EYEPOINT PHARMACEUTICALS

Cover Page Study Protocol

Protocol Title:	A CONTROLLED, MULTI-CENTER STUDY OF THE UTILIZATION AND SAFETY OF THE MK II INSERTER AND THE SAFETY OF THE FAI INSERT IN SUBJECTS WITH NON-INFECTIOUS UVEITIS AFFECTING THE POSTERIOR SEGMENT OF THE EYE
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PROTOCOL PSV-FAI-006

A CONTROLLED, MULTI-CENTER STUDY OF THE UTILIZATION AND SAFETY OF THE MK II INSERTER AND THE SAFETY OF THE FAI INSERT IN SUBJECTS WITH NON-INFECTIOUS UVEITIS AFFECTING THE POSTERIOR SEGMENT OF THE EYE

IND Number 113140

Protocol Release Date: April 4, 2016

Version 3.0

pSivida Corp.
480 Pleasant Street
Watertown, MA 02472 USA

CONFIDENTIALITY STATEMENT

PROTOCOL APPROVAL PAGE

Protocol Title: A CONTROLLED, MULTI-CENTER STUDY OF THE UTILIZATION AND SAFETY OF THE MK II INSERTER AND THE SAFETY OF THE FAI INSERT IN SUBJECTS WITH NON-INFECTIOUS UVEITIS AFFECTING THE POSTERIOR SEGMENT OF THE EYE

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Date: April 4, 2016

This protocol has been reviewed and approved by pSivida Corp.

_____ _____

Flavio Leonin, MD Date

Senior Manager, Clinical Affairs

_____ _____

Gerard E. Riedel, PhD Date

Vice President, Regulatory Affairs

_____ _____

Paul Ashton, PhD Date

Chief Executive Officer

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 FDA regulations (21 CFR Parts 50, 54, 56 and 312) and 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 pSivida Corp. 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

1. PERSONNEL CONTACT INFORMATION

Role in Study	Name	Address and Telephone Number
Sponsor	pSivida Corp.	480 Pleasant Street, Suite B300 Watertown, MA 02472 USA Telephone: 1-617-926-5000 Telefax: 1-617-926-5050
Medical Monitor	PPD Steven Gross, MD	3900 Paramount Parkway Morrisville, NC 27540 USA Telephone: 1-888-483-7729
Drug Safety Physician	PPD Steven Gross, MD	3900 Paramount Parkway Morrisville, NC 27540 USA Telephone: 1-888-483-7729
24-Hour Emergency Contact	PPD Support Center	Medical Support Center Telephone: 1-888-483-7729 Telefax: 1-888-529-3580
Contract Research Organization (CRO)	PPD Suzanne Pio Project Manager	3900 Paramount Parkway Morrisville, NC 27540 USA Telephone: 1-919-428-5231

2. SYNOPSIS

Name of Sponsor/Company:
pSivida Corp.

Name of the Investigational Product:
Fluocinolone Acetonide Intravitreal (FAI) Insert,
administered using either the Mk I inserter or the Mk II inserter

Name of Active Ingredient:
Fluocinolone Acetonide

Title of Study: A controlled, multi-center study of the utilization and safety of the Mk II inserter and the safety of the FAI insert in subjects with non-infectious uveitis affecting the posterior segment of the eye.

Studied Period (years): 1 year	**Phase of Development:** 3

Objectives: To evaluate the utilization and safety of the Mk II inserter and to evaluate the safety of the FAI insert in subjects with non-infectious uveitis affecting the posterior segment of the eye.

Primary Objective:

To assess the utilization and the safety of the Mk II inserter, and the safety of the FAI insert, from the day of treatment through 7 days following treatment.

Secondary Objective:

To assess the safety of the FAI insert during 12 months following treatment.

Methodology: A 12 month, multi-center, randomized, controlled, single masked utilization and safety study.

Number of Subjects (planned): One or both eyes in each subject will be designated as the study eye(s); the study will enroll approximately 30 eyes (20 Mk II inserter: 10 Mk I inserter) at approximately 3-10 sites.

Diagnosis and Main Criteria for Inclusion:

Diagnosis:

Unilateral or bilateral non-infectious uveitis affecting the posterior segment of the eye

Inclusion Criteria:

1. Male or non-pregnant female at least 18 years of age at time of consent
2. At least one eye has a history of non-infectious uveitis affecting the posterior segment
3. Subject has ability to understand and sign the Informed Consent Form
4. Subject is willing and able to comply with study requirements

Exclusion Criteria:

1. Allergy to fluocinolone acetonide or any component of the FAI insert
2. Ocular malignancy in either eye, including choroidal melanoma
3. Uveitis with infectious etiology
4. Current viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella
5. Current mycobacterial infections of the eye or fungal diseases of ocular structures
6. Subjects who yield, during screening, a confirmed positive test for human immune deficiency virus (HIV) or syphilis
7. Systemic infection within 30 days prior to study Day 1
8. Peripheral retinal detachment in area of insertion

9. Elevated intraocular pressure (IOP) > 21 mmHg, or chronic hypotony < 6 mmHg
10. Concurrent therapy at screening with IOP-lowering pharmacologic agent in the study eye
11. Current diagnosis of any form of glaucoma or ocular hypertension in study eye at Screening, unless study eye has been previously treated with an incisional surgery procedure that has resulted in stable IOP in the normal range (10-21 mmHg)
12. Known history of clinically significant IOP elevation in response to steroid treatment in either eye, unless study eye has been previously treated with an incisional surgery procedure that has resulted in stable IOP in the normal range (10-21 mmHg)
13. Ocular surgery or capsulotomy performed on the study eye within 30 days prior to study Day 1
14. Intravitreal treatment of study eye: with FAI insert within 36 months prior to study Day 1;with Retisert within 30 months prior to study Day 1; with Ozurdex within 90 days prior to study Day 1; or with Triesence or Trivaris within 30 days prior to study Day 1
15. Peri-ocular or subtenon steroid treatment of study eye within 30 days prior to study Day 1
16. Treatment with an investigational drug or device within 30 days prior to study Day 1, except the FAI insert within this protocol
17. Pregnant or nursing females; females of childbearing potential who are unwilling or unable to use an acceptable method of contraception as outlined in this protocol from at least 14 days prior to study Day 1 until the Month 12 Visit
18. Any condition which, in the judgment of the Investigator, could make the subject inappropriate for entry into this study

Treatment Assignment:

All study subjects will receive the FAI insert in the designated study eye(s). Eyes will be randomized (2:1) to receive the FAI insert by administration with either the Mk II inserter or the Mk I inserter, respectively. Randomization will be stratified on the basis of the Investigator administering the FAI insert.

Designation of Study Eye:

For subjects with unilateral uveitis, the study eye will be the affected eye; for subjects with bilateral uveitis, the study eye(s) will be the eye(s) satisfying the inclusion/exclusion criteria.

Treatment of Study Eye or Non-Study Eye:

If a subject experiences an adverse event or persistence/worsening of uveitis in a study eye or a non-study eye, the Investigator should administer appropriate treatment, consistent with the subject's medical need and the Investigator's standard care. Subjects who experience an adverse event or persistence/worsening of uveitis will continue in the study.

IOP Reduction Therapy:

The treatment of elevated IOP must be instituted whenever the IOP is > 30 mmHg, or at a lower IOP level based on the Investigator's discretion and in accordance with the Investigator's standard of care. Treatment may include referral to another ophthalmologist. If the elevated IOP does not respond to pharmacologic treatment, alternative treatment should be considered.

Investigational Product (Test Article), Dosage and Mode of Administration:

Test article therapy: Administration of test article on study Day 1, followed by standard care.
The test article is the Fluocinolone Acetonide Intravitreal (FAI) insert, which contains 0.18 mg FA and delivers FA into the vitreous humor for 36 months, at a nominal rate of approximately 0.2 µg FA/day. The FAI insert will be administered to the study eye as an intravitreal injection through the pars plana, using either the Mk I inserter or the Mk II inserter.

Study Procedures:

Screening (within 60 days prior to study Day 1):

Informed consent, eligibility determination, medical history, ophthalmic history including history of non-infectious uveitis, demographics, vital signs, clinical labs, ophthalmic examination (includes BCVA, IOP, dilated ophthalmoscopy and anterior, posterior and intermediate slit lamp examination), visual field, concomitant medications and a pregnancy test, as appropriate.

Treatment Day (Day 1):

Eligibility confirmation, including meeting the eligibility criteria, vital signs, ophthalmic exam, pregnancy test. Following study number assignment, subjects will receive the FAI insert in the study eye. Additional assessments on Day 1 will include concomitant medications, adverse events (AEs), post-insertion safety assessment and assessment of the inserter and its instructions for use. Additionally, subjects will be contacted on the next day to identify any complaint or adverse event.

Follow-up Visits:

Following Study Day 1, subjects will return on Study Day 7, Day 28, Month 3 and Month 12 (follow-up visits). Evaluations will include: vital signs, ophthalmic exam, concomitant medications and AEs. All subjects / subject eyes enrolled in the study will be followed for 12 months.

Study Outcomes:

The primary utilization and safety analyses of the inserters will be conducted at Day 7; safety analyses of the FAI insert will be conducted at Day 7 and Month 12. Analyses will be based on individual eyes.

Evaluation of Mk II inserter and Mk I inserter:

A. Utilization evaluation (based on individual eye):

   Utilization will be evaluated on Day 1, by the investigator who administers the FAI insert (Investigator) and by a trained observer (Observer). The Investigator will complete a questionnaire addressing specific aspects of the use of the inserter. The Observer will complete a questionnaire related to the observed procedure and the instructions for use. Elements to be assessed in the evaluations will include:

   a. Inserter operation and ease of use
   b. Instructions for use
   c. Differences between observed procedure and instructions for use

B. Safety evaluation (based on individual eye):

   Safety will be evaluated over one period: Day 1- Day 7, and will include:

   a. Ocular adverse events, including: procedure-related adverse events, IOP increase/decrease, medications/procedures required to treat adverse events, clinically significant ocular changes

Evaluation of the FAI insert:

A. Safety evaluation

   Safety will be evaluated for two periods: through Day 7 and through Month 12. Descriptive statistics will be used to present the results of all safety evaluations and will include:

   a. Ocular adverse events (base on individual eye), including: IOP increase/decrease, medications/procedures required to control elevated/low IOP, development or worsening of cataract, cataract-related procedures, clinically significant ocular changes
   b. Systemic adverse events

Statistical Methods:

Utilization analyses:

The primary endpoint of the study is the ease of intravitreal administration and will be based on individual eyes. The ease of intravitreal administration for each eye studied will be evaluated by the Investigator performing the procedure using either the Mk I or Mk II inserter, and will be reported as:

- Very easy (VE)
- Easy (E)
- Routine (R)
- Difficult (D)
- Very difficult (VD)

The trial will be deemed a success for the Mk II inserter if the following condition is met:

The proportion of Mk II procedures scored as satisfactory (scored as either VE, E or R) is not lower than the corresponding proportion of satisfactory Mk I procedures.

Sample size – With a sample size of 20 eyes in the Mk II inserter group, the 95%, two-sided confidence interval of satisfactory procedures in the Mk II inserter group will be no larger than 27.2% - 72.8% when the exact binomial method and a proportion of 10 satisfactory procedures out of 20 Mk II inserter procedures are employed. All other satisfactory procedure proportions for the Mk II inserter will result in two-sided, 95% confidence bounds that are narrower than that described above.

With a sample size of 10 eyes in the Mk I inserter group, the 95%, a two-sided confidence interval of satisfactory procedures in the Mk I inserter group will be no larger than 18.7% - 81.3% when the exact binomial method and a proportion of 5 satisfactory procedures out of 10 Mk I inserter procedures are employed. All other satisfactory procedures proportions for the Mk I inserter will result in two-sided, 95% confidence bounds that are narrower than that described above.

The secondary utilization outcomes of the study will be analyzed descriptively, will be based on individual eyes and will include:

- Clarity of the instructions for use, as assessed by the Investigator performing the procedure
- Differences between observed procedure and instructions for use, as assessed by an Observer

Safety Analyses:

Safety will be analyzed descriptively and will include:

- Procedure-related safety (based on individual eye):
    - procedure-related ocular adverse events (including IOP increase/decrease), medications/procedures required to treat adverse events, clinically significant ocular changes
- FAI insert safety:
    - Ocular adverse events(based on individual eye): IOP increase/decrease, medications/procedures required to control elevated/low IOP, development or worsening of cataract, cataract-related procedures, clinically significant ocular changes
    - Systemic adverse events

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADR	Adverse Drug Reaction
AE	Adverse Event
AREDS	Age Related Eye Disease Study
BCVA	Best Corrected Visual Acuity
CFR	Code of Federal Regulations
CRF	Case Report Form
DME	Diabetic Macular Edema
EC	Ethics Committee
eCRF	Electronic Case Report Form
ETDRS	Early Treatment Diabetic Retinopathy Study
ExSR	Expedited Safety Report
FA	Fluocinolone Acetonide
FAI Insert	Fluocinolone Acetonide Intravitreal Insert
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practices
hpf	High power field
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IOP	Intraocular Pressure
IRB	Institutional Review Board
ITT	Intent to Treat
IWRS	Interactive Web Response System
NDA	New Drug Application
Observer	A staff member in the study site who has been trained in the instructions for use for both inserters that are being evaluated in PSV-FAI-006 and who has been trained in completing the questionnaires described in Section 20 .
PVA	Polyvinyl Alcohol
SAE	Serious Adverse Event
SOC	System Organ Class
SOP	Standard Operational Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
VA	Visual Acuity

5. INTRODUCTION

pSivida Corp. is developing a drug product candidate to treat chronic non-infectious uveitis affecting the posterior segment of the eye. This includes posterior uveitis, intermediate uveitis with or without anterior uveitis, and panuveitis.

pSivida's product candidate is an intravitreal insert that contains 0.18 mg of Fluocinolone Acetonide (FA) and releases FA into the vitreous humor for 36 months, at a nominal rate of approximately 0.2 µg FA/day. In this protocol, this specific drug product candidate is abbreviated as "FAI insert" (for Fluocinolone Acetonide Intravitreal insert).

The clinical trial described in this protocol will be conducted in compliance with the protocol, Good Clinical Practices (GCP) as well as all applicable regulatory requirements.

5.1. Uveitis

Uveitis is defined as inflammation of the uveal tract (iris, ciliary body, choroids) or adjacent structures. The cause of inflammatory reaction of 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 has been estimated to be responsible for approximately 10% of blindness in the United States (Suttorp-Schulten 1996). Generally, posterior uveitis occurs in all age groups and affects people of different ethnic origins. The inflammation that affects the choroid and retina may be a primary intra-ocular process or may be an ocular manifestation of systemic disease. Posterior uveitis accounts for most of the loss of vision in eyes with uveitis, due to any one or more of the following: cystoid macular edema, choroidal neovascularization, glaucoma, retinal detachment, subretinal fibrosis, cataract, or optic disk atrophy.

A product that is relatively simple to administer and delivers corticosteroid locally for an extended period of time may offer significant benefits over existing local and systemic steroid therapies.

5.2. Summary of Data for Intravitreal Fluocinolone Acetonide

The FAI insert to be used in the present study contains the same drug product as Iluvien™, an intravitreal fluocinolone acetonide product candidate that is commercially available in the United States and Europe for the treatment of diabetic macular edema (DME) [Iluvien prescribing information (December 2014)].

Additionally, Retisert®, a larger FDA-approved intraocular product that requires surgical implantation, also contains the same active ingredient as the FAI insert. Compared to the FAI insert, Retisert delivers approximately 3 times as much FA at rates approximately 3 times faster. Retisert has been approved by FDA for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye [Retisert prescribing information (June 2011)].

5.2.1. Nonclinical Data

Details of the nonclinical pharmacology, pharmacokinetics and toxicology data that support the clinical use of the FAI insert are presented in the Investigator's Brochure (IB).

5.2.2. Clinical Data

There are two products related to the FAI insert (Retisert and Iluvien) for which there is considerable previous human experience that is relevant to the clinical evaluation of the FAI insert. Additionally, the FAI insert is currently being evaluated in PSV-FAI-001, a phase III clinical study in subjects with chronic non-infectious uveitis affecting the posterior segment of the eye.

5.2.2.1. Previous Human Experience with Retisert

Retisert is a sustained release intravitreal product indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye [Retisert Prescribing Information (June 2011)]. Retisert contains 0.59 mg FA and is surgically inserted into the affected eye through a pars plana incision. Retisert is designed to release FA at a nominal initial rate of 0.6 µg FA/day decreasing over the first month to a steady state between 0.3-0.4 µg FA/day over approximately 30 months. Because Retisert and the FAI insert both utilize FA as the active ingredient, previous human experience with Retisert identifies potential FA-related safety issues that are relevant to the clinical studies proposed for the FAI insert. Details of the clinical experience with Retisert are presented in the IB.

5.2.2.2. Previous Human Experience with Iluvien

Iluvien is an intravitreal product candidate that is administered by injection and is designed to provide long term delivery of FA. Iluvien was invented by pSivida and licensed to Alimera Sciences, Inc. for certain ophthalmic indications, excluding uveitis. Two Iluvien product candidates were evaluated in clinical trials; both contained 0.18 mg FA. A "high dose" Iluvien insert was designed to provide a nominal initial release rate of 0.5 µg FA/day slowing to 0.2 µg FA/day. A "low dose" Iluvien insert was designed to provide a constant nominal release rate of approximately 0.2 µg FA/day for 36 months. Both inserts were administered by intravitreal injection. The low dose Iluvien insert has been approved for the treatment of DME, both in Europe and in the US [Iluvien prescribing information (December 2014)].

The "low dose" Iluvien insert and the FAI insert contain the same drug product. Consequently, previous human experience with Iluvien is highly relevant to the clinical studies that evaluate the FAI insert.

Pharmacokinetics

The pharmacokinetics of FA release from high dose or low dose Iluvien inserts in human subjects with DME was assessed using plasma and aqueous humor sampling (Campochiaro 2013). This three year study demonstrated that Iluvien inserts release FA continuously within the eye for 36 months, and that FA is not measurable in the plasma at any time through 36 months.

FA levels in the aqueous humor of subjects receiving a low dose Iluvien insert (the same drug product as the FAI insert) were initially 2 ng/mL (month 1), gradually decreasing to 0.5 ng/mL (month 36).

Systemic FA levels were below the level of detection at all time points. This observation is consistent with the low systemic bioavailability of FA associated with an intraocular route of administration and the low intraocular daily dose released by the Iluvien inserts.

Additional details of the clinical experience with Iluvien are presented in the IB.

5.2.2.3. Previous Human Experience with the FAI insert in uveitis subjects

The FAI insert is currently being evaluated in two phase 3 trials (PSV-FAI-001 and PSV-FAI-005) in subjects with chronic non-infectious uveitis affecting the posterior segment. In both studies, subjects are randomized (2:1) to receive either an intravitreal administration of the FAI insert or sham injection, respectively. Following treatment, subjects are being followed for three years. As of August 1, 2015, PSV-FAI-001 has completed enrollment (N=129) and is following subjects, and PSV-FAI-005 is actively enrolling subjects.

All study data are currently masked to treatment assignment. As of August 1, 2015, a total of 42 serious adverse events (SAEs) have been reported from both studies; none of these events was considered to be a suspected unexpected serious adverse reaction (SUSAR) that requires expedited safety reporting. Eight of the 42 SAE reports were non-ocular events judged by the investigator to be unrelated to study treatment. The remaining 34 SAE reports involved ocular events, of which 17 events were reported in the non-study eye and judged by the investigator to be unrelated to study treatment. The remaining 17 ocular events were reported in the study eye: 9 events were assessed by the investigator as not related to study treatment [sterile endophthalmitis (two events), uveitis (two events), macular edema (two events), cataract worsening, neovascular glaucoma, optic disc swelling], and 8 events were assessed by the investigator as possibly or probably related to study treatment [elevated IOP (three events), cataract (two events), hypotony (two events), and cystoid macular edema]. Additional information may be found in the IB.

5.2.3. Current benefit-risk profile of the FAI insert

Because the efficacy and safety of the FAI insert in uveitis subjects have not yet been fully evaluated, the current benefit-risk profile is based primarily upon previous human experience with Retisert and Iluvien, as well as the (masked) experience to date in PSV-FAI-001. Currently, all data are consistent with the expected benefit-risk profile of the FAI insert; subjects are expected to experience a significant decrease in the frequency of recurrence of uveitis, and are expected to most frequently experience an adverse event associated with cataract or elevated IOP.

5.3. Study Rationale

Based on information reported in the Iluvien phase 3 trials and in PSV-FAI-001, pSivida Corp. has modified the inserter used in intravitreal administration of the FAI insert. This modified inserter (the Mk II inserter) is expected to be easier to use than the Mk I inserter used in PSV-FAI-001.

PSV-FAI-006 is designed to assess the utilization and safety of the Mk II inserter (compared to the Mk I inserter) and to also assess the safety of the FAI insert.

5.4. Description of the FAI insert

5.4.1. Drug Name

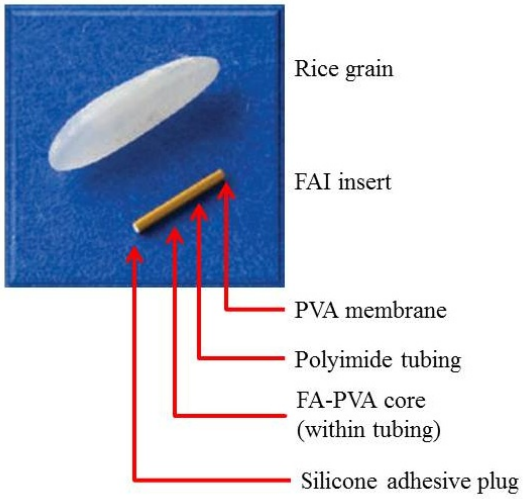
Fluocinolone acetonide is the active ingredient in the FAI insert.

Fluocinolone acetonide is a member of a class of fluorinated synthetic corticosteroids that includes dexamethasone, triamcinolone acetonide and fluocinolone acetonide.

5.4.2. Drug Formulation

FA is combined with one excipient, polyvinyl alcohol (PVA), to form a FA-PVA core (3.5 mm length x 0.34 mm diameter) that is contained within a polyimide tube. The polyimide tube has a permeable PVA membrane at one end and an impermeable silicone adhesive plug on the other end. Figure 1 shows the FAI insert adjacent to a grain of rice.

Figure 1: FAI Insert



5.4.3. Route of Administration

The FAI insert is administered as an intravitreal injection through the pars plana. For this study, the FAI insert will be provided in one of two sterile preloaded inserters: the Mk I inserter (25 gauge needle) or the Mk II inserter (27 gauge needle).

5.4.4. Dose and Duration

The FAI insert is designed to release FA for a period of 36 months at a nominal rate of approximately 0.2 µg FA/day.

5.5. Description of the Mk I Inserter

The Mk I inserter is a sterile, pre-loaded, modified syringe that uses a 25 gauge XX-thin wall needle to penetrate the conjunctiva and sclera; the needle is not retracted after intravitreal injection has been completed. The Mk I inserter has been used previously in clinical study PSV-FAI-001.

5.6. Description of the Mk II Inserter

The Mk II inserter is a sterile, pre-loaded applicator that uses a 27 gauge standard wall needle to penetrate the conjunctiva and sclera; the needle is retracted during intravitreal injection.

6. TRIAL OBJECTIVES AND PURPOSE

To evaluate the utilization and safety of the Mk II inserter and to evaluate the safety of the FAI insert in eyes with non-infectious uveitis affecting the posterior segment of the eye.

6.1. Primary Objective

To assess the utilization and the safety of the Mk II inserter, and the safety of the FAI insert, from the day of treatment through 7 days following treatment.

6.2. Secondary Objective

To assess the safety of the FAI insert over a period of 12 months following treatment.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This trial is a 12 month, phase 3, multi-center, randomized, single-masked (subject), controlled study designed to evaluate the utilization and safety of the Mk II inserter and the safety of the FAI insert, in subjects with non-infectious uveitis affecting the posterior segment of the eye.

As depicted in Figure 2, all subjects will receive the FAI insert on Day 1 of the study, administered using either an Mk I inserter or an Mk II inserter. If both eyes in a subject with bilateral uveitis satisfy the study's inclusion/exclusion criteria, both eyes may be enrolled in the study. In this case, randomization of a subject's second eye will occur independently and will occur no earlier than the study Day 7 visit for the subject's first study eye. Subjects will receive standard care in the study eye(s) and any non-study eye for 12 months following enrollment, in accord with medical need and the Investigator's standard practice. Eyes will be assessed according to the schedule presented in Table 2. The primary utilization and safety analyses of the inserters will be conducted at Day 7; safety analyses of the FAI insert will be conducted at Day 7 and Month 12.

7.2. Number of Subjects

A total enrollment of approximately 30 eyes is planned for this study. Enrollment of approximately 25 subjects is expected, and will continue until:

- at least 20 and 10 study eyes each have been treated using the Mk II and Mk I inserters, respectively, and
- at least 10 different investigators each have performed at least one administration procedure.

7.3. Control (Reference)

FAI insert administered with an Mk I inserter.

7.4. Test Article

FAI insert administered with an Mk II inserter.

7.5. Measures Taken to Minimize Bias

At least 10 different investigators will administer the FAI insert, and randomization will be stratified by investigator.

Each time a subject's eye is enrolled in the study, one investigator will serve as the treating investigator (Investigator); another person will serve as the trained observer (Observer). On study Day 1, the Investigator will administer the FAI insert, and the Observer will observe the procedure used by the Investigator to administer the FAI insert. The Investigator and the Observer will complete questionnaires related to the administration of the FAI insert on Day 1. The Investigator (or designee) will perform all subsequent study assessments. Study personnel will not disclose to the subject which inserter was used for intravitreal administration of the FAI insert.

7.6. Number of Study Sites and Investigators

This study will be conducted in at least 3 study sites; intravitreal administrations will be performed by at least 10 Investigators. Each study site must have at least one Investigator and one Observer; sites are permitted to have more than one Investigator and/or more than one Observer.

7.7. Study Duration

All subjects will be followed for 12 months after treatment.

Figure 2: Study Design

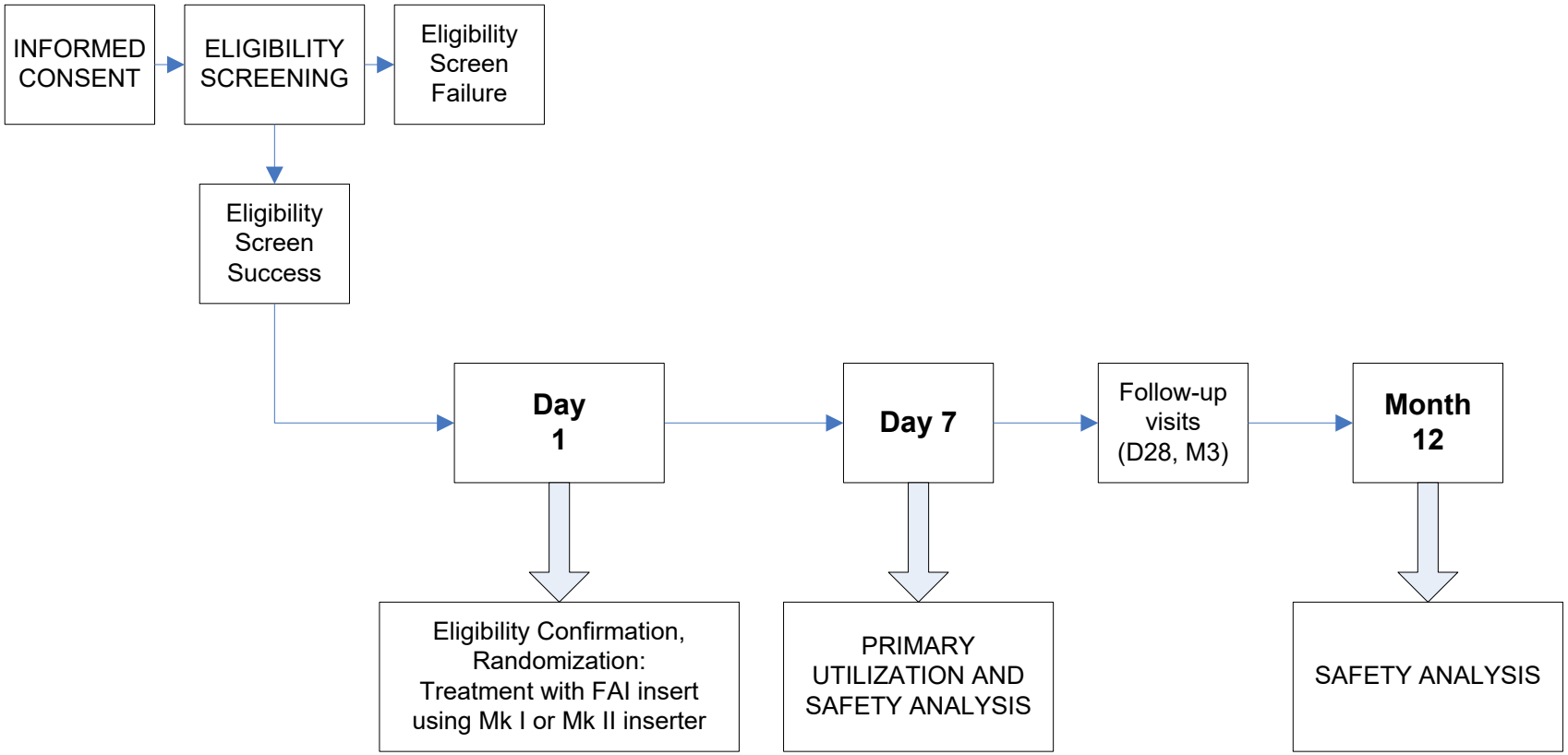


Table 2: Schedule of Procedures and Assessments

Assessments	Screening	Day 1	Day 7	Day 28	Month 3	Month 12
Timing/Interval	-60 to	1	±3D	±14D	±21D	±28D
Medical/Ophthalmic History	X					
Demographics	X					
Inclusion/Exclusion Criteria	X	X				
Vital Signs[a]	X	X	X	X	X	X
Clinical Labs[b]	X					
Ophthalmic Examination[c]	X	X	X	X	X	X
Visual Field	X					X
Pregnancy Test[d]	X	X				X
Randomization		X				
FAI Insert Administration		X				
Post-Administration Assessment[e]		X				
Questionnaire[f]		X				
Concomitant Medications	X	X	X	X	X	X
Adverse Events (AEs)		X	X	X	X	X

[a] Includes systolic/diastolic blood pressure and pulse rate after subject is in the sitting position for at least 5 minutes. Height and weight at screening visit only.
[b] HIV and syphilis serology testing.
[c] Ophthalmic examination includes: BCVA, IOP [recorded as the mean of three measurements], dilated indirect ophthalmoscopy, and anterior, posterior and intermediate slit lamp examinations.
[d] Females of child-bearing potential only: urine test conducted only at Screening, Day 1 and Month 12.
[e] Includes indirect opththalmoscopy to verify adequate central retinal artery perfusion, absence of any other complications, verification of insert placement; IOP [recorded as the mean of three measurements]; follow-up contact with the subject the day following Study Day 1 regarding the subject's ocular condition, and any complaint and/or adverse event.
[f] Following each administration of the FAI insert, the Investigator and the Observer will each complete a questionnaire related to the administration procedure.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

1. Male or non-pregnant female at least 18 years of age at time of consent
2. At least one eye has a history of non-infectious uveitis affecting the posterior segment
3. Subject has ability to understand and sign the Informed Consent Form
4. Subject is willing and able to comply with study requirements

8.2. Subject Exclusion Criteria

1. Allergy to fluocinolone acetonide or any component of the FAI insert
2. Ocular malignancy in either eye, including choroidal melanoma
3. Uveitis with infectious etiology
4. Current viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella
5. Current mycobacterial infections of the eye or fungal diseases of ocular structures
6. Subjects who yield, during screening, a confirmed positive test for human immune deficiency virus (HIV) or syphilis
7. Systemic infection within 30 days prior to study Day 1
8. Peripheral retinal detachment in area of insertion
9. Elevated intraocular pressure (IOP) > 21 mmHg, or chronic hypotony < 6 mmHg
10. Concurrent therapy at Screening with IOP-lowering pharmacologic agent in the study eye
11. Current diagnosis of any form of glaucoma or ocular hypertension in study eye at Screening, unless study eye has been previously treated with an incisional surgery procedure that has resulted in stable IOP in the normal range (10-21 mmHg)
12. Known history of clinically significant IOP elevation in response to steroid treatment in either eye, unless study eye has been previously treated with an incisional surgery procedure that has resulted in stable IOP in the normal range (10-21 mmHg)
13. Ocular surgery or capsulotomy performed on the study eye within 30 days prior to study Day 1
14. Intravitreal treatment of study eye: with FAI insert within 36 months prior to study Day 1; with Retisert within 30 months prior to study Day 1; with Ozurdex within 90 days prior to study Day 1; or with Triesence or Trivaris within 30 days prior to study Day 1
15. Peri-ocular or subtenon steroid treatment of study eye within 30 days prior to study Day 1
16. Treatment with an investigational drug or device within 30 days prior to study Day 1, except the FAI insert within this protocol

17. Pregnant or nursing females; females of childbearing potential who are unwilling or unable to use an acceptable method of contraception as outlined in this protocol from at least 14 days prior to study Day 1 until the Month 12 Visit
18. Any condition which, in the judgment of the Investigator, could make the subject inappropriate for entry into this study

8.3. Subject Withdrawal Criteria

Subjects have the right to withdraw from the study at any time, for any reason, without jeopardizing their medical care. The following are examples of criteria for considering withdrawal from this study:

- Withdrawal of subject consent
- Intercurrent illness (including death) that prevents continuation of regular follow-up visits

All subjects will be followed for safety through the final visit unless the subject is withdrawn from the study.

The Investigator, IRB/EC and pSivida Corp. also have the right to withdraw subjects from the study for the following reasons: when continuation may jeopardize the health of the subject, protocol violations, AEs or concurrent conditions, administrative or other reasons.

Subjects who withdraw for any reason from the study following randomization and administration of study treatment will not be replaced.

9. STUDY PROCEDURES

9.1. Subject Informed Consent and Screening

The Investigator will obtain written informed consent from each subject as a condition of enrollment in the study. Informed consent will be obtained after providing the prospective study participant with an adequate explanation of the protocol procedures and prior to the subject's participation in the study (including screening procedures).

The content of the informed consent form (ICF) will conform to FDA regulations as defined in 21 CFR Part 50, other necessary regulations, and must have current Institutional Review Board (IRB)/ Ethics Committee (EC) approval.

The subject will sign the ICF before any study procedure is initiated. The subject or guardian will sign and date one or two copies of the ICF in the presence of the Investigator or designee, 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 another signed original of the ICF will be given to the subject, in accordance with applicable local requirements.

9.2. Assignment of Subject/Eye Identification Number

Once a subject has provided written informed consent and it has been determined that the subject will undergo screening, a subject/eye identification number (ID number) will be assigned by the

study site. The first 3 digits of the ID number will be the assigned site number, followed by a 3-digit subject number in sequential order (i.e., 201001, etc.), followed by a 1-digit eye identification number: the subject's first eye (if eligible) to be randomized will be assigned the additional digit "1" (e.g., 201001-1); the subject's second eye (if eligible) to be randomized will be assigned the additional digit "2" (e.g., 201001-2).

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

9.3. Screen Failures

Study sites will document all screen failures on the Subject Screening/Enrollment Log with the reason for the failure to be enrolled. Subjects who fail to meet inclusion/exclusion criteria during the screening period or on study Day 1 may be rescreened.

9.4. Randomization

Following confirmation of eligibility at Day 1, eyes will be randomly assigned (2:1) to receive the FAI insert using either the Mk II inserter or the Mk I inserter, respectively. Randomization assignments will be administered through a central Interactive Web Response System (IWRS). Randomization will be stratified on the basis of the investigator administering the treatment.

The randomization schedule will be prepared using a blocked randomization and will be generated by an independent statistician. Only those subjects who have been enrolled in the study will have data recorded on the electronic case report forms (eCRF).

9.5. Study Schedule

See Table 2 for the schedule of visits and assessments. The screening visit and Day 1 (administration of study treatment) are to be within a 60-day period. The windows for the follow-up visits are Day 7: +/- 3 days; Day 28: +/- 14 days; Month 3: +/- 21 days; Month 12: +/- 28 days.

9.6. Screening, Day -60 to Day 0

All study data will be collected for all subject eyes, at screening and subsequent study visits.

After obtaining informed consent, the following assessments will be performed:

- Demographic information, medical history and ophthalmic history including a history of the subject's uveitis and its management over the previous 12 months
- Height, weight and vital signs (includes systolic/diastolic blood pressure and pulse rate after subject is in the sitting position for at least 5 minutes)
- HIV and syphilis serology testing
- Ophthalmic exam, including: BCVA, IOP (recorded as the mean of three measurements), dilated indirect ophthalmoscopy and anterior, posterior and intermediate slit lamp examinations

- Visual field
- Collect urine for urine pregnancy test (females of childbearing potential)
- Concomitant medications
- Verification that the subject satisfies all inclusion and exclusion criteria. Investigators should not continue screening any subject who does not meet the screening eligibility requirements

When screening assessments have been completed, the Investigator should schedule the subject to return for the Day 1 visit.

9.7. Procedures on Day of Treatment (Day 1)

9.7.1. Designation of Study Eye and Randomization

For subjects with unilateral uveitis, the study eye will be the affected eye.

For subjects with bilateral uveitis, the study eye(s) will be the eye(s) meeting eligibility criteria. If both eyes satisfy eligibility criteria, both eyes may be enrolled in the study. In a subject with both eyes eligible for enrollment, randomization of the subject's second study eye may occur no sooner than the study Day 7 visit of that subject's first study eye, and no later than the last day of the study Day 7 visit window of that subject's first study eye. .

If the subject's eye meets the inclusion and exclusion criteria at Screening and Day 1, randomization will be performed via the IWRS. Randomization will be stratified on the basis of the investigator administering treatment.

Treatment assignments will be masked to study subjects. Any non-study eye may receive any standard treatment at the discretion of the Investigator.

9.7.2. Data Collection Prior to Intravitreal Administration of FAI Insert

- Vital signs (blood pressure and pulse rate after subject is in the sitting position for at least 5 minutes)
- Ophthalmic exam , including: BCVA, IOP (recorded as the mean of three measurements), dilated indirect ophthalmoscopy and anterior, posterior and intermediate slit lamp examinations
- Urine Pregnancy test
- Concomitant medications
- Verification that the subject/study eye satisfies all other inclusion and exclusion criteria

9.7.3. FAI Insert Administration Procedure

9.7.3.1. Administration using the Mk I Inserter

The intravitreal injection procedure should be carried out 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.

1. Optimal placement of the FAI insert 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.
2. Using sterile procedure, open the sterile foil pouch containing the Mk I inserter.
3. Remove the Mk I inserter from the sterile pouch by grasping the barrel of the inserter; do not grasp the plunger.
4. Remove the black plunger stop from the plunger.
5. Carefully remove the protective cap from the needle and inspect the needle tip to ensure it is not bent.
6. Remove the trombone wire from the distal end of the needle. Prior to injection, keep the inserter tip above the horizontal plane to ensure that the FAI insert does not fall out of the inserter.
7. 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.
8. Insert the needle through the conjunctiva and sclera up to the positive stop of the inserter.
    a. If the Investigator is unable to insert the needle through the conjunctiva and sclera, please contact the monitor and sponsor immediately.
9. Depress the plunger at the back of the inserter fully to deliver the FAI insert into the back of the eye.
10. Remove the Mk I inserter from the eye and discard.
11. 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 insert.
    a. If the FAI insert is observed to be misplaced within the eye, please contact the monitor and sponsor immediately. Administration of a second FAI insert within the study eye is not permitted in this protocol.
12. Following the injection, monitor the subject for elevation in intraocular pressure and for endophthalmitis. Determine IOP (recorded as a mean of three measurements) within 10 to 30 minutes following the injection. Prescribe a topical antibiotic for the subject to self-administer 4 times per day for 3-5 days. Instruct the subject to report without delay any symptoms suggestive of endophthalmitis.

13. Contact the subject on the next day to determine the subject's ocular condition and to identify any complaint or adverse event.

9.7.3.2. Administration using the Mk II Inserter

The intravitreal injection procedure should be carried out 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.

1. Optimal placement of the FAI insert 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.
2. Using sterile procedure, open the sterile foil pouch containing the Mk II inserter in its tray.
3. Remove the sterile tray lid and then remove the Mk II inserter from the sterile tray.
4. Carefully remove the protective cap from the needle and inspect the needle tip to ensure it is not bent.
5. Visually check through the viewing window of the inserter to confirm that the amber-colored FAI insert is present.
6. 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.
7. Insert the needle through the conjunctiva and sclera up to the hub of the inserter.
    a. If the Investigator is unable to insert the needle through the conjunctiva and sclera, please contact the monitor and sponsor immediately.
8. Press the button on the top of the inserter and confirm that the spring-loaded slide retracts with an audible "click".
9. Depress the plunger at the back of the inserter fully to deliver the FAI insert into the back of the eye.
10. Remove the Mk II inserter from the eye and discard.
11. 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 insert.
    a. If the FAI insert is observed to be misplaced within the eye, please contact the monitor and sponsor immediately. Administration of a second FAI insert within the study eye is not permitted in this protocol.
12. Following the injection, monitor the subject for elevation in intraocular pressure and for endophthalmitis. Determine IOP (recorded as a mean of three measurements) within 10 to 30 minutes following the injection. Prescribe a topical antibiotic for the subject to self-administer 4 times per day for 3-5 days. Instruct the subject to report without delay any symptoms suggestive of endophthalmitis.

13. Contact the subject on the next day to determine the subject's ocular condition and to identify any complaint or adverse event.

9.8. Criteria for FAI Insert Removal

Investigators should consider removing the FAI insert 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 FAI insert and with Iluvien, the likelihood that insert removal will become necessary is very small.

9.9. Follow-up Visits

The subject will return to the study site on Day 7, Day 28, Month 3 and Month 12, for a total follow-up duration of 12 months. Subjects may be seen more frequently if medically indicated. Table 2 provides descriptions of the procedures to be performed, as indicated, at the scheduled visits.

All assessments will be made for both eyes of each subject. Data from study eyes, and adverse event data from non-study eyes, will be entered in the study's electronic case report forms (eCRFs).

9.9.1. Visit on Day 7 (±3 Days)

Assessments include:

- Vital signs (systolic and diastolic blood pressure and pulse rate after subject is in the sitting position for at least 5 minutes)
- Ophthalmic exam: BCVA, IOP (recorded as the mean of three measurements), dilated indirect ophthalmoscopy and anterior, posterior and intermediate slit lamp examinations
- Concomitant medications
- Adverse events

9.9.2. Visits on Day 28 (±14 Days) and Month 3 (±21 Days)

Assessments include:

- Vital signs (systolic and diastolic blood pressure and pulse rate after subject is in the sitting position for at least 5 minutes)
- Ophthalmic exam: BCVA, IOP (recorded as the mean of three measurements), dilated indirect ophthalmoscopy and anterior, posterior and intermediate slit lamp examinations
- Concomitant medications
- Adverse events

9.9.3. Visit at Month 12 (±28 Days)

Assessments include:

- Vital signs (systolic and diastolic blood pressure and pulse rate after subject is in the sitting position for at least 5 minutes)
- Ophthalmic exam: BCVA, IOP (recorded as the mean of three measurements), dilated indirect ophthalmoscopy and anterior, posterior and intermediate slit lamp examinations
- Visual Field
- Pregnancy test (females of child bearing potential)
- Concomitant medications
- Adverse events

9.10. Unscheduled Follow-up Visits

Additional examinations may be conducted as necessary to ensure the safety and well-being of subjects during the study period. Electronic case report forms (eCRFs) should be completed for each unscheduled visit or test that the subject completes.

9.11. Treatment of Worsening/Recurrence of Uveitis

In the event of a worsening/recurrence of uveitis in either eye, standard therapy will be administered, continued and ended in a manner that follows the Investigator's standard practice. Subjects who experience a worsening/recurrence of uveitis will continue in the study.

9.12. Treatment of Elevated IOP

Pharmacologic treatment (eye drops) of elevated IOP must be instituted whenever IOP is > 30 mmHg, and may be instituted at lower IOP levels, at the discretion of the 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. The Investigator should obtain information on the treatment administered by non-study ophthalmologists for inclusion in the study records.

9.13. Cataract Removal and Other Elective Ocular Surgery

Cataracts occurring in the study subjects during the study should be removed by extra-capsular extraction with phacoemulsification. Any other elective ocular surgery should be managed according to the Investigator's standard practice.

9.14. Concomitant Medications/Procedures

At screening, information on prior and concomitant medications taken within the previous 30 days (whether continuing or not) will be collected. All prior and concomitant medications, including pre- and post-ocular procedure medications, will be listed in the subject's medical record and on the concomitant medication eCRF page. At each study visit, each subject should

be questioned concerning any new medications or changes in the subject's current medications since the previous study visit.

For all medications, the generic name, indication, route of administration, frequency, dose, start date and stop date (if applicable) will be collected.

9.15. Description of Procedures

Refer to Table 2 and the appendices (Section 18, Section 19 and Section 20) for details about the following procedures.

9.15.1. Slit Lamp Examination

Slit lamp examination should be performed using the Investigator's standard procedure. This procedure should be the same for all subjects examined at the site and use the same equipment. Observations should be made to indicate the absence or presence of findings for conjunctiva, cornea, iris, and anterior and posterior chambers. All findings are to be documented in the source documentation and the appropriate eCRF.

9.15.2. Dilated Indirect Ophthalmoscopy

Dilated indirect ophthalmoscopy should be performed as part of each ophthalmic examination. This procedure should be the same for all subjects examined at the site and use the same equipment. All findings are to be documented in the source documentation and the appropriate eCRF.

9.15.3. Visual Acuity

BCVA will be measured according to the standard procedure developed for ETDRS at 4 meters (or at 3 meters if the electronic ETDRS system is employed). Corrected-distance VA is to be reported as number of letters read correctly by the subject. The details of refraction and VA determination procedures are provided in Section 18.

9.15.4. Intraocular Pressure

IOP will be reported as an average of 3 measurements (preferably using Goldmann applanation tonometry), using the Investigator's standard procedure.

9.16. Laboratory Testing

Clinical laboratory testing will include HIV and syphilis serology testing, and urine pregnancy tests (for females of childbearing potential).

9.17. Protocol Deviations

The Investigator will not deviate from the requirements from this protocol without prior approval from pSivida Corp. unless necessitated by a medical emergency (i.e., those that impact subject safety or the validity of the study). All other significant changes to the protocol will be made by pSivida Corp. as a protocol amendment and approved by IRB/EC and the appropriate regulatory authority prior to implementation.

9.18. Study Termination or Suspension

If the trial is prematurely terminated or suspended for any reason, the Investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority.

In addition, if the Investigator terminates or suspends a trial without prior agreement of pSivida, the Investigator should inform the institution where applicable, and the Investigator/institution should promptly inform pSivida and the IRB/EC, and should provide pSivida and the IRB/EC a detailed written explanation of the termination or suspension.

If pSivida terminates or suspends this trial, the Investigator should promptly inform the institution where applicable and the Investigator/institution should promptly inform the IRB/EC and provide the IRB/EC a detailed written explanation of the termination or suspension.

If the IRB/EC terminates or suspends its approval/favorable opinion of this trial, the Investigator should inform the institution where applicable and the Investigator/institution should promptly notify pSivida and provide pSivida with a detailed written explanation of the termination or suspension.

10. INVESTIGATIONAL MATERIALS

10.1. FAI Insert

The FAI insert is an injectable intravitreal sustained-release FA delivery system pre-loaded into an injection device. Each insert contains a drug core of FA as the active ingredient within a cylindrical polyimide polymer tube 3.5 mm long with an external diameter of 0.37 mm. One end of the tube is capped with an impermeable polymer (silicone adhesive); the other end is capped with a permeable polyvinyl alcohol membrane. FA release occurs through the permeable end of the cylinder. Each FAI insert contains 0.18 mg FA and delivers FA into the vitreous humor for 36 months, as demonstrated in a clinical pharmacokinetics study of Iluvien (Campochiaro 2013). In vitro data demonstrate that initial FA release occurs at a rate of approximately 0.2 µg FA/day, gradually decreasing over three years to a rate of approximately 0.1 µg FA/day. The FAI insert is designed to be injected through the pars plana into the vitreous.

10.2. FAI Insert in Mk I Inserter

The FAI insert in the Mk I inserter will be supplied as an individual finished product in primary, secondary and tertiary packaging. The primary packaging is the applicator, which includes a 25 gauge needle that is attached to the applicator. The FAI insert is pre-loaded in the applicator. The pre-loaded 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 as investigational drug in accordance with applicable regulations. The assembled units are subsequently sterilized by gamma irradiation, resulting in a sterile, single-use product. Each unit is placed in a SBS shelf carton for shipment.

10.3. FAI Insert in Mk II Inserter

The FAI insert in the Mk II inserter will be supplied as an individual finished product in primary, secondary and tertiary packaging. The primary packaging is the applicator, which includes a 27 gauge needle that is attached to the applicator. The FAI insert is pre-loaded in the applicator, which is then placed in a tray with cover. This assembly is then placed into the secondary packaging, a 6" x 14.3" foil chevron pouch and heat-sealed. Lastly, the foil pouch is placed into a 7.5" x 18" Tyvek chevron pouch. The outer chevron pouch will be labeled as investigational drug in accordance with applicable regulations. The assembled units are subsequently sterilized by gamma irradiation, resulting in a sterile, single-use product. Each unit is placed in a SBS shelf carton for shipment.

10.4. Investigational Product Storage

Investigational product must be stored at controlled room temperature [15°-25ºC (59-77ºF)] in a secured location accessible only to study personnel.

10.5. Supply and Accountability of Investigational Materials

pSivida Corp. will supply the finished product units (Mk I inserter or Mk II inserter) for this study. A log will be maintained at each study site, showing the subject/eye ID number for which each unit is dispensed, the date and who dispensed the unit. Sufficient finished product units will be supplied to each investigative site to allow replacement, as necessary, of any damaged unit.

The Investigator must maintain records of all shipments of study materials and account for all used and unused materials. All unused and damaged study materials must be returned to pSivida Corp. or destroyed on site, with an accounting of all materials supplied, used, and returned, and an explanation for any discrepancies.

11. ASSESSMENT OF SAFETY

11.1. Adverse and Serious Adverse Events

The following are specific definitions of terms guided by the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP) and the U.S. Code of Federal Regulations (CFR) that apply to this section.

11.1.1. Adverse Event

An adverse event (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; an AE does not necessarily have a causal relationship with this treatment. 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 investigational product, whether or not considered related to the investigational product.

11.1.2. Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that:

- Results in death
- 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 or prolongs existing hospitalization
- Results in persistent or significant disability / incapacity
- Is a congenital anomaly / birth defect
- Is a medically important event or reaction
  (Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above.)

The following hospitalizations are not considered SAEs:

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

- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission for purpose other than remedying ill health state 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 requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative)

11.1.3. Protocol-Defined Ocular Adverse Events

The following ocular events must be reported as AEs during this trial:

- decrease in visual acuity of ≥15 letters, compared to the most recent previous measurement of visual acuity
- moderate or severe (grade 3 or 4) ocular findings compared to the last ophthalmic examination
- worsening of ≥ 2 steps in anterior chamber cell count or vitreous haze, compared to the last ophthalmic examination
- increase in IOP of ≥ 10 mmHg at two visits at least 1 week apart or an increase in IOP to ≥ 25 mmHg

11.1.4. Protocol-Defined Ocular Serious Adverse Events

The following ocular events must be reported as SAEs during this trial:

- An AE which causes a decrease in visual acuity of ≥ 30 letters, compared to the most recent previous measurement of visual acuity, lasting more than 1 hour
- An AE which causes a decrease in visual acuity to light perception or worse, lasting more than 1 hour
- An AE which requires surgical intervention (e.g., 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 which is associated with severe intraocular inflammation (i.e., 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 glaucoma medications
- An IOP < 6 mmHg requiring medical intervention
- An AE which in the opinion of the Investigator requires medical or surgical intervention to prevent permanent loss of sight

11.1.5. Laboratory Test Abnormalities

All laboratory test values captured as part of the study should be recorded on the appropriate laboratory test results pages of the eCRF.

In addition, the following laboratory abnormalities should also be captured on the non-serious AE CRF page (paper or electronic) or SAE paper CRF page as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to receive specific corrective therapy

It is expected that, wherever possible, the clinical rather than the laboratory term would be used by the reporting Investigator (e.g., anemia versus low hemoglobin value).

11.1.5.1. Pregnancy

Sexually active women of child bearing potential (WOCBP) must be encouraged to use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized.

All WOCBP MUST have a negative urine pregnancy test within 48 hours prior to receiving the investigational product. If the pregnancy test is positive, the subject must not receive the investigational product and must not be enrolled in the study.

Pregnancy testing must also be performed on all WOCBP throughout the study as specified and the results of all pregnancy tests (positive or negative) recorded on the eCRF.

Any female subject of child-bearing potential should be instructed to contact the Investigator immediately if the subject suspects that she may be pregnant (e.g., missed or late menstrual period) at any time during study participation. NOTE: Pregnancy is not classified as an adverse event in this trial.

11.2. Adverse Event Assessment

11.2.1. Relationship to Study Treatment

The study treatment relationship to each AE should be determined by the Investigator using these explanations:

Unrelated: Evidence indicates no plausible direct relationship to the study medication, device or procedure, or there is a reasonable causal relationship between non-investigational product, concurrent disease, or circumstance and the AE.

Possibly Related: There is reasonable causal relationship between the investigational product, device or procedure and the AE suggests that the association of the event with the study medication, device, or procedure is unknown; however, the adverse event is not reasonably supported by other conditions.

Probably Related: Suggests that a reasonable temporal sequence of the event with medication administration, device usage or the index procedure exists and, based upon the

Investigator's clinical experience, the association of the event with study medication, device or procedure is likely.

The Investigator will make the determination of relationship to the investigational product for each AE (Unrelated, Possibly Related or Probably Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product, device or procedure. If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated".

If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered as related.

If the relationship between the AE/SAE and the investigational product is determined to be "possible" or "probable" the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

11.2.2. Severity

AE severity is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported to him/her by the subject. The assessment of severity is made irrespective of test article relationship or seriousness of the event and should be evaluated according of the following scale:

Mild: Awareness of event but easily tolerated. Usually transient, requiring no special treatment, and does not interfere with the subject's daily activities.

Moderate: Discomfort enough to cause some interference with usual activity. Traditionally introduces a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually relieved by simple therapeutic measures.

Severe: Causes an interruption of the subject's usual daily activity and traditionally requires systemic drug therapy or other treatment.

11.3. 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 can be spontaneously reported or elicited at each study visit through open-ended questioning, examination or evaluation of a subject. In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.

The Investigator will record all AEs of enrolled subjects in the appropriate eCRF. If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms.

The following information should be captured for all AEs: onset and end date, severity, seriousness, relationship to investigational product, action taken, treatment required and outcome. If treatment for the AE was administered, it should be recorded on the appropriate eCRF page.

Completion of supplemental eCRF pages may be requested for AEs and/or laboratory abnormalities that are reported / identified during the course of the study.

The Investigator will take or organize all appropriate and necessary therapeutic measures required for resolution of the adverse event. Any medication necessary for the treatment of an adverse event must be recorded on the concomitant medication eCRF. If more than one distinct AE occurs, each event should be recorded separately.

11.4. Adverse Event Reporting

All subjects enrolled in the study will be evaluated for adverse events. For the individual subjects, adverse events will be collected from Day 1 until study completion.

All AEs will be evaluated from their onset until resolution, stabilization, last day of participation in the study of the patient or the last day of the study, 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 IRB/EC with any additional requested information, notably for reported deaths of subjects.

11.4.1. Reporting of Serious Adverse Event

All SAEs that occur during the course of the study, including death, ***must be reported within 24 hours following the site's knowledge of the SAE*** and recorded on the Serious Adverse Event eCRF (or use a back-up paper form if the eCRF system is not functioning). SAEs will also be reported to regulatory authorities and IRBs/ECs based on the applicable regulatory requirements.

Minimal information to be provided includes:

- Identification of the study
- Identification of the initial reporter
- Patient identification number
- Event term
- Date of onset of the event
- Severity criteria of the event
- Reporting criteria
- Narrative description of the event
- Outcome if known
- Causal relationship to the investigational medication, device and procedure
- Additional and follow-up information as requested by the medical monitor

11.4.2. Reporting of Pregnancy

To ensure patient safety, each pregnancy in a female subject must be reported by the Investigator, within 24 hours of learning of its occurrence. The pregnancy will also be reported to regulatory authorities and Ethics Committees based on the applicable regulatory requirements. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal or newborn complications.

Pregnancy should be recorded on the Pregnancy Report Form. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported as appropriate.

If any male subject's partner becomes or is found to be pregnant during the male subject's treatment with the investigational product, the Investigator must record and submit this information on a Pregnancy Report Form as described above.

11.4.3. Other Safety Considerations

Any significant changes noted during interim/final examinations, procedures or any other potential safety assessment should also be recorded on the appropriate AE or SAE eCRF.

For additional information, Investigators should contact:
PPD Medical Support Center
Telephone: 1-888-483-7729
Telefax: 1-888-529-3580

11.5. Expedited Safety Reporting

Adverse drug reactions (ADRs) that are suspected, serious, and unexpected are subject to expedited reporting. Reports which add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events. For example, an event more specific or more severe than described in the protocol under safety assessments would be considered "unexpected". Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

The purpose of expedited reporting is to make regulators, investigators, and other appropriate people aware of new, important information about serious adverse product reactions. Therefore, such reporting will generally involve events previously unobserved or undocumented. Accordingly, expedited reporting will ordinarily be inappropriate for adverse drug reactions that are serious but expected.

In accordance with local regulations, pSivida will notify investigators of all SAEs that are suspected (probably or possibly related to the investigational product) and unexpected (i.e., not previously described in the Investigator's Brochure).

Investigators will be notified about these events through the use of an expedited safety report (ExSR).

Other important findings which may be reported by the sponsor as an ExSR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (e.g., animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ExSR from pSivida, the Investigator must review and retain the ExSR with the Investigator's Brochure. Where required by local regulations or when there is a central IRB/EC for the study, the sponsor will submit the ExSR to the appropriate IRB/EC. The Investigator and IRB/EC will determine if the informed consent requires revision. The Investigator should also comply with the IRB/EC procedures for reporting any other safety information.

12. REPORTING OF TECHNICAL COMPLAINTS

Technical complaints include quality complaints reported in writing, electronically, or orally involving the use or attempted use of this product that identify any defects in the product (e.g., failure of the inserter to deliver the FAI insert), or dissatisfaction with any other characteristic(s) of the product (labeling, packaging, etc.).

Any technical complaint should be reported within 24 hours by telefax (1-617-926-5050) to Marty Nazzaro at pSivida Corp.

The complaint report should include the following information:

- Product identification number
- Investigator name, study site name, and contact 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 an AE is associated with the complaint, refer to Section 11.)

The unit that is the subject of the complaint should be returned for analysis to:

pSivida Corp.
Attention: Marty Nazzaro or Gerard Riedel
480 Pleasant Street, Suite B300
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.

13. ASSESSMENT OF UTILIZATION AND SAFETY

13.1. Primary Utilization Endpoint

The primary utilization endpoint is defined as the proportion of intravitreal insertion procedures that are assessed by the Investigator as satisfactory. A satisfactory procedure is defined as one receiving a score from the Investigator as either Very Easy (VE), Easy (E), or Routine (R), according to the following categories:

- Very Easy (VE)
- Easy (E)
- Routine (R)
- Difficult (D)
- Very Difficult (VD)

Please refer to Section 20 for additional information.

13.2. Secondary Utilization Endpoints

Secondary endpoints include:

- Clarity of the Instructions for Use, as assessed by the Investigator
- Differences between observed procedure and instructions for use, as assessed by an Observer

13.3. Safety

Safety endpoints include:

- Procedure-related adverse events, including: ocular adverse events (including IOP increase/decrease), clinically significant ocular changes, medications/procedures required to treat adverse events
- All other adverse events, including: ocular adverse events, IOP increase/decrease, medications/procedures required to control elevated/low IOP; development or worsening of cataract; cataract-related procedures; clinically significant ocular changes, systemic adverse events, medications/procedures required to treat adverse events

14. DATA ANALYSES

14.1. Sample Size

With a sample size of 20 eyes in the Mk II inserter group, the 95%, two-sided confidence interval of the satisfactory procedures proportion will be no larger than 27.2% - 72.8% when the exact binomial method and a satisfactory procedures proportion of 10 out of 20 are employed.

All other satisfactory procedures proportions for the Mk II inserter will result in two-sided, 95% confidence bounds that are narrower than that described above.

With a sample size of 10 eyes in the Mk II inserter group, the 95%, two-sided confidence interval of the satisfactory procedures proportion will be no larger than 18.7% - 81.3% when the exact binomial method and a satisfactory procedures proportion of 5 out of 10 are employed. All other satisfactory procedures proportions for the Mk I inserter will result in two-sided, 95% confidence bounds that are narrower than that described above.

These confidence bounds, based on eye, are thought to adequately characterize the ease of use and other performance characteristics of the two inserters being studied.

The study will continue until at least 20 Mk II and 10 Mk I inserter attempts have been randomized and performed, and at least 10 different investigators have attempted at least one administration procedure.

14.2. Study Populations

14.2.1. Intent to Treat (ITT) Population

The ITT population will include all eyes randomized into the study; analyzed as randomized.

14.2.2. Safety Population

The safety population will include all eyes randomized into the study; analyzed as treated.

14.3. Analyses

14.3.1. Analyses of Demographic and Baseline Data

Demographic and baseline characteristics of the ITT population will be presented in tabular summaries by treatment group. Continuous variables will be summarized using the mean, standard deviation, median, minimum and maximum; categorical variables will be summarized using counts and percentages of eyes in each category. The number of subjects will also be presented and have this data described.

14.3.2. Disposition and Exposure

Tabulation of study completion and premature study termination along with reasons for termination will be provided by treatment group. Duration of study participation and insert duration will also be tabulated by treatment group. The number of subjects will also be presented and have this data described.

14.3.3. Schedule of Analyses of Utilization and Safety

Analyses of study data will be performed at the following two time points during the study:

1. After all eyes have completed the Day 7 visit (or have been discontinued from the study prior to this visit). The primary analysis of utilization will occur at the Day 1 time point.
2. After all eyes have completed the Month 12 visit (or have been discontinued from the study prior to this visit).

14.3.4. Analyses of Utilization

Utilization analyses will be performed on the ITT population, at Day 1. All primary and secondary utilization endpoints will be analyzed using the ITT population. Descriptive statistics will be used in all utilization analyses.

14.3.4.1. Primary Utilization Variable and Analysis

The primary utilization analysis will be performed on the ITT population at Day 1 and will present the ease of intravitreal administration reported by Investigators, including the satisfactory ratings proportion, for the Mk I inserter and the Mk II inserter groups of eyes employing descriptive statistics including 95% confidence intervals using the exact binomial methodology.

The primary utilization analysis will be conducted after all eyes in the study have completed study Day 7 or have discontinued study participation.

The trial will be deemed a success for the Mk II inserter if the following condition is met:

> The proportion of Mk II procedures scored as satisfactory (i.e., VE, E or R) is not numerically lower than the corresponding proportion of Mk I procedures.

14.3.5. Secondary Utilization Analyses

The following endpoints will be analyzed employing descriptive statistics:

- Clarity of the instructions for use, as assessed by the Investigator
- Differences between observed procedure and instructions for use, as assessed by an Observer

14.3.6. Analyses of Safety

Safety analyses will be performed on the safety population at Day 7 and Month 12. Eyes randomized but not receiving treatment will have all safety data listed only but will not be included in safety tabulations. Descriptive statistics will be provided for all adverse events. Frequency counts and percentage of eyes within each category will be provided for categorical data. Treatment Emergent Adverse Events (TEAEs; those that occurred on the day or after treatment) will be coded to a corresponding preferred term from the MedDRA coding dictionary.

Ocular safety will be assessed by evaluating ocular TEAEs, visual acuity, IOP, concomitant medications, and slit lamp / dilated indirect ophthalmoscopy exams. Systemic safety will be assessed by evaluating all TEAEs, vital signs, concomitant medications and clinical laboratory tests by treatment group.

Adverse events will be summarized by presenting the number and percentage of eyes having at least one occurrence of any TEAE during the study, having at least one occurrence of a TEAE within each system organ class, and having at least one occurrence of each individual TEAE (preferred term) in each treatment group. Occurrence of TEAEs using MedDRA preferred term, System Organ Class (SOC), by severity and relationship will be provided by treatment group. If a patient experiences multiple events that map to a single preferred term, the greatest severity and strongest Investigator assessment of relation to the investigational product will be assigned to the SOC and preferred term for the appropriate summaries.

Treatment-emergent serious adverse events (SAEs) and TEAEs related to FAI insert treatment will be provided by preferred term, SOC and severity for each treatment group. Again, if a patient experiences multiple events that map to a single preferred term, the greatest severity and strongest Investigator assessment of relation to the investigational product will be assigned to the SOC and preferred term for the appropriate summaries. Adverse events leading to study discontinuation and any deaths will be listed.

Vital signs will be presented using descriptive statistics by visit in each treatment group. Concomitant medication will be summarized by presenting the number and percentage of subjects receiving each medication by term and treatment after coding with WHO-Drug Dictionary terms. Laboratory assessments will be presented by descriptive statistics.

15. ADMINISTRATIVE AND REGULATORY CONSIDERATIONS

15.1. Quality Control and Quality Assurance

pSivida Corp. 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 pSivida Corp. 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.

15.2. Institutional Review Boards / Ethics Committees

Prior to the initiation of the study, the protocol, the ICF and the Investigator's Brochure will be submitted to the IRB/EC for approval. By signing the "Statement of Investigator" form (FDA form 1572), the Investigator is assuring that an IRB/EC which complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review of the proposed 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 pSivida Corp. or its designee prior to release of investigational supplies to the study site. The approval letter must refer to the specific protocol and informed consent form. 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 pSivida Corp. 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 pSivida Corp. 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 pSivida Corp. 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 pSivida Corp. 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.

15.3. 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 to 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. The subject must have a copy of the signed and dated ICF, which will be either a copy of the signed original or another signed original, in accordance with applicable local requirements.

A signed original copy of the ICF must be retained by the study site.

15.4. 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 pSivida Corp. 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 pSivida Corp. 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 relevant 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 links 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 to whether the subject completed the study or discontinued study participation, including the reason for discontinuation.

15.5. Electronic Case Report Forms

All study data must be incorporated in the corresponding electronic case report forms. The Investigator will be responsible for recording all data in the eCRFs.

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.

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

15.6. 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 U.S. (or Product License outside the U.S.) for this drug or 2 years after the withdrawal of the IND. These records include the protocol and copies of all documents submitted to pSivida Corp., or to government authorities, subject records (including signed informed consent forms, 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 pSivida Corp.

15.7. Monitoring of the Study

pSivida Corp. representatives will contact the Investigator and site 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 site's readiness to conduct the trial.

Monitors may observe all aspects of subject treatment as frequently as necessary to ensure adherence to the protocol. The Investigator and site staff will cooperate with pSivida Corp. representatives and will provide any missing information and grant access to all study documentation.

pSivida Corp. representatives may audit the study periodically to ensure that all records are correct and complete.

15.8. Discontinuation of the Study

pSivida Corp. reserves the right to discontinue this study for administrative reasons at any time.

The trial may also be discontinued at a site before study completion, if unexpected adverse events occur or if the Investigator does not adhere to the protocol.

15.9. Policy for Publications

Procedures for the review of publications associated with this trial are described in the clinical trial agreement between the Investigator/institution and pSivida Corp.

16. ETHICS

16.1. 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 Principal Investigator must submit written approval from an IRB/EC to pSivida Corp. or its representative before the Principal 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/EC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. pSivida Corp. representatives 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.

16.2. 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.

16.3. Written Informed Consent

The Principal Investigator(s) at each site will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue participation in the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated ICF must be obtained before conducting any study procedures. The subject must have a copy of the signed and dated ICF, which will be either a copy of the signed original or another signed original, in accordance with applicable local requirements.

A signed original copy of the ICF must be retained by the study site.

17. REFERENCES

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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: 509-16.

Nussenblatt RB, Palestine AG, Chan CC, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. Ophthalmology 1985; 92: 467–71.

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Suttorp-Schulten MS, Rothova A. The possible impact of uveitis in blindness: a literature survey. Br J Ophthalmol 1996; 80: 844-848.

18. APPENDIX 1: MEASUREMENT OF BCVA BY ETDRS

Introduction:

The procedure for performing the testing of best-corrected distance visual acuity is described in this appendix. Visual acuity is always tested with the subject's best correction. Visual acuity should be measured without the pupils being dilated and before slit lamp biomicroscopy examination or any drops or ointments are used.

Equipment and Facilities:

The best-corrected visual acuity (BCVA) of participants will be measured according to the standard procedure originally developed for Early Treatment Diabetic Retinopathy Study (ETDRS) and adapted for the Age Related Eye Disease Study (AREDS) protocol. To ensure best-corrected visual acuity measurement, manifest refraction must be completed prior to visual acuity testing. The study requires a set of three Lighthouse Distance Visual Acuity Test Charts (Lighthouse 2nd edition or Precision Vision "ETDRS") and a rear illuminated box providing standardized chart illumination. For participants who are illiterate or not familiar with the English alphabet, BCVA will be determined using the Tumbling E ETDRS charts.

The charts and the box are manufactured by:

Lighthouse Low Vision Products

36-02 Northern Boulevard

Long Island City, New York 11101

Telephone: (718) 937-6959

Or

Precision Vision

745 North Harvard Ave.

Villa Park, IL 60181

Telephone: (630) 833-1454

Visual acuity testing in this study is required at a distance of 4 meters and for participants with reduced vision, at 1 meter. The 4-meter distance should be clearly and permanently marked. The 1-meter distance is to be measured with a 1-meter stick with the participant seated in a chair.

Visual acuity charts:

Chart R is used for refraction. Chart 1 is used for testing visual acuity of the right eye. Chart 2 is used to test visual acuity of the left eye. The features of the charts are 5 high-contrast Sloan letters in each of the 14 lines. Lines are of equal difficulty, and follow a geometric progression of letter size from line to line. Further, charts 1, 2 and R have different letter sequences to avoid memorization by the participants. Participants should be prevented from seeing Chart 1 and Chart 2 until refraction has been completed, and the visual acuity testing is to begin.

Rear illumination box:

The dimensions of the light box are 24 ¾ inches by 25 ¾ inches by 7 inches. The box can be mounted on a wall or on a 5-pronged wheel-based stand, manufactured by Lighthouse Low Vision Products. Each prong is about 14 inches long, and 2 of the 5 wheels are lockable. When the box is mounted on the stand, the height can be varied. The charts are stored in the back of the light box.

Room lights should be off during refraction and visual acuity testing. The box itself provides sufficient illumination for the examiner to record the test results. Additional light can have an adverse effect. If absolutely necessary, a small desk type light may remain on; however, the light beam should be directed away from the light box and the subject. The light box is equipped with two General Electric Cool Daylight 20-watt fluorescent tubes and ballast. As the illumination of fluorescent tubes diminishes by 5% during the first 100 hours and by another 5% during the next 2,000 hours, the following should be done:

- New tubes should be kept on for about four days (approx. 96 hours) to "warm-up", time "on" does not have to be continuous.
- All tubes should be replaced once a year.
- It is advisable to periodically check the fluorescent tubes for proper function. Replacement tubes can be purchased at a local hardware store or Lighthouse Low Vision Product.

Visual acuity lanes (4-meter and 1-meter):

A distance of exactly 4 meters (13 feet, 1 ½ inches, or 157 ½ inches) is required between the participant's eye and the visual acuity chart for the 4-meter test. A distance of exactly 1 meter (39 ⅜ inches) is required for the 1-meter test.

The room for visual acuity testing must have enough room for the 4-meter lane as well as the light box and the participant.

Mounting the light box:

The light box should be mounted at such a height that the top of the third row of letters (0.8 Log MAR) is 49 ± 2 inches from the floor.

Wall mounting: In addition to the 4-meter lane, 7 inches must be allowed for the depth of the box, plus space for the participant to sit or stand.

Stand mounted box: In addition to the 4-meter lane, 13 inches must be allowed for two of the stand's casters to touch the rear wall or a line marked on the floor if there is no wall, plus space for the participant to sit or stand.

Marking the distance (4 meters):

If the chair and visual acuity box are permanently affixed, distance measurements need only to be made once. If the box is mounted on the wall, but the participant's chair is not permanently affixed, the 4-meter distance from the participant's eye to the chart must be clearly and permanently marked.

If the box is mounted on a movable stand, the 4-meter distance must be clearly and permanently marked on the floor. The location of the box must also be clearly and permanently marked on the floor and placement should be checked between participants. When the stand touches the rear wall, two of the casters should touch the wall.

Marking the distance (1 meter):

The 1-meter distance is measured from the eye of the participant, with his or her back firmly against the back of the chair, to the second or fourth letter of the third line of the eye chart. A 1-meter measuring stick should be used.

18.1. Refraction Technique

All visual acuity will be measured with the participant's best-corrected vision. No pinhole testing will be done. It is strongly advised that the refraction be done with the 4-meter distance. If for practical reasons, the 10-foot distance must be used, the same refraction procedure should be performed as for the 4-meter distance (visual acuity scores will be adjusted accordingly). The right eye should be refracted first, then the left eye.

If the participant wears contact lenses and has glasses, the participant should be reminded that the participant would be unable to wear contact lenses for the duration of the BCVA procedure. At the screening visit, if the participant is wearing contact lenses, the lenses should be removed and refraction and visual acuity should not be determined for at least half an hour for soft lenses and one hour for hard lenses.

18.1.1. Approximate Refraction

If results of a previous subjective refraction are available, they can be used as the beginning of approximate refraction. Otherwise the following procedures should be used:

- If the participant's uncorrected visual acuity is 20/200 or better, and the participant does not have glasses for distance vision, the beginning approximate refraction is no lens correction (plano).
- If the participant's uncorrected visual acuity is less than 20/200 in either eye with the participant's present distance glasses, or without correction if the subject does not have glasses, retinoscopy should be performed by an examiner proficient in this procedure. An acceptable alternative is to conduct an arbitrary trial with any lens to bring visual acuity to 20/200 or better. The lens corrections obtained are used as the beginning approximate refraction for determining best-corrected acuity.
- If the participant's visual acuity is 20/200 or better with participant's current distance glasses, the glasses are measured with a lensometer, and these measurements are to be used as the beginning approximate refraction.

18.1.2. Subjective Refraction

The trial frame is placed and adjusted on the subject's face so that the lens cells are parallel to the anterior plane of the orbits and centered in front of the pupil. The left eye is occluded and the beginning approximate refraction, as previously determined, is placed in the right lens cells with the cylindrical correction anterior.

- It is permissible to use a Phoropter for subjective refraction. However, for testing visual acuity, the lenses from the last Phoropter refraction must be placed in trial frames and the final sphere must be rechecked as described in "Refining Final Spherical Power" (Section 18.1.5).
- If the participant's visual acuity is too poor to see the largest letters on the chart at the 4-meter distance, refer to "Refraction for Participants with Poor Visual Acuity" (Section 18.1.7).

18.1.3. Determination of Spherical Refraction

With the beginning refraction in place, the visual acuity of the right eye is assessed and noted. A +0.50 sphere is then held in front of the right eye and the participant is asked if the vision is "better", "worse", or "no different", while looking at the smallest line the participant can read well.

- If vision is improved, or there is no change, the sphere in the trial frame is replaced with one that is one-half diopter more plus. The +0.50 sphere is held in front of the study eye and participant is asked again if the vision is "better", "worse" or "no different". This process is repeated until the participant says that the additional +0.50 sphere makes the vision worse. The lens should be left in place for 10 to 15 seconds in an attempt to evaluate whether the participant is accommodating. If the vision clears during this period, the +0.50 sphere may be added again. Successive attempts to evaluate additional plus lenses should be made with the 10 to 15 second delay. If there is no evidence of unrelaxed accommodation, the delay period is no longer necessary.
- Whenever the participant says that the vision is worse and no longer improves, the +0.50 sphere is removed from the front of the trial frame. By this process, the highest plus sphere that is tolerated without blurring the participant's vision has been determined.
- Next, a –0.37 sphere is held in front of the trial frame and the participant is asked if vision is "better", "worse" or "no different". If vision is improved, the participant is requested to read the chart, and if at least one more letter is read on the smallest line noted previously or the next smaller line, the sphere in the trial is replaced by a sphere that is 0.25 diopter less. In certain situations, the participant is unable to read more letters, but is convinced that the vision is actually improved. If the examiner believes that this is the case, the additional minus sphere lens can be added. At any stage in the examination, no more than 0.25 diopters of minus sphere should be added without an increase in the number of letters read correctly. The additional minus sphere lens should not be added if the participant reads fewer letters but states that visual acuity is better.
- If the participant says the vision is "no different" or "worse", no minus power should be added and the determination of the sphere correction is complete.

18.1.4. Determination of Cylindrical Refraction

- Cylinder Axis Determination

  If the beginning approximate refraction contains a cylinder correction, changes in cylindrical axis are tested by adding a 0.25, 0.37 or 0.50 diopter cross-cylinder axis, first

with the positive axis at 45 degrees to one side of the cylinder axis and then with the positive axis 45 degrees to the opposite side of the cylinder axis. Since neither position may produce a clear image, the participant is encouraged to select the position producing less blur while focusing on a single round letter on the line above the lowest line on the chart the participant can read when the cross cylinder is not held up before the trial frame. If the participant cannot choose between the two positions of the cross-cylinder at the beginning of this test, the axis is moved 5 to 15 degrees, first in one direction and then in the other, with the cross-cylinder being checked in each position to confirm that the original axis was correct. If the participant prefers one position of the cross-cylinder to the other and the cylinder in the trial frame is plus, the axis of the cylinder is moved 5 to 15 degrees toward the positive axis of the cross-cylinder when it is in the position found to be less blurry by the participant.

When the power of the cylinder is low or the participant's discrimination is poor, larger shifts will produce more clear-cut answers. The cross-cylinder is held again with the positive axis 45 degrees, first to one side, then to the opposite of the new cylinder axis, to determine which position produces less blur.

- Cylinder Power Determination

Change in cylinder power is tested by adding the cross-cylinder, first with the positive axis and then with the negative axis coincident with the cylinder axis. The participant is requested to focus on a round letter on the lowest line of the chart the participant can read. If the participant prefers the positive axis coincident with the cylinder axis, the power of the correcting plus cylinder is increased by a +0.25 diopter. If the participant prefers the negative axis coincident with the cylinder axis, the total power of the correcting plus cylinder is reduced by 0.25 diopter. This process is repeated until the participant finds neither position is better than the other. As the plus cylinder is added, the examiner should notice that the spherical equivalent of the refraction is changed. More minus sphere may be needed as the plus cylinder is added. For every 0.50 diopter of cylinder power added, the sphere changes by –0.25 diopter. If the beginning refraction is a pure sphere, the presence of an astigmatism is tested by arbitrarily placing a +0.25 cylinder at 180 degrees in the trial frame, after having determined the highest-plus or least-minus sphere producing minimal blurring of vision, as described previously in Section 18.1.3. The refraction is continued by using the cross-cylinder to test for the axis and the cylinder power using the cross-cylinder technique outlined above.

18.1.5. Refining Final Spherical Power

When neither the power nor the axis of the cylinder can be improved, the power of the sphere is refined by testing with +0.25 sphere and –0.37 sphere and changing the spherical power as indicated previously in Section 18.1.3. If the sphere is changed at this point, the cylinder should be rechecked.

This process is repeated until no further significant lens changes are made.

18.1.6. Summary of Refraction Protocol

At the end of the refraction, the sphere is checked and the participant neither tolerates increased plus nor improves with increased minus spheres. Then the axis is checked and no change in this is indicated. At this point, the refraction is considered complete.

If, at the time of the refraction, the subject's pupil is dilated it must be noted on the visual acuity worksheet.

18.1.7. Refraction for Participants with Poor Visual Acuity

If it is not possible to perform a subjective refraction at 10 feet or 4 meters because visual acuity is too poor for the participant to see the largest letters on the chart at this distance, the refraction should be attempted at 1 meter. The procedure at 1 meter is the same as the procedure for 4 meters. However, the increments of lens power can be larger. For the sphere, ± 1.00 diopter or more can be tested. Cylindrical refraction can be assessed with the 0.5 or 1.00 diopter. If subjective refraction can be performed successfully at 1-meter, a +0.75 sphere should be subtracted from the 1-meter refraction to make the correction appropriate for the 4-meter distance.

18.2. 4-Meter Test and 1-Meter Test

18.2.1. 4-MeterTest:

The distance from the participant's eyes to the visual acuity chart must be exactly 4 meters (13 feet and 1.5 inches).

- The examiner should insure that the participant is sitting or standing comfortably, and that the head does not move back and forth during the test. The participant's eyes should always remain at the 4-meter distance.
- The participant should be told the chart contains only letters and no numbers. Should the participant forget these instructions and read a number, the examiner will remind the participant that the chart contains letters only and request a letter response in lieu of a number.
- The examiner should ask the participant to read slowly.
- The examiner should never point to the chart or to specific letters on the chart or read any letters during the test.
- Each letter is scored as correct or wrong. If the participant changes a response aloud before he or she has read the next letter aloud, that response is acceptable. If the participant changes the response after the next letter has been read aloud, that next response is unacceptable.
- Participants should be encouraged to guess. The reasons are: a) it will help maximize the participant's effort and help ensure uniformity among different clinical sites; b) it will help prevent bias if the participant has become unmasked.
- The participant should be requested to give only one letter as a response.

- The participant can turn or shake his or her head if this improves visual acuity while the fellow eye remains securely covered.

18.2.2. 1-Meter Test:

Eyes reading less than 20 letters correctly at 4 meters will be tested at 1 meter.

- Before testing at 1-meter, a +0.75 sphere should be added to the 4-meter correction already in the trial frame to compensate for the closer distance.
- The participant will be asked to read only the first six lines at 1 meter, making 30 the highest possible score at this distance.
- After the test of the right eye with chart 1 is completed, repeat the test for the left eye with chart 2, starting at 4 meters. When testing of the left eye is completed, chart 1 and 2 should be removed from view and chart R mounted. At this time refraction used for the right and left eyes should be introduced to the trial frame or the Phoropter and binocular visual acuity should be assessed using the same protocol as noted above.

18.2.3. Scoring Best Corrected Visual Acuity:

The examiner will record each letter correctly identified by circling the corresponding letter on the Visual Acuity Worksheet. Letters read incorrectly or for which there was no guess will be marked with a slash mark through the corresponding letter.

- Each letter read correctly is scored as one point.
- The score of each line (which is zero if no letter was read) is recorded on the Visual Acuity Worksheet.
- If testing at 1 meter is not required, 30 points are automatically added to the total number of letters read correctly.
- If testing at 1 meter is done the score is determined by adding the total number of letters read at 4 meters to the total number read correctly at 1 meter.

The total combined score (sum of the 4-meter and 1-meter test scores) is recorded on the Visual Acuity Worksheet. Snellen-equivalent is calculated from the lowest line read with ≤ 2 letter errors (≥ 3 letters correct).

18.2.4. Visual Acuity Grading Scale

Measurement of best corrected visual acuity is measured with logarithmic visual acuity charts at a distance of 4 meters, and at 1 meter if visual acuity is worse than 20/100. Participants are encouraged to make a maximum effort to read as many lines as possible.

19. APPENDIX 2: METHODS OF CLINICAL EVALUATION

19.1. Ophthalmoscopy and Grading of Vitreous Haze

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

Vitreous Haze Grading Scale
The following scale will be used to define the extent of vitreous haze:

Grade	Description
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

19.2. Anterior Chamber Cells Grading

Anterior Chamber Cells 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 2005).

Field size: 1 mm by 1 mm slit beam

Grade	Description
0	<1 cell / high power field (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

19.3. 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.

19.4. Intraocular Pressure

Intraocular pressure will be assessed, preferably by Goldmann applanation tonometry, 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 measurements for a given subject, using the same instrument. Measurement should be performed before dilated ophthalmoscopy.

19.5. Visual Field Measurement

The 24-2 program will be used. The same program should be used for all measurements for a given subject, using the same instrument. Measurement should be performed before ophthalmoscopy.

20. APPENDIX 3: QUESTIONNAIRES

20.1. Mk I Questionnaires

20.1.1. Investigator Questionnaire

1. Were the instructions for the use of the **Mk I inserter** clear and understandable?

   If not, please explain.

2. The ease of intravitreal administration using the **Mk I inserter** was:
   a. Very easy
   b. Easy
   c. Routine
   d. Difficult
   e. Very difficult

3. Were you able to deliver the insert into the vitreous using the **Mk I inserte**r?

   If not, please explain.

20.1.2. Observer Questionnaire

1. Was sterile technique used to remove the **Mk I inserter** from the pouch?

   If not, please explain.

2. Did the Investigator follow the **Mk I inserter** instructions for use?

   If not, please explain.

3. Did you observe any difficulty experienced by the Investigator during use of the **Mk I inserter**?

   If yes, please explain.

4. Do you have any other observations to report?

   If yes, please explain.

20.2. Mk II Inserter Questionnaires

20.2.1. Investigator Questionnaire

1. Were the instructions for the use of the **Mk II inserter** clear and understandable?

   If not, please explain.

2. The ease of intravitreal administration using the **Mk II inserter** was:
   a. Very easy
   b. Easy
   c. Routine
   d. Difficult
   e. Very difficult

3. Were you able to deliver the insert into the vitreous using the **Mk II inserter**?

   If not, please explain.

20.2.2. Observer Questionnaire

1. Was sterile technique used to remove the **Mk II inserter** from the tray?

   If not, please explain.

2. Did the Investigator follow the **Mk II inserter** instructions for use?

   If not, please explain.

3. Did you observe any difficulty experienced by the Investigator during use of the **Mk II inserter**?

   If yes, please explain.

4. Do you have any other observations to report?

   If yes, please explain.