baseline at Weeks 1, 2, 3, and 4 in the VAS of ODS estimated using all data collected from the mITT population.
- The difference between IVW-1001 and Vehicle in the mean change from baseline at Weeks 1, 2, 3, and 4 in the SAnDE scores estimated using all data collected from the mITT population.
- The difference between IVW-1001 and Vehicle in the mean change from baseline at Weeks 1, 2, 3, and 4 in the CFS inferior zone score estimated using all data collected from the mITT population.
- The difference between IVW-1001 and Vehicle in the mean change from baseline at Weeks 1, 2, 3, and 4 in the CFS total score estimated using all data collected from the mITT population.
- The difference between IVW-1001 and Vehicle in the mean change from baseline in the study eye at Week 4 in the anesthetized Schirmer's test score estimated using all data collected from the mITT population.
- The difference between IVW-1001 and Vehicle in the proportion of subjects with a ≥10 mm increase in the study eye at Weeks 1, 2, 3, and 4 in the unanesthetized Schirmer's test score estimated using all data collected from the mITT population.
- The difference between IVW-1001 and Vehicle in the proportion of subjects with a ≥10 mm increase in the study eye at Week 4 in the anesthetized Schirmer's test score estimated using all data collected from the mITT population.

7.4.3. Exploratory Efficacy Analytical Approach

For the analysis of the exploratory efficacy endpoints, two distinct approaches will be employed, depending on the parameter and desired output. The exploratory endpoints referencing "change from baseline" (unanesthetized and anesthetized Schirmer's test; VAS; SAnDE; CFS) will be evaluated using the methodology outlined in Section 7.3.3.

For parameters referencing comparisons of proportions between the treatment groups, a Cochran-Mantel-Haenszel chi-square test will be evaluated at each visit. Comparisons will be made between each of the IVW-1001 groups and Vehicle.

7.5. Sensitivity Analysis

Population: PP

To evaluate the robustness of the primary endpoint analysis, a sensitivity analysis will be performed using the PP Population, as defined in Section 4.3. Any differences between the results of the primary efficacy analysis and sensitivity analysis will be presented and investigated.

7.6. Interim Analysis

No formal interim analysis is planned for the study.

7.7. Changes to Protocol-Planned Analyses

Changes to the protocol-planned analyses include the following:

- The protocol indicates that as a sensitivity analysis, the primary and secondary efficacy endpoints will be analyzed using the PP population. The secondary endpoints were meant to be defined as 'exploratory' as no efficacy endpoints are defined in the protocol as secondary. Since the primary objective of the study is safety and all the exploratory endpoints will be analyzed at all visits using the mITT population, only the primary endpoint will be analyzed using the PP population.
- The protocol indicates that for the efficacy endpoints, missing data will be imputed using last observation carried forward. Since the amount of missing efficacy data throughout the study is very small, no imputation for missing data will be performed.
- The protocol indicates that for the efficacy endpoints, appropriate methods will be used to control the Type I error rate for multiple comparisons of the 2 dose groups versus the control. Since this is an early phase study where the primary objective is safety, and because there are many endpoints being tested at all visits (primary and exploratory), no multiplicity adjustments will be performed.

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