CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210331Orig1s000

SUMMARY REVIEW

Division Director and Cross-Discipline Team Leader Review
NDA 210331

Date	October 12, 2018
From	Wiley A. Chambers, M.D., and William M. Boyd, M.D.
Subject	Division Director and Cross-Discipline Team Leader Review
NDA	210331
Applicant	Eyepoint Pharmaceuticals Inc.
Date of Submission	1/5/2018
PDUFA Goal Date	11/5/2018
Proprietary Name	Yutiq
Established or Proper Name	fluocinolone acetonide intravitreal implant, 0.18 mg
Dosage Form(s)	intravitreal implant
Indication(s)/Population(s)	treatment of chronic non-infectious uveitis affecting the posterior segment of the eye
Dosing Regimen(s)	Single intravitreal injection of implant 0.18 mg
Recommendation on Regulatory Action	Approval

1. Benefit-Risk Assessment

Yutiq (fluocinolone acetonide intravitreal implant) 0.18 mg will be approved for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

The results from the clinical development program for Yutiq, administered as an intravitreal implant, demonstrate that the product is safe and effective for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye. A risk management plan is not necessary given the known risks of this class of products.

The primary efficacy endpoint in Studies PSV-FAI-001 and PSV-FAI -005 was the proportion of subjects who experienced a recurrence of uveitis in the study eye within 6 months of follow-up. In both studies, the recurrence rate of uveitis within 6 months was significantly lower in the Yutiq group compared to that in the sham group: 18% vs. 79% in Study 01 and 22% vs. 54% in Study 05.

Adverse reactions associated with ophthalmic steroids including Yutiq include cataract formation necessitating subsequent cataract surgery, elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, secondary ocular infections from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. In controlled studies, the most common adverse reactions reported were cataract development and increases in intraocular pressure.

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment
The data contained in this submission establishes the efficacy of Yutiq (fluocinolone acetonide intravitreal implant) 0.18 mg by demonstrating that the recurrence rate of chronic non-infectious uveitis within 6 months was significantly lower in the Yutiq group compared to that in the sham group: 18% vs. 79% in Study 01 and 22% vs. 54% in Study 05. The most commonly reported adverse reactions occurring in Yutiq (fluocinolone acetonide intravitreal implant) 0.18 mg subjects were cataract development and increases in intraocular pressure. The potential benefits of Yutiq (fluocinolone acetonide intravitreal implant) 0.18 mg through reduction in the recurrence of posterior uveitis outweigh the identified risks as demonstrated in the clinical studies submitted with this new drug application.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The inflammation seen chronic non-infectious uveitis affecting the posterior segment of the eye can lead to permanent vision threatening damage to the eye and to elevations of intraocular pressure which can damage the optic nerve.	The inflammation associated with chronic non-infectious uveitis affecting the posterior segment of the eye must be controlled in order to minimize loss of vision.
Current Treatment Options	• Currently available treatments for chronic non-infectious uveitis affecting the posterior segment of the eye include the use of steroid drug products.	This product would provide an alternative steroid preparation, administered as an intravitreal implant.
Benefit	• Reduction in the recurrence rate of chronic non-infectious uveitis decreases the chances of vision loss.	Yutiq (fluocinolone acetonide intravitreal implant) 0.18 mg was superior to sham in reducing the recurrence rate of chronic non-infectious uveitis during a 6 month period of time
Risk and Risk Management	• Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Use of steroids is also associated with increased risk of posterior subcapsular cataract formation. Prolonged use may also suppress the host immune response and increase the hazard of secondary ocular infections.	Fluocinolone acetonide is expected to have the same potential adverse event profile as other corticosteroids. Routine post-implantation monitoring is expected to identify these adverse events if they were to occur.

2. Background

Eyepoint Pharmaceuticals Inc. submitted this 505(b)(1) application relying on its two Phase 3 studies to assess the safety and effectiveness of 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 sustained release non-bioerodible intravitreal implants designed to release drug for up to 3 years.

FA has been used for more than 30 years as a topical steroid for dermatologic conditions and is contained in Retisert (fluocinolone acetonide intravitreal implant) available since 2006, and in Iluvien (fluocinolone acetonide intravitreal implant), available since 2010.

Approved Drugs for the Treatment of Posterior 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

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

- May 7, 2015 - Type C meeting was held referencing IND 113140 to discuss the clinical data package that the sponsor (pSivida)[1] should include in its NDA submission.

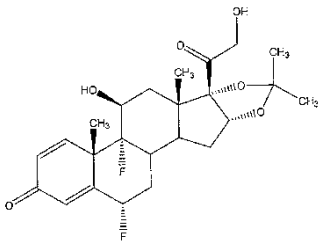
- July 20, 2017 – Type B Pre-NDA meeting was held to discuss the necessary components/format to file the NDA.

3. Product Quality

From the original Office of Product Quality Review dated 10/5/2018:

Drug Substance

The chemical name for fluocinolone acetonide is (6α,11β, 16α)-6,9-difluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis-(oxy)]-pregna-1,4-diene-3,20-dione. Its chemical structure is:



Drug Substance is manufactured by (b) (4) Reference is made to DMF# (b) (4) (refer to Module 1, Section 1.4.2, (b) (4) Letter of Authorization) for information pertaining to the specifications for commercially available (b) (4) Fluocinolone Acetonide from (b) (4)

Table 1: Specifications for Fluocinolone Acetonide Drug Substance

Test	Acceptance Criteria	Method	Test Site
Physical Appearance	(b) (4)	Visual	(b) (4) (for pSivida)
Identification			
- Identification A – Infrared Absorption	Compares to Standard	Current USP/NF <197K>	(b) (4) (for pSivida)

[1] In correspondence dated April 17, 2018, to IND 113140, the IND sponsor's corporate name was updated from pSivida Corp. to Eyegate Pharmaceuticals.

Test	Acceptance Criteria	Method	Test Site
- Identification B – Thin Layer Chromatography	Compares to Standard	Current USP/NF <201>	(b) (4) (for pSivida)
- Identification by HPLC	Retention Time Compares to Standard (b) (4)%)	SP-026-001	pSivida US, Inc
Specific Rotation	Between (b) (4)	Current USP/NF <781s>	(b) (4) (for pSivida)
Loss on Drying	Not more than (b) (4)%	Current USP/NF <731>	(b) (4) (for pSivida)
Assay (Dried Basis)	(b) (4)%	SP-026-001	pSivida US, Inc
Related Substances			
- Any Specified Impurity	Not more than (b) (4)%	SP-026-001	pSivida US, Inc
- Any Unspecified Impurity	Not more than (b) (4)%	SP-026-001	pSivida US, Inc
- Total Impurities	Not more than (b) (4)%	SP-026-001	pSivida US, Inc
Residual Solvents			
(b) (4)	Not more than (b) (4) ppm Not more than (b) (4) ppm Not more than (b) (4) pm	HS-GLC (as listed in CoA from (b) (4))	(b) (4) CoA
Polymorph Content			
(b) (4)	Not less than (b) (4)%	High Resolution X-Ray Powder Diffraction and/or Differential Scanning Calorimetry (as listed in CoA from (b) (4))	(b) (4)
Particle Size			
- Particl (b) (4) µm	Not less than (b) (4)% of total volume	Microchem or IMS (as listed in CoA from (b) (4))	(b) (4)
- Particl µm	Not less than (b) (4)% of total volume		
- Particl m	Not less than (b) (4)% of total volume		
Bioburden			
- Total Aerobic Count	Not more than (b) (4) CFU/g or mL	USP/NF <61> and <62>	(b) (4) (for pSivida)
- Yeast/Mold Count	Not more tha (b) (4) CFU/g or mL		

Test	Acceptance Criteria	Method	Test Site
- Specific Organisms	Absence of *S. aureus, E. coli, P. aeruginosa, Salmonella* species		

Source: Module 3.2.S.4.

Drug Product

Yutiq (fluocinolone acetonide intravitreal implant) 0.18 mg (Figure 1) is a sterile drug delivery system that is designed to release fluocinolone acetonide (FA) into the ocular vitreous. Yutiq is manufactured (b) (4)

(b) (4)

Figure 1 - Implant

(b) (4)

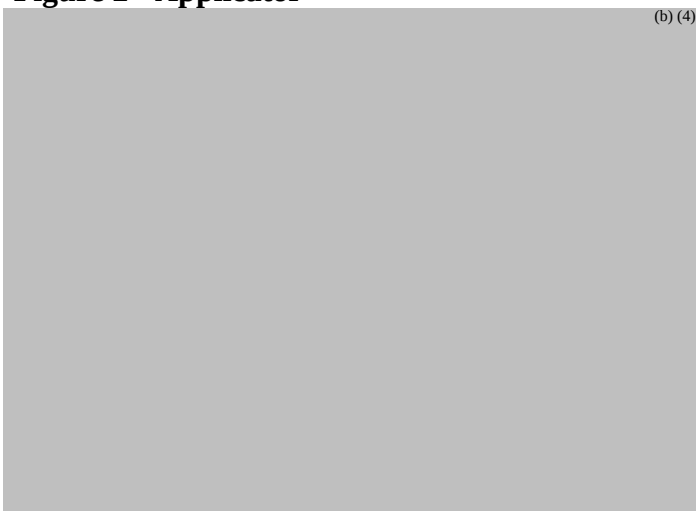
Source: Module 3.2.P.1.

CDER Product Quality requested that CDRH review the biocompatibility test reports provided for the polyimide tube and "address the biocompatibility and safety of the syringe system." CDRH (in their review dated 7/6/2018) found the biocompatibility profile of the polyimide tubing acceptable

and recommended conducting biocompatibility tests (cytotoxicity, sensitization and irritation) for the applicator. The applicant submitted cytotoxicity test result on 9/21/2018 which was found acceptable by CDRH on 10/3/2018.

Regarding the additional requested biocompatibility tests, the applicant has used the drug products (Batch 13-0014, Batch 14-0001 and Batch 15-0016) which have been stored for about 12 months for use in clinical trial studies PSV-FAI-001 and PSVFAI-006, using the proposed applicators. The lack of any reported adverse events caused by the applicator with the drug suggests compatibility. Additionally, the non-clinical studies support the biocompatibility for the applicator. Therefore, the biocompatibility of the applicator is considered of low risk.

Figure 2 - Applicator



Source: Module 3.2.P.1.

Note: From the applicant's 6/19/2018 submission, the to-be-marketed (b) (4) I applicator, shown above, was used to treat 87 and 12 study eyes, in PSV-FAI-001 and PSV-FAI-006, respectively.

In addition, the (b) (4) I applicator was also used to treat a total of 805 study eyes in three Iluvien DME clinical studies reported in NDA201923. EyePoint incorporates information relevant to the safety of the (b) (4) I applicator from those studies by right of reference to NDA2 01923.

Table 2: Composition of Yutiq (b) (4)

Component	Function	Amount per Implant	Quality Standard
Fluocinolone Acetonide (FA), USP	Active ingredient	0.180 mg	USP
Polyvinyl Alcohol	(b) (4)		USP

Water for Injection (sterile, WFI)	(b) (4)	USP
		(b) (4)

Source: Module 3.2.P.1.

(b) (4)

Source: Module 3.2.P.1.

Table 4: Applicator Components

Component	Specifications	Materials
25gauge Needle Assembly	(b) (4)	
Applicator		

(b) (4)

Source: Module 3.2.P.1.

Yutiq drug product batch release specifications are listed in Table 1; Yutiq regulatory (shelf life) specifications are listed in Table 2. The specifications listed in Table 2 are identical to their corresponding specifications in Table 1.

Table 5: Yutiq Drug Product Release Specifications

Test	Limit	Method
Physical Appearance	Light brown, 3.5 mm (b) (4)	Visual SP-023-059
Identification (TLC)	R_f of the sample and standard correspond	TLC SP-026-028 USP <201>
Identification (HPLC)	Retention of the sample and standard correspond	HPLC SP-023-059
Assay of Fluocinolone Acetonide (FA)	(b) (4) mcg (b) (4) % label claim)	HPLC SP-023-059
Release Rate	(b) (4) mcg/day	HPLC SP-023-060
Degradation Products		HPLC SP-023-059
Specified and identified degradation products (b) (4)	NMT (b) (4)% NMT % NMT % NMT %	
Specified and unidentified degradation products Unknown 1 (b) (4) Unknown 2 Unknown 3 Unknown 4 Unknown 5 Unknown 6	NMT % NMT % NMT % NMT % NMT % NMT %	

Test	Limit	Method
Unspecified and unidentified degradation product	NMT (b) (4)%	
Total degradation products	NMT (b) (4)%	
Content Uniformity (finished product)	USP <905> content uniformity acceptance criteria	HPLC SP--023-059 USP <905>
Content Uniformity (drug (b) (4)		

Test	Limit	Method
Bacterial Endotoxins	≤ (b) (4) EU/implant	Gel Clot C-0112, T-0008 USP <85>
Container Closure Integrity	Pass	Bubble Leak Test ASTM 2096
Sterility (verification dose samples)	Sterile	AAMI VDmax 25
Sterility (finished product)	Sterile	C-0110 USP <71>

Source: Module 3.2.P.5.

Table 6: Yutiq Drug Product Regulatory Specifications (Shelf-Life)

Test	Limit	Method
Physical Appearance	Light brown, 3.5 mm (b) (4)	Visual SP-023-059
Identification (HPLC)	Retention of the sample and standard correspond	HPLC SP-023-059
Assay of Fluocinolone Acetonide (FA)	(b) (4) µg (b) (4)% label claim)	HPLC SP-023-059
Release Rate	(b) (4) µg/day	HPLC SP-023-060
Degradation Products		HPLC SP-023-059
Specified and identified degradation products		
(b) (4)	NMT (b) (4)	
	NMT	
	NMT	
	NMT	
Specified and unidentified degradation products		

Test	Limit	Method
Unknown 1 (b) (4)	NMT (b) (4) %	
Unknown 2	NMT %	
Unknown 3	NMT %	
Unknown 4	NMT %	
Unknown 5	NMT %	
Unknown 6	NMT %	
Unspecified and unidentified degradation product	NMT %	
Total degradation products	NMT	
Sterility (finished product)	Sterile	C-0110 USP <71>

Source: Module 3.2.P.5.

Inspections

Following a review of the inspectional histories of the drug substance and drug product manufacturing and testing facilities, there are no outstanding concerns related to the demonstrated manufacturing and testing capabilities. The overall facility review recommendation is adequate for approval.

Summary of Facility Information:

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Risks Identified	Final Recommendation
(b) (4)			• DMF (b) (4) • The last three cGMP conducted were classified as VAI.	Acceptable – based on inspectional history and manufacturing capability
			• (b) (4) of DS only	Acceptable – based on inspectional history and manufacturing capability
			• (b) (4) of DS only	Acceptable – based on inspectional history and manufacturing capability
			• (b) (4) of DS only	Acceptable – based on inspectional history and manufacturing capability

Recommendation and Conclusion on Approvability from OPQ

Satisfactory information and response have been submitted to support the quality of the drug substance, drug product, manufacturing process, biopharmaceutics, and quality micro aspects. The Office of Process and Facilities has issued an overall acceptable recommendation on 10/1/2018. In agreement with the above recommendation, NDA 210331 is recommended for Approval from Product Quality perspective.

4. Nonclinical Pharmacology/Toxicology

From the original Pharmacology/Toxicology review dated 10/1/2018:

The Applicant, EyePoint Pharmaceuticals, Inc (previously named pSivida Corp) submitted NDA 210331 under the 505(b)(1) pathway for Yutiq (fluocinolone acetonide intravitreal implant) 0.18 mg, to treat chronic non-infectious uveitis affecting the posterior segment of the eye, which included proposed labeling text to comply with the "Pregnancy and Lactation Labeling Rule" (PLLR). Applicant has the right of reference to NDA 201923 for Iluvien (fluocinolone acetonide intravitreal implant) 0.19 mg.

QSAR assessment of mutagenic potential was conducted for degradation products (b) (4) In Applicant's responses to Agency information request (IR), dated 8/8/18 and 08/13/2018, the Applicant stated that a referenced mutagenicity study provides support that impurities were not mutagenic under study conditions.

The originally proposed specification levels (b) (4) The Applicant has revised the limits to NMT (b) (4)% in the drug product specification.

5. Clinical Pharmacology

Due to the difficulty in sampling the vitreous humor in humans and lack of measurable amounts of FA in the systemic circulation, the ability to assess bioavailability by pharmacokinetic (PK) means is limited. Clinical Pharmacology, therefore, did not conduct a formal review for this application. The Division of Biopharmaceutics completed a review dated 8/9/2018. From that review:

Drug Release Method and Acceptance Criterion: The Applicant's proposed method [1.7 mL micro centrifuge tube filled with 1 ml of 0.1M phosphate buffer solution, pH 7.4 immersed into a water bath at 37°C] which was also used for another similar approved product is

acceptable to monitor drug release from the implant. The proposed drug release acceptance criterion of (b) (4) µg/day is acceptable. An appropriate level of drug release characterization was done during product development stage while manufacturing the clinical study batches.

The formulation of the drug product used in the pivotal clinical studies is reported to be the same as that of the commercial drug product. The manufacturing site of the drug product-batches used in the Phase 3 clinical and registration stability studies is the proposed commercial site. Therefore, bridging between the clinical and commercial formulation-products is not needed. Acceptable.

6. Clinical Microbiology

Not applicable. This product is not an anti-infective.

7. Clinical/Statistical- Efficacy

From the original Medical Officer review dated 10/4/2018:

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

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%)
Prohibited 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.

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 trended lower ($P=0.084$) in FAI insert treatment group compared with the sham injection treatment group.

Applicator

The applicator proposed for approval for the Yutiq (fluocinolone acetonide intravitreal implant) 0.18 mg is the (b) (4) I (see amendment to application dated 6/19/2018).

PSV-FAI-006 was 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.

8. Safety

From the original Medical Officer review dated 10/4/2018:

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.

Deaths

No deaths were reported during any trial of YUTIQ.

Common Adverse Events

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%)	

Event	FAI Insert Study -001 N=87	FAI Insert Study -005 N=101	Sham Study -001 N=42	Sham Study -005 N=52
Hypertension		3 (3%)		1 (2%)

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.

Pooled Common Adverse Events

Ocular Adverse Reactions Reported by ≥ 1% of Uveitis Subjects and Non-Ocular Adverse Reactions Reported by ≥ 2% of Uveitis Subjects (Study -001 and -005)

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 Hemorrhage	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 Hyperemia	7 (4%)	4 (4%)
Vitreous Floaters	6 (3%)	5 (5%)
Vitreous Haze	6 (3%)	3 (3%)
Conjunctival Hyperemia	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%)

Ocular		
EVENT	**Yutiq (N=188) n (%)**	**Sham Injection (N=94) n (%)**
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 Hemorrhage	3 (2%)	0
Corneal Abrasion	2 (1%)	0
Corneal Deposits	2 (1%)	0
Diplopia	2 (1%)	0
Episcleritis	2 (1%)	0
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 Hemorrhage	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 edema and cystoid macular edema
3. includes hypotony, intraocular pressure decreased and procedural hypotension
4. includes eye pain and procedural pain
5. includes conjunctivitis, conjunctivitis allergic and conjunctivitis viral

In controlled studies, the most common adverse reactions reported were cataract development and increases in intraocular pressure.

9. Advisory Committee Meeting

There were no issues raised during the review of this application that were believed to benefit from discussion at an Advisory Committee meeting.

10. Pediatrics

The safety of Yutiq has not been established in pediatric patients. A Pediatric Research Equity Act (PREA) safety and effectiveness assessment was not triggered by NDA 210331 because there is no new active ingredient, new indication, new dosage form, new route of administration or new dosing regimen.

11. Other Relevant Regulatory Issues

Biostatistics
Per the original Biostatistics review dated 8/28/2018:

Studies 01 and 05 were of almost identical design. They were multi-center, randomized, masked, sham-controlled, 36-month, superiority studies. While Study 01 was conducted in US, UK, Germany, Hungary, Israel, and India, Study 05 was conducted only in India. To be eligible for the studies, the study eye had to have either received treatment for uveitis or experienced recurrence of uveitis during the 12 months prior to enrollment. A total of 129 subjects in Study 01 and a total of 153 subjects in Study 05 were randomized in a 2:1 ratio to the FAI insert or sham injection. Randomization was stratified by systemic treatment to control uveitis at the time of study entry (no treatment, corticosteroids, or immuno-suppressant). The primary endpoint was assessed at Month 6. While the studies are ongoing, this submission includes data up to 12 months.

The primary efficacy endpoint of the two studies was the proportion of subjects who experience a recurrence of uveitis in the study eye within 6 months following treatment. For any visit, a recurrence of uveitis was defined as either a decrease of at least 15 letters in best-corrected visual acuity (BCVA) or an increase of at least 2 steps in vitreous haze score compared to baseline or any prior visit. In addition to this definition, the following subjects were also counted as having a recurrence of uveitis: subjects with missing data required to assess recurrence at Month 6 and subjects who took a prohibited medication or rescue medication prior to Month 6. Table 1 summarizes the primary analysis results.

Table 1: Subjects with recurrence of uveitis in the study eye within 6 months (ITT population)

	PSV-FAI-001		PSV-FAI-005	
	FAI Insert N = 87	Sham Injection N = 42	FAI Insert N = 101	Sham Injection N = 52
Subjects with recurrence, n (%)	16 (18.4%)	33 (78.6%)	22 (21.8%)	28 (53.8%)
Difference (Sham - FAI) [95% CI] [1]	60.2% [41.4%, 73.0%]		32.1% [14.9%, 47.6%]	
P-value [2]	< 0.0001		0.0001	
Recurrence by type, n (%)				
a. Recurrence by BCVA or VH [3]	2 (2.3)	10 (23.8)	11 (10.9)	9 (17.3)
b. Prohibited/rescue medication [4]	15 (17.2)	32 (76.2)	16 (15.8)	24 (46.2)
- Subjects who met both a and b	1 (1.1)	9 (21.4)	7 (6.9)	7 (13.5)
c. Missing data [5]	0 (0.0)	1 (2.4)	2 (2.0)	2 (3.8)

[1] The 95% CIs (confidence intervals) were estimated using the Newcombe method with continuity-correction.
[2] P-values were computed using continuity-corrected Chi-squared tests.
[3] Subjects with decrease of ≥ 15 letters in BCVA or increase of ≥ 2 steps in vitreous haze score within 6 months.
[4] Subjects who used prohibited or rescue medications prior to Month 6.
[5] Subjects who had no eye examination data at Month 6 required to assess recurrence of uveitis.
Source: Reviewer's analysis and Table 11-6 of the clinical study reports for Studies 01 and 05.

Division of Medication Error Prevention and Analysis (DMEPA)

The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of originally proposed proprietary name, (b) (4), and found the name unacceptable in correspondence to the sponsor (IND 113140) dated 11/16/2017. Their proprietary name risk assessment found that the proposed name would broaden the indication of the drug.

The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of the alternate proprietary name, Yutiq, and granted conditional acceptance on 4/5/2018. Their proprietary name risk assessment did not find the name vulnerable to confusion that would lead to medication errors and did not consider the name promotional.

DMEPA completed a formal review of the package insert and container labeling on 7/2/2018.

Office of Prescription Drug Promotion (OPDP)

The Office of Prescription Drug Promotion (OPDP) completed reviews of the package insert and carton and containers (10/5/2018) and had suggested revisions. These have been not incorporated into the labeling: the suggestion to add "Glaucoma" as a contraindication, c/w Iluvien, is not appropriate for this indication since posterior uveitis is potentially vision-threatening and concurrent glaucoma would not be a contraindication; the suggestion to remove or modify "lasting 36 months" in Section 3 because it is promotional is not appropriate for this indication since the prescribing physician needs this dosing information to appropriately monitor the uveitis.

Office of Scientific Investigations (OSI)

A routine Office of Scientific Investigations (OSI) audit was requested.

Per the OSI review dated 8/20//2018:

An inspection was requested for the following protocol in support of this application:

Protocol PSV-FAI-001: "A Phase 3, Multi-national, Multi-center, Randomized, Masked, Controlled, Safety and Efficacy Study of a Fluocinolone Acetonide Intravitreal (FAI) Insert in Subjects with Chronic Non-Infectious Uveitis Affecting the Posterior Segment of The Eye."

The clinical site of Dr. Foster was selected for inspection because of its relatively large enrollment and lack of previous inspections.

Site #/ Name of CI/ Address	**Protocol #/ # of Subjects (enrolled)**	**Inspection Dates**	**Classification**
Site #18 **C. Stephen Foster, M.D.** Ocular Immunology and Uveitis Foundation 1440 Main Street, Suite 201 Waltham, MA 02451 Ph: (781) 891-6377 Previously: Ocular Immunology and Uveitis Foundation 5 Cambridge Center, 8th Floor Cambridge, MA 02142	PSV-FAI-001 Subjects: 13	9-21 May 18	VAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.

A Form FDA 483 was issued at the conclusion of the inspection. The 483 noted that the protocol-specified blinding process was not followed. In brief, the protocol stated that one investigator would be unblinded to the treatment arm and would perform the study procedure on Day 1 while a blinded investigator would perform all safety and efficacy assessments after Day 1. The unblinded investigator (Dr. Foster) not only did the procedures on Day 1 but also conducted follow up safety and efficacy assessments on at least 32 occasions for seven of thirteen enrolled subjects.

DTOP performed a sensitivity analyses excluding this investigator site to evaluate the effect on the efficacy and safety results. Exclusion of this investigational site in a separate sensitivity analysis had no significant effect on efficacy and safety results.

Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.* Four investigators with disclosable financial interests/arrangements.

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

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

12. Labeling

NDA 210331 Yutiq (fluocinolone acetonide intravitreal implant) 0.18 mg will be approved for treatment of chronic non-infectious uveitis affecting the posterior segment of the eye with the labeling attached as an Appendix in this review.

13. Regulatory Action

NDA 210331 Yutiq (fluocinolone acetonide intravitreal implant) 0.18 mg will be approved for treatment of chronic non-infectious uveitis affecting the posterior segment of the eye. There are no recommended postmarketing risk evaluation and management strategies (i.e., REMS) for this drug product. There are no additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

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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/

WILLIAM M BOYD
10/12/2018

WILEY A CHAMBERS
10/12/2018