EyePoint Pharmaceuticals, Inc.

Protocol Number: EYP-2102-001

A Phase 3, Multicenter, Prospective, Randomized, Masked, Controlled, Safety and Efficacy Study of Fluocinolone Acetonide (FA) Intravitreal 0.05 mg Insert (Yutiq 0.05 mg) in Subjects with Chronic Non-Infectious Uveitis Affecting the Posterior Segment of the Eye

Statistical Analysis Plan

Version: 1.0 08MAY2023

Author Signature Page

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Approved by: ___ 5/12/2023

PPD Date

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Version History

SAP Version	Date	Change	Rationale
1.0	08MAY2023	Not applicable	Original version

1. Introduction

This document presents the statistical analysis plan (SAP) for the protocol EYP-2102-001, a phase 3, multicenter, prospective, randomized, masked, controlled, safety and efficacy study of fluocinolone acetonide (FA) intravitreal 0.05 mg insert (Yutiq 0.05 mg) in subjects with chronic non-infectious uveitis affecting the posterior segment of the eye.

This SAP was developed in accordance with ICH E9 guideline. This SAP is to provide details of the statistical analyses based on the protocol version 3.0, dated July 20, 2022. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock and reasons for such deviations will be described and documented in the clinical study report.

The Sponsor decided to stop enrollment in early May 2022. Subjects who were randomized to Yutiq 0.05 mg will continue to be monitored on a modified-protocol schedule. The subjects who had been treated with sham injection were discontinued from the study. Consider the fact that the study was terminated early, the analyses described in this SAP has been limited to the scope per the interest of EyePoint Pharmaceuticals, Inc. For such a reason, the list of endpoints and analyses in this SAP is a reduced list from the study protocol.

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	Primary Efficacy Endpoint
To evaluate the safety and efficacy of Yutiq 0.05 mg in the management of subjects with chronic non-infectious uveitis affecting the posterior segment of the eye.	The proportion of subjects who have a recurrence of uveitis in the study eye within 24 weeks (6 months) after receiving study treatment
Secondary	Secondary Efficacy Endpoints
	• Proportion of subjects who have a recurrence of uveitis in the study eye within 52 weeks • Mean change from baseline in best corrected visual acuity (BCVA) letter score in the study eye at 24 and 52 weeks • Number of recurrences of uveitis within 24 and 52 weeks • Proportion of subjects with resolution of macular edema as measured by Spectral-domain Optical Coherence Tomography (SD-OCT) imaging at Day 28 and at Months 2, 3, 6, 9, and 12.
Safety	

	• Systemic Adverse Events (AEs) • Ocular AEs, including IOP elevation • Medications/procedures required to control elevated IOP • Development or worsening of cataract • Cataract-related procedures • Clinically significant ocular changes • Procedure related AEs • Subjective ocular tolerability and discomfort assessments • Vital signs • Clinical laboratory assessments • Use of rescue and concomitant medications

1.2. Study Design

The protocol was originally planned to be a 52-week, prospective, randomized, masked (subject and outcome assessor), controlled, safety and efficacy study of intravitreal Yutiq 0.05 mg compared to sham injection with a primary efficacy and safety readout at 24 weeks. A total of approximately 60 subjects (30 subjects in the Yutiq 0.05 mg group and 30 in the sham treatment group) were to be enrolled at approximately 40 sites in the US. One eye in each subject will be designated as the study eye.

The Sponsor decided to stop enrollment in early May 2022 for reasons other than safety or efficacy, following FDA advice received on January 24, 2022. Subjects who were randomized to Yutiq 0.05 mg will continue to be monitored on a modified-protocol schedule through Month 12 (or ET) and evaluated for efficacy and safety. Those subjects who had been treated with sham injection were discontinued from the study and subsequently had their End of Study (EOS) evaluation.

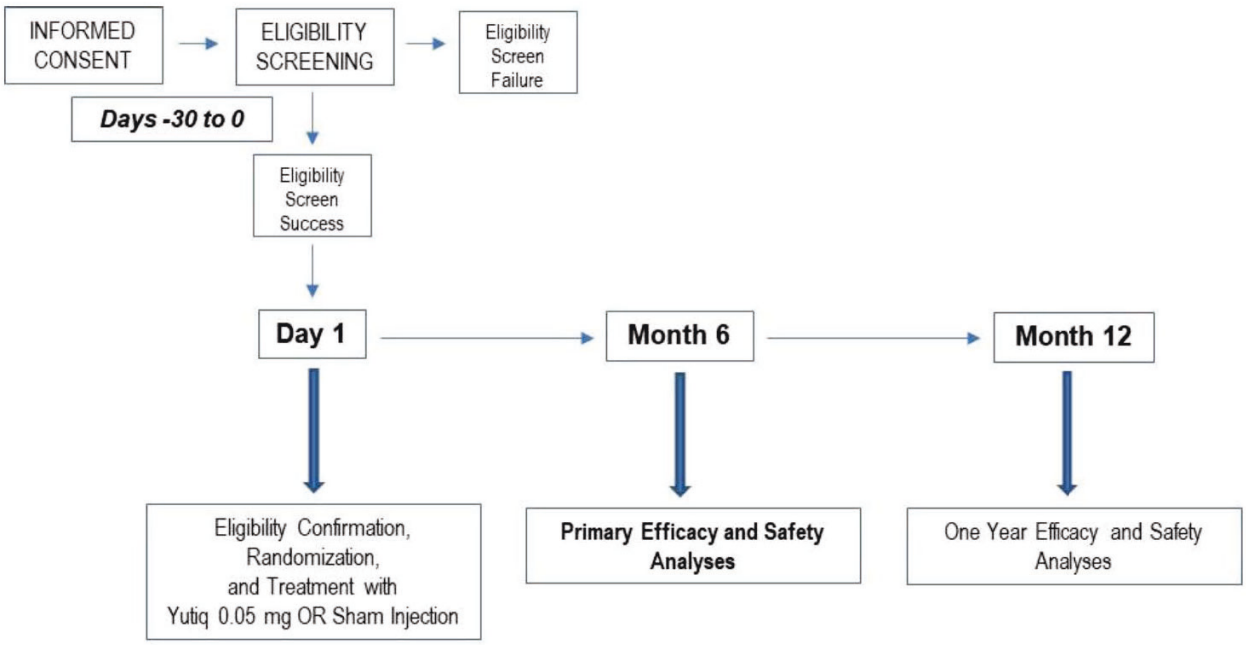
Subjects will receive either Yutiq 0.05 mg or a sham injection on Day 1 of the study on the study eye and will be assessed over the following 52 weeks according to the schedule of study procedures and assessment.

Yutiq 0.05 mg is a non-erodible intravitreal implant in a drug delivery system that contains 0.05 mg of FA and is designed to release FA at a rate of 0.25 µg/day into the vitreous humor for at least 6 months. Yutiq 0.05 mg is preloaded into a single-dose applicator to facilitate injection of the implant directly into the vitreous.

To ensure the health of both eyes, observations of both the study eye and non-study (fellow) eye

should be made at all visits as described in the schedule of study procedures and assessments. Ocular data will be collected for both eyes at all visits except for the SD-OCT assessments.

Figure 1. Study Design Schema



1.2.1. Randomization

One eye in each subject will be designated as the study eye. Following confirmation of eligibility on Day 1, subjects will be randomly assigned in a 1:1 ratio to either Yutiq 0.05 mg or sham injection through a central Interactive Voice Response System (IVRS). Randomization will be stratified based on whether the subject is receiving systemic treatment to control uveitis at the time of study entry.

2. Statistical Hypotheses

Not applicable.

2.1. Multiplicity Adjustment

Not applicable.

3. Analysis Sets

For the purposes of analysis, the following analysis populations are defined:

3.1. Intent-to-Treat Analysis Set

The Intent-to-Treat (ITT) analysis set will include all subjects who are randomized. Subject will be classified according to the assigned treatment. The ITT set will be used for analysis of efficacy, unless otherwise specified.

3.2. Safety Analysis Set

The Safety Analysis Set (SAS) will include all subjects who are randomized and received Yutiq 0.05 mg or sham injection. Subjects will be classified according to the actual treatment received. The SAS set will be used for the analysis of safety data.

4. Statistical Analyses

4.1. General Considerations

4.1.1. Data Summarization

The Sponsor decided to stop enrollment in early May 2022. Subjects who were randomized to Yutiq 0.05 mg will continue to be monitored on a modified-protocol schedule. The subjects who had been treated with sham injection were discontinued from the study. Consider the fact that the study was terminated early, no statistical hypothesis testing will be performed. All data summaries will be descriptive only, based on observed data.

Tabular data summaries for variables measured on a continuous scale will include descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) by treatment group and visit.

For variables evaluated on a categorical scale, data summaries will include the number and percentage of subjects who provide each possible category, by treatment group and visit when applicable. The 95% confidence interval (CI) of the proportions will be constructed for each treatment group, as appropriate.

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

4.1.2. Definition of Baseline

Baseline measurements are those taken at Screening or prior to receiving study treatment on Day 1, whichever is the latest.

4.1.3. Analysis Visit Windows

There will not be visit date re-mapping for the data analyses. All analyses will be descriptive. Descriptive summary tables will be based on nominal visits.

- Efficacy endpoints labelled as Week 24 endpoint will use the assessments from Month 6 visit.
- Efficacy endpoints labelled as Week 52 endpoints will use the assessments of Month 12 visit.

4.1.4. Handling of Missing Data

In general, missing data will not be imputed, unless otherwise specified. For missing and partial dates imputation, refer to section 6.3.1.

4.1.5. Multicenter Considerations

Up to 40 investigative study centers will participate in the study. All centers will be in the United States. Data will be pooled for all study centers for data analysis, unless otherwise specified.

4.1.6. Adjustment for Covariates

Not applicable.

4.1.7. Multiple Comparisons and Multiplicity

Not applicable.

4.1.8. Statistical Software

All statistical summaries and analyses will be produced using SAS, Release 9.4 or higher.

4.2. Primary Efficacy Endpoint Analysis

4.2.1. Definition of Endpoint

The primary efficacy endpoint is the proportion of subjects who have a recurrence of uveitis in the study eye within 24 weeks (6 months) after receiving study treatment. Recurrence is defined as:

- An increase in the vitreous haze of ≥2 steps compared to baseline at the Week 24 visit, or any visit time point prior to the Week 24 visit after the Study Day 7 visit

Or

- A deterioration in visual acuity of at least 15 letters BCVA compared to baseline at the Week 24 visit, or any visit time point prior to the Week 24 visit after the Study Day 7 visit.

Any criterion used to define recurrence must be attributable only to noninfectious uveitis. To prevent post-procedural inflammatory reactions from being reported as uveitis recurrences, assessments for recurrence of uveitis begin after the Study Day 7 visit.

The study protocol stated to impute subjects who don't complete Week 24 eye examinations and subjects who take prohibited medications as having a recurrence. Consider the fact that the study was terminated early, no imputation will be implemented. Summary of the primary efficacy endpoint will be based only on the observed data from the subjects who reached Week 24.

4.2.1.1. Vitreous Haze

Dilated indirect ophthalmoscopy will be performed to assess retinal and choroid appearances and vitreous haze for study eye and fellow eye at all study visits.

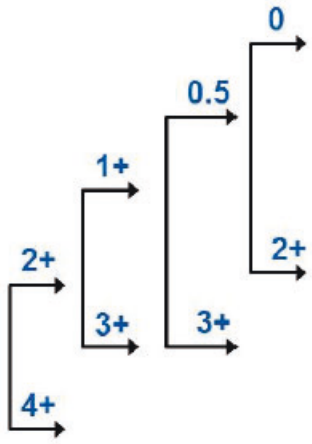
The following scale will be used to define the extent of vitreous haze.

Vitreous Haze Grading Scale

Absent	Clear view of optic disc, retinal vessels and nerve fiber layer
Trace	Slight blurring of optic disc margin and of normal striations and reflex of nerve fiber layer
1+	Mild blurring of optic disc margin and slight loss of retinal vessel definition
2+	Moderate blurring of optic disc margin and loss of retinal vessel definition
3+	Optic nerve head and large vessels visible but borders quite (very) blurry
4+	Optic nerve head obscured

The diagram below presents the scoring convention that will be used to identify a minimum of "> 2 step increase" of vitreous haze for the primary efficacy endpoint.

Vitreous Haze Scoring Convention



Score*	Characteristics*
Absent [0]	Clear view of optic disc, retinal vessels and nerve fiber layer
Trace [0.5]	Slight blurring of optic disc margin and of normal striations and reflex of nerve fiber layer
1+	Mild blurring of optic disc margin and slight loss of retinal vessel definition
2+	Moderate blurring of optic disc margin and loss of retinal vessel definition
3+	Optic nerve head and large vessels visible but borders quite (very) blurry
4+	Optic nerve head obscured

* Nussenblatt et al 1985

4.2.1.2. Measurement of BCVA by ETDRS

Visual acuity testing in this study is required at a distance of 4 meters, and for subjects with reduced vision at 1 meter. Visual acuity is always tested with the subject's best correction and should be measured prior to pupil dilation and slit lamp biomicroscopy examination or any drops or ointments being used. BCVA by ETDRS will be measured at every study visit.

4.2.2. Analytical Approach for Primary Efficacy Endpoint

The recurrence of uveitis rate will be summarized with the number and percentage of subjects with the recurrence and 95% confidence interval (CI) based on binomial distribution using the Clopper-Pearson (Exact) method.

The vitreous haze score and measurement of BCVA results will be summarized by treatment group at each scheduled visit. Mean change from baseline and proportion of subjects who have an increase of vitreous haze score of ≥2 steps, and proportion of subjects who have a deterioration of at least 15 letters BCVA from baseline will be presented at each scheduled visit.

Abnormal vitreous haze for the study eye and fellow eye will be summarized by treatment group and visit.

4.2.3. Sensitivity Analysis

No sensitivity analysis will be performed.

4.3. Secondary Endpoints Analysis

4.3.1. Definition of Secondary Endpoints

The secondary efficacy endpoints will include the following endpoints:

4.3.1.1. Proportion of subjects who have a recurrence of uveitis in the study eye within 52 weeks

The recurrence of uveitis will be assessed the same as the primary efficacy endpoint within 52 weeks.

4.3.1.2. Mean change from baseline in BCVA letter score in the study eye at 24 and 52 weeks

The change from baseline in BCVA as measured by ETDRS letter at each visit will be calculated.

4.3.1.3. Number of recurrences of uveitis within 24 and 52 weeks

The recurrences of uveitis on the study eye will be assessed as described in the primary efficacy endpoint and the incidence will be counted.

4.3.1.4. Proportion of subjects with resolution of macular edema as measured by SD-OCT imaging at Day 28 and at Months 2, 3, 6, 9, and 12.

The number and percentage of subjects who had macular edema from SD-OCT imaging will be summarized for each assessment timepoint through Week 24 and Week 52.

4.3.2. Analytical Approach for Secondary Efficacy Endpoints

The secondary efficacy analyses will be conducted using the ITT analysis set based on observed data.

- The proportion of subjects with recurrent of uveitis will be summarized for the timepoint of interest using the same method described for the primary efficacy endpoint.
- The mean change from baseline in BCVA as measured by ETDRS letter score at each visit will be summarized for week 24 and 52 using descriptive statistics.

4.4. Safety Analyses

Safety data will include adverse events reported after screening, data collected from ocular examinations and IOP measurements, ocular tolerability and discomfort assessments, vital sign measurements, clinical laboratory tests, and the use of rescue and concomitant medications.

All safety analyses will be performed on the safety analysis set based on actual treatment received. Ocular safety data will be summarized on the study eye and fellow eye separately, where applicable.

4.4.1. Extent of Exposure

Subjects will receive either intravitreal Yutiq 0.05 mg or sham injection in the designated study eye on Day 1 and will be followed for 52 weeks after treatment for change in IOP and for endophthalmitis. The number and percentage of subjects who remain on the study will be summarized for each visit by treatment group. The number of subjects in each treatment group will be presented based on the actual treatment they have received.

4.4.2. Adverse Events

Adverse event data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The severity of each AE will be graded by the investigator per CTCAE v5.0 criteria.

Descriptive statistics will be provided for all treatment-emergent adverse events (TEAEs). Both ocular and non-ocular TEAEs are defined as events that start after the study drug administration, and occur before termination of the study, or were present before study drug administration and worsened after dose administration.

Frequency counts and percentage of subjects within each treatment group will be provided by system organ class (SOC) and preferred term (PT) by treatment. Within each level of summarization (SOC, PT), subjects who experience more than one occurrence will only be counted once. Adverse events will also be presented by severity (mild, moderate, severe, life- or sight-threatening), and by relationship to study drug (not related, possibly related, probably related). Listings of deaths, and AEs leading to withdrawal will be presented.

Summaries will be sorted in descending order of frequency in the Yutiq 0.05 mg arm, when applicable. A listing of treatment-emergent AEs, treatment-emergent ocular events, and serious AEs will be provided.

Ocular Adverse Events

The following ocular events will be considered AEs for the purposes of this study:

- Decrease in BCVA of at least ≥15 letters or ≥3 lines from the previous BCVA measurement
- Moderate or severe (Grade 3 or 4) ocular findings compared to the last ocular examination
- Worsening of >2 steps in anterior chamber cell count or vitreous haze compared to the last ocular examination
- Increase in IOP of >10 mmHg at two visits at least 1 week apart or an increase in IOP to >25 mmHg

4.4.3. Subjective Ocular Tolerability and Discomfort Assessment

Ocular discomfort will be measured using a 6-point scale (from "absent" to "intolerable") and ocular tolerability will be measured using a visual analog scale. Subjects will be asked to grade ocular tolerability and discomfort for the study eye and fellow eye at all study visits.

Subjective Ocular Discomfort Grading

Subjects will assess discomfort using the following subjective scale (Maca et al. 2010). This parameter will consist of questioning about superficial pain, foreign body, or gritty sensation, itching, burning, and other forms of non-specific discomfort.

- Grade 0: Absent
- Grade 0.5: Very mild
- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe
- Grade 4: Intolerable

Subjective Tolerability Using a Visual Analog Scale for Pain

Subjects will assess tolerability using the following subjective visual analog scale (Scoville et al. 1985). A visual analogue scale is performed by asking subjects to indicate on an unmarked 100-mm line the intensity of their pain. A mark of "0" represents no sensation while "100" indicates the worst imaginable pain. The location of the mark on the line is then measured with a ruler (in mm) to provide a numeric score.

The number and percentage of subjects in each ocular discomfort grading will be summarized by treatment group and visit. The VAS pain scale and change from baseline will be summarized using descriptive statistics by treatment group and visit.

4.4.4. Intraocular Pressure

Intraocular pressure (IOP) will be measured after slit lamp examination has been completed at every study visit. The mean of 3 measurements per eye will be recorded as the IOP. Measurement should be performed before dilated ophthalmoscopy. The IOP measurement and change from baseline will be summarized using the descriptive statistics by treatment group and visit.

4.4.5. Slit Lamp Examination

A routine slit lamp examination will collect clinical findings from the anterior and posterior segment of both study and fellow eye with pupil dilation and should be conducted after IOP measurement has been completed.

Abnormal slit-lamp biomicroscopy results for the study eye and fellow eye will be summarized by treatment group and visit through week 24 and 52, respectively.

4.4.5.1. Anterior Chamber Cell Grading Scale

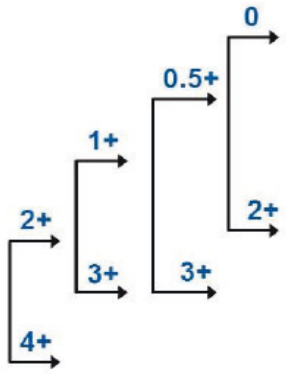
Anterior chamber cells will be measured at all study visits and assessment will be made using the following scale (Jabs et al. 2005).

Field size: 1 mm by 1 mm slit beam

0	<1 cells/hpf
0.5+	1-5 cells/hpf
1+	6-15 cells/hpf
2+	16-25 cells/hpf
3+	26-50 cells/hpf
4+	>50 cells/hpf

Anterior Chamber Cell Scoring Convention
The diagram presents the scoring convention that will be used to identify a minimum of "≥ 2 step increase" of anterior chamber cells compared to baseline at the Week 24 visit, or any visit time point prior to the Week 24 visit after the Study Day 7 visit.

Anterior Chamber Cell ≥2 Step Increase:



Score *	Cell Count*
0	<1 cells/hpf
0.5+	1-5 cells/hpf
1+	6-15 cells/hpf
2+	16-25 cells/hpf
3+	26-50 cells/hpf
4+	>50 cells/hpf

*** Jabs et al 2005**

The grading scale and measurement of anterior chamber cell results will be summarized by treatment group at each scheduled visit. The proportion of subjects who have an increase of anterior chamber cell of ≥2 step increase will be presented.

Abnormal anterior chamber assessment results will be summarized by treatment group and visit.

4.4.6. Indirect Ophthalmoscopy

Indirect ophthalmoscopy will be performed to assess retinal and choroid appearances and vitreous haze (Nussenblatt et al. 1985). Indirect ophthalmoscopy will be performed for study eye and fellow eye with pupil dilation and should be conducted after IOP measurement has been completed.

Abnormal indirect ophthalmoscopy results for the study eye and fellow eye will be summarized by visit through week 24 and 52 separately.

4.4.7. Prior and Concomitant Medications

Prior and concomitant medications for both ocular and non-ocular indications will be coded using the World Health Organization (WHO) Drug Dictionary. These medications (prescription, OTC, and nutritional supplements) will be summarized by anatomical therapeutic chemical (ATC) classification level 2 term, WHO generic name, and treatment group. Subjects will only be counted once at each level of the generic name or ATC level.

4.4.7.1. Use of Rescue and Prohibited Medications

All prohibited medications used concurrently (from Day 1 through Month 12) must be documented in the eCRF. During the study, some subjects may require rescue treatments in the study eye as a result of AEs or lack of efficacy of the study treatment. Prior to database lock, the Sponsor will conduct a data review to classify concomitant treatments as either rescue or prohibited. The proportion of subjects receiving these medications will be summarized by treatment type (rescue or prohibited), treatment group, and time point.

4.4.8. Clinical Laboratory Evaluation

Clinical laboratory results of hematology, chemistry, and urinalysis will be presented by treatment group using descriptive statistics. For hematology, shift tables of the worst on-study laboratory toxicity based on CTCAE grading relative to baseline will be presented. Subject incidence tables of grade ≥ 3 laboratory toxicities will be provided for hematology and chemistry.

Laboratory values will be listed by subject, and values outside of a normal reference range will be flagged.

4.4.9. Vital Signs, Physical Findings and Other Observations Related to Safety

Observed and change from baseline for each vital sign parameter will be summarized descriptively by treatment group.

4.5. Interim Analysis

No formal interim analyses are planned for this study.

4.6. Primary Analysis

Not applicable.

4.7. Final Analysis

The final analysis will be performed at the end of study when all subjects have completed the week 52 visit or terminate early from the study.

4.8. Changes to Protocol-planned Analyses

There are modifications from the clinical study protocol amendment (protocol version 3.0, 20 July 2022) that impact statistical analysis.

- Hypothesis testing using the exact binomial test will not be conducted to test the difference between the proportion of subjects with a recurrence using a 2-sided alpha = 0.05 due to insufficient sample size. Instead, the number and proportion of subjects who experience the uveitis recurrence will be summarized by treatment group.
- Analysis populations are defined to include subjects who are randomized for the study.

5. Sample Size Determination

A total of approximately 60 subjects will be enrolled in the study and receive either Yutiq 0.05 mg or a sham injection. The Sponsor decided to stop enrollment for reasons other than safety or efficacy, following FDA advice received on January 24, 2022. In early May 2022, subject enrollment into the study has been stopped; therefore, the sample size will represent the number of subjects enrolled at the time of the Sponsors decision to stop enrollment.

6. Supporting Documentation

6.1. Appendix 1: List of Abbreviations

Abbreviation / Acronym	Definition / Expansion
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
BCVA	Best corrected visual acuity
BMI	Body Mass Index
CI	Confidence interval
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
EDTRS	Early Treatment Diabetic Retinopathy Study
FA	Fluocinolone acetonide
IOP	Intraocular pressure
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
MedDRA	Medical Dictionary for Regulatory Activities
OTC	Over-the-counter
PD	Protocol deviation
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD-OCT	Spectral-domain Optical Coherence Tomography
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
WHO-DD	World Health Organization - Drug Dictionary

6.2. Appendix 2: Supporting Study Information

6.2.1. Disposition of Subjects

A summary table will be prepared indicating the number and percentage of subjects in each treatment group who are included in each analysis population. Within the ITT population, the number and percentage of subjects who did/did not complete the study will be presented. Screen failures, including reasons for failing to satisfy eligibility criteria will also be summarized. In addition, randomization stratification and subgroups will be summarized.

Subjects who discontinue any time during the study will be summarized by reason for termination. Duration of study participation and insert duration will also be tabulated.

6.2.2. Demographics

Demographics and baseline characteristics data include age (in years, at time of signing informed consent) and age category (< 65 vs ≥ 65), race, sex, childbearing potential, ethnicity, height, weight, calculated BMI, and geographic region, and will be summarized by treatment group using descriptive statistics for the ITT population.

6.2.3. Baseline and Disease Characteristics

Optical baseline characteristics include dilated indirect ophthalmoscopy results, baseline BCVA group (≤ 64 vs > 64 letters), BCVA ETDRS letter score, intraocular pressure, ocular tolerability, and anterior, posterior and intermediate slit lamp examinations, and SD-OCT, and will be summarized by treatment group using descriptive statistics with the ITT analysis set.

6.2.4. Protocol Deviations

Protocol Deviations (PDs) data will be identified and recorded. The study team will conduct on-going reviews of the PD data throughout the study. A summary of incidence of major PDs will be tabulated using number and percentage of subjects by deviation type.

Listings of subjects with PDs will be provided.

6.2.5. Medical History and Concurrent Illnesses

Medical history data including ophthalmic history will be coded using the MedDRA version 24.1 or higher and summarized by SOC and PT for each treatment group.

6.2.6. Prior/Concomitant Medications

Prior medications are defined as all prescription, vaccinations, supplements, herbal therapies, any

prohibited medications, and over-the-counter (OTC) medications taken within the 30 days to day 1 whether subjects continue to take or not. All prior medications must be documented on the concomitant medications eCRF.

Concomitant Medications are all prescription and OTC concomitant medications used concurrently from the time of ICF signing through Month 12 and documented on the concomitant medication eCRF.

Information on the concomitant medication/therapy eCRF includes the name of the medication/therapy, dose, frequency, route, dates of use, and indication for use.

Prior and concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) version September 2021 B3 and will be summarized by preferred name.

The number and percentage of subjects using each medication will be presented by treatment group using the safety analysis set. Subjects taking more than one medication in the same preferred name will be counted once for the number of subjects taking that preferred name.

6.3. Appendix 3: Data Handling Conventions

6.3.1. Missing Date Imputation

6.3.1.1. Missing/Incomplete AE and Medication Start Date

For AEs and Prior/Concomitant medications, the following imputation rules will be applied to impute partial or missing start dates.

- If year, month, and day are all missing, then assign the date of study drug administration.
- If month and day are missing and year is:
  - the same as the year of study drug administration then assign the month-day of study drug administration
  - earlier than the year of study drug administration then assign December 31
  - after the year of study drug administration then assign January 1.
- If only day is missing, and month-year is:
  - the same as the month-year of study drug administration then assign the day of study drug administration
  - earlier than the month-year of study drug administration then assign the last day of the month
  - after the month-year of study drug administration then assign the first day of the month.

If the imputed start date is after the stop date, then there is a data error and do not impute the start date.

The imputed dates will be used to assess whether AEs should be considered as treatment emergent and if medications should be included in the safety summaries as prior or concomitant. The original, partial dates will be included in data listings.

6.3.1.2. Missing/Incomplete AE and Medication End Date

Imputation rules for partial or missing stop dates

- if day is missing, assign the last day of the month.
- if month-day is missing, assign December 31 of the year.
- if year, month, and day are all missing, do not impute.

If the stop date imputation leads to a date that is after the death date, then impute the stop date as the death date.
If the stop date imputation leads to a date that is before the start date, then there is a data error and do not impute the stop date.

6.3.1.3. Missing/Incomplete Death Date

Imputation rules for partial or missing death dates

- If death year and month are available but day is missing:
  - If "mmyyyy" for last contact date = "mmyyyy" for death date, set death date to the day after the last contact date.
  - If "mmyyyy" for last contact date < "mmyyyy" for death date, set death date to the first day of the death month.
  - If "mmyyyy" for last contact date > "mmyyyy" for death date, data error and do not impute.
- If both month and day are missing for death date or a death date is totally missing, set death date to the day after the last contact date.

7. References

YUTIQ® US Prescribing Information, May 2021.

Jung SH. Stratified Fisher's Exact Test and its Sample Size Calculation. Biom J. 2014 January; 56(1): doi:10.1002/bimj.201300048.

SAS/STAT® 13.1 User's Guide. The FREQ Procedure.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonized Tripartite Guideline. Structure and Content of Clinical Study Reports (E3). Current Step 4 Version dated 30 November 1995.
Statistical Principles for Clinical Trials (E9). Current Step 4 version dated 5 February 1998.

Maca SM, Amon M, Findl O, Kahraman G, Barisani-Asenbauer T. Efficacy and tolerability of preservative-free and preserved diclofenac and preserved ketorolac eyedrops after cataract surgery. Am J Ophthalmol. 2010; 149: 777-784.

Scoville B, Krieglstein GK, Then E, Yokoyama S, Yokoyama T. Measuring drug-induced eye irritation: a simple new clinical assay. J Clin Pharmacol. 1985; 25: 210-218.

Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of Uveitis Nomenclature (SUN) Working Group: Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140:509-516.

Nussenblatt RB, Palestine AG, Chan CC, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. Ophthalmol. 1985;92:467-471.