CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210331Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	210331
Priority or Standard	Standard
Submit Date(s)	January 5, 2018
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Division / Office	DTOP/OAP
Reviewer Name(s)	Martin P Nevitt, M.D., M.P.H.
Review Completion Date	October 2, 2018
Established Name	Fluocinolone acetonide intravitreal implant, 0.18 mg
(Proposed) Trade Name	YUTIQ
Therapeutic Class	Corticosteroid
Applicant	Eyepoint Pharmaceuticals Inc.
Formulation(s)	Intravitreal implant
Dosing Regimen	One insert per affected eye
Indication(s)	Treatment of chronic non-infectious uveitis affecting the posterior segment of the eye
Intended Population(s)	Patients with non-infectious uveitis affecting the posterior segment of the eye

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

YUTIQ (fluocinolone acetonide intravitreal implant), 0.18 mg is recommended for approval for the treatment of non-infectious uveitis affecting the posterior segment (NIU-PS) of the eye.

1.2 Risk Benefit Assessment

YUTIQ has been shown to be effective for the treatment of non-infectious uveitis affecting the posterior segment of the eye based on two adequate and well controlled clinical trials.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A risk management plan is not necessary given the known risks of this class of products (such as cataract formation and the increase in Intraocular Pressure (IOP)).

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended Post-Marketing Requirements or Commitments.

2 Introduction and Regulatory Background

Eyepoint Pharmaceuticals Inc. is submitting this application as a 505(b)(1) application relying on its two Phase 3 studies to assess the findings of safety and effectiveness to seek approval for YUTIQ, an intravitreal insert that is nearly identical to Iluvien, another intravitreal insert approved for diabetic macular edema in NDA 201923. Eyepoint Pharmaceuticals Inc. has a Letter of Authorization to reference and use all ILUVIEN data in NDA 201923. YUTIQ contains 0.18 mg of fluocinolone acetonide (FA) compared to ILUVIEN which has 0.19 mg of fluocinolone acetonide. Both drugs are sterile and are a sustained release non-bioerodible intravitreal implant designed to release drug for up to 3 years.

Fluocinolone acetonide (FA) has been used for more than 30 years as a topical steroid for dermatologic conditions, and since 2005 it has been available in the US as a surgically administered intravitreal implant, RETISERT, for chronic non-infectious posterior uveitis. RETISERT contains 0.59 mg FA and is designed to release FA over approximately 30 months.

2.1 Product Information

2.2 Tables of Currently Available Treatments for Proposed Indication

Approved Drugs for the Treatment of Uveitis

Drug	Endpoint	Treatment Effect	Intended Population
Adalimumab (Humira)	Time to treatment failure	Trial 1 Failures: placebo (79%) vs. (55%) adalimumab Trial 2 Failures: placebo (55%) vs. (39%) adalimumab	Patients ≥ 18 y.o. with non-infectious intermediate or posterior uveitis
fluocinolone acetonide implant (Retisert)	recurrence of uveitis (i.e. ≥ 2 step increase in cells or flare) in the study eye within 34 weeks following implantation	54% vs. 7% (trial 1) 40% vs. 14% (trial 2)	Patients, age 7 and older, with chronic recurrent non-infectious posterior uveitis
dexamethasone intravitreal implant (Ozurdex)	proportion of patients with vitreous haze score of 0 (no inflammation) at week 8	47% vs. 12%	Patients ≥ 18 y.o. with non-infectious intermediate or posterior uveitis
Triamcinolone	DESI		Inflammatory conditions of the eye
Prednisone	DESI		Inflammatory conditions of the eye
Dexamethasone	DESI		Inflammatory conditions of the eye

2.3 Availability of Proposed Active Ingredient in the United States

FA has been used for more than 30 years as a topical steroid for dermatologic conditions and is contained in RETISERT available since 2006 as an intravitreal insert and in ILUVIEN available since 2010 as an intravitreal implant.

2.4 Important Safety Issues With Consideration to Related Drugs

YUTIQ, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in myocbacteria infection of the eye and fungal diseases of ocular structures.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following meetings/correspondence was held with the sponsor during the course of the drug's development process:

May 7, 2015 - Type C meeting was held referencing IND 113,140 to discuss the clinical data package that the former sponsor (pSivida) should include in its NDA submission.

July 20, 2017 – Type B Pre-NDA meeting was held to discuss the necessary components/format to file their NDA.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission was of sufficient quality to allow for a substantive review without requiring additional clinical information from the sponsor.

3.2 Compliance with Good Clinical Practices

The clinical studies contained in this application were conducted in accordance with International Conference on Harmonization (ICH) guidelines and Good Clinical Practice (GCP).

3.3 Financial Disclosures

Investigator	Site	Eyes Enrolled in Study PSV-FAI-001	Eyes Enrolled in Study PSV-FAI-005
(b) (6)			

<u>Reviewer's comments:</u>

A total of 282 eyes were included in the ITT population with no site driving the overall results of the clinical trials.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

YUTIQ is a sterile non-bioerodible intravitreal implant containing 0.18 mg fluocinolone acetonide in a 36-month sustained-release drug delivery system. YUTIQ is preloaded into a single-use applicator to facilitate injection of the implant directly into the vitreous. The drug substance is a synthetic corticosteroid, fluocinolone acetonide.

Each YUTIQ consists of a light brown 3.5mm x 0.37mm implant containing 0.18 mg of the active ingredient fluocinolone acetonide and the following inactive ingredients: polyimide tube, polyvinyl alcohol, silicone adhesive and water for injection.

4.2 Clinical Microbiology

Not applicable. There is no clinical microbiology review for this product. It is not an anti-infective.

4.3 Preclinical Pharmacology/Toxicology

Long-term animal studies have not been conducted to determine the carcinogenic potential or the effect on fertility of YUTIQ.

Fluocinolone acetonide was not genotoxic in vitro in the Ames test (S. typhimurium and E. coli) and the mouse lymphoma TK assay, or in vivo in the mouse bone marrow micronucleus assay.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Corticosteroids inhibit inflammatory responses to a variety of inciting agents including multiple inflammatory cytokines. They inhibit edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation.

Corticosteroids are thought to act by inhibition of phospholipase A2 via induction of inhibitory proteins collectively called lipocortins. It is postulated that these proteins control biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting release of the common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A2.

4.4.3 Pharmacokinetics

In a human pharmacokinetic study of ILUVIEN, fluocinolone acetonide concentrations in plasma were below the lower limit of quantitation of the assay (100 pg/mL) at all post-administration time points from Day 7 through Month 36 following intravitreal administration of an ILUVIEN implant. A pharmacokinetic study of Yutiq has not been conducted.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Number of Subjects	Diagnosis of Patients	Duration of Treatment
PSV-FAI-001	Efficacy and Safety	Prospective, multi-center, randomized (2:1), double masked, comparison FAI insert to sham injection (control), followed by standard of care and 36-month follow-up.	129 eyes randomized As of M6: 129 completed 0 discontinued As of M12: 126 completed 3 discontinued	Male and female subjects age ≥18 years who had non-infectious uveitis affecting the posterior segment of the eye	Primary endpoint at Month 6

PSV-FAI-005	Efficacy and Safety	Prospective, multi-center, randomized (2:1), double masked, comparison FAI insert to sham injection (control), followed by standard of care and 36-month follow-up.	153 eyes randomized As of M6: 151 completed 2 discontinued	Male and female subjects age ≥18 years who had non-infectious uveitis affecting the posterior segment of the eye	Primary endpoint at Month 6
PSV-FAI-006	Safety and Utilization	Prospective, randomized (1:2), single masked, multi-center comparison of FAI insert administered with one of two applicators followed by standard care and 12-month follow-up.	26 randomized (38 eyes) As of Day 7: 26 (38 eyes) completed, 0 discontinued	Non-infectious uveitis affecting the posterior segment of the eye	Day 7 report

5.2 Review Strategy

The safety and efficacy of YUTIQ a sterile non-bioerodible intravitreal implant containing 0.18 mg fluocinolone acetonide in a 36-month sustained-release drug delivery system for the proposed indication of non-infectious uveitis affecting the posterior segment of the eye was based on the review of 2 randomized, double-masked, sham-controlled studies (Studies PSV-FAI-001 and -005) studies. The (b) (4) I applicator was studied in Study PSV-FAI-001 and the (b) (4) II applicator was studied in Study PSV-FAI-005. Description of the trial design for the studies is included in section 5.3.

NOTE: Throughout this document FAI insert refers to (b) (4) I applicator for study PSV-FAI-001 and to (b) (4) II applicator for study PSV-FAI-005.

5.3 Discussion of Individual Studies/Clinical Trials

Studies PSV-FAI-001 and -005 were prospective, multi-center, randomized, double masked, comparisons of the FAI insert to sham injection (control), followed by standard of care and 36-month follow-up.

Study PSV-FAI-001, using the (b) (4) I applicator, enrolled subjects at a total of 33 sites in the US, United Kingdom, Germany, Hungary, Israel and India. Study PSV-FAI-005, using the (b) (4) II applicator, enrolled subjects at 15 sites in India.

The inclusion/exclusion at both sites was similar with both studies having enrolled males and non-pregnant females at least 18 years old, with a history of NIU-PS of ≥ 1 year duration. In the twelve months prior to enrollment, subjects were required to have received systemic corticosteroid or other treatment for at least 3 months and/or at least 2 intra- or periocular corticosteroid treatments to manage uveitis, or have had at least 2 separate recurrences requiring systemic, intra- or periocular corticosteroid. On Day 1, the study eye was required to have < 10 anterior chamber cells/high powered field, vitreous haze (VH) ≤ grade 2 and BCVA of at least 15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters. Subjects with glaucoma or ocular hypertension were only permitted if the study eye had previously had an incisional surgical procedure resulting in an IOP of 10-21 mmHg.

Subjects received a single FAI insert or a sham injection on Day 1 and had additional visits scheduled on Study Days 7, 28 and Months 2, 3, 6, 9, 12, 18, 24, 30 and 36.

The primary efficacy endpoint was defined as the proportion of subjects who had a recurrence of uveitis in the study eye within 6 months following treatment.

Recurrence was defined as:

- An increase in the vitreous haze of ≥2 steps compared to baseline or any visit time point prior to Month 6

OR

- A deterioration in visual acuity of at least 15 letters in Best-Corrected Visual Acuity (BCVA) associated with recurrence of uveitis, compared to baseline or any visit time point prior to Month 6.

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

6 Review of Efficacy

6.1 Indication

YUTIQ is recommended for approval for the treatment of non-infectious uveitis affecting the posterior segment (NIU-PS) of the eye.

6.1.1 Methods

The description of the clinical trial design is contained in section 5.3.

The 2 studies (PSV-FAI-001 and -005) had similar inclusion and exclusion criteria and similar study populations were enrolled in each trial. Across the two trials, 282 subjects were enrolled and included in the ITT populations and safety populations. Of these, 188 subjects were randomized to the drug treatment group and 94 subjects were randomized to sham injection treatment group. Since only one eye/subject could be treated in each study the number of eyes is equal to the number of subjects.

In the Phase 3 trials two different types of insertion applicator systems were used, in study PSV-FAI-001 87 subjects were enrolled using the (b) (4) I applicator with 42 subjects receiving sham injections, and in study PSV-FAI-005 101 subjects were enrolled using the (b) (4) II applicator with 52 subjects receiving sham injections.

Additionally, a Phase 3b Safety and Utilization study was performed in a Prospective, randomized ([(b) (4)] I: [(b) (4)] II/1:2), single masked, multi-center comparison of FAI insert administered with one of two applicators followed to Day 7. For Phase 3b results refer to Section 7.4.5.

List of Investigators for Study PSV-FAI -001 and Subjects Enrolled

PSV-FAI-001 Investigator	Site #	Address	Subjects Enrolled
Germany			
Christoph Deuter, PD, Dr.med	21	Universitäts- Augenklinik, Abteilung Augenheilkunde Schleichstraβe 12-16, Tübingen, 72076 Germany	0
Carsten Heinz, PD, Dr. med	23	Augenklinik am St. Franziskus Hospital Hohenzollernring 74 Muenster, 48145 Germany	11
Hungary			
János Németh, MD, Prof.	31	Semmelweis Egyetem Mária u. 39. Szemészeti Klinika Budapest, 1085 Hungary	0
András Berta, MD, Prof.	32	Debreceni Egyetem Orvos-ós Rgészségtudományi Centrum Nagyordel körút 98, Szemklinika Debrecen, 4032	0
Ágnes, Kerényi, MD, PhD	33	Maglódi út 89-91, Budapest, 1106 Hungary	1
India			
Mudit Tyagi, MS, MBBS Previous Principle Investigator:	70	Smt Kanuri Santhamma Centre for VitreoRetinal Diseases, L.V. Prasad Eye Institute Kallam Anji Reddy Campus, LV Prasad Marg, Banjara Hills, Hyderabad, Telangana, 500034 India, L.V. Prasad Eye Institute, Kallam Anji Reddy Campus, L.V. Pasad Marg, Banjara Hills Hyderabad,	5
Nilesh Kakade, MBBS, DO, DNB Previous Principal Investigator:	71	PBMA'S, H.V. Desai Eye Hospital S No 93, Tarawade Vasti, Mohammadwadi Rd, Hadapsar Pune, Maharashtra, 411060 India	8
Tejas Himanshu Desai, MBBS, MS	73	Retina Department, C.H. Nagri Municipal Eye Hospital, Ellisbridge, Ahmedabad, Gujarat, 380006 India	3
Kokila G. Kamath, MBBS, MS	74	Department of Ophthalmology, Seth G.S. Medical College & K.E.M. Hospital, Parel Mumbai, Maharashtra, 400012 India	2
Soumyava Basu, MBBS, MS	75	L.V. Prasad Eye Institute Patia Bhubaneswar, Odisha, 751024 India	3
Vishal Katiyar, MBBS, MS	76	Department of Ophthalmology, King George Medical University Shah Mina Rd, Chowk, Lucknow, Uttar Pradesh, 226003 India	10
Israel			
Michal Kramer, MD	41	Department of Ophthalmology, Rabin Medical Center Beilinson Hospital, 39 Jabotinski St Petah Tikva, 49100 Israel	2
Amer Radgonde, MD, MBBS	42	Department of Ophthalmology Hadassah University Hospital, Ein Kerem, Kiryat Hadassah Jerusalem, 91120	4
Gill Sartani, MD	44	Department of Ophthalmology, Emek Medical Center 21 Yitshak Rabin Boulevard Afula, 18101 Israel	0
Vicktoria Vishnevskia- Dai, MD	46	Department of Ophthalmology The Chaim Sheba Medical Center, Tel Hashomer Ramat Gan, 52621 Israel	4
United Kingdom			
Carlos Pavesio, MD	51	Moorfields Eye Hospital 162 City Rd London, EC1V 2PD England, United Kingdom	6
Helen Devonport, FRCOphth	52	Bradford Royal Infirmary Duckworth Ln Bradford, BD9 6RJ England, United Kingdom	2
Philip Murray, MBBS, DO(RCS), PhD, FRCP, FRCS,	53	Birmingham and Midland Eye Centre, City Hospital Dudley Rd, Birmingham, B18 7QU England United	2

Antonis Kaintatzis, MD, CCT, EBOd, MSHSM Previous Principle Investigator: Ahmed Sallam, MD, PhD, MB Ch.B, MRCSI, FRCS,	54	Gloucestershire Royal Hospital Great Western Rd Gloucester, GL1 3NN England United Kingdom	2
Giuliana Silvestri, MD, FRCOphth, FRCS, MRCP,	55	The Queen's University of Belfast, Royal Group of Hospitals Grosvenor Rd Belfast, BT12 6BA Northern Ireland	3
Miles Stanford, PhD, MD, FRCOphth, FRCS, MB, MSc	56	St Thomas' Hospital Lambeth Palace Rd London, SE1 7EH England United Kingdom	5
USA			
J. Brian Reed, MD	01	Retinal Consultants Medical Group, Inc 5775 Greenback Ln Sacramento, CA 95841 USA	1
Mark E. Chittum, MD	02	Retina Consultants of Southern Colorado, PC 2770 N. Union Blvd Ste #140, Colorado Springs, CO 80909 USA	4
Daniel Virgil Alfaro III, MD	03	Charleston Neuroscience Institute 9565 Hwy 78, Building 300, Ladson, SC 29456 USA	1
Mark E. Kleinman, MD	04	Department of Ophthalmology and Visual Sciences 740 S. Limestone, Lexington, KY 40536-0284 USA	1
Pravin Dugel, MD	05	Retinal Consultants of Arizona 1101 E. Missouri Ave Phoenix, AZ 85014, USA	0
Careen Lowder, MD, PhD	08	Cleveland Clinic 9500 Euclid Ave I-30 Cleveland, OH 44195 USA	6
Glenn J. Jaffe, MD	09	Duke Eye Center, 2351 Erwin Rd, Box 3802, Durham, NC 27710 USA	5
David G. Callanan, MD	11	Texas Retina Associates, 801 W. Randol Mill Rd., Ste 101 Arlington, TX 76012, USA	4
Naomi Falk, MD, OD	12	Retina Consultants, PLLC 1220 New Scotland Rd Ste 201 Slingerlands, NY 12159 USA	3
Ron P. Gallemore, MD, PhD	13	Retina Macula Institute, 4201 Torrance Blvd., Ste 220 Torrance, CA 90503 USA	1
Eric B. Suhler, MD, MPH	14	Oregon Health & Science University Casey Eye Institute 3375 SW Terwilliger Blvd. Portland, OR 97239 USA	3
David K. Scales, MD	17	Foresight Studies, LLC 9623 Huebner Rd, Ste 101 San Antonio, TX 78240 USA	4
C. Stephen Foster, MD, FACS, FACR	18	Ocular Immunology and Uveitis Foundation 1440 Main St, Ste 201, Waltham, MA 02451 USA Previously: Ocular Immunology and Uveitis Foundation 5 Cambridge Center, 8th Floor	13
Quan Dong Nguyen, MD, MSc	19	UNMC Truhlsen Eye Institute, 985540 Nebraska Medical Center (Mailing only) Omaha, NE 68198 USA	3
Rosa Y. Kim, MD	90	Retina Consultants of Houston, PA 6560 Fannin, Ste 750 Houston, TX 77030 USA	3
Pouya Dayani, MD	92	Retina-Vitreous Associates Medical Group 9001 Wilshire Boulevard, Ste 301, Beverly Hills, CA 90211 USA	1
Thomas M. Aaberg, Jr., MD	94	Retina Specialists of Michigan 2757 Leonard NE, Suite 200 Grand Rapids, MI 49525 USA	0
Debra A. Goldstein, MD, FRCSC	95	Northwestern Medical Group, Department of Ophthalmology, 675 N. St. Clair St Ste 15-150 Chicago, IL	3

List of Investigators for Study PSV-FAI -005 and Subjects Enrolled

PSV-FAI-005 Investigator	Site #	Address	Subjects Enrolled
India			
Mudit Tyagi, MBBS Previous Principal Investigator:	101	L.V. Prasad Eye Institute, Kallam Anji Reddy Campus, L.V. Prasad Marg, Banjara Hills, Hyderabad, Telangana, 500034, AP, India	10
Asokan Paramasivam, MBBS Previous Principal Investigator:	102	Vitero Retinal Services, Vasan Eye Care Hospital, No. 383, Anna Salai, Saidapet, Chennai - 600015, Tamil Nadu, India	2
Atul Hegade, MBBS, DOMS Previous Principal	103	Retina Department, Room No 110, PBMA's H.V. Desai Eye Hospital S No 93, Tarawade Vasti, Mohammadwadi Road, Hadapsar Pune, Maharashtra, 411060 India	14
Arjun Ahuja, MS Previous Principal Investigator:	105	Department of Ophthalmology, OPD No.36, Ground Floor, Seth G.S. Medical College & KEM Hospital, A.D. Marg, Parel Mumbai, Maharashtra, 400012 India	7
Jyotirmay Biswas, MBBS, MS	106	Director of Uveitis & Head of the Department of Ocular Pathology, Sankara Nethralaya, New No 41, Old No 18, College Road Chennai, Tamil Nadu,	17
Tejas Himanshu Desai, MBBS, MS	107	Retina Department, C.H. Nagri Municipal Eye Hospital	3
Shahana Mazumdar, MBBS, MS, DNB	108	ICARE Eye Hospital & Post Graduate Institute ICARE Research Centre, E3A, Sector-26 Noida, Uttar Pradesh, 201301 India	12
Manisha Agarwal, MBBS, MS	109	Vitreo - Retina Department, Dr. Shroff's Charity Eye Hospital 5027, Kedarnath Road, Daryaganj New Delhi, 110002 India	13
Jayanta Dutta, MBBS Previous Principal Investigators: Himadri Datta, MS, PhD	110	Department of Ophthalmology, 4th Floor, Regional Institute of Ophthalmology, 88 College Street, Kolkata, West Bengal, 700073 India	7
Vishal Katiyar, MBBS, MS	111	Department of Ophthalmology, Room No.103 and 104 King George Medical University, Shah Mina Road, Chowk	24
Aparna Mahendru, MBBS, MS	112	Dept. of Ophthalmology, J.L. Rohatgi Memorial Eye Hospital 117/52, G.T. Road, Sarvodaya Nagar Kanpur, Uttar Pradesh, 208005 India	9
Nilesh Mohan, MD, MBBS, DNB	113	Regional Institute of Ophthalmology, OPD Block, First Floor, Indira Gandhi Institute of Medical Sciences, Sheikhpura Patna, Bihar, 800014 India	19
Radha Annamalai, MBBS, DO, DNB	114	1st Floor, Department of Ophthalmology, G Block Sri Ramachandra Hospital, No 1, Ramachandra Nagar, Porur	4

Dipankar Das, MBBS, MS	115	Department of Ocular Pathology, Uvea & Neuro-Ophthalmology Services, Sri Sankaradeva Nethralaya, 96, Basistha Road, Beltola Guwahati, Assam, 781028 India	8
Aratee Palsule, MBBS, MS	116	2nd Floor, Ophthalmology Department Deenanath Mangeshkar Hospital and Research Centre, Erandwane Pune, Maharashtra, 411004 India	4

List of Investigators for Study PSV-FAI -006 and Subjects Enrolled

PSV-FAI-006 Investigator	Site #	Address	Subjects (Eyes)[a] Enrolled
USA			
C Stephen Foster, MD, FACS, FACR	201	Massachusetts Eye Research and Surgery Institution Ocular Immunology & Uveitis Foundation 1440 Main St, Ste 201 Waltham, MA 02451 USA	4 (5)
David Callanan, MD	202	Texas Retina Associates, 801 W. Randol Mill Rd, Ste 101 Arlington, TX 76012, USA	7 (12)
Sunil K Srivastava, MD	204	Cleveland Clinic Foundation Cole Eye Institute 9500 Euclid Ave I-32, Cleveland, OH 44195 USA	8 (10)
Ramin Sarrafizadeh, MD, PhD	205	Retina Consultants of Southern Colorado, PC 2770 North Union Blvd, Ste #140, Colorado Springs, CO 80909 USA	4 (7)
Daniel Virgil Alfaro III, MD	206	Charleston Neuroscience Institute 9565 Hwy 78 Building 300, Ladson, SC 29456 USA	3 (4)
[a] PSV-FAI-006 permitted enrollment of one or two study eyes per subject.			

Reviewer's comments:

No individual site enrolled a disproportionate number of subjects in either clinical trial.

6.1.2 Demographics

PSV-FAI-001 and -005

For the population, no important differences were observed between treatment groups for any of the demographic characteristics (i.e., age, sex, and race).

POPULATION	FAI Insert N=87	Sham N=42	FAI Insert N=101	Sham N=52
Age (yrs) n Mean (SD) Median Min, max	 87 48.3 (13.90) 48.0 20,77	 42 48.3 (13.71) 48.0 18,73	 101 39.9 (12.87) 38.0 20,80	 52 40.6 (13.74) 38.0 18, 85

Age categories (yrs), n (%) ≤ 20 20 to <40 40 to 60 ≥60	 1 (1.1) 24 (27.6) 40 (46.0) 22 (25.3)	 2 (5%) 8 (19%) 22 (52%) 10 (24%)	 0 57 (56%) 34 (34%) 10 (10%)	 2 (4%) 25 (48%) 21 (40%) 4 (8%)
Sex, n (%) Male Female	 37 (42.5) 50 (57.5)	 13 (31%) 29 (69%)	 39 (39%) 62 (61%)	 18 (35%) 34 (65%)
Race, n (%) White Black Asian American Indian / Alaska Native Hawaiian/Pacific Islander Other	 60 (69.0) 4 (4.6) 21 (24.1) 0 0 2 (2.3)	 26 (62%) 3 (7%) 12 (29%) 0 0 1 (2%)	 0 5 (5%) 96 (95%) 0 0 0	 0 3 (6%) 49 (94%) 0 0 0
Ethnicity, n (%) Hispanic or Latino Not Hispanic or Latino	 3 (3.4) 84 (96.6)	 3 (7%) 39 (93%)	 0 101 (100%)	 0 52 (100%)
Iris color Black Brown Hazel Green Blue Grey Other	 8 (9.2) 42 (48.3) 8 (9.2) 5 (5.7) 23 (26.4) 1 (1.1) 0	 2 (5%) 28 (67%) 2 (5%) 3 (7%) 7 (17%) 0 0	 57 (56%) 44 (44%) 0 0 0 0 0	 32 (62%) 20 (38%) 0 0 0 0 0
Height (cm) n Mean (SD) Median Min, max	 86 167.4 (9.36) 167.6 146, 196	 41 165.1 (8.88) 164.0 149, 183	 101 160.5 (9.82) 160.0 142, 183	 52 158.3 (9.94) 158.0 135, 183

FAI, fluocinolone acetonide intravitreal; ITT, intent-to-treat, SD, standard deviation
Note: Iris color refers to the color of both eyes

6.1.3 Subject Disposition

Subject Disposition for Phase 3 Trials PSV-FAI-001 and PSV-FAI-005

Population	PSV-FAI-001		PSV-FAI-005	
	FAI Insert N=87	Sham N=42	FAI Insert N=101	Sham N=52
Intent-to-Treat	87	42	101	52
Safety	87	42	101	52
Per-Protocol (at Month 6)	87	42	101	52

Reasons for Exclusion from the Per Protocol Population

	FAI Insert (N=188) n (%)	**Sham Injection (N=94) n (%)**
Number of subjects included in the PP Population through Month 6	154 (82%)	50 (53%)
Number of subjects excluded from PP Population through Month 6	34 (18%)	44 (47%)

Reasons for Exclusion from PP population		
Received Systemic Treatment for Recurrence of Uveitis in the Fellow Eye	2 (1%)	1 (1%)
Has an Imputed Endpoint for the Study Eye at the 6 Month Endpoint of the Study	26 (14%)	44 (47%)
Failed Screening, without Exemption, but Received FAI Insert	7 (4%)	2 (2%)
Had a Major Protocol Deviation	7 (4%)	5 (5%)

A total of 282 (100%) subjects were included in the ITT and safety population. Of these, 188 received the FAI insert treatment group and 94 the sham injection treatment. Four subjects discontinued from the study prior to the Month 6 visit (3 [1.6%] in the FAI insert treatment group and 1 [1.1%] subject in the sham injection group).

In the PP population, there was a higher proportion of subjects excluded from the sham injection group compared with the FAI insert treatment group through Month 6: (34 [18.1%] subjects and 44 subjects [46.85%] in the FAI insert and sham injection treatment groups, respectively).

6.1.4 Analysis of Primary Endpoint(s)

Proportion with Recurrence of Uveitis within 6 Months (ITT Population)

	PSV-FAI-001		PSV-FAI-005	
	FAI Insert N=87	**Sham N=42**	**FAI Insert N=101**	**Sham N=52**
Recurrence within 6 months, n (%)	16 (18%)	33 (79%)	22 (22%)	28 (54%)
Protocol-defined recurrence	2 (2%)	9 (21%)	10 (10%)	8 (15%)
Imputed recurrence	14 (16%)	24 (57%)	12 (12%)	20 (39%)
Missing data[a]	0	0	2 (2%)	2 (4%)
Proh bited medication	14 (16%)	24 (57%)	10 (10%)	18 (35%)
Systemic steroid or immunosuppressant	12 (14%)	7 (17%)	9 (9%)	7 (13%)
Intra/peri-ocular steroid	2 (2%)	17 (41%)	1 (1%)	11 (21%)
Difference from sham injection[b] Odds Ratio (95% CI)	16.3 (6.5, 40.6)		4.2 (2.0, 8.6)	
Difference rate[c] (95% CI)	60.2 (41.4, 73.0)		32.1 (14.9, 47.6)	
P value [d]	<0.001		<0.001	

Abbreviations: FAI, fluocinolone acetonide intravitreal; ITT, intent-to-treat.

[a] One study eye in the sham injection treatment group in study 001 was missing a recurrence assessment (BCVA) but was not imputed for recurrence at Month 6,because the study eye had prior imputed recurrences due to treatment with prohibited medications.

[b] The odds ratio (FAI insert/sham) and 95% confidence interval for no recurrence within 6 months are based on Mantel-Haenszel.

[c] The difference rate and 95% confidence interval are based on the method of Newcombe.

Subjects with no recurrence prior to Month 6 who do not have recurrence assessed at Month 6 (for any reason) or who took a proh bited or rescue concomitant medication prior to Month 6 are counted as having a recurrence of uveitis.

[d] P-value is from a continuity corrected Chi-square test comparing the number of subjects with and without recurrence within 6 Months between treatment conditions

Proportion with Recurrence of Uveitis within 6 Months (PP Population)

	PSV-FAI-001		PSV-FAI-005	
	FAI Insert N=67	Sham N=18	FAI Insert N=101	Sham N=52
Recurrence within 6 months, n (%)	2 (3%)	9 (50%)	9 (10%)	8 (25%)
Protocol-defined recurrence	2 (3%)	9 (50%)	9 (10%)	8 (25%)
Difference from sham injection[a] Odds Ratio (95% CI)	32.50 (6.04, 174.96)		2.89 (1.00, 8.31)	
P value[b]	< 0.001		0.084	

Abbreviations: FAI, fluocinolone acetonide intravitreal; ITT; intent-to-treat; Protocol-defined recurrence.

Note: Subjects with no recurrence prior to Month 6 who did not have recurrence assessed at Month 6 (for any reason) or who took a prohibited systemic or local concomitant medication prior to Month 6 were counted as having a recurrence of uveitis.

[a]The odds ratio (FAI insert/sham) and 95% confidence interval for no recurrence within 6 months were based on Mantel-Haenszel.

[b]*P* value was from a continuity-corrected Chi-square test comparing the number of subjects with and without recurrence within 6 Months between treatment conditions.

Reviewer's comments:

For the ITT population in PSV-FAI-001 and PSV-FAI-005 studies, the recurrence of uveitis within 6 months was statistically significantly lower (P<0.001) in the FAI insert treatment group compared with the sham injection treatment group.

For the PP population in study PSV-FAI-001, the recurrence of uveitis within 6 months was statistically significantly lower (P<0.001) in FAI insert treatment group compared with the sham injection treatment group. For the PP population in study PSV-FAI-005 the recurrence of uveitis in the study eye within 6 months was not statistically significantly lower (P=0.084) in FAI insert treatment

group compared with the sham injection treatment group, but it did trend in right the direction with a 10% recurrence in FAI insert group compared with a 25% recurrence rate in the sham group.

6.1.5 Analysis of Secondary Endpoints(s)

Time to First Recurrences of Uveitis within 6 months (ITT Population) Pooled Data

	FAI Insert (N=188)	**Sham Injection (N=94)**
Median Time to recurrence (days) [a] 95% confidence interval for median	NE (NE, NE)	129 (91, 181)
Probability (SE) of recurrence		
1 month (30 days)	0.04 (0.01)	0.10 (0.03)
2 months (60 days)	0.07 (0.02)	0.21 (0.04)
3 months (90 days)	0.10 (0.02)	0.38 (0.05)
4 months (120 days)	0.15 (0.03)	0.49 (0.05)
5 months (150 days)	0.17 (0.03)	0.52 (0.05)
6 months (180 days)	0.19 (0.03)	0.59 (0.05)

Abbreviations: FAI, fluocinolone acetonide intravitreal; ITT, intent-to-treat; NE, not evaluable; SE, standard error.
Note: Time to first recurrence of uveitis within 6 months was calculated as the number of days between the date of injection (Day 1) and the visit date of the first reported recurrence of uveitis in the study eye or the Month 6 visit date for subjects who did not experience a recurrence. Subjects with no recurrence prior to Month 6 who did not have recurrence assessed at Month 6 (for any reason), or who took a prohibited systemic or local concomitant medication prior to Month 6 were counted as having a recurrence of uveitis.
a The median, 95% CI for the median, probability of recurrence, and SE were obtained from Kaplan-Meier estimates.

In the ITT population, the median time to first recurrence of uveitis in the study eye was not evaluable in the FAI insert treatment group, due to an insufficient number of recurrences, and was 129 days in the sham injection treatment group.

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

Evaluations of primary efficacy endpoints were conducted in subgroups defined by gender (male, female) and age group (< 20 years, 20 to < 40 years, 40 to < 60 years and ≥ 60 years). There was no evidence of any relevant differences in efficacy by age group or gender.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

YUTIQ is a non-bioerodable intravitreal implant in a drug delivery system containing 0.18 mg fluocinolone acetonide, designed to release fluocinolone acetonide at an initial rate of 0.25 µg/day, (b) (4) over a total period of approximately 36 months.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

Subgroup analyses were performed for the ITT population based on three major geographic regions (US, Europe/Middle East, India). In all three regions, the recurrence of uveitis was lower in the FAI insert treatment group compared with the sham injection treatment group through Month 6: 16.2% compared with 78.9% (US), 26.7% compared with 100% (Europe/Middle East) and 19.8% compared with 54.0% (India), respectively.

7 Review of Safety

Safety Summary

7.1 Methods

The safety profile of YUTIQ for the proposed indication is based on data derived from two Phase 3 Trials PSV-FAI-001 and PSV-FAI-005.

PSV-FAI-001 has completed enrollment, and data through Month 12. The study will continue through Month 36 to evaluate long term safety and the rate of recurrence of non-infectious uveitis affecting the posterior segment (NIU-PS). PSV-FAI-005 has completed enrollment, and data through Month 6. The study will continue through Month 36 to evaluate long term safety and the rate of recurrence of NIU-PS.

Ocular Adverse Events occurring in greater than 5% of patients

Event	FAI Insert Study -001 N=87	FAI Insert Study -005 N=101	Sham Study -001 N=42	Sham Study -005 N=52
Anterior Chamber Flare	0	8 (8%)	3 (7%)	3 (6%)
Cataract	24 (28%)	6 (6%)	2 (5%)	7 (13%)
Cataract subcapsular	5 (6%)	4 (4%)	3 (7%)	4 (8%)
Conjunctival hemorrhage	11 (13%)		4 (10%)	
Cystoid macular edema/macular edema	13 (15%)	8 (8%)	22 (52%)	8 (15%)
Dry eye	7 (8%)		2 (5%)	
Eye pain	11 (13%)	2 (2%)	7 (17%)	3 (6%)
Foreign body sensation	7 (8%)		7 (17%)	
Hypotony		9 (9%)		
Iridocyclitis	1 (1%)	0	3 (7%)	3 (6%)
Ocular discomfort	5 (6%)		1 (2%)	
Ocular hyperemia	6 (7%)		4 (10%)	
Uveitis	9 (10%)	7 (7%)	17 (40%)	11 (21%)
Vision blurred	2 (2%)		3 (7%)	
Visual acuity reduced	17 (20%)	5 (5%)	5 (12%)	4 (8%)
Vitreous floaters/vitreous opacities	8 (9%)	3 (3%)	9 (21%)	4 (8%)
Vitreous haze		6 (6%)		3 (6%)
Elevated intraocular pressure	23 (26%)	27 (27%)	11 (26%)	2 (4%)
Vitritis		2 (2%)		4 (8%)

Non-ocular Adverse Events (reported in greater than 2% of patients)

Event	FAI Insert Study -001 N=87	FAI Insert Study -005 N=101	Sham Study -001 N=42	Sham Study -005 N=52
Nasopharyngitis	9 (10%)		5 (10%)	
Nausea	2 (2%)		4 (10%)	
Fatigue			3 (7%)	
Cough	1 (1%)		3 (7%)	
Hypertension		3 (3%)		1 (2%)

Reviewer's comments:

In Study PSV-FAI-001, the most frequent ocular events reported in the treated eye were cataract (24[27%] subjects and increased IOP (23[26%] subjects in the FAI insert treatment group and uveitis (17[41%] subjects and macular edema (14[33%] subjects in the sham injection treatment group. Cataract formation and increased IOP are well known side effects of ocular steroid treatments.

In Study PSV-FAI-005 the most frequent ocular events reported in the treated eye were increased IOP (27[27%] subjects in the FAI insert treatment group and uveitis (11[21%] subjects in the sham injection treatment group. Increased IOP is a well known side effect of ocular steroid treatments.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Refer to Section 7.1.

7.1.2 Categorization of Adverse Events

MedDRA was used to code adverse events. The number and percent of patients reporting adverse events was tabulated based on the system organ class and preferred term.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The pooled includes all clinical data from PSV-FAI-001 collected through Day 388 (which is the last day of the Month 12 visit window) and PSV-FAI-005 collected through Day 208 (which is the last day of the Month 6 visit window). This data 3 was also used to analyze all safety or tolerability risks of treatment with the FAI insert compared to sham injection.

The most frequently reported ocular TEAEs in the FAI insert group for the study eye were increased IOP (50 [27%] subjects), cataracts (30 [16%] subjects), and reduced visual acuity (22 [12%] subjects). The peak incidence in cataract development would not be expected until approximately 18 months after implantation. The most frequently reported ocular TEAEs in the sham injection group were uveitis (28[30%] subjects), macular edema (18 [19%] subjects), and increased IOP (13 [14 %] subjects).

7.2 Adequacy of Safety Assessments

The duration of exposure was only assessed for subjects who received the FAI insert for studies 001 and 005 through Day 388 and Day 208, respectively. The mean (SD) duration of exposure was 261.2 (92.11) days. The duration of exposure was 61 to 90 days (2 [1%] subjects), 91 to 180 days (50 [27%] subjects), 181 to 208 days (49 [26%] subjects, 271 to 360 days (50 [27%] subjects), or 361 to 388 days (37 [20%] subjects).

The mean (SD) duration of study participation was similar between the treatment groups (261.2 [92.11] days and 257.1 [89.62] days for the FAI insert and sham injection treatment groups, respectively). The duration of study participation was 61 to 90 days (2 [1%] subjects in the FAI insert group), 91 to 180 days (50 [27%] and 29 [31%] subjects in the FAI insert and sham injection groups, respectively), 181 to 208 days (49 [26%] and 23 [25%] subjects in the FAI insert and sham injection groups, respectively), 271 to 360 days (50 [27%] and 20 [21%] subjects in the FAI insert and sham injection groups, respectively), or 361 to 388 days (37 [20%] and 20 [21%] subjects in the FAI insert and sham injection groups, respectively).

7.2.2 Explorations for Dose Response

Refer to Section 6.1.8.

7.2.3 Special Animal and/or In Vitro Testing

Long-term animal studies have not been conducted to determine the carcinogenic potential or the effect on fertility of YUTIQ. Fluocinolone acetonide was not genotoxic in vitro in the Ames test (S. typhimurium and E. coli) and the mouse lymphoma TK assay, or in vivo in the mouse bone marrow micronucleus assay.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported during any trial of YUTIQ.

7.3.2 Nonfatal Serious Adverse Events

The most commonly reported severe ocular AE in the FAI insert group was hypotony of the eye experienced by 5 (3%) subjects, while in the sham injection group severe uveitis was experienced by 2 (2%) subjects.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Ocular Adverse Reactions Reported by ≥ 1% of Uveitis Subjects and Non-Ocular Adverse Reactions Reported by ≥ 2% of Uveitis Subjects

Ocular		
EVENT	**Yutiq (N=188) n (%)**	**Sham Injection (N=94) n (%)**
Cataract[1]	39/103 (38%)	15/56 (27%)
Increased IOP	36 (19%)	9 (9%)
Visual Acuity Reduced	22 (12%)	10 (11%)
Macular Oedema[2]	21 (11%)	30 (32%)
Uveitis	17 (9%)	28 (30%)
Conjunctival Haemorrhage	15 (8%)	5 (5%)
Hypotony Of Eye[3]	15 (8%)	1 (1%)
Eye Pain[4]	15 (8%)	10 (11%)
Anterior Chamber Cell	10 (5%)	4 (4%)
Dry Eye	10 (5%)	2 (2%)
Conjunctivitis[5]	8 (4%)	4 (4%)
Foreign Body Sensation In Eyes	7 (4%)	2 (2%)
Ocular Hyperaemia	7 (4%)	4 (4%)
Vitreous Floaters	6 (3%)	5 (5%)
Vitreous Haze	6 (3%)	3 (3%)
Conjunctival Hyperaemia	5 (3%)	1 (1%)
Eye Pruritus	5 (3%)	2 (2%)
Ocular Discomfort	5 (3%)	1 (1%)
Vitreous Opacities	5 (3%)	8 (8%)
Vitritis	5 (3%)	5 (5%)
Macular Fibrosis	4 (2%)	2 (2%)
Photopsia	4 (2%)	2 (2%)
Posterior Capsule Opacification	4 (2%)	3 (3%)
Choroiditis	3 (2%)	1 (1%)
Eye Inflammation	3 (2%)	2 (2%)
Eye Irritation	3 (2%)	1 (1%)
Visual Field Defect	3 (2%)	0
Vitreous Haemorrhage	3 (2%)	0
Corneal Abrasion	2 (1%)	0
Corneal Deposits	2 (1%)	0
Diplopia	2 (1%)	0
Episcleritis	2 (1%)	0

Ocular		
EVENT	**Yutiq (N=188) n (%)**	**Sham Injection (N=94) n (%)**
Eye Discharge	2 (1%)	0
Eyelid Ptosis	2 (1%)	0
Lacrimation Increased	2 (1%)	0
Macular Hole	2 (1%)	0
Maculopathy	2 (1%)	0
Optic Disc Haemorrhage	2 (1%)	0
Papilloedema	2 (1%)	0
Photophobia	2 (1%)	1 (1%)
Vision Blurred	2 (1%)	3 (3%)
Non-ocular		
Nasopharyngitis	9 (5%)	5 (5%)
Arthralgia	5 (3%)	1 (1%)
Hypertension	5 (3%)	1 (1%)
Headache	4 (2%)	3 (3%)

1. includes cataract, cataract subcapsular and lenticular opacities in subjects who were phakic at baseline. 103 of the 188 UVIEY subjects were phakic at baseline; 56 of 94 sham-controlled subjects were phakic at baseline.
2. includes macular oedema and cystoid macular oedema
3. includes hypotony, intraocular pressure decreased and procedural hypotension
4. includes eye pain and procedural pain
5. includes conjunctivitis, conjunctivitis allergic and conjunctivitis viral

7.4.2 Laboratory Findings

No additional laboratory studies were conducted.

7.4.3 Vital Signs

No additional safety studies were conducted to address a specific safety concern.

7.4.4 Electrocardiograms (ECGs)

No additional safety studies were conducted to address a specific safety concerns.

7.4.5 Special Safety Studies/Clinical Trials

PSV-FAI-006 is a Phase 3b, multi-center, randomized, single-masked (subject), controlled study designed to evaluate the utilization and safety of the (b) (4) I (used in PSV-FAI-001) and (b) (4) II (used in PSV-FAI-005) inserters, and the safety of the FAI insert in subjects with NIU-PS of the eye. Clinical sites in the US participated in this study.

Applicators used in PSV-FAI-001, PSV-FAI-005 and PSV-FAI-006

Clinical Study	Study Eyes Treated With (b) (4) I Applicator	Study Eyes Treated With (b) (4) II Applicator
PSV-FAI-001	87	0
PSV-FAI-005	0	101
PSV-FAI-006	12	26

The primary objective of this study was to assess the utilization and the safety of the (b) (4) II inserter, and the safety of the FAI insert, from the day of treatment through 7 days following treatment.

Overall, the utilization results for the (b) (4) II inserter treatment group were comparable with the (b) (4) I inserter treatment group, therefore the study was deemed a success. The (b) (4) II inserter treatment group had a higher proportion of satisfactory assessments compared with the (b) (4) I inserter treatment group. The investigator and observer questionnaire responses were comparable between treatment groups.

From Section 6.1.4 Analysis of Primary Endpoint(s) the (b) (4) I applicator was utilized in Study PSV-FSA-001 and the (b) (4) II applicator was utilized in Study PSV-FSA-005.

	PSV-FAI-001		PSV-FAI-005	
	FAI Insert N=67	Sham N=18	FAI Insert N=101	Sham N=52
Recurrence within 6 months, n (%)	2 (3.0)	9 (50.0)	9 (10.3)	8 (25.0)
Protocol-defined recurrence	2 (3.0)	9 (50.0)	9 (10.3)	8 (25.0)
Imputed recurrence	0	0	0	0
No recurrence within 6 months, n (%)	65 (97.0)	9 (50.0)	78 (89.7)	24 (75.0)
Difference from sham injection Odds Ratio (95% CI)	32.50 (6.04, 174.96)		2.89 (1.00, 8.31)	
P value	< 0.001		< 0.084	

Reviewer's comments:
The results were similar regardless which applicator was used as demonstrated in Study PSV-FSA-001 and Study PSV-FSA-005.

7.4.6 Immunogenicity

N/A

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

N/A

7.5.2 Time Dependency for Adverse Events

As to be expected the cataract and IOP increased with the duration of exposure to the FAI insert.

7.5.3 Drug-Demographic Interactions

The assessment of the AEs reported during trials of YUTIQ showed no evidence of any clinically relevant differences by gender or age group.

7.5.4 Drug-Disease Interactions

Use of corticosteroids including YUTIQ may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

7.5.5 Drug-Drug Interactions

This is minimal systemic exposure after administration; therefore, it is not expected that any drug-drug interaction would occur.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Long-term animal studies have not been conducted to determine the carcinogenic potential or the effect on fertility of YUTIQ.

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies of YUTIQ. in pregnant women. Animal reproduction studies have not been conducted with fluocinolone acetonide.

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. YUTIQ.should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety of YUTIQ.has not been established in pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

YUTIQ. is non-narcotic and does not have abuse potential as it is given by an intravitreal injection by a care provider.

7.7 Additional Submissions / Safety Issues

The 120 Safety Update was submitted on May 4, 2018. The Safety Update Report includes the 12 Month report for Phase 3 Study PSV-FAI-005 and the Phase 3b Study PSV-FAI-006, a Safety and Utilization study.

The Phase 3 Study PSV-FAI-001 had a 12 Month report which was included with the original NDA submission. No additional information was included as this study had completed its 12 Month report at the time of the initial NDA submission.

For the Phase 3 Study PSV-FAI-005 which included follow-up data through Month12, the safety profile of the FAI insert showed no new or unexpected safety risks. Study PSV-FAI-005 used the (b) (4) II applicator.

For the Phase 3b Study PSV-FAI-006, a Safety and Utilization Study which compared using the (b) (4) I to the (b) (4) II applicator with follow-up data through Month12, the (b) (4) II inserter showed no new or unexpected safety risks.

8 Postmarketing Experience

Because the FAI insert has not been approved for commercial use in patients with uveitis, there is no post-marketing experience.

9.0 Appendices

9.1 Literature Review/References

N/A

9.2 Labeling Recommendations

Refer to attached label with recommend revisions to the package insert.

9.3 Advisory Committee Meeting

No new issues that were thought to benefit from an Advisory Committee discussion.

9.4 Clinical Investigator Financial Disclosure Review Template

Application Number: 210331
Submission Date(s): January 5, 2018
Applicant: Eyepoint Pharmaceuticals Inc.
Product: Fluocinolone acetonide intravitreal implant, 0.18 mg
Reviewer: Martin P Nevitt, M.D., M.P.H.
Date of Review: September 10, 2018
Covered Clinical Study (Name and/or Number): PSV-FAI-001 and PSV-FAI-005.

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 55		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 4		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

To minimize potential bias the studies were randomized with the investigators and subjects masked to treatment and mulit-center where no investigator enrolled a majority of subjects.

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARTIN P NEVITT
10/03/2018

WILLIAM M BOYD
10/04/2018