Yutiq 0.05 mg
(Fluocinolone Acetonide Intravitreal 0.05 mg Insert)

PROTOCOL EYP-2102-001

A Phase 3, Multicenter, Prospective, Randomized, Masked, Controlled, Safety and Efficacy Study of a 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

IND Number	113140
Sponsor:	EyePoint Pharmaceuticals, Inc. 480 Pleasant Street Watertown, MA 02472 USA
Version:	3.0
Protocol Release Date:	20 Jul 2022

PROTOCOL APPROVAL PAGE

Protocol Title: **A Phase 3, Multicenter, Prospective, Randomized, Masked, Controlled, Safety and Efficacy Study of a 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**

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This protocol has been reviewed and approved by EyePoint Pharmaceuticals, Inc.

PPD MD PPD PPD EyePoint Pharmaceuticals, Inc.	Date

INVESTIGATOR'S AGREEMENT

I have read the attached protocol, concur that it contains all information necessary to conduct the study, and agree to follow the study procedures as outlined in this protocol.

I agree to comply with United States (US) Food and Drug Administration (FDA) regulations (21 CFR Parts 50, 54, 56 and 312) and International Conference on Harmonization (ICH) guidelines. I will not initiate the study until I have obtained written approval by the appropriate Institutional Review Board/Ethics Committee and have complied with all financial and administrative requirements of the governing body of the clinical institution. I will obtain written informed consent from all study participants prior to performing any screening procedures.

This protocol and related information is subject to the Confidentiality Agreement between myself and EyePoint Pharmaceuticals, Inc. and as such must be held in confidence and not disclosed to any third party for a period of seven (7) years from the date of the Confidentiality Agreement, or until said information shall become a matter of public knowledge, or until a formal written agreement for that purpose has been entered into by the parties.

Principal Investigator Signature	Date
Print Name	

PERSONNEL CONTACT INFORMATION

Role in Study	Name	Address and Telephone Numbers
Sponsor	EyePoint Pharmaceuticals, Inc.	EyePoint Pharmaceuticals, Inc. 480 Pleasant Street Watertown, MA 02472 USA Phone: (833) 393-7646 Fax: (617) 926-5050
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SYNOPSIS

Name of Sponsor/Company: EyePoint Pharmaceuticals, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(for National Authority Use only)*
Name of Investigational Product: EYP-2102 (Fluocinolone Acetonide Intravitreal 0.05 mg Insert [Yutiq 0.05 mg])		
Name of Active Ingredient: Fluocinolone Acetonide		

Title of Study: A Phase 3, Multicenter, Prospective, Randomized, Masked, Controlled, Safety and Efficacy Study of a 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

Protocol Number: EYP-2102-001 | **Phase of Development:** 3

Study Centers: Up to 40 study sites in the United States (US)

Studied Period: Up to 52 weeks of follow-up

Objectives: 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.

Methodology: A 52-week, prospective, randomized, masked, 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.

Number of Subjects (planned): Approximately 60 subjects (30 subjects in the Yutiq 0.05 mg group and 30 in the sham treatment group) 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. The Sponsor is reevaluating the development program of Yutiq 0.05 mg.

Key Inclusion Criteria:

1. Male or non-pregnant female at least 18 years of age at time of consent.
2. One or both eyes having a history of recurrent non-infectious uveitis affecting the posterior segment of the eye (intermediate, posterior, or panuveitis) with or without anterior uveitis >1 year duration.
3. During the 52 weeks prior to enrollment (Day 1), the subject must have received treatment for uveitis in the study eye with:
   a) Systemic corticosteroid or other systemic therapies for at least 12 consecutive or non-consecutive weeks,

      AND/OR

   b) at least 2 intra- or peri-ocular administrations of corticosteroid for management of uveitis

      OR

   c) the study eye has experienced recurrence of uveitis at least 2 separate times requiring systemic, intra- or peri-ocular injection of corticosteroid.

4. At the time of enrollment (Day 1), the study eye has <10 anterior chamber cells/HPF (high-power field) and a vitreous haze ≤ grade 2.
5. Visual acuity of study eye ≥15 letters on the ETDRS chart.
6. Not planning to undergo elective ocular surgery during the study.
7. Able to understand and sign the Informed Consent Form (ICF).
8. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Key Exclusion Criteria:

Ocular Exclusion Criteria (for the study eye, unless indicated otherwise):

1. History of posterior uveitis only that is not accompanied by vitritis or macular edema.
2. History of iritis only associated with no vitreous cells, anterior chamber cells, or vitreous haze at Day 1.
3. Uveitis with infectious etiology.
4. Vitreous hemorrhage.
5. Intraocular inflammation associated with a condition other than noninfectious uveitis (eg, intraocular lymphoma).
6. Uveitis limited to the anterior segment, ie, anterior uveitis only.
7. Ocular malignancy **in either eye**, including choroidal melanoma.
8. Previous viral retinitis.
9. Toxoplasmosis scar or scar related to previous viral retinitis in the study eye.
10. Current viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, mycobacterial infections of the eye, or fungal diseases of ocular structures.
11. Media opacity precluding evaluation of retina and vitreous.
12. Peripheral retinal detachment in area of insertion.
13. Intraocular pressure ≥ 22 mmHg or uncontrolled glaucoma (open angle or angle closure) in the study eye at Screening; subjects are not excluded if IOP is ≤ 22 mmHg in the study eye with no more than 2 classes of IOP lowering medications.
14. Chronic hypotony (<6 mmHg).
15. Ocular surgery within 12 weeks prior to Day 1.
16. Capsulotomy within 30 days prior to Day 1.
17. Prior intravitreal treatment with Retisert®, ILUVIEN®, or YUTIQ® (0.18 mg) within 156 weeks prior to Day 1.
18. Prior intravitreal treatment with OZURDEX® or sub-choroidal injection with XIPERE™ within 24 weeks prior to Day 1.
19. Prior intravitreal treatment with Triesence® or TRIVARIS™ within 12 weeks prior to Day 1.
20. Peri-ocular or subtenon steroid treatment within 12 weeks prior to Day 1.

21. Significant structural issues that put the subject at risk for implant migration to the anterior chamber (e.g. large iris defects or an anterior chamber lens).

All other Exclusion Criteria:

22. Allergy to fluocinolone acetonide or any component of Yutiq 0.05 mg.
23. Requirement for chronic systemic or inhaled corticosteroid therapy (>15mg prednisone daily) or chronic systemic immunosuppressive therapy.
24. History of certain skin cancers (specifically, basal cell carcinoma and squamous cell carcinoma), any malignancy receiving treatment, or in remission less than 5 years prior to Day 1.
25. Positive test for human immunodeficiency virus (HIV) or syphilis during Screening.
26. Mycobacterial uveitis or chorioretinal changes of either eye which, in the opinion of the Investigator, result from infectious mycobacterial uveitis.
27. Systemic infection within 30 days prior to Day 1.
28. Any severe acute or chronic medical or psychiatric condition that could increase the risk associated with study participation or could interfere with the interpretation of study results and, in the judgment of the Investigator, could make the subject inappropriate for study enrollment.
29. Any other systemic or ocular condition which, in the judgment of the Investigator, could make the subject inappropriate for study enrollment.
30. Treatment with an investigational drug or device within 30 days prior to Day 1.
31. Pregnant or nursing females; females of childbearing potential who are unwilling or unable to use an acceptable method of contraception as outlined in the protocol from at least 14 days prior to Day 1 until the 52-week Visit.
32. Unlikely to comply with the study protocol or who are likely to be lost to follow-up within 52 weeks.

Treatment Assignment: Study subjects will be randomly assigned to receive either Yutiq 0.05 mg (the test article) or an intravitreal sham injection in the designated study eye.

Control: Intravitreal sham injection

Duration of Treatment: Twenty-four weeks (based on *in vivo* release rates of Yutiq 0.05 mg in nonclinical study data) with expected tapering of FA release through 52 weeks.

Test Article Therapy: Fluocinolone acetonide intravitreal 0.05 mg insert (Yutiq 0.05 mg). Yutiq 0.05 mg contains 0.05 mg FA and is designed to deliver FA into the vitreous humor for at least 24 weeks. Yutiq 0.05 mg will be administered to the study eye by injection through the pars plana using a pre-loaded applicator with a 25-gauge needle.

Designation/Randomization of Study Eye: For subjects with unilateral uveitis, the study eye will be the affected eye; for subjects with bilateral uveitis, the study eye will be the more severely affected eye fitting the inclusion/exclusion criteria (ie, the eye having suffered more recurrences in the previous year, or if equal, the eye having received more therapy in the previous year, or if equal, the eye having the worse VA, or if equal, the eye clinically judged to be the more severely affected eye.) If the eyes are symmetrically affected, the study eye will be the right eye.

Study Procedures:

Screening (within 30 days prior to injection):

Eligibility determination, informed consent, demographics, medical and ophthalmic history (including a detailed history of the management of their uveitis over the previous 52 weeks), vital signs, clinical laboratory testing, ophthalmic examinations (includes BCVA, IOP, dilated ophthalmoscopy, and anterior, posterior and intermediate slit lamp examination), subjective ocular tolerability and discomfort assessment, concomitant medications, and pregnancy testing as appropriate.

Treatment Day (Day 1):

Eligibility confirmation including meeting the entry criteria for anterior chamber cells, vitreous haze, IOP, and visual acuity on Study Day 1, and then randomization to either intravitreal Yutiq 0.05 mg or sham injection. Following determination of study eye, subjects will receive either Yutiq 0.05 mg or the sham injection. Assessments on that day will include vital signs, ophthalmic examinations, spectral-domain – optical coherence tomography (SD-OCT), subjective ocular tolerability and discomfort assessment, pregnancy test if appropriate, concomitant medications, and adverse events (AEs).

Follow-up Visits:

Following injection on Study Day 1, subjects who were treated with Yutiq 0.05 mg will return for study visits on Days 7, 28, and at Months 2, 3, 6, and 12. Evaluations on these days will include: review of concomitant medications, vital signs, ophthalmic examinations, IOP, SD-OCT, subjective ocular tolerability and discomfort assessment, and AEs. All subjects treated with Yutiq 0.05 mg in the study will be followed for 52 weeks. In early May 2022, those subjects who had been treated with sham injection were discontinued from the study. Sham-treated subjects subsequently had their End of Study (EOS) evaluation.

Masking: Study subjects will receive either Yutiq 0.05 mg or a sham injection. Subjects and study staff conducting clinical study assessments, except for the clinician performing the injection procedure, will be masked to randomized treatment assignment.

Concomitant Medications:

Subjects may be treated prior to study entry in order to meet study inclusion criteria and obtain a relatively quiet eye prior to enrollment. If a subject is receiving a systemic treatment regimen or topical steroids to control uveitis prior to study enrollment, that subject will have such treatment ended within 12 weeks following Study Day 1, in a manner that follows the standard of care for ending the specific treatment. For example, some systemic treatments may be ended immediately, while others require a period of gradual dose reduction (tapering).

If a subject experiences a recurrence of uveitis in either eye that requires treatment during the study, local (topical, periocular, or intraocular) treatment will be used as the first line of therapy. Systemic immunosuppressants or systemic steroids will be used only if local therapy fails. Subjects who experience a recurrence of uveitis will continue in the study; once the subject's recurrence is controlled, treatment will be ended in a manner that follows the standard of care for the specific treatment regimen.

Criteria for Evaluation:

Efficacy

Primary Efficacy Endpoint: 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 or any visit time point prior to the Week 24 visit;
  OR
- A deterioration in visual acuity of at least 15 letters BCVA compared to baseline or any visit time point prior to the Week 24 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.

Secondary Efficacy Endpoints:

- Proportion of subjects who have a recurrence of uveitis in the study eye within 52 weeks
- Proportion of subjects who have a recurrence of uveitis in the fellow eye within 24 and 52 weeks
- Mean change from baseline in BCVA letter score in the study eye at 24 and 52 weeks
- Number of recurrences of uveitis within 24 and 52 weeks
- Time to recurrence of uveitis through 24 and 52 weeks
- Number of adjunctive treatments required to treat recurrences of uveitis at 24 and 52 weeks
- Proportion of subjects with recurrence of iridocyclitis defined as a >2-step increase in anterior chamber cells per HPF (1.6 × using a 1-mm beam) in the study eye compared to baseline at 24 and 52 weeks.
- Proportion of subjects with resolution of macular edema as measured by SD-OCT imaging at Day 28 and at Months 2, 3, 6, and 12.

Safety

- Systemic 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

Statistical Methods:

Sample Size:

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.

Analysis Populations:

The intent-to-treat (ITT) population will include all subjects enrolled in the study. The Safety population will include all subjects enrolled in the study who received Yutiq 0.05 mg. The per protocol (PP) population will be defined separately for the Week 24 and Week 52 analyses, and will exclude all subjects in the ITT population who meet any of the following criteria:

- Received systemic treatment for recurrence of uveitis in fellow eye
- Received an imputed endpoint at the Weeks 24 or 52 endpoints of the study
- Failed screening, without exemption, but received Yutiq 0.05 mg
- Had a major protocol deviation

Efficacy Analyses:

Efficacy analyses will be performed on both the ITT and PP populations at 24 and 52 weeks. The primary efficacy analysis will be performed on the ITT population at 24 weeks and will be the proportion of subjects who have a recurrence of uveitis. The exact 95% confidence interval for the proportion will be derived. Hypothesis testing using the exact binomial test will be conducted to test the difference between the proportion of subjects with a recurrence using a 2-sided alpha = 0.05. The primary efficacy analysis will be conducted after all subjects in the study have completed at least 24 weeks of study or have discontinued.

In addition to recurrence based on vitreous haze increase or BCVA loss as defined above, recurrence will also be imputed in the following circumstances:

- A subject who has not previously experienced a recurrence and does not complete the required eye examinations at Week 24 (or at Week 52 for the Week 52 analyses) for any reason will be considered as having a recurrence.
- A subject who has not previously experienced a recurrence and takes a prohibited systemic concomitant medication or a prohibited local concomitant medication in the study eye at any time during the study prior to Week 24 (or prior to Week 52 for the Week 52 analyses) will be considered as having a recurrence.

Systemic medications or topical steroids administered as part of gradual dose reduction (tapering) will not be considered prohibited medications. Topical steroids, including those administered as part of short-term standard treatment following an ocular surgical procedure, will also not be considered prohibited medications.

Safety Analyses:

Safety analyses will be performed on the safety population at Weeks 24 and 52. Descriptive statistics will be provided for all treatment-emergent adverse events (TEAEs). Frequency counts and percentage of subjects within each treatment group will be provided by using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) by treatment. Clinical laboratory results will be presented by treatment group using descriptive statistics. Vital signs will be presented using descriptive statistics by treatment group and visit. Subjective ocular tolerability and discomfort assessment results will be presented using descriptive statistics by treatment group and visit. Concomitant medications will be presented by treatment group after coding with the World Health Organization (WHO) Drug Dictionary terms.

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List of Abbreviations

Table 1–1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical
BCVA	Best corrected visual acuity
BUN	Blood urea nitrogen
CFP	Color fundus photography
CFR	(US) Code of Federal Regulations
CI	Confidence interval
CPR	Cardiopulmonary resuscitation
CRA	Clinical Research Associate
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
eCRF	Electronic case report form
ESR	Erythrocyte sedimentation rate
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluocinolone acetonide
FDA	Food and Drug Administration
GCP	Good Clinical Practice (guidelines)
HIV	Human immunodeficiency virus
HPF	High-power field
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug application
IOP	Intraocular pressure
IRB	Institutional Review Board
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
MedDRA	Medical Dictionary for Regulatory Activities
OTC	Over-the-counter
PT	Preferred term
PVA	Polyvinyl alcohol
SAE	Serious adverse event
SAP	Statistical analysis plan
SD-OCT	Spectral-domain – optical coherence tomography
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected, unexpected serious adverse reaction
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
US/USA	United States of America
USPI	US prescribing information
WHO	World Health Organization

1 INTRODUCTION

1.1 Background

YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg (180 mcg) is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye (intermediate, posterior, or panuveitis), and was approved for marketing by the United States (US) Food and Drug Administration (FDA) in Oct 2018. In Mar 2019, the product received approval under the ILUVIEN® brand in the 17 countries under the Mutual Recognition Procedure for prevention of relapse in recurrent non-infectious uveitis affecting the posterior segment of the eye. EyePoint Pharmaceuticals, Inc. (the Sponsor) developed this injectable intravitreal implant in a drug delivery system that contains 0.18 mg of fluocinolone acetonide (FA) designed to release FA at an initial rate of 0.25 µg/day into the vitreous humor for 36 months. YUTIQ® was designed to provide local steroid therapy to the eye for an extended period with the goals of eliminating the need for surgical implantation, providing extended, effective control of inflammation with an acceptable benefit/risk profile, and reducing the side effects associated with systemic administration of corticosteroids or immunomodulating drugs.

The Sponsor is now developing Yutiq 0.05 mg (FA intravitreal implant) with 0.05 mg (50 mcg) of FA for the same indication as that noted above for YUTIQ® 0.18 mg. 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 delivered through a siliconized 25-gauge needle using a pre-loaded injector.

1.2 Uveitis

Uveitis is defined as inflammation of the uveal tract (iris, ciliary body, choroids) or adjacent structures of the eye. The cause of an inflammatory reaction in the inner eye can be infectious, traumatic, neoplastic, or autoimmune. According to the classification scheme recommended by the International Uveitis Study Group, the disease can be classified on the basis of anatomic locations: anterior, intermediate, posterior, or panuveitis.

Uveitis affecting the posterior segment of the eye is responsible for approximately 10% of blindness in the US. Chronic non-infectious uveitis affecting the posterior segment of the eye can occur at any age and affects people of different ethnic origins. The inflammation that affects the choroid and retina may be a primary intraocular process or an ocular manifestation of systemic disease. Uveitis of the posterior segment accounts for most of the loss of vision in patients with uveitis due to cystoid macular edema, glaucoma, retinal detachment, subretinal fibrosis, cataract, and optic disk atrophy.

1.3 Current Treatments for Uveitis

Uveitis is often a chronic disease requiring long-term medical therapy. Currently, medical management of uveitis of the posterior segment includes the local administration of corticosteroid (topical, periocular, intravitreal) and/or systemic steroids or immunosuppressants. Immunosuppressive therapy is used for patients with severe uveitis who cannot tolerate or do not respond to systemic corticosteroid therapy. The goal of therapy is to suppress the inflammation in the back of the eye.

There are disadvantages associated with these treatments and/or their routes of administration. All corticosteroid therapy, including systemic, is associated with ocular side effects, in particular cataract and corticosteroid-induced increased intraocular pressure (IOP), but these side effects are more commonly seen with local therapy. Topical delivery is not effective for the treatment of uveitis of the posterior segment due to its limited intraocular penetration. Periocular or intravitreal corticosteroid injections may be required frequently; however, injections have additional potential risks such as globe perforation, orbital fibrosis, endophthalmitis, and ptosis.

In addition to Yutiq®, corticosteroids currently approved for the intravitreal treatment of chronic non-infectious uveitis affecting the posterior segment of the eye include Retisert® (invented by Eyepoint and licensed to Bausch and Lomb), OZURDEX®, and TRIVARIS®. Despite the availability of these approved products as intravitreal therapy of uveitis of the posterior segment, systemic corticosteroids remain the mainstay of uveitis therapy (MUST Group 2011). However, long-term use of systemic corticosteroids is associated with significant side effects (Brunton et al. 2006) and may not be a practical option for many patients.

Yutiq 0.05 mg, a product that is relatively simple to administer and delivers the corticosteroid locally for at least 6 months, may offer significant benefits over existing local and systemic steroid therapies in the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

For more complete information regarding the safety profile and efficacy of Yutiq 0.05 mg, please refer to the current Yutiq Investigator's Brochure (IB).

2 STUDY OBJECTIVES

The primary objective is 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 (intermediate, posterior, or panuveitis).

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

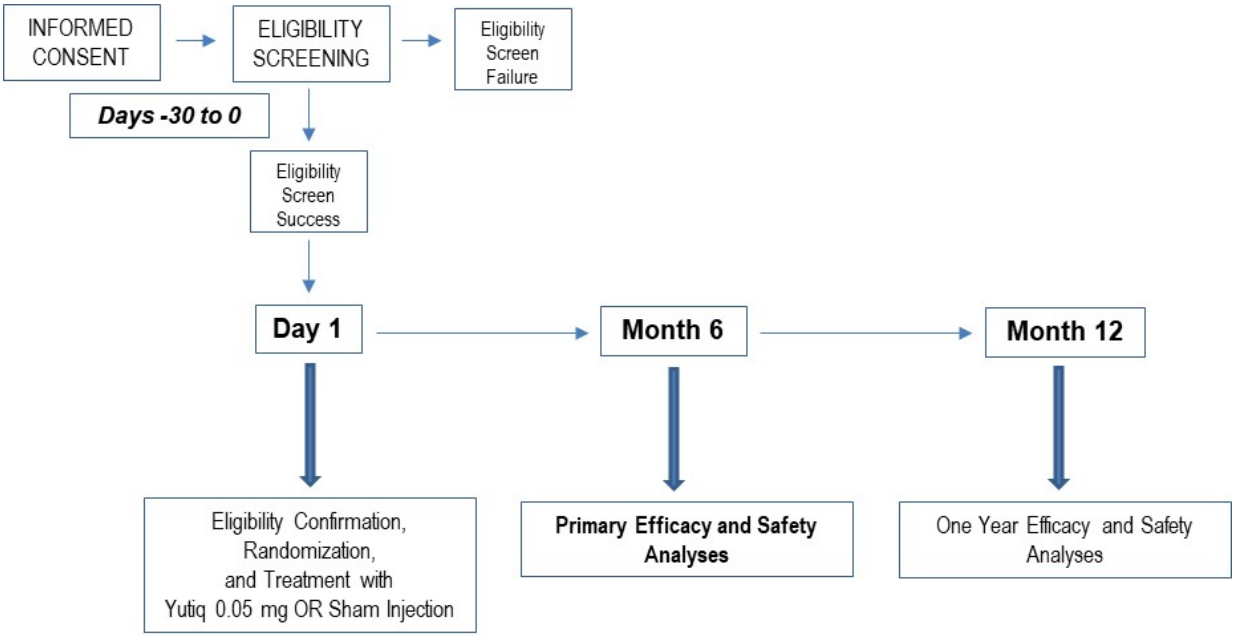
The protocol was originally planned to be a 52-week, prospective, randomized, masked (subject and outcome assessor), controlled, safety and efficacy study of intravitreal Yutiq 0.05 mg compared to sham injection with a primary efficacy and safety readout at 24 weeks.

The Sponsor has decided to stop enrollment for reasons other than safety or efficacy in early May 2022, following FDA advice received on January 24, 2022. The Sponsor is reevaluating the development program of Yutiq 0.05 mg. Subject enrollment has been stopped, and all subjects have been unmasked. Subjects who were randomized to the sham injection were discontinued from the study and underwent their EOS visit. Subjects who were randomized to sham injection may have been treated with standard of care medication, if necessary. Subjects who were randomized to Yutiq 0.05 mg will be followed on a modified protocol schedule through Month 12 (or ET) and evalulated for efficacy and safety.

As depicted in Figure 3-1, subjects will receive either Yutiq 0.05 mg or a sham injection on Day 1 of the study. Subjects who were treated with Yutiq 0.05 mg will be assessed over the following 52 weeks on a modified protocol schedule according to the schedule presented in

Table 5–1. Subjects who were randomized to the sham injection were discontinued from the study and underwent their EOS visit.

Figure 3-1: Study Design Schema, Study EYP-2102-001



Note: The sponsor decided to stop enrollment for reasons other than safety or efficacy in early May 2022, following FDA advice received on January 24, 2022. The Sponsor is reevaluating the development program of Yutiq 0.05 mg Subject enrollment in the study has been stopped. All subjects who were currently enrolled have been unmasked. Subjects who were to receive Yutiq 0.05 mg will be followed on a modified protocol schedule through Month 12 (or ET).

3.2 Discussion of Study Design, Including the Choice of Control Groups

A randomized, multicenter, masked, controlled study design has been selected in order to assess the safety and efficacy of the study treatment. This study will utilize a sham injection as the control. To minimize bias, two Investigators will be used at each study site. One Investigator will serve as the unmasked treating Investigator (Investigator 1) and the other Investigator will serve as the masked assessing Investigator (Investigator 2). On Day 1, Investigator 1 will inject Yutiq 0.05 mg or perform a sham injection. Either the Investigator 1 or a trained and delegated site staff member may also perform all Day 1 procedures and assessments. At all other visits, study assessments will be performed by Investigator 2. Only Investigator 1 will know the assigned treatment and should perform the post-injection indirect ophthalmoscopy to avoid unmasking of additional investigators. Study personnel will use every reasonable effort to maintain the study mask.

3.3 Duration of Study

All subjects who were randomized to Yutiq 0.05 mg will be followed for 12 months after treatment on a modified protocol schedule. Subjects who were randomized to the sham injection have been discontinued from the study and underwent their EOS visit. After the initial Screening

visit, subjects will have up to 30 days to be enrolled. Study treatment will be administered on Day 1. Eligible subjects who are enrolled in this study and randomized to receive Yutiq 0.05 mg will be seen for 8 scheduled study visits over approximately 12-14 months depending on the time between initial Screening, Day 1, and the final study visit at Month 12. Screen failures will be recorded along with the reason(s) for not meeting the eligibility criteria.

3.4 Assignment of Subject Identification Number

Once a subject has provided written informed consent, and it has been determined that the subject will undergo screening, a Subject Identification (ID) Number will be assigned by the study site. The first 2 digits of the ID number will be the assigned site number as followed by a 3-digit number in sequential order (ie, 01-001, 01-002, etc.).

The ID number is to be recorded on all study documents and will link the documents to the subject's medical record. To maintain confidentiality, the subject's name should not be recorded on any study document other than the informed consent form (ICF).

Only those patients who have been randomized will have Exclusion/Inclusion data recorded on the electronic case report form (eCRF).

3.5 Designation of Study Eye and Randomization

One eye in each subject will be designated as the study eye. For subjects with unilateral uveitis, the study eye will be the affected eye; for subjects with bilateral uveitis, the study eye will be the more severely affected eye fitting the inclusion/exclusion criteria (ie, the eye having suffered more recurrences in the previous year, or if equal, the eye having received more therapy in the previous year, or if equal, the eye having the worse VA, or if equal, the eye clinically judged to be the more severely affected eye.) If the eyes are symmetrically affected, the study eye will be the right 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 on the basis of whether the subject is receiving systemic treatment to control uveitis at the time of study entry.

The randomization schedule will be prepared using a blocked randomization and will be generated by an independent statistician.

The treatment assignment will be revealed to the assessing Investigator only in emergency situations when medical/supportive care cannot be provided without determining which study treatment the subject.

3.5.1 Unmasking

Unmasking a subject's treatment to the assessing Investigator should only be done in emergency situations for reasons of subject safety.

At the initiation of the study, the clinical sites will receive instructions for unmasking a subject.

In the event that an emergency unmasking is required, the assessing Investigator/medically qualified designee has the authority to unmask a subject's treatment using IVRS, or its back-up

system if IVRS is not functioning. If possible, the assessing Investigator/medically qualified designee should contact the Medical Monitor or designee before breaking the mask.

When the masked treatment code is broken, the date and time of unmasking, name of person doing the unmasking, and the reason for unmasking must be fully documented in the source documentation.

3.6 Recording of Injection Procedure

The injection procedure of Yutiq 0.05 mg may be photographed or video-recorded according to the site's standard procedures. Images and/or video will be provided to the Sponsor who may distribute them to other participating sites or other appropriate parties. Subject-identifying information must be redacted from all images and video prior to distribution.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

Subject enrollment has been stopped for reasons other than safety or efficacy, following FDA advice received on January 24, 2022. See Section 3.1 for further details. Subjects will be enrolled in the study only if they meet all the following eligibility criteria.

4.1 Inclusion Criteria

Subjects will be considered eligible for participation in the study if all of the following inclusion criteria are satisfied:

1. Male or non-pregnant female at least 18 years of age at time of consent.
2. One or both eyes having a history of recurrent non-infectious uveitis affecting the posterior segment of the eye (intermediate, posterior, or panuveitis) with or without anterior uveitis >1 year duration.
3. During the 52 weeks prior to enrollment (Day 1), the subject must have received treatment for uveitis in the study eye with:
   a) Systemic corticosteroid or other systemic therapies for at least 12 consecutive or non-consecutive weeks,

      AND/OR

   b) at least 2 intra- or peri-ocular administrations of corticosteroid in the study eye,

      OR

   c) the study eye has experienced recurrence of uveitis at least 2 separate times requiring systemic, intra- or peri-ocular injection of corticosteroid.
4. At the time of enrollment (Day 1), the study eye has <10 anterior chamber cells/HPF (high-power field) and a vitreous haze ≤ grade 2.
5. Visual acuity of study eye ≥15 letters on the ETDRS chart.
6. Not planning to undergo elective ocular surgery during the study.
7. Able to understand and sign the ICF.
8. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

4.2 Exclusion Criteria

Subjects who fulfill any of the following criteria will not be recruited into the study:

Ocular Exclusion Criteria (for the study eye, unless indicated otherwise):

1. History of posterior uveitis only that is not accompanied by vitritis or macular edema.
2. History of iritis only associated with no vitreous cells, anterior chamber cells, or vitreous haze at Day 1.
3. Uveitis with infectious etiology.
4. Vitreous hemorrhage.

5. Intraocular inflammation associated with a condition other than noninfectious uveitis (eg, intraocular lymphoma).
6. Uveitis limited to the anterior segment, ie, anterior uveitis only.
7. Ocular malignancy **in either eye**, including choroidal melanoma.
8. Previous viral retinitis.
9. Toxoplasmosis scar or scar related to previous viral retinitis in the study eye.
10. Current viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, mycobacterial infections of the eye, or fungal diseases of ocular structures.
11. Media opacity precluding evaluation of retina and vitreous.
12. Peripheral retinal detachment in area of insertion.
13. Diagnosis of any form of glaucoma or ocular hypertension at Screening, unless previously treated with an incisional surgery procedure that has resulted in stable intraocular pressure (IOP) in the normal range (10-21 mmHg).
14. IOP >21 mmHg or concurrent therapy at Screening with any IOP-lowering pharmacologic agent.
15. Chronic hypotony (<6 mmHg).
16. Ocular surgery within 12 weeks prior to Day 1.
17. Capsulotomy within 30 days prior to Day 1.
18. Prior intravitreal treatment with Retisert®, ILUVIEN®, or YUTIQ® (0.18 mg) within 156 weeks prior to Day 1.
19. Prior intravitreal treatment with OZURDEX® or sub-choroidal injection with XIPERE™ within 24 weeks prior to Day 1.
20. Prior intravitreal treatment with Triesence® or TRIVARIS™ within 12 weeks prior to Day 1.
21. Peri-ocular or subtenon steroid treatment within 12 weeks prior to Day 1.

All other Exclusion Criteria:

22. Allergy to fluocinolone acetonide or any component of Yutiq 0.05 mg.
23. Requirement for chronic systemic or inhaled corticosteroid therapy (>15mg prednisone daily) or chronic systemic immunosuppressive therapy.
24. History of certain skin cancers (specifically, basal cell carcinoma and squamous cell carcinoma), any malignancy receiving treatment, or in remission less than 5 years prior to Day 1.
25. Positive test for human immunodeficiency virus (HIV) or syphilis during Screening.
26. Mycobacterial uveitis or chorioretinal changes of either eye which, in the opinion of the Investigator, result from infectious mycobacterial uveitis.

27. Systemic infection within 30 days prior to Day 1.
28. Any severe acute or chronic medical or psychiatric condition that could increase the risk associated with study participation or could interfere with the interpretation of study results and, in the judgment of the Investigator, could make the subject inappropriate for study enrollment.
29. Any other systemic or ocular condition which, in the judgment of the Investigator, could make the subject inappropriate for study enrollment.
30. Treatment with an investigational drug or device within 30 days prior to Day 1.
31. Pregnant or nursing females; females of childbearing potential who are unwilling or unable to use an acceptable method of contraception as outlined in the protocol from at least 14 days prior to Study Day 1 until the 52-week Visit.
32. Unlikely to comply with the study protocol or who are likely to be lost to follow-up within 52 weeks.

4.3 Pregnancy and Contraception

Women of childbearing potential must be practicing and willing to continue using a highly effective method of birth control during the course of the study, such as: oral contraceptive pill (eg, Ortho Tri-Cyclen®); injection (eg, Depo Provera®); implant (eg, Norplant®); patch (eg, Ortho Evra Patch®); vaginal ring (eg, NuvaRing®); intrauterine coil (eg, Mirena® coil); intrauterine device (IUD); or a barrier method (eg, latex condom, diaphragm, or cap) used **with an additional form of contraception, ie, two methods** (eg, sponge, spermicide, hormonal contraceptive pill, or injection). A female is considered to be of childbearing potential UNLESS she is post-menopausal (no menses for two consecutive years) or without a uterus and/or both ovaries.

Before enrolling a woman of childbearing potential, Investigators must review with the subject the following:

- Pregnancy prevention information
- Risks to unborn child(ren)
- Risks if currently nursing
- Any drug interactions with hormonal contraceptives
- Contraceptives in current use; and
- Guidelines for the follow-up of a reported pregnancy

Subjects who become pregnant during the study should be discontinued from the study immediately. Positive urine pregnancy results will be confirmed by a serum pregnancy test. Subjects should be instructed to notify the Investigator if it is determined after completion of the study that they became pregnant while participating in the study. However, it is the Investigator's responsibility to pursue the follow-up. Whenever possible, a pregnancy should be followed to term, any premature terminations of pregnancy should be reported, and the status of the mother and the child should be reported to the Medical Monitor after delivery.

Urine pregnancy testing will be done in female subjects of childbearing potential at Screening, Day 1, and Month 12 as shown in Table 5–1.

Subjects who are not of childbearing potential meeting one or both of the following criteria will not be required to be tested for pregnancy or use contraception:

- Amenorrheic for >2 years without a hysterectomy and bilateral oophorectomy and a FSH value in the postmenopausal range upon pre-trial (screening) evaluation.
- Post-hysterectomy, bilateral oophorectomy, or tubal ligation. Tubal ligation must be confirmed with medical records of the actual procedure.

If the Investigator becomes aware of a pregnancy occurring in any male subject's partner during the male subject's treatment with the investigational product, the Investigator must submit this information to the Sponsor on the Pregnancy Report Form.

4.4 Study Termination Criteria

Each subject will be informed that they are free to withdraw from the study at any time. The Investigator, the Investigator in consultation with the Medical Monitor, or the Medical Monitor may exercise his or her medical judgment to terminate a subject's participation in the study if it is in the best interest of the subject.

If a subject withdraws from the study during the follow-up period, the Investigator should make every effort to have the subject return to the clinic for the end of study safety evaluations.

Medical Monitoring for this study will be conducted by:

PPD MD
PPD
EyePoint Pharmaceuticals, Inc.
480 Pleasant Street, Suite B300
Watertown, MA 02472 USA
Cell: PPD
PPD

The Sponsor reserves the right to terminate the study at any time. Every effort should be made to collect all data required by the protocol during or following the subject's early termination visit.

In cases of early termination, every effort should be made to complete the case report forms and report the results as thoroughly as possible. A termination eCRF page should be completed for every subject who received study treatment whether or not the subject completed the study. The reason for any early termination from the study should be indicated on this form. The primary reason for a subject's early termination should be selected from the following standard categories:

Adverse Event (AE): Clinical or laboratory events occurred that in the medical judgment of the Investigator for the best interest of the subject are grounds for discontinuation. This includes serious AEs (SAEs) and non-serious AEs regardless of the relationship to study drug.

Subjects who are withdrawn due to AEs must be followed until there is either:

- resolution
- stabilization or severity to mild
- returned to baseline status
- subject is lost to follow-up
- the event is otherwise explained by the Investigator

Death: The subject died during the study.

Withdrawal of Consent: The subject desired to withdraw from further participation in the study in the absence of a medical need to withdraw as determined by the Investigator. If the subject gave a reason for this desire, this should be recorded.

Major Protocol Violation: There was failure to meet the protocol entry criteria or the subject failed to adhere to the protocol requirements or received prohibited medication (eg, subject failure to follow instructions, or inability to complete study assessments). The violation necessitated premature termination from the study.

Other: The subject was terminated for a reason other than those listed above, such as termination of study by the Sponsor or a regulatory authority. The Investigator must specify the reason.

5 STUDY PROCEDURES

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 (Table 5–1). Data will be collected for both eyes at all visits except for the SD-OCT assessments, which will be collected in the fellow eye only at Day 1, Day 28, and at the early termination or Month 12 (end of study) visit.

BCVA by ETDRS: The equipment and procedures necessary for testing BCVA are presented in Appendix 1. 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 (Table 5–1). Visual acuity testing in this study is required at a distance of 4 meters, and for subjects with reduced vision at 1 meter. Each site should have at least one certified refractionist available for the use of ETDRS charts. **An ETDRS-certified refractionist** should perform all protocol refraction and BCVA measurements required by the protocol.

Slit lamp Biomicroscopy: Anterior chamber evaluation will be conducted using a slit beam of 1 mm height and 1 mm width with maximum luminance through the highest powered lens using the Investigator's standard slit lamp equipment and procedure. This procedure will be the same for all subjects observed at the Investigator's site. Ocular structures, including vitreous haze, the presence of anterior chamber cells, and fundus examination will be measured according to the scales and conventions presented in Appendix 2. Ocular examinations will be done at the study visits noted in (Table 5–1).

Dilated Ophthalmoscopy: Will be performed according to the Investigator's preferred procedure. This procedure will be the same for all subjects observed at the Investigator's site (Appendix 2). Ocular examinations will be done at the study visits noted in Table 5–1.

Intraocular Pressure/Tonometry: IOP will be measured as described in Appendix 2 at the study visits noted in (Table 5–1).

SD-OCT Assessments: Spectral-domain – optical coherence tomography assessments of both eyes will be taken by a study-certified OCT technician according to the standardized procedures described in the Study Manual. Because the eye must be dilated for OCT, it must be performed after testing visual acuity if these procedures are performed on the same day. SD-OCT testing will be done at the study visits noted in (Table 5–1).

Ocular and Non-ocular TEAEs: Adverse events will be recorded at each study visit by asking the subject "How are you feeling today?" and additional questions as necessary, making an assessment of the reason for use of new concomitant medications or concurrent procedures (see Section 8.1).

5.1 Measurements and Evaluations by Visit

The schedule of study procedures and assessments by visit is presented in Table 5–1. The Sponsor decided to stop enrollment for reasons other than safety or efficacy, following FDA advice received on January 24, 2022. The Sponsor is reevaluating the development program of Yutiq 0.05 mg. All subjects have been unmasked. Subjects who had been assigned to sham were discontinued from the study in early May 2022 and were treated with standard of care medication, if necessary. Subjects who had been treated with Yutiq 0.05 mg will be followed at Month 6 and 12 (or ET).

Table 5–1: Schedule of Study Procedures and Assessments, Study EYP-2102-001

	Screening	Day 1	Day 7	Day 28	Months 2, 3	Months 6, 12 or ET
Timing/Interval:	*-30 to 0*	*1*	*±2 days*	*±3 days*	*±7 days*	*±28 days*
Informed Consent	X					
Medical/Ophthalmic/Medication History	X					
Demographics	X					
Inclusion/Exclusion Criteria	X	X				
Randomization		X				
Pregnancy Test[a]	X	X				X[gh]
Vital Signs[b]	X	X	X	X	X	X
Clinical Laboratories[cd]	X					X[g]
ETDRS BCVA	X	X	X	X	X	X
Ophthalmic Examinations[de]	X	X	X	X	X	X
Intraocular Pressure (IOP)[e]	X	X	X	X	X	X
SD-OCT[f]		X		X	X	X
Subjective Ocular Tolerability/Discomfort	X	X	X	X	X	X
Yutiq 0.05 mg Placement or Sham Injection		X				
Concomitant Medications	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X

BCVA = Best corrected visual acuity; ET = Early termination; ETDRS = Early treatment diabetic retinopathy study; HIV = Human immunodeficiency virus; SD-OCT = Spectral domain – optical coherence tomography

Note: Yutiq 0.05 mg = Fluocinolone acetonide (FA) intravitreal 0.05 mg insert

Note: For subjects with unilateral uveitis, the study eye will be the affected eye; for subjects with bilateral uveitis, the study eye will be the more severely affected eye fitting the inclusion/exclusion criteria (ie, the eye having suffered more recurrences in the previous year, or if equal, the eye having received more therapy in the previous year, or if equal, the eye having the worse VA, or if equal, the eye clinically judged to be the more severely affected eye.) If the eyes are symmetrically affected, the study eye will be the right eye.

Note: All ocular procedures and assessments will be performed on both the study eye and non-study (fellow) eye and data will be collected for both eyes with the exception of SD-OCT assessments (see footnote “g” below).

(table footnotes on next page)

Footnotes for Table 5-1:

a. Females of child-bearing potential only. Urine pregnancy test done at Screening, Day 1, and Month 12.

b. Vital signs will include systolic/diastolic blood pressure and pulse rate measured after the subject is in the sitting position for at least 5 minutes, height and weight (at Screening only).

c. Routine clinical laboratory tests will include: hematology (including erythrocyte sedimentation rate); serum chemistry; urinalysis; HIV and syphilis serology testing; tuberculosis testing (Screening only).

d. Ophthalmic examinations will include: dilated indirect ophthalmoscopy, and anterior, posterior, and intermediate slit lamp examinations.

e. IOP will be recorded in the eCRF as the mean of three measurements.

f. SD-OCT assessments will only be collected in the fellow eye at Day 1, Day 28, Month 6, and Month 12 (end of study) visits or at ET.

g. To be done at Month 12 (end of study) visit, or for ET only.

5.1.1 Days -30 to 0 (Screening Period)

The following procedures must be completed during the initial Screening period (Table 5–1).

Informed Consent: Properly executed informed consent (written and verbal) is to be obtained prior to completion of any trial related procedures. A subject may take as long as needed to review the ICF and consider trial participation; they may take the document with them and return for Day 1 at a later date (provided the study is still open for enrollment). The subject must review, sign and date the document and receive a copy.

Inclusion/Exclusion Criteria: Inclusion/exclusion criteria (Section 4.1 and Section 4.2, respectively) will be reviewed to determine the subject's eligibility to participate in the trial with the Investigator verifying enrollment eligibility.

Demography, Medical/Ophthalmic History, and Medication History: Demography, medical history, complete ophthalmic surgical and medical history, and recent (previous 30 days) ophthalmic and systemic concomitant medications are to be recorded. Please document current contact lens use or ocular trauma in the study eye.

Ocular Procedures to be Performed with Data Collected for Both Eyes:

- BCVA (Appendix 1)
- Intraocular pressure (Appendix 2)
- Ocular examination – dilated ophthalmoscopy and slit lamp biomicroscopy (Appendix 2)
- Subjective ocular tolerability and discomfort assessment (Appendix 3)

Non-Ocular Procedures to be Performed:

- Collect urine sample for pregnancy testing in female subjects of childbearing potential (Section 4.3)
- Vital sign measurements (Section 8.4)
- Collect blood and urine samples for clinical laboratory evaluations (Section 8.2)
- Prior and concomitant mediations (Section 7.1 and Section 7.5, respectively)
- Adverse events, which will be collected from the time the ICF is signed (Section 8.1)

5.1.2 Day 1 (Study Treatment)

The following procedures will be completed during the Day 1 visit (Table 5–1).

Inclusion/Exclusion Criteria: Will be reviewed again (Section 4.1 and Section 4.2, respectively) to confirm the subject's eligibility to keep participating in the trial with the Investigator verifying eligibility.

Randomization and Study Eye: If still meeting the eligibility criteria, study subjects will then be randomized using the IVRS to receive either intravitreal Yutiq 0.05 mg or sham injection in the designated study eye on Day 1 (Section 3.5).

Study Treatment Administration: Yutiq 0.05 mg will be administered to the designated study eye by injection through the pars plana into the vitreous humor using a pre-loaded applicator with a

25-gauge siliconized needle. The complete intravitreal injection procedure is presented in Section 6.2.1. The intravitreal injection procedure is the same as that described in the current US prescribing information (USPI) for the marketed product YUTIQ® 0.18 mg (YUTIQ® USPI, 2021).

Subjects assigned to the sham injection control group will be prepared for injection in the same manner as subjects in the Yutiq 0.05 mg treatment group and will receive the same post-treatment evaluations and medications. However, when the Investigator opens the treatment packaging for a subject assigned to the sham injection control group, the package will contain an empty syringe with a blunt needle attached. The sham injection will consist of pressing the blunt needle against the sclera of the eye with approximately the same pressure as would be used during the injection of Yutiq 0.05 mg (Section 6.4.3).

Ocular Procedures to be Performed with Data Collected for Both Eyes (unless otherwise specified):

- BCVA (Appendix 1)
- Intraocular pressure (Appendix 2)
- Ocular examination – dilated ophthalmoscopy and slit lamp biomicroscopy (Appendix 2)
- SD-OCT assessment
- Subjective ocular tolerability and discomfort assessment (Appendix 3)

Non-Ocular Procedures to be Performed:

- Vital sign measurements (Section 8.4)
- Collect urine sample for pregnancy testing in female subjects of childbearing potential (Section 4.3)
- Prior and concomitant mediations (Section 7.1 and Section 7.5, respectively)
- Adverse events (Section 8.1)

5.1.3 Day 7

The following procedures will be completed during the Day 7 visit (Table 5–1).

Ocular Procedures to be Performed with Data Collected for Both Eyes (unless otherwise specified):

- BCVA (Appendix 1)
- Intraocular pressure (Appendix 2)
- Ocular examination – dilated ophthalmoscopy and slit lamp biomicroscopy (Appendix 2)
- Subjective ocular tolerability and discomfort assessment (Appendix 3)

Non-Ocular Procedures to be Performed:

- Vital sign measurements (Section 8.4)
- Concomitant and rescue mediations (Section 7.5 and Section 7.6, respectively)

- Adverse events (Section 8.1)

Unscheduled visit assessments may be performed as necessary at the discretion of the Investigator following Sponsor approval.

5.1.4 Day 28

The following procedures will be completed during the Day 28 visit (Table 5–1).

Ocular Procedures to be Performed with Data Collected for Both Eyes (unless otherwise specified):

- BCVA (Appendix 1)
- Intraocular pressure (Appendix 2)
- Ocular examination – dilated ophthalmoscopy and slit lamp biomicroscopy (Appendix 2)
- SD-OCT assessment
- Subjective ocular tolerability and discomfort assessment (Appendix 3)

Non-Ocular Procedures to be Performed:

- Vital sign measurements (Section 8.4)
- Concomitant and rescue mediations (Section 7.5 and Section 7.6, respectively)
- Adverse events (Section 8.1)

Unscheduled visit assessments may be performed as necessary at the discretion of the Investigator following Sponsor approval.

5.1.5 Months 2 and 3

The following procedures will be completed during the Month 2 and Month 3 visits (Table 5–1).

Ocular Procedures to be Performed with Data Collected for Both Eyes (unless otherwise specified):

- BCVA (Appendix1)
- Intraocular pressure (Appendix 2)
- Ocular examination – dilated ophthalmoscopy and slit lamp biomicroscopy (Appendix 2)
- SD-OCT assessment (study eye only)
- Subjective ocular tolerability and discomfort assessment (Appendix 3)

Non-Ocular Procedures to be Performed:

- Vital sign measurements (_Vital_Signs_1)
- Concomitant and rescue mediations (_Concomitant_Medications and _Rescue_Medications, respectively)
- Adverse events (_Adverse_Events)

5.1.6 Month 6

The following procedures will be completed during the Month 6 visit (Table 5–1).

Ocular Procedures to be Performed with Data Collected for Both Eyes (unless otherwise specified):

- BCVA (
- Intraocular pressure (Appendix 2)
- Ocular examination – dilated ophthalmoscopy and slit lamp biomicroscopy (Appendix 2)
- SD-OCT assessment (study eye only)
- Subjective ocular tolerability and discomfort assessment (Appendix 3)

Non-Ocular Procedures to be Performed:

- Vital sign measurements (_Vital_Signs_1)
- Concomitant and rescue mediations (_Concomitant_Medications and _Rescue_Medications, respectively)
- Adverse events (_Adverse_Events)

5.1.7 Month 12 (End of Study) or Early Termination

The following procedures will be completed during the Month 12 (End of Study) visit, or at early termination (Table 5–1). Subjects who terminate the study prior to the Month 12 visit should undergo all procedures noted below.

Ocular Procedures to be Performed with Data Collected for Both Eyes (unless otherwise specified):

- BCVA (Appendix 1)
- Intraocular pressure (Appendix 2)
- Ocular examination – dilated ophthalmoscopy and slit lamp biomicroscopy (Appendix 2)
- SD-OCT assessment
- Subjective ocular tolerability and discomfort assessment (Appendix 3)

Non-Ocular Procedures to be Performed:

- Collect urine sample for pregnancy testing in female subjects of childbearing potential (Section 4.3)
- Vital sign measurements (Section 8.4)
- Collect blood and urine samples for clinical laboratory evaluations (Section 8.2)
- Concomitant and rescue mediations (Section 7.5 and Section 7.6, respectively)
- Adverse events (Section 8.1)

5.2 Appropriateness of Measurements

The efficacy and safety assessments to be utilized in this study (eg, BCVA by ETDRS, slit lamp biomicroscopy, dilated ophthalmoscopy, IOP measurements, SD-OCT, collection of ocular and non-ocular AEs, clinical laboratory evaluations, vital signs) are standard measures in studies evaluating intravitreal investigational products like Yutiq 0.05 mg.

6 INVESTIGATIONAL MATERIALS

6.1 Study Drug Identification and Description

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.

6.1.1 Yutiq 0.05 mg Composition

Yutiq 0.05 mg intravitreal insert contains fluocinolone acetonide (FA), a synthetic corticosteroid, as the active drug substance. Fluocinolone acetonide is combined [redacted], polyvinyl alcohol (PVA), [redacted] contained within a polyimide tube. [redacted]

The drug delivery system is placed into a one-time-use siliconized needle attached to an injector delivery system. The drug product is sterilized after packaging and prior to distribution.

6.1.2 Yutiq 0.05 mg Packaging

Yutiq 0.05 mg is packaged at EyePoint Pharmaceuticals in a controlled temperature cleanroom. The intravitreal insert is supplied as a sterile, single-use unit in primary, secondary, and tertiary packaging. The insert is provided in a sterile preloaded applicator with a 25-gauge needle. Depression of the syringe plunger is controlled by a stop collar that prevents over-insertion. The applicator is placed into the secondary packaging, a 2.5" x 9" foil chevron pouch and heat-sealed. Finally, the foil pouch is placed into a 3.5" x 12" Tyvek chevron pouch and heat-sealed. The final product is terminally sterilized by gamma irradiation. The outer chevron pouch is labeled as an investigational drug in accordance with applicable regulations and placed inside a similarly labeled carton box.

6.2 Yutiq 0.05 mg Administration

Yutiq 0.05 mg will be administered by intravitreal injection through the pars plana into the vitreous humor of the eye using a 25-gauge siliconized needle applicator that controls the insertion depth and creates a self-healing wound. The injection procedure and the applicator are the same as used with the commercial YUTIQ® 0.18 mg product (YUTIQ® USPI, 2021).

6.2.1 Yutiq 0.05 mg Injection Procedure

The intravitreal injection procedure must be performed under aseptic conditions, which include use of sterile gloves, a sterile drape, a sterile caliper, and a sterile eyelid speculum (or

equivalent). Adequate anesthesia and a broad-spectrum microbicide should be given prior to the injection. The injection procedure for Yutiq 0.05 mg is as follows:

1. Just prior to injection, administer topical and/or subconjunctival anesthesia at the injection site (inferotemporal quadrant recommended).
2. Administer 2-3 drops of a broad-spectrum microbicide into the lower fornix. The lids may be scrubbed with cotton-tipped applicators soaked with a broad-spectrum microbicide. Place a sterile lid speculum. Have the patient look up and apply additional microbicide solution to the injection site. Allow 30-60 seconds for the topical antiseptic to dry prior to injection of Yutiq 0.05 mg.
3. Optimal placement of Yutiq 0.05 mg is inferior to the optic disc and posterior to the equator of the eye. Measure 4 millimeters inferotemporal from the limbus with the aid of calipers for point of entry into the sclera.
4. Using sterile procedure, open the sterile foil pouch containing Yutiq 0.05 mg.
5. Remove the Yutiq 0.05 mg applicator from the sterile pouch by grasping the barrel of the applicator; do not grasp the plunger.
6. Remove the black plunger stop from the plunger.
7. Carefully remove the protective cap from the needle and inspect the needle tip to ensure it is not bent.
8. Remove the trombone wire from the distal end of the needle. Prior to injection, keep the applicator tip above the horizontal plane to ensure that the Yutiq 0.05 mg implant does not fall out of the applicator.
9. Gently displace the conjunctiva so that after withdrawing the needle, the conjunctival and scleral needle entry sites will not align. Care should be taken to avoid contact between the needle and the lid margin or lashes.
10. Insert the needle through the conjunctiva and sclera up to the positive stop of the applicator.
11. Depress the plunger at the back of the applicator fully to deliver the Yutiq 0.05 mg implant into the back of the eye.
12. Remove the Yutiq 0.05 mg applicator from the eye and discard in a biohazard sharps container.
13. Remove the lid speculum and perform indirect ophthalmoscopy to verify adequate central retinal artery perfusion, absence of any other complications, and to verify the placement of the implant. Scleral depression may enhance visualization of the implant. Immediate measurement of IOP may be performed at the discretion of the Investigator.

Following the injection, subjects should be monitored for change in IOP and for endophthalmitis. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection, tonometry within 30 minutes following the injection, and biomicroscopy. Subjects should be instructed to report without delay any symptoms suggestive of endophthalmitis.

6.3 Criteria for Yutiq 0.05 mg Removal

The Investigator should consider removing Yutiq 0.05 mg if any of the following events occur:

- Apparent intolerance to insert
- Endophthalmitis
- Partial extrusion or exposure of insert

Based on prior human experience with the marketed product YUTIQ® 0.18 mg, the likelihood that insert removal will become necessary is very small.

6.4 Sham Injector

6.4.1 Description

The sham applicator is an empty 1-mL syringe attached to a blunt needle; it does not contain an intravitreal insert.

6.4.2 Sham Injector Packaging and Labeling

Sham injectors will be supplied as individual finished products in primary, secondary, and tertiary packaging. The primary packaging is the sham applicator, which includes a blunt needle. The sham applicator is placed into the secondary packaging, a 2.5" x 15" foil chevron pouch and heat-sealed. Lastly, the foil pouch is placed into a 3.5" x 18" Tyvek chevron pouch. The outer chevron pouch will be labeled for investigational use in accordance with applicable regulations. The assembled units are subsequently sterilized by gamma irradiation, resulting in the sham injector, a sterile, single-use product.

6.4.3 Sham Injection Procedure

The sham injection will consist of pressing the blunt needle against the sclera of the eye with approximately the same pressure as would be used during the injection of Yutiq 0.05 mg.

6.5 Storage and Dispensing of Study Treatments

Yutiq 0.05 mg and the sham injectors must be stored in a secure place and at controlled room temperature (15°C to 30°C/59°F to 86°F) and in the original containers.

The Investigator has the overall responsibility for ensuring that study treatments are stored in a safe location with limited-access under the specified storage conditions. Limited responsibility may be delegated to a pharmacy representative; however, this delegation must be documented.

6.6 Drug Accountability

The Investigator is responsible for ensuring adequate accountability of all used and unused study treatments. While the Investigator may delegate components of drug accountability tasks to documented designee(s) (eg, pharmacist or staff designee), the ultimate responsibility for drug control and accountability resides with the Investigator. This includes acknowledgment of receipt of each shipment (quantity and condition), maintenance of subject dispensing records and returned (as required) documentation. Dispensing records will document quantities received from the Sponsor (or designee) and quantities dispensed to subjects, including treatment

kit/package number, date dispensed, subject identification number, subject initials, and the initials of the person dispensing drug will be recorded on the drug accountability log.

During study initiation, the study monitor (Clinical Research Associate, CRA) will evaluate and obtain a copy of each site's written standard operating procedure for study drug disposal/ destruction or return to ensure that it complies with Sponsor requirements if supplies will not be returned.

An inspection for inventory and accounting purposes, and the assurance of proper storage, will also be conducted during monitoring visits. Any significant accounting or storage discrepancy will be recorded and reported to the Sponsor and a plan for resolution will be documented. After the monitor has checked and verified drug accountability during interim site visits and at the end of the study, any expired, partially-used, and used product should be handled according to the Sponsor's instructions (ie, returned or destroyed).

7 CONCOMITANT MEDICATIONS/PROCEDURES

7.1 Prior 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 (whether continuing or not) prior to Day 1. All prior medications must be documented on the concomitant medications eCRF.

7.2 Tapering/Ending Systemic or Topical Uveitis Treatment Following Day 1

Subjects may be treated prior to entry in order to meet study inclusion criteria. The objective of prior treatment is to obtain a relatively quiet eye prior to enrollment. If a subject is receiving systemic corticosteroids or immunosuppressants, or topical steroids to control uveitis prior to study enrollment, that subject will have such treatment ended within 3 months following Day 1, in a manner that follows the standard of care for ending the specific treatment. For example, some systemic treatment regimens may be ended immediately, while others require a period of gradual dose reduction (tapering). Systemic medications or topical steroids administered as part of gradual dose reduction are not considered prohibited medications.

7.3 IOP Reduction Therapy

Pharmacologic treatment (eyedrops) of elevated IOP must be instituted whenever the IOP is >30 mmHg, and may be instituted at lower IOP levels at the discretion of Investigator and in accordance with the Investigator's standard of care. Treatment may include referral to another ophthalmologist. If IOP does not adequately respond to pharmacologic treatment, alternative treatment should be considered (laser, trabeculectomy). The Investigator should obtain information on the treatment administered by non-study ophthalmologists for inclusion in the study records.

7.4 Cataract Removal and Other Elective Ocular Surgery

Cataracts are recommended to be removed by extra-capsular extraction with phacoemulsification. A cataract may be removed prior to a subject's enrollment. Because of the importance of VA evaluations in this study, the timing of cataract removal or any elective surgery

during the post-treatment follow-up period should be scheduled at least 4 weeks prior to any study visit involving VA assessment.

7.5 Concomitant Medications

All prescription and OTC concomitant medications used concurrently (from the time of ICF signing through Month 12) must be 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. Subjects should be instructed not to take any medication including OTC products, without first consulting with the Investigator. Any AE(s) that result(s) from taking a concomitant medication/therapy following the first study dose should be recorded on the AE eCRF.

7.6 Rescue Treatment of Recurrence of Uveitis

In the event of a uveitis recurrence in either eye (defined as an "Endpoint"), peri-ocular or intraocular corticosteroid injections, or topical medications should be administered as first line local therapy, in accordance with the protocol. Investigators should consider treatment with topical steroids as first line therapy for a recurrence that involves only an increase in anterior chamber cells with no increase in vitreous opacity. Systemic immunosuppressants or systemic steroids should be used only if local therapy fails.

Subjects who experience a recurrence of uveitis will continue participation in the study. Once the subject's recurrence is controlled, the treatment regimen (local or systemic therapy) will be ended in a manner that follows the standard of care for ending the specific treatment regimen.

Details of each recurrence and its treatment will be documented in the eCRF.

7.7 Prohibited Medications

Other than the exceptions described in Section 7.2, Section 7.6, or below, the following concomitant medications are not permitted during the study:

- Oral, systemic, injectable, or topical steroids
- Systemic immunosuppressants

Systemic medications or topical steroids administered as part of gradual dose reduction (tapering), as described in Section 7.2, are not considered prohibited medications. Additionally, topical steroids administered as short-term standard treatment following an ocular surgical procedure are not considered prohibited medications.

It is advisable for the Investigator to discuss treatment with the Medical Monitor before administering any prohibited medication unless it is an emergency.

Any medications or therapies that the subject is using during the study period and that would preclude eligibility as indicated in the Exclusion Criteria (Section 4.2), are prohibited medications.

All prohibited medications used concurrently (from Day 1 through Month 12) must be documented in the eCRF.

8 ASSESSMENT OF SAFETY

Safety assessments will include the incidence and severity of TEAEs reported after Screening, safety 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.

8.1 Adverse Events

The following are specific definitions of terms guided by the International Conference on Harmonization (ICH E2) Guidelines for Good Clinical Practice (GCP) and the US Code of Federal Regulations (CFR) that apply to the following sections. The severity of AEs will be graded by the Common Terminology Criteria for Adverse Events (CTCAE), version 5 (Appendix 4).

Definition of Adverse Event:

An AE is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.

AEs may also include pre- or post-treatment complications that occur as a result of protocol-specified procedures (eg, invasive procedures such as venipuncture, delivery procedure, etc). Pre-existing conditions that increase in severity or change in nature during (or as a consequence of use of a medicinal product in) the study will also be considered AEs.

An AE Will Not Include:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion) for events that led to the procedure
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected prior to the Screening visit, unless they worsen during the study
- Situations where an AE or untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)

Associated with the Use of the Drug (Causality):

There is a reasonable possibility that the event may have been caused by the investigational drug (and/or the administration procedure).

Unexpected Adverse Event:

Any event that is not identified in nature, severity, or frequency in the current version of the IB. For example, if the IB referred to elevated hepatic enzymes or hepatitis, then an event of hepatic necrosis would be considered unexpected by the virtue of the greater severity. The Sponsor or designee will determine AE expectedness.

8.1.1 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

8.1.2 Serious Adverse Events

An SAE is any AE that results in one of the following outcomes:

- Death/Fatal
- Is life-threatening (the term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more intense).
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons for any length of time), or prolongs existing hospitalization.
- Results in a persistent or significant disability/incapacity, or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect (in the child of a subject who was exposed to the study treatment).
- Other important medical event. Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization but required medical intervention in order to prevent a SAE outcome. However, if it is determined that the event may jeopardize the subject and/or may require intervention to prevent one of the other SAE outcomes, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The following hospitalizations will not be considered SAEs:

- A visit to the emergency room or other hospital department for <24 hours that does not result in in-patient admission (unless considered an "important medical event" or a "life-threatening event").
- Elective surgery or planned surgery prior to signing the ICF.
- Admissions as per protocol for a planned medical/surgical procedure.

- Routine health assessments requiring admission for baseline/trending of health status (eg, routine colonoscopy).
- Medical/surgical admission for a purpose other for healthcare purposes and was planned prior to entry into the study (appropriate documentation is required in these cases).
- Admission encountered for another life circumstance that carries no bearing on health status and/or requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

Clarification of SAEs:

- Death is an outcome of an AE, and not an AE in itself.
- All deaths, regardless of cause or relationship, must be reported.
- Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization, it is an SAE.
- "In-patient hospitalization" means the subject has been formally admitted to a hospital for medical reasons for any length of time. This may or may not be overnight. It does not include presentation to, and/or care within, an emergency department.
- The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information.

8.1.3 Sight-Threatening Ocular Events Defined as SAEs in This Study

In addition to the standard SAE categories described above, this study defines these additional ocular events as SAEs:

- An AE that causes a decrease in visual acuity of ≥30 letters or ≥6 lines from the most recent previous measurement of visual acuity, lasting more than 1 hour.
- An AE that causes a decrease in visual acuity to light perception or worse, lasting more than 1 hour.
- An AE that requires surgical intervention (eg, conventional surgery, vitreous tap or biopsy with intravitreal injection of anti-infectives, or laser or retinal cryopexy with gas) to prevent permanent loss of sight.
- An AE that is associated with severe intraocular inflammation (ie, 4.0 anterior chamber cell score, 4+ flare or 4+ vitritis).
- Two consecutive IOP measurements of 30 mmHg or higher taken at least 72 hours apart when a subject is already being treated with two IOP-lowering medications.
- An IOP <6 mmHg requiring medical intervention.
- An AE that in the opinion of the Investigator requires medical or surgical intervention to prevent permanent loss of sight.

The Investigator must employ all necessary therapeutic measures to resolve the SAE. Any medications or therapies used to treat the SAE must be recorded in the eCRF.

8.1.4 Clinical Laboratory Adverse Events

An abnormal laboratory result should be considered an AE if it:

- Results in the initiation or change of an intervention (eg, increased dose of medication), based on medical evaluation (eg, packed red cells for low hemoglobin).
- Results in any out of range laboratory value that in the Investigator's judgment fulfills the definitions of an AE.
- Increases in severity compared to baseline.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the AE eCRF. It is the responsibility of the Investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

All laboratory AEs should be repeated and reassessed by the Investigator to track resolution and especially to confirm if they meet the definition of serious. If serious, they will be reported as SAEs.

The Investigator or a licensed designee must review all laboratory results in a timely manner as demonstrated by signature/date.

8.1.5 Adverse Event Severity and Relationship

Adverse event severity is defined as a qualitative assessment of the intensity of an AE as determined by the Investigator. The assessment of severity is made irrespective of the relationship or seriousness of the event to study treatment or the injection device.

In the absence of an assigned severity per the CTCAE v5.0 (Appendix 4) grading criteria, the Investigator will grade AEs according to the following severity criteria:

Mild/Grade 1:	The event may be noticeable to subject; does not influence daily activities; usually does not require intervention.
Moderate/Grade 2:	The event may be of sufficient severity to make subject uncomfortable; performance of daily activities may be influenced; intervention may be needed.
Severe/Grade 3:	The event may cause severe discomfort; usually interferes with daily activities; subject may not be able to continue in the study; treatment or other intervention usually required.
Life- or Sight-Threatening/Grade 4:	The event requires urgent intervention to preserve life and/or permanent loss of vision.
Death/Grade 5:	The event resulted in the subject's death.

The relationship of study treatment (ie, Yutiq 0.05 mg), the injector, or the injection procedure, to each AE must be determined by the Investigator according to the following:

Not Related:	Evidence indicates no plausible direct relationship to the study treatment, device, or procedure, or there is a reasonable causal relationship between non-investigational product, concurrent disease, or circumstance and the AE; and/or a causal relationship is considered biologically implausible.
Possibly Related:	There is reasonable causal relationship between the study treatment, device, or procedure and the AE. There may or may not be a clinically-plausible temporal sequence between the onset of the AE and study treatment, device, or procedure; the AE is not reasonably supported by other conditions.
Probably Related:	The study medication, device, or procedure and AE occurrence are reasonably related in time; a clinically-plausible temporal sequence between the onset of the AE and study treatment, device, or procedure is likely; based upon the Investigator's clinical experience, the association of the AE with study medication, device, or procedure is likely; all other potential causes have been ruled out.

If the relationship between the AE/SAE and the sequence study treatment, device, or procedure is determined to be "possible" or "probable", the event will be considered related for the purposes of expedited regulatory reporting.

8.2 Recording of Adverse Events

Medical conditions or diseases present before a subject starts study treatment are only considered AEs if they worsen after the start of the study treatment.

Adverse events may be spontaneously reported or elicited at each study visit through open-ended questioning, examination, or evaluation of a subject. To prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.

The Investigator will record all AEs in the eCRF. Where a diagnosis is possible, it is preferable to report the diagnosis rather than a series of terms (signs/symptoms) relating to the diagnosis. If a definitive diagnosis is not possible, the individual symptoms and signs should be recorded.

The following information must be captured for all AEs:

- onset and end date
- severity
- seriousness
- relationship to study treatment or the injection device, procedure
- action taken

- any treatment required
- outcome

If treatment for the AE was administered, it should be recorded on the appropriate concomitant medication/procedure eCRF page. Each distinct AE should be recorded separately.

8.3 Adverse Event Reporting

All subjects enrolled in the study will be evaluated for AEs, which will be collected from the time the ICF is signed until study completion (Table 5–1).

All AEs will be evaluated from onset until resolution or stabilization, whichever is first. Adverse events that continue after the subject's discontinuation or completion of the study will be followed until their medical outcomes are determined or until no further change in the condition is expected. The event and outcome will be reported in writing by the Investigator to the Sponsor. The Investigator shall supply the Sponsor and Institutional Review Board (IRB)/Ethics Committee (EC) with any additional requested information, notably for reported deaths.

8.3.1 Reporting of Serious Adverse Events

All SAEs, regardless of cause(s) or relationship to study drug, must be recorded on the appropriate eCRF page and **reported to the Sponsor within 24 hours of the Investigator's first awareness** using the study's designated SAE Report Form.

Minimal information to be provided on the SAE Report Form includes:

- Protocol number
- Site and Investigator identifiers
- Subject number
- Brief description of the event(s)
- Onset date of the event
- Outcome of the event as of the date of report, if known
- Resolution date and time, if the event(s) resolved
- Any medication administered to treat the event
- Investigator's assessment of the causal relationship of the SAE to the investigational product
- Additional and follow-up information as requested by Sponsor or its designee

SAEs must be reported using the study's designated SAE Report Form and sent to:

Email: PPD

Fax: PPD

The Investigator will also compile with urgent priority other relevant documentation (eg, copies of test results, hospital discharge summary, autopsy report, etc.) and send this information to the Sponsor (or Sponsor's designee).

The FDA and all participating Investigators shall be notified by a written Investigational New Drug Application (IND) safety report of any AE associated with the use of the investigational product that is both serious and unexpected no later than 15 calendar days from the Sponsor's awareness date of the event. An SAE is considered to be associated with the use of the investigational product if the relationship between the SAE and the investigational product is classified by the Investigator as "possibly related" or "probably related" (ie, suspected, unexpected serious adverse reaction [SUSAR]). Any unexpected fatal or life-threatening SAE associated with the use of the investigational product will be reported to the FDA by the Sponsor within 7 calendar days.

The IRB/EC should be notified of SAEs as required in accordance with the local institutional policy.

All Investigators participating in the study will be notified of unexpected SAEs determined to be related to study treatment/injection procedure.

Pregnancy Reporting

Pregnancy that occurs during the study must be immediately reported to the Investigator who will immediately notify the Sponsor or designee within 24 hours of first awareness using the study's designated Pregnancy Report Form. This includes any pregnancy following maternal or paternal exposure to the investigational product.

The pregnancy should be followed to term. The outcome, including premature termination must also be reported to the Sponsor or designee within 24 hours of the Investigator's awareness using the Pregnancy Report Form. All live births must be followed for a minimum of 4 weeks or to the first well-baby visit. All reports of congenital abnormalities/birth defects and spontaneous abortions/miscarriages should be reported as SAEs. Elective abortion procedures without complications should not be considered as AEs.

If the Investigator becomes aware of a pregnancy occurring in any male subject's partner during the male subject's treatment with the investigational product, the Investigator must submit this information to the Sponsor on the Pregnancy Report Form.

The Pregnancy Report Form should be sent to:

Email: PPD

Fax: PPD

Special Situations

Notification must be made to the Sponsor or designee of any special situation that includes the following, regardless of any associated AE:

- A medication error, defined as any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider or subject.
- Abuse, defined as persistent or sporadic intentional excessive use of a medicinal or other product.
- Misuse, defined as any intentional or inappropriate use of a medicinal product that is not in accordance with the protocol instructions or local prescribing information.

- An overdose, defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose per protocol or in the product labeling. In cases of a discrepancy in drug accountability, overdose will be determined only when it is clear that the subject received an excess dose(s).

Special situations should be reported on the study's designated Special Situation Report Form except pregnancies for which there is a dedicated form. If any special situation results in clinical sequela(ae)/AE(s), the event(s) must be recorded on the AE eCRF. If the AE is serious, the SAE eCRF must be completed and a SAE Report Form must be completed and submitted to the Sponsor or designee within 24 hours of first awareness.

Special situations involving concomitant medication do not need to be reported on the Special Situation report form. However, special situations involving concomitant medication that result in clinical sequelae/AEs should be reported on the AE eCRF. In addition, any inappropriate use of prohibited concomitant medications should not be reported as "misuse" but may be more appropriately documented as a protocol deviation.

The Special Situation Report Form should be sent to:

Email: PPD

Fax: PPD

8.4 Clinical Laboratory Evaluations

The routine clinical laboratory tests noted below will be performed at Screening and Month 12 (or early termination) only (Table 5–1):

- Hematology (standard tests)
- Erythrocyte sedimentation rate (ESR)
- Serum electrolytes: sodium, potassium, chloride, calcium, bicarbonate
- Renal function tests: serum creatinine, blood urea nitrogen (BUN)
- Hepatic function tests: serum bilirubin, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), albumin, total protein
- HIV and syphilis serology testing
- Screening test for latent mycobacterium tuberculosis (TB) infection (Screening only)
- Urinalysis (standard tests)
- Urine pregnancy test (for female subjects of childbearing potential)

Investigators must review and document laboratory test results, as well as address the clinical significance and causality (for significant abnormalities). Clinically significant abnormal laboratory results should be repeated as soon as possible. Section 7.1.4 provides further guidance as to when abnormal laboratory results are to be reported as AEs.

8.5 Vital Signs

Vital signs, including measurements of height and weight, will include systolic/diastolic blood pressure and pulse rate measured after the subject is in the sitting position for at least 5 minutes at the visits indicated in Table 5–1.

8.6 Subjective Ocular Tolerability and Discomfort Assessment

These subject assessments will be measured as described in Appendix 3. 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. These subject assessments will be measured at every study visit (Table 5–1).

9 REPORTING OF TECHNICAL PRODUCT COMPLAINTS

A Product Complaint is defined as any written, electronic, or verbal expression of dissatisfaction regarding the identity, quality, reliability, safety, purity, potency, effectiveness, or performance of an investigational or commercial product after it is released for distribution. (eg, any failure of the applicator to deliver the intravitreal insert), or dissatisfaction with any other characteristic(s) of the drug product (eg, labeling, packaging, etc).

Any/all Product Complaints should be reported to EyePoint within 24 hours using the designated Product Complaint Report Form. The complaint report should include the following information:

- Product identification number
- Investigator name, study center name, and contact phone number
- Date the complaint occurred
- Brief description of the complaint
- Subject involved? (yes or no); if yes, were any AEs associated with the complaint? (yes or no). If (yes) an AE is associated with the complaint, please refer to Section 8.1.

Once all information is collected please report to:

Email: PPD

Phone: PPD

The drug container (applicator, foil pouch, and carton) for which the complaint was initiated should be retained for return to EyePoint for analysis.

Attention:

Product Returns
EyePoint Pharmaceuticals, Inc.
480 Pleasant Street
Watertown, MA 02472 USA

Any complaint about an investigational product must be reported regardless of whether the defect or deficiency had any effect on a subject or on study personnel.

10 ASSESSMENT OF EFFICACY

10.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be 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 or any visit time point prior to the Week 24 visit;

OR

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

Refer to Appendix 2 for additional information.

10.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints will include:

- Proportion of subjects who have a recurrence of uveitis in the study eye within 52 weeks
- Proportion of subjects who have a recurrence of uveitis in the fellow eye within 24 and 52 weeks
- Mean change from baseline in BCVA letter score in the study eye at 24 and 52 weeks
- Number of recurrences of uveitis within 24 and 52 weeks
- Time to recurrence of uveitis through 24 and 52 weeks
- Number of adjunctive treatments required to treat recurrences of uveitis at 24 and 52 weeks
- Proportion of subjects with recurrence of iridocyclitis defined as a >2-step increase in anterior chamber cells per HPF (1.6 × using a 1-mm beam) in the study eye compared to baseline at 24 and 52 weeks.
- Proportion of subjects with resolution of macular edema as measured by SD-OCT imaging at Day 28 and at Months 2, 3, 6, and 12.

11 STATISTICAL METHODS AND DATA ANALYSIS

Detailed methodology for statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be developed and maintained by the Sponsor.

The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

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

11.1 Determination of Sample Size

Subject enrollment has been stopped due to reassons other than safety or efficacy. See Section 3.1 for further details.

11.2 Analysis Populations

The intent-to-treat (ITT) population will include all subjects enrolled in the study. The Safety population will include all subjects enrolled in the study who received Yutiq 0.05 mg. The per protocol (PP) population will be defined separately for the Week 24 and Week 52 analyses, and will exclude all subjects in the ITT population who meet any of the following criteria:

- Received systemic treatment for recurrence of uveitis in fellow eye
- Received an imputed endpoint at the Weeks 24 or 52 endpoints of the study
- Failed screening, without exemption, but received Yutiq 0.05 mg
- Had a major protocol deviation

11.3 General Statistical Considerations

11.3.1 Data Summarization

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.

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. The 95% confidence interval (CI) of the proportions will be constructed for each dose cohort, as appropriate.

11.3.2 Definition of Baseline

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

11.3.3 Handling of Missing Data

In general, missing data will not be imputed, unless otherwise specified. Early termination visits will be mapped to the next scheduled visit for inclusion in summary tables, where appropriate. Every effort will be made to ensure completeness of data collection.

11.3.4 Multicenter Considerations

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

11.3.5 Adjustment for Covariates

Not applicable.

11.3.6 Interim Analyses

No formal interim analyses are planned for this study.

11.3.7 Multiple Comparisons and Multiplicity

Not applicable.

11.3.8 Examination of Subgroups

Subgroup analyses will be performed on the primary efficacy variable. Analyses will be performed to determine the treatment effect within specific subgroups of interest, and to determine if the treatment effect is consistent across different subgroup levels. Subgroups will be defined on the basis of baseline characteristics, including severity of edema, duration of disease, lens status, IOP, presence/absence of vitrectomy, and BCVA. Further details will be provided in the SAP.

11.3.9 Statistical Software

All statistical summaries and analyses will be produced using SAS, Release 9.3 or higher.

11.4 Analyses

11.4.1 Subject Disposition

A summary table will be prepared indicating the number and percentage of subjects in each treatment group who were 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.

Subjects who discontinue any time during the study will be categorized by reason for termination, and the percentage within each category will be provided. Duration of study participation and insert duration will also be tabulated.

11.4.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group using descriptive statistics for the ITT population.

11.4.3 Medical/Ophthalmic/Medication History

Medical history data will be coded and listed by treatment group.

11.4.4 Efficacy Analyses

Efficacy analyses will be performed on both the ITT and PP populations at 24 and 52 weeks. The primary efficacy analysis will be performed on the ITT population at 24 weeks and will be the proportion of subjects who have a recurrence of uveitis. The exact 95% CI for the proportion will be derived. Hypothesis testing using the exact binomial test will be conducted to test the

difference between the proportion of subjects with a recurrence using a 2-sided alpha = 0.05. The primary efficacy analysis will be conducted after all subjects in the study have completed at least 24 weeks of study or have discontinued.

In addition to recurrence based on vitreous haze increase or BCVA loss as defined above, recurrence will also be imputed in the following circumstances:

- A subject who has not previously experienced a recurrence and does not complete the required eye examinations at Week 24 (or at Week 52 for the Week 52 analyses) for any reason will be considered as having a recurrence.
- A subject who has not previously experienced a recurrence and takes a prohibited systemic concomitant medication or a prohibited local concomitant medication in the study eye at any time during the study prior to Week 24 (or prior to Week 52 for the Week 52 analyses) will be considered as having a recurrence.

Systemic medications or topical steroids administered as part of gradual dose reduction (tapering) will not be considered prohibited medications. Topical steroids, including those administered as part of short-term standard treatment following an ocular surgical procedure, will also not be considered prohibited medications.

11.4.5 Use of Rescue and Prohibited Medications

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 blinded data review to classify concomitant treatments as either rescue (Section 7.6) or prohibited (Section 7.7). The proportion of subjects receiving these medications will be summarized by treatment type (rescue or prohibited), treatment group, and time point.

11.4.6 Safety Analyses

Safety analyses will be performed on the Safety population at Weeks 24 and 52. 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 using the Medical Dictionary for Regulatory Activities (MedDRA) 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, SAEs, and withdrawals due to AEs will be presented.

Clinical laboratory results will be presented by treatment group using descriptive statistics. Laboratory values will be listed by subject, and values outside of a normal reference range will be flagged. Pregnancy test results will be summarized separately.

Vital signs will be presented using descriptive statistics by treatment group and visit.

Subjective ocular tolerability and discomfort assessment results will be presented using descriptive statistics by treatment group and visit.

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 levels, WHO generic name, and treatment group. Subjects will only be counted once at each level of the generic name or ATC level.

12 ADMINISTRATIVE AND REGULATORY CONSIDERATIONS

12.1 Quality Control and Quality Assurance

The Sponsor's employees and/or their contracted representatives utilize standard operating procedures (SOPs) designed to ensure that research procedures and documentation are consistently conducted/prepared to the highest quality standards. These SOPs also require compliance with Health Authority regulations and GCP guidance.

A Quality Assurance audit may be conducted by the Sponsor or a designee at any time during or after completion of this study. The Investigator will be given adequate notice if he/she is selected for an audit. The audit will include, but is not limited to, a review of all ICFs, a review of eCRFs, associated source documents and medical records, a review of regulatory documentation, an assessment of study conduct and protocol compliance, and a review of the investigational drug accountability. At the conclusion of an audit, the auditor will conduct a brief meeting with the Investigator to review the audit findings.

12.2 Institutional Review Boards/Independent Ethics Committee

Prior to the study initiation, the protocol and ICF will be submitted to the IRB/EC for approval. The IB may also be submitted as supplemental information. By signing the "Statement of Investigator" form (FDA Form 1572), the Investigator is assuring that an IRB/EC that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review of the clinical study. A copy of the IRB/EC approval letter for the protocol, and the informed consent, as well as the protocol signature page must be submitted to the Sponsor or its designee prior to release of investigational supplies to the study site. The approval letter must refer to the specific protocol and ICF. The study site must maintain an accurate and complete record of all reports, documents, and other submissions made to the IRB/EC concerning this protocol. A list of the IRB/EC members, their titles or occupations, and their institutional affiliation, or an IRB/EC assurance number must be provided to the Sponsor or its designee prior to release of study supplies.

FDA/relevant health authority regulations require that all advertisements for subject recruitment be approved by an IRB/EC prior to implementation. The complete text and format must be submitted to the Sponsor or designee for approval prior to IRB/EC submission.

The Investigator is responsible for notifying the IRB/EC of any SAEs. A copy of the notification must be forwarded to the Sponsor or its designee.

Status reports must be submitted to the IRB/EC at least once a year (or more frequently as required by the IRB/EC) and the IRB/EC must be notified of study completion or termination.

A final report must be provided to the IRB/EC and the Sponsor within 6 months of study completion or termination. This report should include: any protocol deviations, the number of subjects evaluated, the number of subjects who withdrew or were withdrawn and the reasons for withdrawal, any significant AEs, and the Investigator's summation of the study.

12.3 Informed Consent Process

It is the responsibility of the Investigator to inform each subject, prior to the Screening evaluation, of the purpose of this clinical trial, including possible risks and benefits and document the informed consent process in the subject's chart. Prior to entry into the study or initiation of any study-related procedures, the subject must read, sign and date the IRB/EC approved ICF. The person executing the consent must also sign and date the final consent form page. One or two signed originals of the ICF will be prepared, in accordance with applicable local requirements. A signed original copy will be retained with the subject records, and either a copy of the signed original or the other signed original of the ICF will be given to the subject, in accordance with applicable local requirements.

12.4 Source Documentation

The Investigator must maintain adequate and accurate source documents upon which eCRFs for each subject are based. These documents are to be separate and distinct from eCRFs, except for cases in which the Sponsor has predetermined that direct data entry into specified pages of the subject's eCRF is appropriate. The Investigator must allow access to the source documents by representatives of the Sponsor and regulatory authorities as needed. These records should include detailed notes on:

- The date the subject entered the study, study protocol number, and name of the Sponsor.
- The oral and written communication with the subject regarding the study treatment (including the risks and benefits of the study). The date of informed consent must be recorded in the source documentation.
- The subject's medical history prior to participation in the study and evidence that the subject meets study eligibility requirements.
- The subject's basic identifying information, such as demographics, that link the subject's source documents with the eCRFs.
- The dates of all study-related subject visits.
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject.
- The subject's exposure to study treatment, and documentation of study treatment accountability.
- All AEs.
- The subject's exposure to any concomitant therapy (including start and stop dates, route of administration, and dosage).
- All relevant observations and data on the condition of the subject throughout the study.

- The date when subject exited the study and a notation as whether the subject competed the study or was discontinued, including the reason for discontinuation.

Upon request, the Investigator will provide the Sponsor with any required background data from the study documentation or clinic records. This is particularly important when source documents are illegible or when errors in data transcription are suspected. In case there are issues or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

12.5 Electronic Case Report Forms

All study data must be incorporated in the corresponding eCRFs which are designed for computer processing and analysis. The Investigator will be responsible for recording all data in the eCRFs and must ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the eCRF and in all required reports.

Data from clinical laboratory reports, etc, will be incorporated into the eCRFs either by direct transcription into appropriate eCRF pages or by inclusion of photocopies of these reports with printouts of the appropriate eCRF pages and stored in the site's Study Binder.

If corrections are made following official final review and sign-off by the Investigator, the Investigator must be made aware of the changes and provide written acknowledgement.

This study will be conducted in compliance with the regulations contained within 21 CFR Part 11, electronic records/electronic signatures regulations.

12.6 Retention of Study Records

GCP regulations require that the Investigator retain all documentation related to this clinical trial for a period of 2 years after the approval of the NDA in the US (or Product License outside the US) for this drug or 2 years after the withdrawal of the IND. These records include the protocol and copies of all documents submitted to the Sponsor or to government authorities, subject records (including signed ICFs, subject charts, eCRFs, and other source documents), IRB/EC approvals and correspondence, records of drug accountability, and all study communications, whether written, telephonic, or electronic. None of the required documents will be destroyed or transferred to the control of another party without the written approval of the Sponsor.

If the Investigator cannot guarantee the archiving requirement at the site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in a sealed container outside of the study site so that they can be returned sealed to the Investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies will be made for storing outside of the study site.

12.7 Monitoring the Study and Data Quality Assurance

Representatives of the Sponsor (or designees) will contact the Investigator and his/her staff prior to the start of the trial to review the procedures to be followed in conducting the study and recording the findings, and to confirm the facility's readiness to conduct the trial.

It will be the monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor must have access to all study related reports and

records needed to verify the entries on the eCRF. The Investigator (or designee) must agree to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved and agree to provide missing information and grant access to all study documentation.

Every attempt must be made to follow the protocol, obtain and record all data requested for each subject at the specified times. However, ethical reasons may warrant the failure to obtain and record certain data or to record data at the times specified. If data is not recorded per protocol, the reasons must be clearly documented on the eCRF/records.

Accurate and reliable data collection will be ensured by the verification of the eCRFs against the Investigator's records by the monitor (source documentation verification). Collected data will be entered into a computer database and subject to electronic and manual quality assurance procedures.

The study data must be verifiable with the source data, which requires access to all original recordings, laboratory reports, product accountability records, including access to the subject electronic medical record, and source data must be made available for all study data. Subjects must also allow access to their medical records. They will be informed of this and must consent to permission by providing their signature on the ICF prior to enrollment.

Representatives of the Sponsor (or designees) may audit the study periodically to ensure that all records are correct and complete. The verification of the eCRF data must be by direct inspection of source documents.

12.8 Discontinuation of the Study

The Sponsor reserves the right to discontinue this study for administrative reasons at any time.

The trial may also be terminated prematurely if unexpected AEs occur or if the Investigator does not adhere to the protocol.

12.9 Policy for Publications

The detailed procedures for the review of publications are set out in the clinical trial agreement entered into with the Sponsor in connection with this study. Results from the study shall not be made available to any third party by the Investigator or staff outside of the publication policy.

13 ETHICS

13.1 Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB/EC as appropriate. The IB may also be provided as required. The Investigator must submit written approval from an IRB/EC to the Sponsor or a designee such as a Contract Research Organization (CRO) before the Investigator may initiate this study.

The Principal Investigator is responsible for informing the IRB/EC of any amendment to the protocol in accordance with local requirements. In addition, the IRB/EC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB/EC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor or the CRO will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB/EC according to local regulations and guidelines.

13.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements.

13.3 Written Informed Consent

A properly executed, written informed consent document, in compliance with 21 CFR 50, the ICH guidelines, and relevant local regulatory requirements, will be obtained from each subject before the subject is enrolled into the study and before any study-related procedure is performed. Attention will be directed to the basic elements required for incorporation into the informed consent under US Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a]) and (21 CFR 50.25[b]).

The informed consent document will be reviewed by the Sponsor or designee for inclusion of all required elements prior to submission to the IRB/EC. The Sponsor must also review any revisions to the approved informed consent document prior to submission to the IRB/EC. The final IRB/EC-approved document must be provided to the Sponsor for regulatory purposes. It is the responsibility of the Investigator, or a person designated by the Investigator, to obtain written informed consent from each subject (or the subject's legally authorized representative) participating in the study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. In the case where the subject is unable to read the form, an impartial witness will be present during the entire informed consent discussion. After the subject has orally consented to participate in the study, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood.

A copy of the fully executed informed consent document must be provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language by the site under the guidance of the Investigator. Signed informed consent documents must remain in each subject's medical record and be made available for verification by the monitor at any time.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated as necessary. All subjects (including those who have already been treated with Yutiq 0.05 mg) will be informed of the new information and given a copy of the revised form to provide their consent in order to continue participation in the study.

14 REFERENCES

Brunton LL, Lazo JS, Parker KL. Adrenocorticotropic hormone: adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones. In:

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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.

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.

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

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.

YUTIQ® US Prescribing Information, May 2021.

APPENDIX 1: Measurement of BCVA by ETDRS

The procedure for carrying out the testing of best-corrected visual acuity (BCVA) measured according to the standard procedure originally developed for Early Treatment Diabetic Retinopathy Study (ETDRS) will be covered in a separate document with instructions provided by the independent certification vendor selected by the Sponsor.

APPENDIX 2: Slit Lamp Biomicroscopy, Ophthalmoscopy, and Intraocular Pressure

Slit Lamp Examination

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

Anterior Chamber Cell Grading Scale

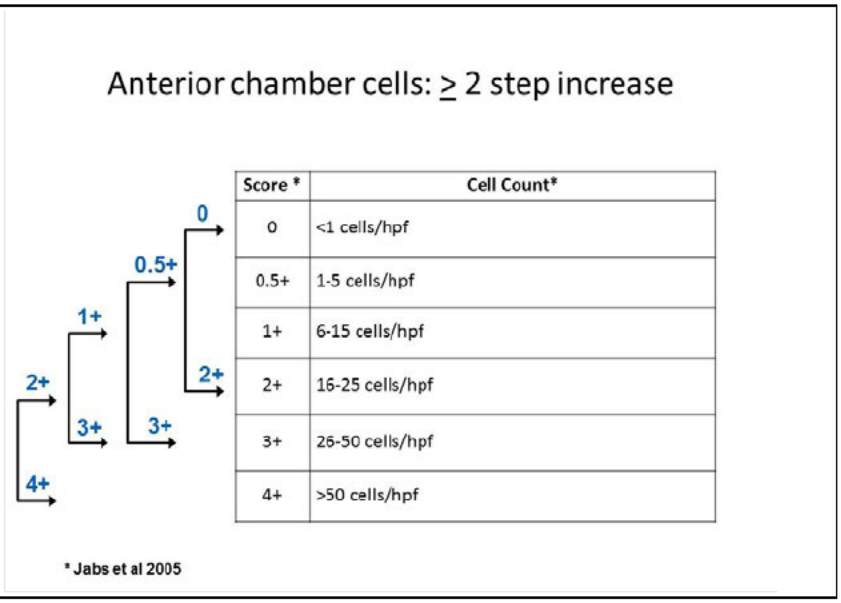
Anterior chamber cells will be measured using a Haag/Streit or similar slit lamp at high magnification (1.6 X) 1-mm beam. The same instrument, and when possible, the same examiner should be used on each patient throughout the study. Assessment will be made using the following scale (Jabs et al. 2005).

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 on the right presents the scoring convention that will be used to identify a minimum of "≥ 2 step increase" of anterior chamber cells for the primary efficacy endpoint.



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

Ophthalmoscopy

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.

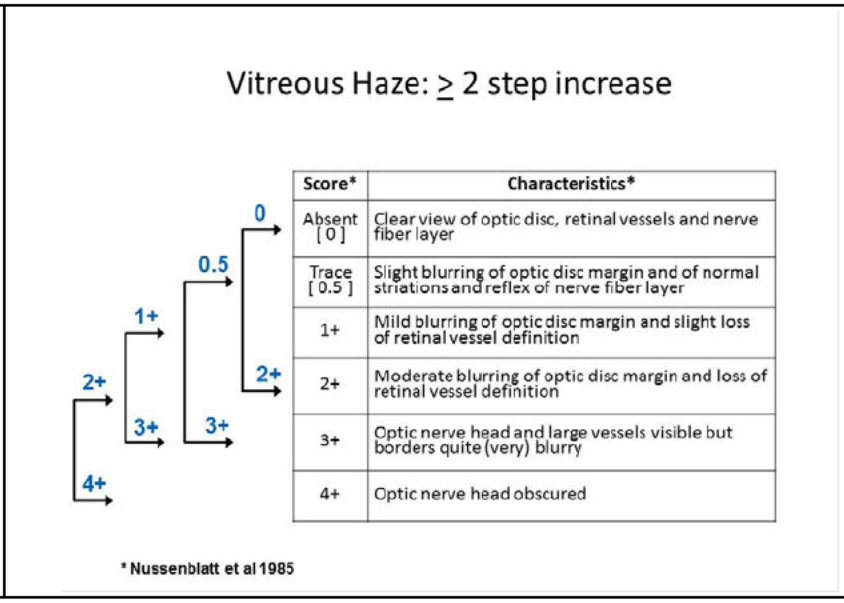
Vitreous Haze Grading Scale

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

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

Vitreous Haze Scoring Convention

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



Fundus Examination

The fundus assessments should be conducted using indirect ophthalmoscopy with a 20 diopter, 28 diopter, or 30 diopter condensing lens. In order to minimize variability, every effort should be made to have a single examiner conduct all assessments on a given subject.

Intraocular Pressure

Intraocular pressure will be assessed by applanation tonometry (preferably, Goldmann) and should be measured only after slit lamp examination has been completed. The mean of 3 measurements per eye will be recorded as the IOP. All reasonable efforts should be made to have the same examiner obtain all IOP measurement for a given subject. Measurement should be performed before dilated ophthalmoscopy.

APPENDIX 3: Subjective Ocular Tolerability and Discomfort Assessment

Subjects will be asked to grade ocular tolerability and discomfort in both eyes at all study visits.

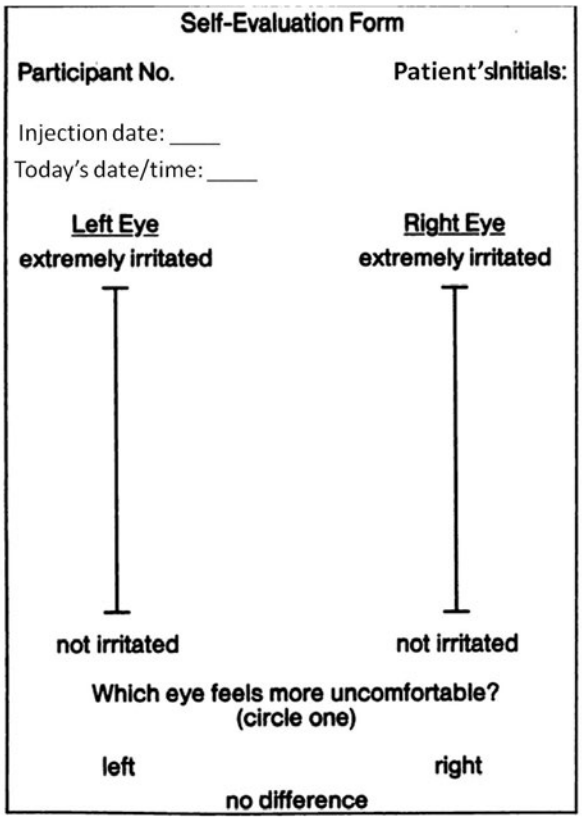
Subjective Ocular Discomfort Grading

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.



APPENDIX 4: Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0

Adapted from:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

APPENDIX 5: Summary of Changes

The following changes were made to Protocol EYP-2102-001 as Amendment 3 (v2.0):

Section(s)	Description of Change / Rationale
Synopsis Section 3.1, Overall Study Design Figure 3-1, Study Design Schema, Study EYP-2102-001 Section 5.1, Measurements and Evaluations by Visit	• Added details to state that the Sponsor has decided to stop subject enrollment and will continue to monitor subjects randomized to Yutiq 0.05 mg. • Enrollment has been stopped due to reasons other than safety or efficacy, following FDA advice received on January 24, 2022. The Sponsor is reevaluating the development program of Yutiq 0.05 mg. • Updated these sections to describe the modified protocol schedule for those subjects randomized to Yutiq 0.05 mg. • Added the information that subjects who were randomized to sham injection will be discontinued from the study and will undergo their EOS visit.
Section 3.2, Discussion of Study Design, Including the Choice of Control Groups	• Clarified the masked versus unmasked personnel requirements that were included in Administrative Letter #2 (dated January 3, 2022).
Section 3.3, Duration of Study	• Clarified the modified protocol scheduled
Section 4, Selection and Withdrawal of Subjects	• Added text to state that subject enrollment has been stopped.
Synopsis Section 4.1, Inclusion Criteria #3	• Clarified the inclusion criteria #3 that was included in Administrative Amendment 3 (March 1, 2022).
Synopsis Section 4.1, Inclusion Criteria #19	• Added the marketed uveitis treatment XIPERE™ that was included in Administrative Amendment 3 (March 1, 2022).
Section 5.1, Measurements and Evaluations by Visit Table 5–1, Schedule of Study Procedures and Assessments, Study EYP-2102-001	• Removed Month 9 to align with modified protocol schedule for the subjects were were treated with Yutiq 0.05 mg.
Table 5–1, Schedule of Study Procedures and Assessments, Study EYP-2102-001 (footnote “c”). Section 8.4, Clinical Laboratory Evaluations	• Added “Screening only” for the tuberculosis testing. Tuberculosis testing will not be performed at the final visit.
Section 6.2.1, Yutiq 0.05 mg Injection Procedure	• Clarified the timing for biomicroscopy post-injection that was provided in the Administrative Letter #2 (dated January 3, 2022).
Section 11.1, Determination of Sample Size	• Added text that the Sponsor has stopped enrollment of the study.

Section(s)	**Description of Change / Rationale**
Appendix 2, Slit Lamp Biomicroscopy, Ophthalmoscopy, and Intraocular Pressure	• Clarified the requirement for dilation for the slit lamp examination assessment that was included in the Administrative Letter #3 dated March 1, 2022.
Appendix 5 Summary of Changes	• Added Appendix 5 due to Amendment 3 changes.
Global protocol changes	• Miscellaneous typographical and formatting issues were corrected, and some hyperlinks were fixed and/or added.