CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 210-331
Supplement #:	Not applicable (Original-1)
Drug Name:	Yutiq (fluocinolone acetonide intravitreal insert), 0.18 mg
Indication:	Treatment of non-infectious uveitis affecting the posterior segment of the eye
Applicant:	EyePoint Pharmaceuticals, Inc.
Dates:	Date Submitted: January 05, 2018
	Primary Review Due Date: September 14, 2018
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Review Priority:	Standard
Biometrics Division:	DB IV
Statistical Reviewer:	Wonyul Lee, Ph.D.
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Keywords: double-masked, non-infectious uveitis, Chi-squared test, Newcombe method

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1 EXECUTIVE SUMMARY

The Applicant seeks approval of Yutiq (fluocinolone acetonide intravitreal [FAI] insert) 0.18 mg for the treatment of non-infectious uveitis affecting the posterior segment of the eye. The FAI insert 0.18 mg delivers fluocinolone acetonide (FA) into the vitreous humor for up to 36 months.

The Applicant conducts two pivotal efficacy studies: PSV-FAI-0**01** and PSV-FAI-0**05**. These studies are hereafter referred to as Study 01 and Study 05, respectively.

Studies 01 and 05 have almost identical designs. They are multi-center, randomized, masked, sham-controlled, 36-month, superiority studies. While Study 01 is conducted in US, UK, Germany, Hungary, Israel, and India, Study 05 is 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 is 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 is 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 are also counted as having a recurrence of uveitis: subjects with missing data required to assess recurrence at Month 6 and subjects who takes 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.

In both studies, the recurrence rate of uveitis within 6 months was significantly lower in the FAI insert group compared to that in the sham group: 18.4% vs. 78.6% in Study 01 and 21.8% vs. 53.8% in Study 05. The difference (sham - FAI) in the recurrence rates was 60.2% [95% CI: (41.4%, 73.0%)] in Study 01 and 32.1% [95% CI: (14.9%, 47.6%)] in Study 05.

The difference in the recurrence rates was mostly driven by the higher proportion of the sham-treated subjects who used prohibited or rescue medication prior to Month 6. In Study 01, the proportion of subjects who used prohibited or rescue medication prior to Month 6 was 17.2% in the FAI insert group and 76.2% in the sham group. In Study 05, this proportion was 15.8% in the FAI insert group and 46.2% in the sham group.

The two pivotal studies also measured the recurrence rates of uveitis within 12 months. The FAI insert group showed lower recurrence rate of uveitis within 12 months compared to the sham group: 27.6% vs. 85.7% in Study 01 and 32.7% vs. 59.6% in Study 05. Similar to the case of the recurrence rate within 6 months, the major component of the recurrence rate within 12 months was the proportion of subjects who used prohibited or rescue medication prior to Month 12. See Section 3.2.4.2 for details.

As an exploratory efficacy endpoint, the two pivotal studies measured time to the first recurrence of uveitis within 12 months. This exploratory endpoint was analyzed using the Kaplan-Meier plots. The plots showed clear separation between the two groups. This indicates that the chance of recurrence was constantly lower in the FAI group over 12 months. See Section 3.2.4.2 for details.

In terms of visual acuity as measured by BCVA letter, the two studies provided no strong evidences supporting better beneficial effect of the FAI insert than the sham. See Section 3.2.4.2 for details.

Regarding safety, the incidence rate of cataract among phakic eyes was higher in the FAI insert group compared with that in the sham group for both studies: 69% vs. 19% in Study 01 and 47.5% vs. 25.7% in Study 05. In Study 05, the FAI insert group also had a higher proportion of subjects who experienced increased intraocular pressure: 28.7% vs. 1.9%. On the other hand, the sham group showed higher rates of uveitis in both studies: 10.3% vs. 40.5% in Study 01 and 10.9% vs. 32.7% in Study 05. Although overall adverse event rates were comparable between the two treatment groups, the reviewer defers to the medical reviews for a comprehensive safety evaluation.

In summary, the reviewer concludes that this application provided adequate statistical evidence of efficacy to support an approval of the FAI insert 0.18 mg for the treatment of non-infectious uveitis affecting the posterior segment of the eye.

2 INTRODUCTION

This section provides an overview of the application, a summary of the clinical studies selected for review, and information on data sources for review.

2.1 Overview

The Applicant seeks approval of Yutiq (fluocinolone acetonide intravitreal [FAI] insert) 0.18 mg for the treatment of non-infectious uveitis affecting the posterior segment of the eye.

Uveitis is the inflammation of uvea, the vascular middle layer of the eye. Uveitis can be classified into anterior, intermediate, posterior, or pan-uveitis depending on anatomic location where it affects (Jabs et al., 2005). Uveitis can also be classified into infectious uveitis (caused by bacteria or a virus) or non-infectious uveitis. Causes for non-infectious uveitis include ocular injury, neoplasia, and autoimmune response.

The most common treatment option for non-infectious uveitis is topical, systemic, or local administration of corticosteroids. For people with severe uveitis who are intolerant of or do not respond to corticosteroid therapies, immunosuppressive agents can be used.

Corticosteroids currently approved for the treatment of non-infectious uveitis include Retisert® (FAI implant) 0.59 mg and OZURDEX® (dexamethasone intravitreal implant) 0.7 mg. Retisert® is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye. OZURDEX® is indicated for the treatment of non-infectious uveitis affecting the posterior segment of the eye. OZURDEX® is also indicated for the treatment of macular edema following retinal vein occlusion and the treatment of diabetic macular edema (DME).

Per the Applicant, the FAI insert 0.18 mg was designed to have an efficacy comparable to that of Retisert®. A safety profile of the FAI insert 0.18 mg was anticipated to be superior to that of Retisert® and comparable to that of ILUVIEN® (FAI implant 0.19 mg). ILUVIEN® is indicated for the treatment of DME in a certain sub-population of DME patients.

2.1.1 Class and Indication

Per the Applicant, the FAI insert contains 0.18 mg FA and delivers FA into the vitreous humor for up to 36 months at an initial rate of 0.2 μg FA/day (b) (4) . FA is a member of a class of synthetic corticosteroids that includes dexamethasone, triamcinolone acetonide, and FA. The indication that the Applicant seeks is to treat non-infectious uveitis affecting the posterior segment of the eye.

2.1.2 History of Drug Development

Under IND 113140, the Applicant filed the initial IND application on April 18, 2012 and proposed to conduct two adequate and well-controlled studies. This IND included the study protocol for the first proposed study (Study 01). The protocol was amended several times and the amendments were reviewed by the former statistical reviewers (See the DARRTS entries on 08/21/2012, 08/19/2013, and 03/21/2014). The primary efficacy endpoint of this study was the proportion of subjects who have a recurrence of uveitis in the study eye within 12 months

following treatment. In the protocol, recurrence was defined as one of the following changes compared to baseline or any time point prior to Month 12:

- An increase of ≥ 2 steps in the number of cells in the anterior chamber **OR**
- An increase of ≥ 2 steps in the vitreous haze score **OR**
- A deterioration of ≥ 15 letters in visual acuity

At the Type C meeting on March 10, 2015, the DTOP did not agree with the first criterion (an increase of ≥ 2 steps in the number of cells in the anterior chamber) as they consider anterior and posterior uveitis to be separate indications (See the meeting minutes dated on April 10, 2015 in DARRTS). To address this issue, the Applicant has prepared two separate statistical analysis plans (SAPs) instead of revising the definition in the protocol: one for the U.S. submission and the other one for submissions to the rest of the world. The SAP for the U.S. submission removed the first criterion from the definition. This review follows the definition in the SAP for the U.S. submission.

The Applicant's initial plan was to submit an NDA with Month 6 interim results. However, the DTOP disagreed with this plan as indicated in the following comment to the Applicant (See the meeting minutes dated on June 05, 2015 in DARRTS):

"The Agency would not expect to approve an application with Month 6 data from an interim analysis; the Agency would accept data for review from a trial with a Month 6 primary efficacy endpoint."

Consequently, the Applicant revised the timing of the primary efficacy endpoint as Month 6 (protocol version 8 dated on July 02, 2015). The DTOP considered the revised timing (Month 6) of the primary efficacy endpoint acceptable (See the meeting preliminary comments dated on September 22, 2015).

In the review of the SAPs for Studies 01 and 05, the former statistical reviewer requested the Applicant to provide the difference in the recurrence rates between the treatment groups and its 95% confidence interval (CI) as the SAPs planned to report only the odds ratio and its 95% CI. To comply with this request, the Applicant proposed the followings in the pre-NDA meeting package submitted on June 16, 2017:

- *pSivida will conduct the requested analysis for both PSV-FAI-001 and PSV-FAI-005, using the Newcombe method (Newcombe 1998).*
- *Each analysis and its results will be reported in an addendum attached to the 6-month clinical study reports, for both PSV-FAI-001 and PSV-FAI-005.*
- *This additional analysis and its result will be included in the ISE analyses of the pooled efficacy data (from PSV-FAI-001 and PSV-FAI-005).*

This proposal was considered acceptable by the former statistical reviewer.

2.1.3 Specific Studies Reviewed

The Applicant conducts the following three ongoing clinical studies:

- PSV-FAI-001: Phase 3 efficacy and safety study
- PSV-FAI-005: Phase 3 efficacy and safety study
- PSV-FAI-006: Safety and utilization study

This review focuses on PSV-FAI-0**01** and PSV-FAI-0**05**. The two studies are hereafter referred to as Study 01 and Study 05, respectively. The primary endpoint of the two pivotal studies was assessed at Month 6. While the studies are ongoing, this submission includes Month 6 and Month 12 clinical study reports with corresponding safety and efficacy data. A summary of the two studies is presented in Table 2. PSV-FAI-006 was not designed as an efficacy study. The primary objective of PSV-FAI-006 was to assess the utilization and safety of the (b) (4) II inserter (intended commercial inserter) used in Study 05 compared to the (b) (4) I inserter used in Study 01.

Table 2: Summary of specific studies reviewed

	PSV-FAI-001	**PSV-FAI-005**
Design	36-month, Phase 3, multi-center, randomized, masked, sham-controlled, superiority	
Site	33 sites in US, UK, Germany, Hungary, Israel, and India	15 sites in India
Treatment / Sample Size	FAI Insert/ 87 Sham Injection/ 42	FAI Insert / 101 Sham Injection / 52
Primary Endpoint	**Proportion of subjects who had a recurrence of uveitis in the study eye within 6 months following treatment**	
Exploratory Endpoints	- Proportion of subjects who had a recurrence of uveitis in the fellow eye - Mean change from baseline in BCVA in the study eye - Number of recurrences of uveitis - Time to recurrence of uveitis in the study eye - Number of adjunctive treatments required to treat recurrences of uveitis - Resolution of macular edema	
Study Population	- Age 18 years or older with a history of recurrent non-infectious uveitis affecting the posterior segment of the eye - During the 12 months prior to enrollment, either the study eye has received treatment for uveitis or the study eye has experienced recurrence requiring treatment - The study eye has < 10 anterior chamber cells/HPF and a vitreous haze ≤ grade 2 - The study eye has visual acuity of ≥ 15 letters	

Source: Reviewer's summary based on the clinical study reports.

2.2 Data Sources

The data sources for this review include protocols, statistical analysis plans (SAPs), clinical study reports (CSRs), the summary of clinical efficacy (SCE), the summary of clinical safety (SCS), and the datasets for the respective studies.

The CSRs can be found at the following locations:

- \\CDSESUB1\evsprod\NDA210331\0001\m5\53-clin-stud-rep: Month 6 and Month 12 CSRs for Study 01 and Month 6 CSR for Study 05
- \\CDSESUB1\evsprod\NDA210331\0009\m5\53-clin-stud-rep: Month 12 CSR for Study 05

The datasets were submitted in the formats of Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) in electronic submission. The datasets can be located at

- \\CDSESUB1\evsprod\NDA210331\0001\m5\datasets: Month 6 and Month 12 data for Study 01 and Month 6 data for Study 05
- \\CDSESUB1\evsprod\NDA210331\0009\m5\datasets: Month 12 data for Study 05

The above locations also include the SAS programs used to generate tables and figures for the efficacy and safety analyses in the clinical study reports.

The data for prohibited/rescue medications (probremd.xpt) for deriving the primary endpoint can be found at \\CDSESUB1\evsprod\NDA210331\0009\m5\datasets\ise\analysis\adam\datasets. An updated draft label including Month 12 results can be found at \\CDSESUB1\evsprod\NDA210331\0009.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The Office of Scientific Investigations (OSI) found that one site (Dr. Foster's site) in Study 01 did not follow the blinding process described in the protocol. More specifically, two investigators were supposed to participate at each site. The first unmasked investigator was to administer study treatments and perform Day 1 assessments. The second masked investigator was to perform all study assessments after Day 1. The OSI determined that the unmasked investigator in the Dr. Foster's site not only performed the procedures on Day 1 but also conducted follow-up safety and efficacy assessments on at least 32 occasions for 7 subjects. Regarding this issue, the medical team leader stated the following:

"The use of two investigators was meant to minimize bias as much as possible, but in actuality the implant is frequently visible after insertion to any observer using a slit lamp. Sometimes it is impossible to fully mask evaluators after surgical procedures. The primary endpoint of the trial, the proportion of subjects who had a recurrence of uveitis in the study eye within 6 months after receiving study treatment, requires evaluation of the eye using the same slip lamp device that would allow visualization of the FAI implant. Although it is clear that Dr. Foster's location did not follow protocol and did not minimize bias by using the blinded investigator to record safety and efficacy assessments, it is unlikely that this had a significant effect on the study results. However, we will perform sensitivity analyses excluding this investigator site to evaluate the effect on the efficacy and safety results. We will include a full discussion within our Clinical review."

In this review, a supportive analysis was conducted to investigate the impact of this issue on the primary efficacy results. Specifically, the reviewer excluded the Dr. Foster's site from the analysis data and computed the recurrence rates. The recurrence rates of uveitis in this supportive analysis were almost the same as the recurrence rates in the primary analysis (See Section 3.2.4.1 for details). Thus, the reviewer found that this issue does not impact the overall efficacy conclusions.

During the above supportive analysis, the reviewer found that the site number for Subject (b) (6) in Study 01 was incorrect in the ADaM dataset "adsl.xpt" and the SDTM dataset "dm.xpt". In these datasets, the site number for this subject was 09 (Dr. Jaffe's site). However, per Appendices 16.1.4 (List of Investigators) and 16.1.6 (List of Subjects) of the Month 6 CSR, the

site number for this subject is 18 (Dr. Foster's site). See Appendix F for a list of the subjects in Dr. Foster's site. In the above supportive analysis, this subject was excluded. The reviewer observed that a supportive analysis including this subject resulted in only negligible numerical differences. Thus, this minor issue had little impact on the conclusion from the supportive analysis.

No other issues were identified regarding the quality and integrity of the submitted SDTM and ADaM datasets. The datasets were well organized. The Applicant's primary efficacy results were reproducible using the ADaM datasets. In general, using SDTM and ADaM datasets, the reviewer was able to conduct the necessary analyses without complex manipulations.

3.2 Evaluation of Efficacy

This section evaluates the efficacy results of Studies 01 and 05.

3.2.1 Study Design and Endpoints

Study Design

Studies 01 and 05 have almost identical design. They are 36-month, Phase 3, multi-center, randomized, masked, sham-controlled, and superiority studies comparing the FAI insert to sham injection for the treatment of non-infectious uveitis affecting the posterior segment of the eye. Randomization was as follows:

- In Study 01, a total of 33 sites in US, UK, Germany, Hungary, Israel, and India enrolled 129 subjects. They were randomized in a 2:1 ratio to the FAI insert (87 subjects) or sham injection (42 subjects).
- In Study 16, a total of 15 sites in India enrolled 153 subjects. They were randomized in a 2:1 ratio to the FAI insert (101 subjects) or sham injection (52 subjects).

The randomization was stratified by systemic treatment to control uveitis at the time of study entry. The three strata were

- Not receiving systemic treatment,
- Receiving systemic treatment - corticosteroid therapy, or
- Receiving systemic treatment - immunosuppressive therapy.

Each study consists of the following three periods (see Appendix A for more details):

- Screening (Day -30 to Day 0)
- Randomization/Treatment (Day 1): subjects receive either the FAI insert or sham injection.
- Follow-up (Day 7, Day 28, Months 2, 3, 6, 9, 12, 18, 24, 30, and 36): the primary efficacy endpoint is assessed at Month 6.

The key inclusion criteria are as follows:

- Male or non-pregnant female at least 18 years of age
- Having a history of recurrent non-infectious uveitis affecting the posterior segment of the eye with or without anterior uveitis ≥1 year duration

- During the 12 months prior to enrollment (Day 1), the study eye had either received treatment for uveitis or experienced recurrence of uveitis
- At the time of enrollment (Day 1), study eye had <10 anterior chamber cells/high powered field (HPF) and a vitreous haze of grade ≤ 2
- Visual acuity (VA) of study eye was at least 15 letters on the early treatment diabetic retinopathy study (ETDRS) chart

If both eyes of a subject are eligible, the more severely affected eye is the study eye (i.e. the eye with more recurrences in the previous year, or if equal, the eye with more therapies in the previous year, or if equal, the eye with worse visual acuity). If the eyes are symmetrically affected, the study eye is the right eye. Study subjects receive assigned study drugs in the designated study eyes.

Masking: Two investigators participate at each site: unmasked treating investigator (investigator 1) and masked assessing investigator (investigator 2). On Day 1, the investigator 1 injects the FAI insert or sham and performs all Day 1 assessments. All other study assessments after Day 1 are performed by investigator 2.

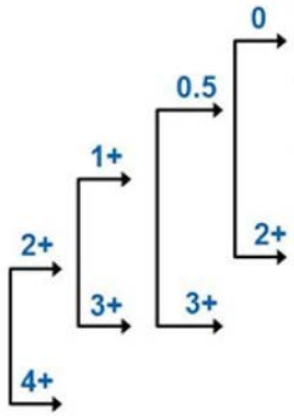
Primary Efficacy Endpoint

The primary efficacy endpoint is **the proportion of subjects who had a recurrence of uveitis in the study eye within 6 months following treatment**. The SAPs define a recurrence of uveitis as follows:

- 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 BCVA letters, compared to baseline or any visit time point prior to Month 6

The figure below depicts the definition of an increase of ≥ 2 steps in vitreous haze.

Figure 9–3 Vitreous Haze: Greater than or Equal to 2-Step Increase



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

Source: Figure 9-3 of the CSR for Study 01.

For concise presentation, the proportion of subjects who had a recurrence of uveitis is referred to as “recurrence rate” in this review.

Use of prohibited/rescue medications: In addition to the definition of recurrence above, a subject who takes prohibited or rescue medications prior to Month 6 is counted as having a recurrence for the primary efficacy analyses. The prohibited or rescue medications defined in the protocols are as follows:

- Prohibited medications: (1) oral, systemic, injectable, or topical steroids, (2) systemic immuno-suppressants.
- Rescue medications: In the event of a uveitis recurrence, peri-ocular or intraocular corticosteroid injections are administered as the first line local therapy. For an increase in anterior chamber cells with no increase in vitreous opacity, topical steroids are the first line therapy. If local therapies fail, systemic immuno-suppressants or systemic steroids are used.

However, the following cases are not considered as prohibited medications:

- Systemic medications or topical steroids administered as part of gradual dose reduction (tapering)
- Topical steroids administered as short term standard treatment following an ocular surgical procedure
- Steroids or systemic immuno-suppressants used as a part of standard care based on Investigator discretion (Study 05 only)
- The SAPs for the US submission also states that topical steroids are not considered as prohibited medications

The data for the use of prohibited or rescue medications (probremd.xpt) can be found at \\CDSESUB1\evsprod\NDA210331\0009\m5\datasets\ise\analysis\adam\datasets.

Exploratory Efficacy Endpoints

The SAP-defined exploratory efficacy endpoints include the followings:

- Proportion of subjects in each treatment group who have a recurrence of uveitis in the fellow eye (within 6 months, within 12 months, and within 36 months)
- Mean change from baseline in BCVA letter score in the study eye in each treatment group (at 6 months, 12 months, and 36 months)
- Number of recurrences of uveitis in each treatment group (within 6 months, within 12 months, and within 36 months)
- Time to recurrence of uveitis in study eye in each treatment group (within 6 months, within 12 months, and within 36 months)
- Number of adjunctive treatments required to treat recurrences of uveitis in each treatment group (within 6 months, within 12 months, and within 36 months)
- Resolution of macular edema, as measured by OCT imaging (at 6 months, 12 months, and 36 months)

3.2.2 Statistical Methodologies

This section primarily focuses on describing statistical methodologies for analyzing the primary efficacy endpoint: the recurrence rate within 6 months. Statistical methodologies for analyzing exploratory efficacy endpoints are also briefly described.

Analysis populations

The protocols and SAPs defined three analysis populations as follows:

1. The intent-to-treat (ITT) population includes all randomized subjects. The primary efficacy analyses are performed on the ITT population. All subjects in the ITT population are analyzed according to the treatment they are randomized.
2. The per-protocol (PP) population is defined separately for the Month 6, Month 12, and Month 36 analyses. The PP population excludes all subjects in the ITT population who meet any of the followings:
   - Received systemic treatment for recurrence of uveitis in fellow eye
   - Had no eye examination data required to assess recurrence of uveitis at Month 6 (or Month 12 or Month 36)
   - Received prohibited/rescue medications within 6 months (or 12 months or 36 months)
   - Failed screening, without exemption, but received FAI insert
   - Had a major protocol violation

   Analyses on the PP population serve as supportive analyses. All subjects in the PP population are analyzed according to the treatment they actually receive.
3. The safety population includes all randomized subjects. All subjects in the safety population are analyzed according to the treatment they actually receive. All safety analyses are performed on the safety population.

Analysis methods for the efficacy endpoints

The primary analysis methods for the primary efficacy endpoint are as follows:

- SAP-defined analyses
  - Chi-squared test with continuity-correction.
  - Odds ratio (FAI/Sham) for no recurrence and its 95% CI.
- Additional analysis requested by FDA
  - Difference in the recurrence rates and its 95% CI.

Reviewer's notes:

1. *Per the CSRs and the submitted SAS codes, the odds ratio and its 95% CI were estimated using the Mantel-Haenszel method (1959) with the Greenland and Robins (1985) variance estimator. As this method is one of the most common methods for the odds ratio and performs well in many cases, the reviewer found this method acceptable.*
2. *The Applicant used the Newcombe (1998) method (with continuity-correction) to obtain a 95% CI for the difference in the recurrence rates. The Newcombe method first obtains a*

95% CI for a single proportion (recurrence rate) in each arm using Wilson (1927) method. Then, the Newcombe method combines the two individual 95% CIs by a certain rule to obtain a 95% CI for the difference in the proportions. The Wilson intervals have been shown to work well even for small proportions and can avoid aberrations such as confidence limits outside [0, 1]. See the theoretical and numerical results in Newcombe (1998) and Brown et al. (2002) for more details. The reviewer also conducted a simulation study to assess the Newcombe method (See Appendix B). The simulated coverages of the Newcombe 95% CIs were greater than the nominal level of 95%. Thus, the reviewer finds the Newcombe method acceptable.

The exploratory efficacy endpoints are analyzed as specified in the SAPs as follows:

- Recurrence rate in the fellow eye, mean change from baseline in BCVA letter, the number of recurrences, the number of adjunctive treatments, and resolution of macular edema are descriptively summarized.
- Time to the first recurrence is analyzed by the Kaplan-Meier method. Median time to the first recurrence is calculated.

Handling of missing values

For the recurrence of uveitis within 6 months (or 12 months), a subject who did not have the required eye examination data to assess recurrence at Month 6 (or Month 12) was considered as having a recurrence. For the other exploratory efficacy measures, no imputations were performed.

3.2.3 Subject Disposition, Demographic, and Baseline Characteristics

Subject disposition and primary reasons for study discontinuation are summarized in Table 3. All subjects in Study 01 completed Month 6. In Study 05, one subject in the FAI insert group withdrew voluntarily prior to Month 6 and one subject in the sham group did not complete Month 6 because of lost to follow-up.

Table 3: Subject disposition, n (%)

	PSV-FAI-001		PSV-FAI-005	
	FAI	**Sham**	**FAI**	**Sham**
Randomized Population	N = 87	N = 42	N = 101	N = 52
Subjects Completed Month 6				
Yes	87 (100.0)	42 (100.0)	100 (99.0)	51 (98.1)
No	0 (0.0)	0 (0.0)	1 (1.0)	1 (1.9)
- Subject Voluntarily Withdrew	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
- Lost to Follow-up	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
Subjects Completed Month 12				
Yes	86 (98.9)	40 (95.2)	97 (96.0)	50 (96.2)
No	1 (1.1)	2 (4.8)	4 (4.0)	2 (3.8)
- Subject Voluntarily Withdrew	1 (1.1)	0 (0.0)	2 (2.0)	0 (0.0)
- Lost to Follow-up	0 (0.0)	2 (4.8)	2 (2.0)	2 (3.8)

Source: Table 10-1 of the Month 6 and Month 12 CSRs for Studies 01 and 05.

Baseline demographic characteristics are summarized in Table 4. In general, the demographic characteristics were balanced between the FAI insert group and the sham group. In terms of age and ethnicity, no notable imbalance was observed between the FAI insert group and the sham group. In Study 01, the proportion of female was lower in the FAI insert group compared to that in the sham group: 57.5% vs. 69.0%. In terms of race, the proportion of White was higher in the FAI insert group: 69.0% vs. 61.9%. However, considering the small sample size in the sham group, these imbalances are not remarkable.

The mean age was 48.3 and 40.1 years in Study 01 and Study 05, respectively. The majority of the subjects were female (61.2% in Study 01 and 62.7% in Study 05). In terms of race, most subjects were White (66.7%) in Study 01 and Asian (94.8%) in Study 05. Recall that Study 05 is conducted in India. Most subjects identified themselves as neither Hispanic nor Latino (95.3% in Study 01 and 100% in Study 05).

Table 4: Baseline demographics

	PSV-FAI-001			PSV-FAI-005		
	All	**FAI**	**Sham**	**All**	**FAI**	**Sham**
Randomized Population	N = 129	N = 87	N = 42	N = 153	N = 101	N = 52
Age (years)						
Mean (SD)	48.3 (13.8)	48.3 (13.9)	48.3 (13.7)	40.1 (13.1)	39.9 (12.9)	40.6 (13.7)
Median	48.0	48.0	48.0	38.0	38.0	38.0
Min - Max	18.0 - 77.0	20.0 - 77.0	18.0 - 73.0	18.0 - 85.0	20.0 - 80.0	18.0 - 85.0
Age Category, n (%)						
< 65	111 (86.0)	75 (86.2)	36 (85.7)	147 (96.1)	97 (96.0)	50 (96.2)
>= 65	18 (14.0)	12 (13.8)	6 (14.3)	6 (3.9)	4 (4.0)	2 (3.8)
Gender, n (%)						
Female	79 (61.2)	50 (57.5)	29 (69.0)	96 (62.7)	62 (61.4)	34 (65.4)
Male	50 (38.8)	37 (42.5)	13 (31.0)	57 (37.3)	39 (38.6)	18 (34.6)
Race, n (%) †						
White	86 (66.7)	60 (69.0)	26 (61.9)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	33 (25.6)	21 (24.1)	12 (28.6)	145 (94.8)	96 (95.0)	49 (94.2)
Black	7 (5.4)	4 (4.6)	3 (7.1)	8 (5.2)	5 (5.0)	3 (5.8)
Other	3 (2.3)	2 (2.3)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity, n (%)						
Not Hispanic or Latino	123 (95.3)	84 (96.6)	39 (92.9)	153 (100.0)	101 (100.0)	52 (100.0)
Hispanic or Latino	6 (4.7)	3 (3.4)	3 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)

† Note that Study 05 is conducted in India whereas Study 01 is multi-national (US, UK, Germany, Hungary, Israel, and India).
Source: Table 11-3 of the CSRs for Studies 01 and 05.

Baseline disease and ocular characteristics are summarized in Table 5. In general, the two groups were comparable with the following exceptions:

- In Study 05, the proportion of subjects with vitreous haze of ≥ 1+ was lower in the FAI insert group compared to the sham group (63.3% vs. 73.1%)

- In Study 01, the FAI insert group had longer duration of uveitis at the time of study entry compared to the sham group (mean duration: 7.9 years vs. 5.6 years).
- In Study 05, the proportion of subjects having phakic lens with cataract present was lower in the FAI insert group (14.9% vs. 23.1%). The proportion of subjects having pseudo-phakic lens was higher in the FAI insert group (38.6% vs. 28.8%).

Baseline ocular characteristics for the fellow eyes are summarized in Table 19 of Appendix C. The two groups were comparable except that in Study 01, the fellow eyes in the FAI insert group had longer duration of uveitis at the time of study entry compared to the fellow eyes in the sham group.

Table 5: Baseline disease and ocular characteristics for the study eye

	PSV-FAI-001		**PSV-FAI-005**	
	FAI	**Sham**	**FAI**	**Sham**
Randomized Population	N = 87	N = 42	N = 101	N = 52
BCVA (letters)				
Mean (SD)	66.94 (15.49)	64.88 (15.53)	66.38 (15.85)	63.63 (16.82)
Median	70.00	65.00	69.00	70.00
Min - Max	19.00 - 89.00	21.00 - 99.00	30.00 - 90.00	20.00 - 90.00
Vitreous haze				
Absent (0)	22 (25.3)	8 (19.0)	10 (9.9)	3 (5.8)
Trace (0.5)	26 (29.9)	13 (31.0)	27 (26.7)	11 (21.2)
1+	29 (33.3)	19 (45.2)	38 (37.6)	30 (57.7)
2+	10 (11.5)	2 (4.8)	26 (25.7)	8 (15.4)
3+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Duration of uveitis (years)				
Mean (SD)	7.85 (6.69)	5.57 (6.82)	3.07 (3.00)	3.59 (3.00)
Median	5.93	2.83	1.79	2.31
Min - Max	0.87 - 28.03	0.93 - 29.52	0.74 - 15.42	0.98 - 15.58
Number of recurrences within 12 months prior to screening, n (%)				
0	2 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
1 - 2	63 (72.4)	34 (81.0)	86 (85.1)	45 (86.5)
> 2	21 (24.1)	8 (19.0)	15 (14.9)	7 (13.5)
Systemic treatment to control uveitis, n (%)				
Not receiving systemic treatment	43 (49.4)	21 (50.0)	62 (61.4)	32 (61.5)
Receiving systemic treatment				
Corticosteroid therapy	27 (31.0)	13 (31.0)	37 (36.6)	19 (36.5)
Immunosuppressive therapy	17 (19.5)	8 (19.0)	2 (2.0)	1 (1.9)
IOP (mmHg)				
Mean (SD)	13.86 (3.12)	13.60 (3.15)	13.29 (3.07)	13.13 (2.60)
Median	14.00	13.00	13.00	12.50
Min - Max	6.00 - 21.00	8.00 - 20.00	8.00 - 23.00	10.00 - 20.00
Severity of edema, n (%)				
CSFT < 300 microns	37 (42.5)	14 (33.3)	70 (69.3)	36 (69.2)

	PSV-FAI-001		PSV-FAI-005	
	FAI	Sham	FAI	Sham
CSFT >= 300 microns	48 (55.2)	27 (64.3)	30 (29.7)	14 (26.9)
Lens status, n (%)				
Phakic	42 (48.3)	21 (50.0)	61 (60.4)	35 (67.3)
Cataract present, n (%)	25 (28.7)	9 (21.4)	15 (14.9)	12 (23.1)
Ahakic	0 (0.0)	0 (0.0)	1 (1.0)	2 (3.8)
Pseudophakic	45 (51.7)	21 (50.0)	39 (38.6)	15 (28.8)

Source: Table 11-4 of the Month 6 CSRs for Studies 01 and 05.

3.2.4 Results and Conclusions

Section 3.2.4.1 provides efficacy results for the primary efficacy endpoint. Section 3.2.4.2 presents the efficacy results for the exploratory endpoints. The reviewer's efficacy conclusion is provided in Section 3.2.4.3.

3.2.4.1 Recurrence of Uveitis within Month 6

Table 6 presents the primary analysis results of the primary efficacy endpoint: the recurrence rate of uveitis in the study eye within 6 months following treatment. In the two studies, the FAI insert group showed lower recurrence rate compared to the sham group: 18.4% vs. 78.6% in Study 01 and 21.8% vs. 53.8% in Study 05. The treatment difference (sham - FAI) in the recurrence rates was statistically significant: 60.2% [95% CI: (41.4%, 73.0%)] and 32.1% [95% CI: (14.9%, 47.6%)] in Study 01 and Study 05, respectively. The p-value from the continuity-corrected Chi-squared test was < 0.0001 in Study 01 and 0.0001 in Study 05. The odds ratio of no-recurrence rates also indicates statistical superiority of the FAI insert in terms of the primary efficacy endpoint.

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

	PSV-FAI-001		PSV-FAI-005	
	FAI	Sham	FAI	Sham
ITT population	N = 87	N = 42	N = 101	N = 52
Recurrence within 6 months, n (%)				
No recurrence	71 (81.6)	9 (21.4)	79 (78.2)	24 (46.2)
Recurrence	16 (18.4)	33 (78.6)	22 (21.8)	28 (53.8)
Treatment Comparison				
Difference [95% CI] [1]	60.2% [41.4%, 73.0%]		32.1% [14.9%, 47.6%]	
Odds Ratio [95% CI] [2]	16.27 [6.52, 40.63]		4.19 [2.04, 8.62]	
P-value [3]	< 0.0001		0.0001	

[1] Difference in the recurrence rates (Sham- FAI); 95% CIs (confidence interval) estimated using the Newcombe method.
[2] Odds ratio of no recurrence rates (FAI/Sham); 95% CIs estimated using the Mantel-Haenszel method.
[3] P-values computed using continuity-corrected Chi-squared tests.
Source: Table 11-6 of the Month 6 CSRs for Studies 01 and 05.

Recall that a subject was considered as having a recurrence of uveitis in any of the following three cases: (1) decrease of ≥ 15 letters in BCVA or increase of ≥ 2 steps in vitreous haze, (2) use of prohibited or rescue medications, or (3) missing eye examination data at Month 6. Table 7 shows the recurrence rates by these three components.

In both studies, the major component of the recurrence rate was the use of prohibited or rescue medications. The difference in the recurrence rates between the two groups was mostly driven by this component. In Study 01, the most frequent use of medication counted as a recurrence was prednisolone (5 subjects) in the FAI insert group and dexamethasone (10 subjects) in the sham group. In Study 05, most cases were prednisolone (13 subjects) for the FAI insert group and either dexamethasone (14 subjects) or prednisolone (10 subjects) for the sham group.

A supportive analysis was performed on the PP population (Table 20 in Appendix D). In this supportive analysis, all recurrence cases due to either missing data or use of prohibited/rescue medications were excluded. In this supportive analysis, the recurrence rate was 3% for the FAI insert group and 50% for the sham group in Study 01. The treatment difference (sham - FAI) was 47% [95% CI: (22.3%, 70.4%)]. In Study 05, the recurrence rate was 10.3% for the FAI group and 25.0% for the sham group. The treatment difference was 14.7% [95% CI: (-1.0%, 34.1%)].

Table 7: Subjects with recurrence of uveitis within 6 months by recurrence type (ITT population)

	PSV-FAI-001		PSV-FAI-005	
	FAI	**Sham**	**FAI**	**Sham**
ITT population	N = 87	N = 42	N = 101	N = 52
Recurrence within 6 months, n (%)	**16 (18.4)**	**33 (78.6)**	**22 (21.8)**	**28 (53.8)**
a. Recurrence by BCVA or VH [1]	**2 (2.3)**	**10 (23.8)**	**11 (10.9)**	**9 (17.3)**
i. Decrease of ≥ 15 letters in BCVA	1 (1.1)	9 (21.4)	10 (9.9)	5 (9.6)
ii. Increase of ≥ 2 steps in vitreous haze	1 (1.1)	4 (9.5)	4 (4.0)	5 (9.6)
Subjects who met both i and ii	0 (0.0)	3 (7.1)	3 (3.0)	1 (1.9)
b. Prohibited/rescue medication [2]	**15 (17.2)**	**32 (76.2)**	**16 (15.8)**	**24 (46.2)**
i. Systemic steroid or immune-suppressant	13 (14.9)	16 (38.1)	14 (13.9)	11 (21.2)
azathioprine	1	2	0	1
ciclosporin	1	0	0	0
dexamethasone sodium phosphate	0	0	1	0
methotrexate	1	1	0	0
methylprednisolone	1	2	0	0
mycophenolate mofetil	1	5	0	0
prednisolone	5	2	13	10
prednisone	3	4	0	0
ii. Intraocular steroid in the study eye	5 (5.7)	24 (57.1)	2 (2.0)	19 (36.5)
dexamethasone	1	10	1	14
fluocinolone acetonide	0	1	0	0
triamcinolone	1	4	0	2
triamcinolone acetonide	3	9	1	3
- Subjects who met a and b	1 (1.1)	9 (21.4)	7 (6.9)	7 (13.5)
c. Missing Data [3]	0 (0.0)	1 (2.4)	2 (2.0)	2 (3.8)

[1] Subjects with decrease of ≥ 15 letters in BCVA or increase of ≥ 2 steps in vitreous haze (VH).
[2] Subjects who used prohibited or rescue medications within 6 months.
[3] 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 Month 6 CSRs for Studies 01 and 05.

<u>Reviewer's note</u>: The CSRs reported the recurrence rate by type (a, b, or c) in a manner that all types are mutually exclusive. More specifically, in the CSRs, the type of recurrence was determined by the first event. For example, suppose that a study eye received a rescue medication prior to Month 6 and lost more than 15 letters in BCVA within 6 months. If the BCVA loss occurred prior to the rescue medication, then the recurrence was categorized into a. If the rescue medication occurred prior to the BCVA loss, then the recurrence was categorized into b.

Special Sensitivity Analysis

As mentioned in Section 3.1, the OSI revealed that one site (Dr. Foster's site) in Study 01 did not follow the blinding process described in the protocol; the unmasked investigator conducted assessments even after Day 1 for at least 32 occasions for 7 subjects. To evaluate the effect of this issue on the efficacy results, the reviewer conducted a sensitivity analysis by excluding the subjects in the Dr. Foster's site from the primary analysis population. Consequently, this sensitivity analysis excluded a total of 13 subjects in this site (11 in the FAI group and 2 in the sham group; see Appendix F for the list of the subjects that were excluded).

Table 8 shows the results of this sensitivity analysis. The recurrence rates were similar between the primary analysis and the sensitivity analysis: 18.4% vs. 18.4% in the FAI group and 78.6% vs. 77.5% in the sham group. The estimated difference (Sham - FAI) in the recurrence rates remained almost the same: 60.2% [95% CI: (41.4%, 73.0%)] in the primary analysis and 59.1% [95% CI: (39.4%, 72.5%)] in the sensitivity analysis. Thus, it does not appear that this issue has a significant impact on the primary efficacy conclusions.

Table 8: Sensitivity analysis for the recurrence rate within 6 months (PSV-FAI-001; ITT population)

	Including the site [4] (Primary Analysis)		**Excluding the site** [4] (Sensitivity Analysis)	
	FAI	**Sham**	**FAI**	**Sham**
Number of Subjects	N = 87	N = 42	N = 76	N = 40
Recurrence within 6 months, n (%)				
No recurrence, n (%)	71 (81.6)	9 (21.4)	62 (81.6)	9 (22.5)
Recurrence, n (%)	**16 (18.4)**	**33 (78.6)**	**14 (18.4)**	**31 (77.5)**
Treatment Comparison				
Difference (95% CI) [1]	**60.2% (41.4%, 73.0%)**		**59.1% (39.4%, 72.5%)**	
Odds Ratio (95% CI) [2]	16.27 (6.52, 40.63)		15.25 (5.95, 39.12)	
P-value [3]	<0.0001		<0.0001	
Recurrence by Type, n (%)				
a. Recurrence by BCVA or VH	2 (2.3)	10 (23.8)	2 (2.6)	10 (25.0)
b. Prohibited/rescue medication	15 (17.2)	32 (76.2)	13 (16.9)	30 (75.0)
c. Missing Data	0 (0.0)	1 (2.4)	0 (0.0)	1 (2.5)

[1] Difference in the recurrence rates (Sham- FAI); 95% CIs (confidence interval) estimated using the Newcombe method.
[2] Odds ratio of no recurrence rates (FAI/Sham); 95% CIs estimated using the Mantel-Haenszel method.
[3] P-values computed using continuity-corrected Chi-squared tests.
[4] Dr. Foster's site
Source: Reviewer's analysis

3.2.4.2 Exploratory Efficacy Endpoints

This section presents the analysis results for the following exploratory efficacy endpoints:

- Recurrence rate of uveitis in the study eye within 12 months
- Recurrence rate of uveitis in the fellow eye
- Mean change from baseline in BCVA
- Time to the first recurrence of uveitis in the study eye within 12 months
- Number of recurrences of uveitis in the study eye within 12 months

Recurrence of uveitis in the study eye within 12 months

Table 9 presents the recurrence rate of uveitis in the study eye within 12 months for the ITT population. In the two studies, the FAI insert group showed lower recurrence rate compared to the sham group: 27.6% vs. 85.7% in Study 01 and 32.7% vs. 59.6% in Study 05. The treatment difference (sham- FAI) in the recurrence rates was 58.1% [95% CI: (39.7%, 70.2%)] in Study 01 and 26.9% [95% CI: (9.3%, 42.7%)] in Study 05. Similar to the recurrence rate within 6 months, the major component of the recurrence rate was the use of prohibited or rescue medications. In Study 01, the proportion of subjects who took a prohibited or rescue medication prior to Month 12 was 21.8% in the FAI insert group and 81.0% in the sham group. In Study 05, this proportion was 18.8% in the FAI insert group and 51.9% in the sham group.

Table 9: Subjects with recurrence of uveitis in the study eye within 12 months (ITT population)

	PSV-FAI-001		PSV-FAI-005	
	FAI	**Sham**	**FAI**	**Sham**
ITT population	N = 87	N = 42	N = 101	N = 52
Recurrence within 12 months, n (%)				
No recurrence	63 (72.4)	6 (14.3)	68 (67.3)	21 (40.4)
Recurrence	24 (27.6)	36 (85.7)	33 (32.7)	31 (59.6)
Treatment Comparison				
Difference [95% CI] [1]	58.1% [39.7%, 70.2%]		26.9% [9.3%, 42.7%]	
Odds Ratio [95% CI] [2]	15.75 [5.89, 42.13]		3.04 [1.52, 6.08]	
P-value [3]	< 0.0001		0.0025	
Recurrence by Type				
a. Recurrence by BCVA or VH	4 (4.6)	11 (26.2)	16 (15.8)	11 (21.2)
b. Prohibited/rescue medication	19 (21.8)	34 (81.0)	19 (18.8)	27 (51.9)
i. Systemic steroid or immune-suppressant	17 (19.5)	17 (40.5)	17 (16.8)	13 (25.0)
ii. Intraocular steroid in the study eye	6 (6.9)	26 (61.9)	3 (3.0)	20 (38.5)
c. Missing Data	2 (2.3)	3 (7.1)	9 (8.9)	5 (9.6)

[1] Difference in the recurrence rates (Sham- FAI); 95% CIs (confidence interval) estimated using the Newcombe method.
[2] Odds ratio of no recurrence rates (FAI/Sham); 95% CIs estimated using the Mantel-Haenszel method.
[3] P-values computed using continuity-corrected Chi-squared tests.
Source: Reviewer's analysis and Table 11-6 of the Month 12 CSRs for Studies 01 and 05.

Recurrence of uveitis in the fellow eye within 6 months and 12 months

Recurrence rates of uveitis for the fellow eyes are summarized in Table 10. In Study 01, the recurrence rate within 6 months for the fellow eyes was higher in the FAI insert group compared to the sham injection group: 71.2% vs. 54.8%. The recurrence rate within 12 months was

comparable between the groups: 72.9% vs. 74.2%. In Study 05, the recurrence rate in the fellow eye was lower in the FAI insert group compared to the sham injection group: 40.9% vs. 54.8% within 6 months and 54.5% vs. 67.6% within 12 months.

Table 10: Subjects with recurrence of uveitis in the fellow eye (ITT population)

	PSV-FAI-001		PSV-FAI-005	
	FAI	**Sham**	**FAI**	**Sham**
ITT population[1]	N = 59	N = 31	N = 66	N = 31
Recurrence within 6 months, n (%)	42 (71.2)	17 (54.8)	27 (40.9)	17 (54.8)
a. Recurrence by BCVA or VH	15 (25.4)	5 (16.1)	10 (15.2)	7 (22.6)
b. Prohibited/rescue medication	38 (64.4)	17 (54.8)	21 (31.8)	14 (45.2)
c. Missing data	2 (3.4)	1 (3.2)	5 (7.6)	1 (3.2)
Recurrence within 12 months, n (%)	43 (72.9)	23 (74.2)	36 (54.5)	21 (67.7)
a. Recurrence by BCVA or VH	21 (35.6)	8 (25.8)	18 (27.3)	11 (35.5)
d. Prohibited/rescue medication	42 (71.2)	19 (61.3)	28 (42.4)	17 (54.8)
e. Missing data	2 (3.4)	3 (9.7)	10 (15.2)	3 (9.7)

[1] Fellow eyes with no occurrence of uveitis prior to the study were excluded.
Source: Reviewer's analysis and Table 11-8 of the Month 6 and Month 12 CSRs for Studies 01 and 05.

The recurrence rate within 6 months in the FAI group was much lower for the study eyes compared to that for the fellow eyes: 18.4% vs. 71.2% in Study 01 and 21.8% vs. 40.9% in Study 05. This may support that the FAI insert is effective in preventing recurrence of uveitis.

Change from baseline in BCVA at Month 6 and Month 12

Table 11 presents mean BCVA change from baseline in the study eye. In Study 01, the FAI insert group showed higher mean change from baseline than the sham injection group: 6.6 vs. 0.8 at Month 6 and 5.8 vs. 3.3 at Month 12. In Study 05, however, the FAI insert group showed lower mean change from baseline than the sham group: 4.9 vs. 7.3 at Month 6 and 3.0 vs. 7.4 at Month 12. Thus, in terms of BCVA improvement, the reviewer found no strong evidences supporting better beneficial effect of the FAI insert compared to the sham.

Table 11: BCVA change from baseline in the study eye (ITT population)

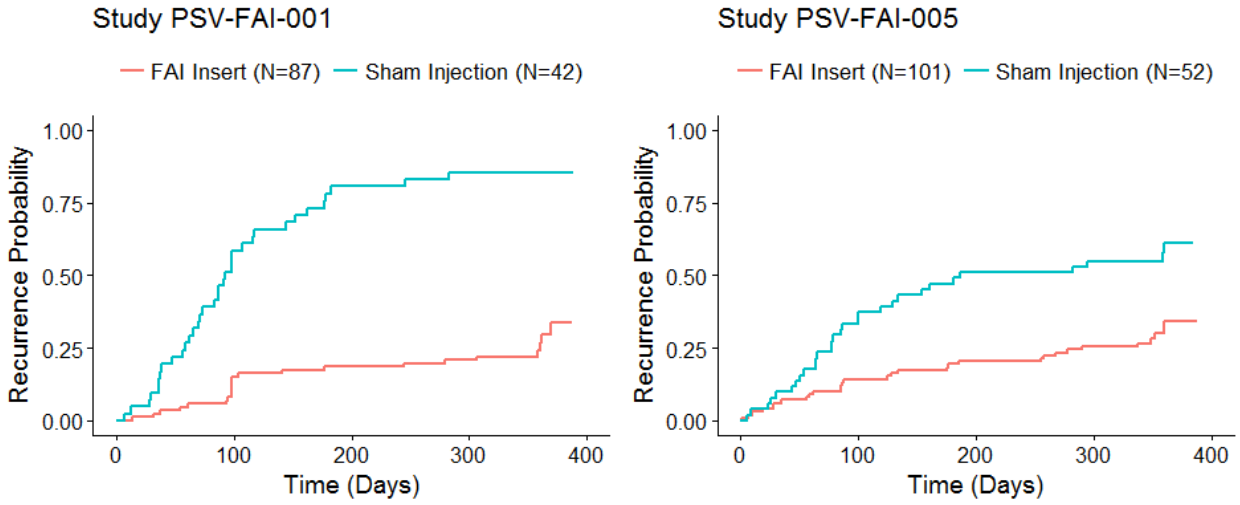
	PSV-FAI-001		PSV-FAI-005	
	FAI	**Sham**	**FAI**	**Sham**
Baseline				
N	87	42	101	52
Mean (SD)	66.9 (15.49)	64.9 (15.53)	66.4 (15.85)	63.6 (16.82)
Change from baseline at Month 6				
N	87	41	99	51
Mean (SD)	6.6 (11.24)	0.8 (11.28)	4.9 (10.57)	7.3 (11.49)
Change from baseline at Month 12				
N	85	39	93	49
Mean (SD)	5.8 (14.36)	3.3 (12.78)	3.0 (12.79)	7.4 (10.77)

Source: Table 11-13 of the Month 6 and Month 12 CSRs for Studies 01 and 05.

Time to first recurrence of uveitis in the study eye within 12 months

Figure 1 depicts the Kaplan-Meier plots of time to the first recurrence of uveitis in the study eye within 12 months. The plots show clear separation between the two groups, indicating that the probability of recurrence was constantly lower in the FAI insert group over 12 months compared with that in the sham group. The median time to the first recurrence was not evaluable for the FAI insert group due to the low number of recurrences for both studies. The median time to the first recurrence for the sham group was 92 days in Study 01 and 187 days in Study 05.

Figure 1: Kaplan-Meier plot of time to first recurrence of uveitis in the study eye (ITT population)



†Subjects who did not have recurrence assessed at Month 12 or took a prohibited or rescue medication prior to Month 12 were also considered as having recurrence. Source: Figure 11-1 of the Month 12 CSRs for Studies 01 and 05.

Number of recurrences of uveitis in the study eye within 12 months

Table 12 summarizes the number of recurrences of uveitis in the study eye within 12 months. In this calculation, each prohibited or rescue medication was counted as a recurrence if it occurred >28 days after any prior recurrence or any prior use of prohibited or rescue medications. In Study 01, the average number of recurrences per subject was lower in the FAI insert group: 0.5 vs. 1.8. In Study 05, however, the average number of recurrences was comparable between the two groups: 0.9 vs. 1.2. In both studies, the proportion of subjects with ≥ 2 recurrences was lower in the FAI insert group: 10.3% vs. 50.0% in Study 01 and 18.8% vs. 32.7% in Study 05.

3.2.4.3 Efficacy Conclusion

The two pivotal studies demonstrated evidence of efficacy of the FAI insert for the treatment of non-infectious uveitis affecting the posterior segment of the eye. The recurrence rate of uveitis in the study eye within 6 months was significantly lower in the FAI insert group compared to that of the sham group. The FAI insert group also showed lower recurrence rate of uveitis within 12 months compared with the sham group. The Kaplan-Meier analysis of time to the first recurrence indicated that the probability of recurrence was constantly lower in the FAI insert group over 12 months.

Table 12: Number of recurrences of uveitis in the study eye within 12 months (ITT population)

	PSV-FAI-001		PSV-FAI-005	
	FAI	**Sham**	**FAI**	**Sham**
ITT Population	N = 87	N = 42	N = 101	N = 52
Subjects with at least 1 recurrence	24 (27.6)	36 (85.7)	33 (32.7)	31 (59.6)
Number of recurrences				
Mean (SD)	0.5 (1.0)	1.8 (1.4)	0.9 (1.7)	1.2 (1.4)
Median	0	1	0	1
Min - Max	0 - 7	0 - 5	0 - 12	0 - 7
Number of recurrences, n (%)				
0	63 (72.4)	6 (14.3)	68 (67.3)	21 (40.4)
1	15 (17.2)	15 (35.7)	14 (13.9)	14 (26.9)
≥ 2	**9 (10.3)**	**21 (50.0)**	**19 (18.8)**	**17 (32.7)**

Source: Reviewer's analysis and Table 11-10 of the Month 12 CSRs for Studies 01 and 05.

3.3 Evaluation of Safety

In this section, high-level summaries of adverse events within 12 months are provided; see the FDA medical reviews for a comprehensive safety evaluation.

3.3.1 Summary of Adverse Events

Table 13 presents a high-level summary of adverse events (AE). For both studies, the proportion of subjects with AEs was slightly lower in the FAI insert group compared with that in the sham group: 89.7% vs. 95.2% in Study 01 and 86.1% vs. 90.4% in Study 05. All AEs were treatment-emergent AEs except only 1 case in Study 01: non-ocular mild AE of skin infection for Subject 54001 in the FAI group. In terms of serious AE (SAE), the two groups in Study 01 had similar rates of SAE. However, in Study 05, the SAE rate was higher in the FAI insert group: 12.9% vs. 5.8%.

Table 13: Summary of adverse events (AEs) within 12 months

	PSV-FAI-001		PSV-FAI-005	
	FAI	**Sham**	**FAI**	**Sham**
Safety Population	87	42	101	52
Subjects with AE[1]	**78 (89.7%)**	**40 (95.2%)**	**87 (86.1%)**	**47 (90.4%)**
Subjects with ocular AE	70 (80.5%)	39 (92.9%)	86 (85.1%)	45 (86.5%)
Subjects with non-ocular AE	43 (49.4%)	22 (52.4%)	14 (13.9%)	6 (11.5%)
Subjects with Serious AE (SAE)[2]	**14 (16.1%)**	**7 (16.7%)**	**13 (12.9%)**	**3 (5.8%)**
Subjects with ocular SAE	9 (10.3%)	7 (16.7%)	13 (12.9%)	1 (1.9%)
Subjects with non-ocular SAE	6 (6.9%)	2 (4.8%)	0 (0%)	2 (3.8%)
Subjects withdrawn due to AE	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)

[1] Subjects with ≥ 1 ocular AEs in the study eye or ≥ 1 non-ocular AEs
[2] Subjects with ≥ 1 ocular SAEs in the study eye or ≥ 1 non-ocular SAEs
Source: Reviewer's analysis

Most frequent ocular SAEs are presented in Table 14. The number in the parenthesis is the number of SAE suspected to be related to the study medication. In Study 01, most frequent

ocular SAEs for the FAI insert group were cataract (4), increased intraocular pressure (2), and uveitis (1). In Study 05, 7 subjects in the FAI subjects experienced hypotony of eye (low intraocular pressure) while no subject in the sham group experienced it. See Table 21 of Appendix E for the whole list of SAEs observed in the two studies.

Table 14: Most frequent ocular SAEs (serious AEs) within 12 months

	PSV-FAI-001		PSV-FAI-005	
	FAI	**Sham**	**FAI**	**Sham**
Subjects with SAEs	14	7	13	3
Ocular SAE				
hypotony of eye	0	1	7 (7)	0
cataract	4 (2)	0	1 (1)	0
uveitis	1 (0)	2	1 (0)	1
glaucoma	0	1	1 (1)	0
intraocular pressure increased	2 (2)	0	0	0
macular edema	0	2	0	0
non-infectious endophthalmitis	0	2	0	0

Source: Reviewer's analysis; the number in the parenthesis is the number of SAE suspected to be related to the study medication.

In terms of ocular AE, the FAI insert group and sham group had comparable ocular AE rates: 80.5% vs. 92.9% in Study 01 and 85.1% and 86.5% in Study 05 (Table 15). In Study 05, the FAI insert group showed a higher proportion of subjects who experienced increased intraocular pressure compared with the sham group: 28.7% vs. 1.9%. On the other hand, the sham group showed a higher rate of uveitis compared with the FAI insert group: 10.3% (FAI) vs. 40.5% (sham) in Study 01 and 10.9% (FAI) vs. 32.7% (sham) in Study 05. In Study 01, the sham group also had a higher rate of macular edema compared with the FAI insert group.

Table 15: Most common ocular AEs within 12 months

	PSV-FAI-001				PSV-FAI-005			
	FAI		**Sham**		**FAI**		**Sham**	
	Events	**Subjects**	**Events**	**Subjects**	**Events**	**Subjects**	**Events**	**Subjects**
Safety Population	87		42		101		52	
Subjects with ocular AE	70 (80.5%)		39 (92.9%)		86 (85.1%)		45 (86.5%)	
Ocular AE								
intraocular pressure increased	37	23 (26.4%)	14	11 (26.2%)	46	**29 (28.7%)**	1	**1 (1.9%)**
uveitis	9	**9 (10.3%)**	19	**17 (40.5%)**	18	**11 (10.9%)**	21	**17 (32.7%)**
cataract	29	24 (27.6%)	2	2 (4.8%)	14	12 (11.9%)	8	7 (13.5%)
visual acuity reduced	19	17 (19.5%)	8	5 (11.9%)	7	7 (6.9%)	3	3 (5.8%)
cataract subcapsular	6	5 (5.7%)	3	3 (7.1%)	19	19 (18.8%)	4	4 (7.7%)
macular edema	5	**5 (5.7%)**	20	**14 (33.3%)**	8	7 (6.9%)	6	5 (9.6%)
cystoid macular edema	9	**8 (9.2%)**	14	**8 (19.0%)**	7	5 (5.0%)	8	6 (11.5%)
eye pain	13	11 (12.6%)	9	7 (16.7%)	4	3 (3.0%)	6	5 (9.6%)
conjunctival haemorrhage	12	11 (12.6%)	4	4 (9.5%)	4	4 (4.0%)	1	1 (1.9%)
vitreous opacities	2	2 (2.3%)	5	4 (9.5%)	8	8 (7.9%)	5	4 (7.7%)
anterior chamber cell	2	2 (2.3%)	2	1 (2.4%)	11	9 (8.9%)	7	5 (9.6%)
ocular hyperaemia	6	6 (6.9%)	5	4 (9.5%)	2	2 (2.0%)	3	3 (5.8%)
vitritis	3	3 (3.4%)	2	1 (2.4%)	3	3 (3.0%)	8	7 (13.5%)

	PSV-FAI-001				PSV-FAI-005			
	FAI		Sham		FAI		Sham	
	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects
dry eye	7	7 (8.0%)	2	2 (4.8%)	3	3 (3.0%)	1	1 (1.9%)
hypotony of eye	2	2 (2.3%)	1	1 (2.4%)	11	9 (8.9%)	0	0 (0.0%)
visual impairment	0	0 (0.0%)	1	1 (2.4%)	7	7 (6.9%)	3	3 (5.8%)
vitreous floaters	7	6 (6.9%)	5	5 (11.9%)	0	0 (0.0%)	0	0 (0.0%)

Source: Reviewer's analysis and Tables 14.3.1-1.2 and 14.3.1-2.2 of the Month 12 CSRs for Studies 01 and 05.

The cataract event rate was summarized by baseline lens status in Table 16. In this table, cataract events included cataract, cataract subcapsular, and lenticular opacities. The event rate of cataract among phakic eyes was higher in the FAI insert group compared with the sham group for both studies: 69% vs. 19% in Study 01 and 47.5% vs. 25.7% in Study 05. For the pooled data from Studies 01 and 05, 103 subjects in the FAI insert group and 56 subjects in the sham group were phakic at baseline. The cataract event rate among the phakic eyes was higher in the FAI insert group compared with the sham group: 56.3% vs. 23.2%.

Table 16: Subjects with cataract by baseline lens status

	PSV-FAI-001		PSV-FAI-005		Pooled Data	
	FAI	Sham	FAI	Sham	FAI	Sham
Subjects, N [1]	87	42	101	52	188	94
Lens Status [2]						
phakic	**29/42 (69.0%)**	**4/21 (19.0%)**	**29/61 (47.5%)**	**9/35 (25.7%)**	**58/103 (56.3%)**	**13/56 (23.2%)**
aphakic	0/0 (0.0%)	0/0 (0.0%)	0/1 (0.0%)	2/2 (100.0%)	0/1 (0.0%)	2/2 (100.0%)
pseudophakic	0/45 (0.0%)	1/21 (4.8%)	0/39 (0.0%)	0/15 (0.0%)	0/84 (0.0%)	1/36 (2.8%)

[1]The number of subjects in the safety population; [2] Lens status of the study eye at baseline.
Source: Reviewer's analysis; cataract events were counted through12 months for both Study 01 and Study 05.

In terms of non-ocular AE, no notable differences between the two groups were observed. In Study 01, the proportion of subjects with non-ocular AEs was 49.4% in the FAI insert group and 52.4% in the sham group. In Study 05, it was 13.9% in the FAI insert group and 11.5% in the sham group. See Table 22 of Appendix E for more details.

3.3.2 Safety Conclusion

For both studies, overall AE rates were comparable between the FAI insert group and sham group. Higher proportion of the FAI-treated subjects experienced cataract and increased ocular pressure compared with the sham-treated subjects. On the other hand, the sham group showed higher rates of uveitis and macular edema compared with those of the FAI insert group. Considering that cataract and increased ocular pressure are commonly observed for the treatment of uveitis using steroids, the AE profile of the FAI insert appears as expected; however, deference is made to the FDA medical reviews for a comprehensive safety evaluation and conclusion.

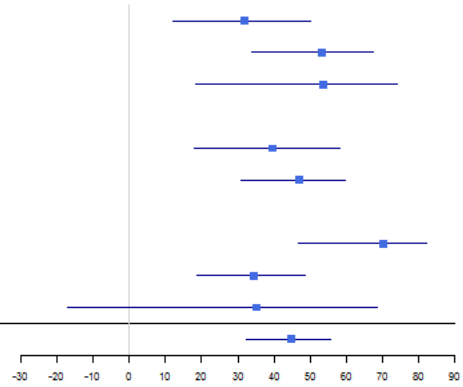
4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The recurrence rate of uveitis in the study eye within 6 months was analyzed across various subgroups: (1) subgroups defined by age (< 40 years, 40 to < 60 years, or ≥ 60 years), gender, race, (2) subgroups by region or systemic therapy at study entry, and (3) subgroups by baseline ocular characteristics. Due to limited sample sizes, the subgroup analyses were performed on the pooled data from Studies 01 and 05. Considering that the studies had almost identical designs and showed consistent efficacy conclusion, the pooling appears reasonable. However, the results of the subgroup analyses on the pooled data need to be interpreted with caution. For each subgroup, a 95% confidence interval for the difference in the recurrence rates was obtained using the Newcombe method mentioned in Section 3.2.2.

Figure 2 shows the results for the subgroup analyses by age, gender, or race. The plots in the right panel present 95% confidence intervals for the differences in the recurrence rates (Sham - FAI). All subgroups consistently show favorable results for the FAI group. The observed difference in recurrence rates between the two groups ranges from 31.8% to 70.1% across the subgroups.

Figure 2: Recurrence of uveitis in the study eye within 6 months by demographic subgroups (ITT population)

Subgroup	FAI	Sham	RD†
Age			
< 40 years	16/82 (19.5%)	19/37 (51.4%)	31.8%
40 to <60 years	14/74 (18.9%)	31/43 (72.1%)	53.2%
>= 60 years	8/32 (25.0%)	11/14 (78.6%)	53.6%
Gender			
Male	14/76 (18.4%)	18/31 (58.1%)	39.6%
Female	24/112 (21.4%)	43/63 (68.3%)	46.8%
Race			
White	11/60 (18.3%)	23/26 (88.5%)	70.1%
Asian	23/117 (19.7%)	33/61 (54.1%)	34.4%
Other	4/11 (36.4%)	5/7 (71.4%)	35.1%
All Subjects	38/188 (20.2%)	61/94 (64.9%)	44.7%



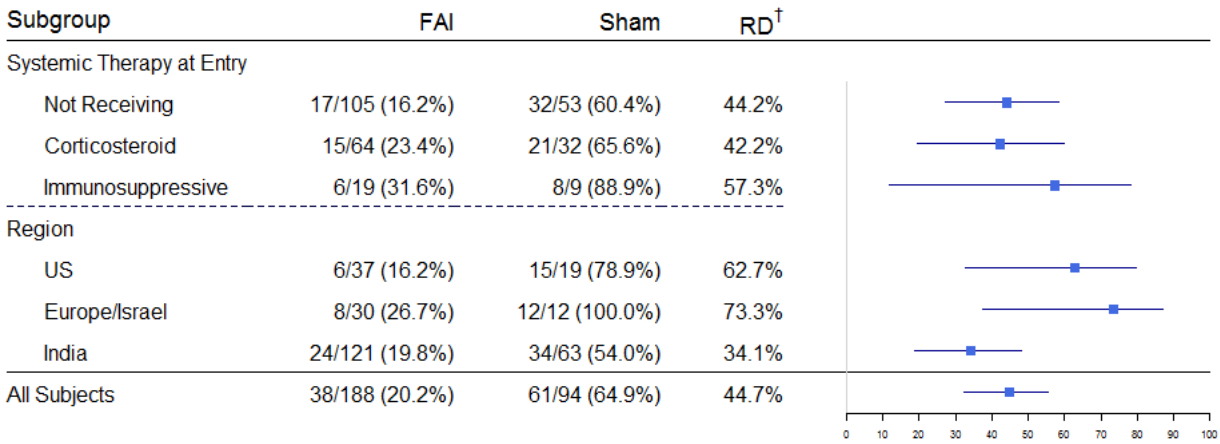
†RD: Risk difference (difference in recurrence rates, Sham - FAI)
Source: Table 16 of the Integrated Summary of Efficacy.

Figure 3 shows the results for the following subgroups:

- Systemic treatments received at the time of study entry: Recall that some subjects had received systemic medications to control uveitis prior to study enrollment.
- Geographic regions: Study 01 was conducted in US, Europe (UK, Germany, and Hungary), Israel, and India.

For all subgroups in these analyses, lower recurrent rates were observed for the FAI group compared to the sham group. Other subgroup analyses by baseline disease characteristics also showed consistently favorable results for the FAI treatment arm (See the Appendix D).

Figure 3: Recurrence of uveitis in the study eye within 6 months by special subgroups (ITT population)



†RD: Risk difference (difference in recurrence rates, Sham - FAI)
Source: Table 16 of the Integrated Summary of Efficacy.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The OSI notified that one site in Study 01 did not follow the masking process described in the protocol. Consequently, for 7 subjects in this site, efficacy assessments were conducted by an unmasked investigator. The reviewer conducted a sensitivity analysis to investigate the impact of this issue on the primary efficacy results. Specifically, the reviewer excluded the subjects in this site from the analysis population and applied the same method used in the primary efficacy analysis. The results of this sensitivity analysis were very similar to the primary analysis results. Thus, this issue does not have a significant impact on the overall efficacy conclusions. The reviewer found no other major statistical issues.

5.2 Collective Evidence

The Applicant seeks approval of the FAI insert 0.18 mg for the treatment of non-infectious uveitis affecting the posterior segment of the eye. Efficacy and safety were evaluated in the two pivotal studies, Study 01 and Study 05.

In terms of recurrence of uveitis within 6 months following treatment, the two pivotal studies demonstrated that the recurrence rate was significantly lower in the FAI insert group compared with that in the sham group: 18.4% vs. 78.6% in Study 01 and 21.8% vs. 53.8% in Study 05. The difference (sham - FAI) in the recurrence rates was 60.2% [95% CI: (41.4%, 73.0%)] and 32.1% [95% CI: (14.9%, 47.6%)] in Study 01 and Study 05, respectively. P-value from a Chi-squared test comparing the recurrence rates in the two groups was less than 0.001 for both studies. The recurrence rate within 12 months was also lower for the FAI insert group: 27.6% vs. 85.7% in Study 01 and 32.7% vs. 59.6% in Study 05.

Kaplan-Meier plots of time to the first recurrence of uveitis in the study eye showed clear separation between the two treatment groups, indicating that the estimated probability of recurrence was constantly lower in the FAI insert group over 12 months.

In terms of AE profile, the FAI insert group showed lower rate of uveitis compared with the sham group: 10.3% vs. 40.5% in Study 01 and 10.9% vs. 32.7% in Study 05. The rate of macular edema was also lower for the FAI insert group in Study 01: 5.7% vs. 33.3%. On the other hand, the FAI insert group had a higher rate of cataract among phakic eyes compared with the sham group: 69% vs. 19% in Study 01 and 47.5% vs. 25.7% in Study 05. In Study 05, The FAI insert group also showed a higher proportion of subjects who experienced increased intraocular pressure: 28.7% vs. 1.9%. The overall AE rates were comparable between the two groups.

5.3 Conclusions and Recommendations

Study 01 and Study 05 demonstrated that the FAI insert 0.18 mg was superior to the sham in preventing recurrence of uveitis and provided adequate evidence of efficacy to support an approval of the FAI insert 0.18 mg for the proposed indication.

5.4 Labeling Recommendations

The Applicant presented the following two tables in Section 14 (Clinical Studies):

Table 5: Uveitis Recurrence Rate (ITT; All Randomized Subjects)

Time point	Uveitis Recurrence	Study 1		Study 2	
		YUTIQ	Sham	YUTIQ	Sham
		N= 87	N= 42	N=101	N=52
6 months	n (%)	16 (18.4%)	33 (78.6%)	22 (21.8%)	28 (53.8%)
	Odds ratio (95% CI)	16.27 (6.52, 40.63)		4.19 (2.04, 8.62)	
	Estimated Difference (95% CI)	60.2% (41.4%, 73.0%)		32.1% (14.9%, 47.6%)	
	P value*	< 0.001		< 0.001	
12 months	n (%)	24 (27.6%)	36 (85.7%)	33 (32.7%)	31 (59.6%)
	Odds ratio (95% CI)	15.75 (5.89, 42.13)		3.04 (1.52, 6.08)	
* continuity corrected Chi-square test					

Table 6: Subjects Receiving Adjunctive Treatments (ITT; All Randomized Subjects)

Time point	Adjunctive treatment	Study 1		Study 2	
		YUTIQ	Sham	YUTIQ	Sham
		N= 87	N= 42	N=101	N=52
6 months	Systemic steroid or immunosuppressant (%)	13 (14.9%)	16 (38.1%)	14 (13.9%)	11 (21.2%)
	Intraocular steroid (in study eye) (%)	5 (5.7%)	24 (57.1%)	2 (2.0%)	19 (36.5%)
12 months	Systemic steroid or immunosuppressant (%)	17 (19.5%)	17 (40.5%)	17 (16.8%)	13 (25%)
	Intraocular steroid (in study eye) (%)	6 (6.9%)	26 (61.9%)	3 (3.0%)	20 (38.5%)

Recurrence of uveitis was defined as a multi-component outcome: (1) deterioration in visual acuity or vitreous haze attributable to non-infectious uveitis, or (2) use of prohibited or rescue medication. Table 6 presents the second component; the reviewer found that the subjects receiving adjunctive treatments presented in Table 6 were identical to the subjects who were considered as having a recurrence due to the use of prohibited/rescue medications. Thus, the statistical team recommends combining these two tables into one table in the format below. The new format presents the recurrence rate by each component. The odds ratios are excluded in the new format as we consider they are not practically helpful for prescribers given that the differences in the recurrence rates are provided.

If the medical review team determines that the information in the Applicant's Table 6 is clinically unnecessary for labeling, we do not have any objection to simply remove Table 6 and keep the Applicant's Table 5. In this case, however, we recommend adding the following text in the label: "Recurrence of uveitis was defined as either deterioration in visual acuity (b) (4) vitreous haze attributable to non-infectious uveitis (b) (4) or rescue medication".

Reviewer's Table: Efficacy Results of Recurrence of Uveitis in Randomized Study Eyes

	Study 1		Study 2	
	YUTIQ N = 87	**Sham N = 42**	**YUTIQ N = 101**	**Sham N = 52**
Eyes with recurrence within 6 months, n (%)	**16 (18%)**	**33 (79%)**	**22 (22%)**	**28 (54%)**
a. Deterioration in BCVA or VH [1]	2 (2%)	10 (24%)	11 (11%)	9 (17%)
b. Use of prohibited/rescue medications	15 (17%)	32 (76%)	16 (16%)	24 (46%)
i. Systemic steroid or immune-suppressant	13 (14.9%)	16 (38.1%)	14 (13.9%)	11 (21.2%)
ii. Intraocular steroid in the study eye	5 (5.7%)	24 (57.1%)	2 (2.0%)	19 (36.5%)
c. Missing data	0 (0.0%)	1 (2%)	2 (2%)	2 (4%)
Difference (95% CI) [2] in recurrence rates	**60% (41%, 73%)**		**32% (15%, 48%)**	
P-value [3]	< 0.001		< 0.001	
Eyes with recurrence within 12 months, n (%)	**24 (28%)**	**36 (86%)**	**33 (33%)**	**31 (60%)**
a. Deterioration in BCVA or VH [1]	4 (4%)	11 (26%)	16 (16%)	11 (21%)
b. Use of prohibited/rescue medications	19 (22%)	34 (81%)	19 (19%)	27 (52%)
i. Systemic steroid or immune-suppressant	17 (19.5%)	17 (40.5%)	17 (16.8%)	13 (25.0%)
ii. Intraocular steroid in the study eye	6 (6.9%)	26 (61.9%)	3 (3.0%)	20 (38.5%)
c. Missing data	2 (2%)	3 (7%)	9 (9%)	5 (10%)
Difference (95% CI) [2] in recurrence rates	**58% (40%, 70%)**		**27% (9%, 43%)**	

[1] Eyes with decrease of ≥ 15 letters in best-corrected visual acuity (BCVA) or increase of ≥ 2 steps in vitreous haze score.
[2] The 95% CIs (confidence intervals) were estimated using the Newcombe method with continuity-correction.
[3] P-values were computed using continuity-corrected Chi-squared tests.

APPENDICES

Appendix A. Schedule of Procedures and Assessments

Table 17: Schedule of procedures in PSV-FAI-001 and PSV-FAI-005

Assessments	Screening	Day 1	Day 7	Day 28	Months 2, 3	Months 6, 9, 12, 18, 24, 30, 36
Timing/Interval	-30 to 0	1	±2D	±3D	±7D	±28D
Medical/Ophthalmic History	X					
Demographics	X					
Inclusion/Exclusion Criteria	X	X				
Randomization		X				
Pregnancy Test[a]	X	X				X[a]
Vital Signs[b]	X	X	X	X	X	X
Clinical Labs[c]	X					
Ophthalmic Examination[d]	X	X	X	X	X	X
Visual Field[e]	X					X[e]
OCT		X		X	X	X
Physical Exam	X					
Subjective Ocular Tolerability & Discomfort Assessment	X	X	X	X	X	X
FAI Insert Placement or Sham Injection		X				
Concomitant Meds	X	X	X	X	X	X
AEs		X	X	X	X	X

[a] Females of child-bearing potential only: urine test conducted only at Screening, Day 1, Month 12, Month 24 and Month 36.
[b] 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 only.
[c] Hematology; ESR; serum chemistry; urinalysis; HIV and syphilis serology testing; TB testing.
[d] Ophthalmic examination includes BCVA, IOP [recorded as the mean of three measurements], dilated indirect ophthalmoscopy, and anterior, posterior and intermediate slit lamp examinations
[e] Conducted only at Months 12, 24 and 36.
†Source: Table 4 of the protocols for Studies PSV-FAI-001 and PSV-FAI-005.

Appendix B. Simulation Study to Assess the Newcombe Method

The reviewer conducted a simulation study to investigate coverage probabilities of the 95% CIs obtained by the Newcombe method. The true recurrence rate assumed for each treatment group ranged from 10% to 90%. For each scenario, 1000 datasets were generated. Each dataset included 129 subjects as Study 01 did (87 subjects in the FAI insert group and 42 subjects in the sham group). Table 18 shows the simulated coverage probabilities of the 95% confidence intervals obtained by the Newcombe method. Among all scenarios considered here, the minimum coverage probability was 0.952 when the recurrence rate was 60% and 50% for the FAI insert group and the sham group, respectively. Thus, it appears that 95% CIs from the Newcombe method have enough coverage (greater than the nominal level of 95%).

Table 18: Simulated coverage probabilities of 95% CIs obtained by the Newcombe method

	Recurrence Rate in Sham Injection								
	10%	**20%**	**30%**	**40%**	**50%**	**60%**	**70%**	**80%**	**90%**
Recurrence Rate in FAI Insert									
10%	0.979	0.969	0.975	0.972	0.964	0.971	0.967	0.964	0.965
20%	0.972	0.964	0.970	0.973	0.967	0.953	0.954	0.974	0.965
30%	0.975	0.972	0.966	0.967	0.959	0.970	0.962	0.966	0.976
40%	0.974	0.968	0.965	0.972	0.966	0.962	0.962	0.959	0.966
50%	0.964	0.973	0.962	0.962	0.960	0.968	0.953	0.972	0.968
60%	0.963	0.977	0.962	0.976	**0.952**	0.958	0.965	0.972	0.964
70%	0.960	0.972	0.969	0.974	0.972	0.960	0.977	0.964	0.975
80%	0.969	0.965	0.959	0.970	0.963	0.968	0.975	0.963	0.972
90%	0.969	0.960	0.962	0.959	0.965	0.962	0.976	0.979	0.974

† For each combination of the recurrence rates in the two groups, 1000 datasets were simulated.

The followings are the R codes used to compute 95% Newcombe CIs.

```
newcombe <- function(y, trt, alpha=0.05){

  ### y: binary response variable (1: success, 0: failure)
  ### trt: factor variable indicating treatment assignment

  N <- tapply(y,trt,length)
  n <- tapply(y,trt,sum)
  p <- n/N

  diff <- p[1] - p[2]
  z <- qnorm(1-alpha/2)

  ### CIs for each proportion (See Method 4 in Section 2 of Newcombe(1998a))
  l.bound <- (2*N*p + z^2 - 1 - z*sqrt(z^2-2-1/N+4*p*(N*(1-p)+1)))/(2*(N+z^2))
  u.bound <- (2*N*p + z^2 + 1 + z*sqrt(z^2+2-1/N+4*p*(N*(1-p)-1)))/(2*(N+z^2))

 ### Final CI (See Method 10 in Section 2 of Newcombe(1998b))
  diff.l <- diff - sqrt((p[1]-l.bound[1])^2+(u.bound[2]-p[2])^2)
  diff.u <- diff + sqrt((u.bound[1]-p[1])^2+(p[2]-l.bound[2])^2)
  ci.newcombe <- c(diff.l, diff.u)

  return(ci.newcombe)
 }
```

Appendix C. Baseline Ocular Characteristics in Fellow Eyes

Table 19: Baseline disease and ocular characteristics for the fellow eye

	PSV-FAI-001		PSV-FAI-005	
	FAI	**Sham**	**FAI**	**Sham**
Randomized Population [1]	N = 59	N = 31	N = 66	N = 31
BCVA (letters)				
Mean (SD)	70.6 (18.9)	72.4 (14.6)	68.7 (20.9)	68.6 (18.7)
Median	76.0	75.0	76.0	75.0
Min - Max	0.0 - 94.0	28.0 - 91.0	18.0 - 95.0	25.0 - 92.0
Vitreous haze				
Absent (0)	35 (59.3)	14 (45.2)	24 (36.4)	16 (51.6)
Trace (0.5)	15 (25.4)	12 (38.7)	17 (25.8)	7 (22.6)
1+	8 (13.6)	5 (16.1)	16 (24.2)	6 (19.4)
2+	1 (1.7)	0 (0.0)	5 (7.6)	2 (6.5)
3+	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)
4+	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Duration of uveitis (years)				
Mean (SD)	8.7 (7.0)	5.6 (6.3)	2.8 (2.8)	3.8 (2.9)
Median	8.2	3.0	2.0	3.4
Min - Max	0.9 - 34.2	0.0 - 23.6	0.0 - 14.5	0.0 - 9.9
Number of recurrences within 12 months prior to screening, n (%)				
0	16 (27.1)	5 (16.1)	7 (10.6)	2 (6.5)
1 - 2	32 (54.2)	23 (74.2)	56 (84.8)	28 (90.3)
> 2	11 (18.6)	3 (9.7)	3 (4.5)	1 (3.2)
Systemic treatment to control uveitis, n (%)				
Not receiving systemic treatment	28 (47.5)	16 (51.6)	41 (62.1)	19 (61.3)
Receiving systemic treatment				
Corticosteroid therapy	19 (32.2)	9 (29.0)	24 (36.4)	11 (35.5)
Immunosuppressive therapy	12 (20.3)	6 (19.4)	1 (1.5)	1 (3.2)
IOP (mmHg)				
Mean (SD)	14.7 (4.3)	14.2 (3.6)	13.4 (3.1)	13.1 (3.1)
Median	14.0	14.0	13.5	12.0
Min - Max	6.0 - 25.0	7.0 - 22.0	7.0 - 21.0	8.0 - 20.0
Severity of edema, n (%)				
CSFT < 300 microns	34 (57.6)	22 (71.0)	50 (75.8)	20 (64.5)
CSFT >= 300 microns	24 (40.7)	8 (25.8)	10 (15.2)	8 (25.8)
Lens status, n (%)				
Phakic	27 (45.8)	18 (58.1)	50 (75.8)	25 (80.6)
Cataract present, n (%)	16 (27.1)	6 (19.4)	21 (31.8)	11 (35.5)
Ahakic	0 (0.0)	0 (0.0)	2 (3.0)	0 (0.0)
Pseudophakic	32 (54.2)	13 (41.9)	14 (21.2)	6 (19.4)

[1] The fellow eyes without occurrence of uveitis were excluded from the summaries.
Source: Table 14.1-4.1 of the Month 6 CSRs for Studies 01 and 05.

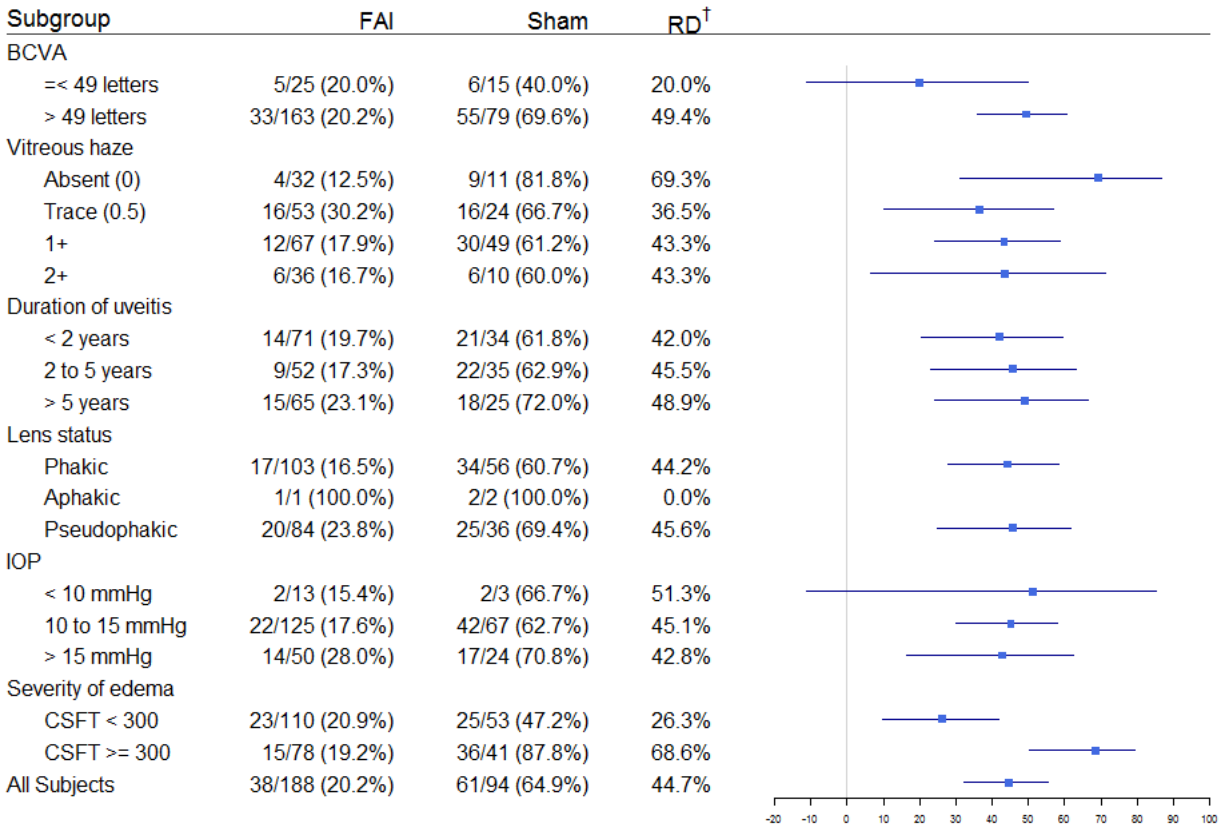
Appendix D. Supportive Efficacy Analyses

Table 20: Proportion of subjects with recurrence of uveitis in the study eye within 6 months (PP population)

	PSV-FAI-001		PSV-FAI-005	
	FAI	**Sham**	**FAI**	**Sham**
ITT population	N = 67	N = 18	N = 87	N = 32
Recurrence within 6 months, n (%)				
No recurrence	65 (97.0)	9 (50.0)	78 (89.7)	24 (75.0)
Recurrence	2 (3.0)	9 (50.0)	9 (10.3)	8 (25.0)
Treatment Comparison				
Difference [95% CI] [1]	47.0% (22.3%, 70.4%)		14.7% (-1.0%, 34.1%)	
Odds Ratio [95% CI] [2]	32.50 (6.04, 174.96)		2.89 (1.00, 8.31)	
P-value [3]	<0.0001		0.0836	

[1] Difference in the recurrence rates (Sham- FAI); 95% CIs (confidence interval) estimated using the Newcombe method.
[2] Odds ratio of no recurrence rates (FAI/Sham); 95% CIs estimated using the Mantel-Haenszel method.
[3] P-values computed using continuity-corrected Chi-squared tests.
Source: Table 11-7 of the CSRs for Studies 01 and 05.

Figure 4: Subgroup analyses of uveitis recurrence by baseline characteristics (ITT population)



†RD: Risk difference (difference in recurrence rates, Sham - FAI)
Source: Table 16 of the Integrated Summary of Efficacy.

Appendix E. Summary Tables for AEs

Table 21: Serious AEs (SAEs) within 12 months

	PSV-FAI-001		PSV-FAI-005	
	FAI	**Sham**	**FAI**	**Sham**
Subjects with SAEs	14	7	13	3
Ocular SAE				
hypotony of eye	0	1 (0)	7 (7)	0
cataract	4 (2)	0	1 (1)	0
uveitis	1 (0)	2 (1)	1 (0)	1 (1)
glaucoma	0	1 (0)	1 (1)	0
intraocular pressure increased	2 (2)	0	0	0
macular edema	0	2 (1)	0	0
non-infectious endophthalmitis	0	2 (0)	0	0
choroiditis	0	0	1 (0)	0
cystoid macular edema	1 (0)	0	0	0
device dislocation	1 (0)	0	0	0
intraocular pressure fluctuation	1 (1)	0	0	0
optic ischemic neuropathy	0	0	1 (0)	0
optic neuritis	1 (0)	0	0	0
post procedural inflammation	1 (0)	0	0	0
retinal detachment	0	0	1 (1)	0
vitreous haemorrhage	0	0	1 (0)	0
vitritis	1 (0)	0	0	0
Non-ocular SAE				
acute kidney injury	0	0	0	1 (0)
duodenitis	1 (0)	0	0	0
foot deformity	1 (0)	0	0	0
hydrocele	1 (0)	0	0	0
myocardial infarction	1 (0)	0	0	0
premature baby	1 (0)	0	0	0
rhabdomyolysis	1 (0)	0	0	0
septic shock	0	0	0	1 (0)
transient ischemic attack	0	1 (0)	0	0
tuberculosis gastrointestinal	0	0	0	1 (0)
upper gastrointestinal haemorrhage	1 (0)	0	0	0
uterine cancer	0	1 (0)	0	0

Source: Reviewer's analysis; The number in the parenthesis is the number of SAEs suspected to be related to the study medication.

Table 22: Most common non-ocular AEs within 12 months

	PSV-FAI-001				PSV-FAI-005			
	FAI		Sham		FAI		Sham	
	Events	Subjects	Events	Subjects	Events	Subjects	Events	Subjects
Safety Population	87		42		101		52	
Subjects with non-ocular AE	43 (49.4%)		22 (52.4%)		14 (13.9%)		6 (11.5%)	
Non-ocular AE								
nasopharyngitis	11	9 (10.3%)	5	5 (11.9%)	0	0 (0.0%)	0	0 (0.0%)
headache	4	3 (3.4%)	3	2 (4.8%)	2	1 (1.0%)	1	1 (1.9%)
nausea	2	2 (2.3%)	6	4 (9.5%)	0	0 (0.0%)	0	0 (0.0%)
arthralgia	5	4 (4.6%)	1	1 (2.4%)	1	1 (1.0%)	0	0 (0.0%)
hypertension	3	2 (2.3%)	0	0 (0.0%)	3	3 (3.0%)	1	1 (1.9%)

Source: Reviewer's analysis and Tables 14.3.1-1.1 and 14.3.1-2.1 of the Month 12 CSRs for Studies 01 and 05.

Appendix F. Thirteen Subjects at Dr. Foster's Site in Study 01

Country	Site #	Subject #	Lot Number	Drug
United States	18	(b) (6)	13-0011 A	FAI Insert
United States	18		13-0011 A	FAI Insert

Country	Site #	Subject #	Lot Number	Drug
United States	18	(b) (6)	13-0011 A	FAI Insert
United States	18		13-0011 A	FAI Insert
United States	18		14-0004 A	FAI Insert
United States	18		13-0009 B	Sham
United States	18		14-0004 A	FAI Insert
United States	18		14-0004 A	FAI Insert
United States	18		14-0004 A	FAI Insert
United States	18		14-0004 A	FAI Insert
United States	18		14-0006 A	FAI Insert
United States	18		14-0006 A	FAI Insert
United States	18		14-0005 B	Sham

Source: Pages 3-4 of Appendix 16.1.6 in the Month 6 CSR for Study 01

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Source: Page 6 of Appendix 16.1.4 in the Month 6 CSR for Study 01

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/

WONYUL N LEE
08/29/2018

YAN WANG
08/29/2018
I concur.