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 206911
Supplement #:	000
Drug Name:	Bromfenac ophthalmic solution, 0.075%
Indication(s):	Treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery
Applicant:	InSite Vision Inc.
Date(s):	Submitted: 06/10/2015 PDUFA date: 04/10/2016
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Keywords: ocular inflammation, anterior chamber cells , ocular pain, cataract surgery, prevention of pain, reduction of pain, treatment of pain

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1 EXECUTIVE SUMMARY

The applicant seeks approval of BromSite™ (bromfenac ophthalmic solution) 0.075% (also known as ISV-303 throughout this review) for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery. The proposed dosage and administration is to instill one drop of ISV-303 to the affected eye twice daily (morning and evening) for 16 days: 1 day prior to surgery, the day of surgery, and 14 days post-surgery.

The NDA included the efficacy and safety results from two identically designed pivotal clinical trials, Studies C-11-303-003 and C-12-303-004 (also referred to as Study 003 and Study 004 throughout this review). Both Studies 003 and 004 were prospective, multicenter, randomized, double-masked, vehicle-controlled, parallel-group studies. For both studies, the primary efficacy endpoint was the proportion of subjects with anterior chamber cell (ACC) grade of 0 without rescue therapy by Day 15; and the secondary endpoint was the proportion of subjects with a pain grade of 0 without rescue therapy in the study eye at each post-surgical visit (Days 1, 8, 15, and 29). The primary analysis set for the evaluation of the primary and secondary efficacy endpoints was the modified intent-to-treat (mITT) population, which included all subjects who were randomized, underwent cataract surgery, and received at least one dose of study treatment.

For Study 003, at Day 15 visit, 57.1% (96/168) of the patients in the ISV-303 group had an ACC grade of 0 without rescue therapy compared with 18.8% (16/85) of the patients in the Vehicle group; the treatment difference 38.3% was statistically significant ($p<0.001$) with a 95% CI of (27.1%, 49.5%). For Study 004, at the Day 15 visit, 38.1% (64/168) of the patients in the ISV-303 group had an ACC grade of 0 without rescue therapy compared with 22.4% (19/85) of the patients in the Vehicle group; the treatment difference 15.7% was statistically significant ($p=0.035$) with a 95% CI of (4.2%, 27.3%).

In Study 003, at each of the postsurgical visits (Days 1, 8, 15, and 29), proportionally more ISV-303-treated subjects (76.8%, 90.5%, 92.9% and 85.1%, respectively) had no pain (VAS score of 0 without rescue therapy), compared with vehicle-treated subjects (48.2%, 38.8%, 42.4% and 47.1%, respectively), and the differences in proportions (28.6%, 51.7%, 50.5%, and 38.1%, respectively) were statistically significant ($p < 0.001$) with 95% CI of (16.2%, 40.9%), (40.4%, 62.9%), (39.3%, 61.7%), and (26.2%, 50.0%), respectively. In Study 004, proportionally more ISV-303-treated subjects (82.1%, 86.3%, 86.9% and 83.3%, respectively) were pain free (VAS score of 0 without rescue therapy) compared with vehicle-treated subjects (62.4%, 50.6%, 57.6% and 60.0%, respectively). The differences in proportions (19.8%, 35.7%, 29.3%, and 23.3%, respectively) were statistically significant ($p < 0.001$) with 95% CI of (8.0%, 31.6%), (23.9%, 47.6%), (17.6%, 40.9%), and (11.5%, 35.2%), respectively.

In conclusion, ISV-303 (BromSite™ (bromfenac ophthalmic solution) 0.075%) is superior to Vehicle in terms of:

- The percentage of patients who achieved an ACC score of 0 at Day 15;
- And the percentage of patients who achieved a pain score of 0 at each post-surgical visit (Days 1, 8, 15, and 29).

Therefore, the statistical reviewer finds evidence of efficacy for BromSite™ (bromfenac ophthalmic solution) 0.075%.

Table 1: Summary of the Primary and Secondary Efficacy Results (mITT)

Proportion of Subjects with an ACC Score of 0 Without Rescue Therapy						
	Study 003			Study 004		
Visit	ISV-303 (N=168)	Vehicle (N=85)	ISV-303 vs. Vehicle Difference (95% CI)[a]	ISV-303 (N=168)	Vehicle (N=85)	ISV-303 vs. Vehicle Difference (95% CI)[a]
Day 1	3 (1.8%)	2 (2.4%)	-0.6% (-4.4%, 3.2%)	5 (3.0%)	1 (1.2%)	1.8% (-1.6%, 5.2%)
Day 8	54 (32.1%)	7 (8.2%)	23.9% (14.7%, 33.1%)	40 (23.8%)	8 (9.4%)	14.4% (5.5%, 23.3%)
Day 15	**96 (57.1%)**	**16 (18.8%)**	**38.3% (27.1%, 49.5%)**	**64 (38.1%)**	**19 (22.4%)**	**15.7% (4.2%, 27.3%)**
Day 29	108 (64.3%)	23 (27.1%)	37.2% (25.3%, 49.1%)	95 (56.5%)	36 (42.4%)	14.2% (1.3%, 27.1%)
Proportion of Subjects Who Were Pain Free (VAS Score of 0) Without Rescue Therapy						
	Study 003			Study 004		
Visit	ISV-303 (N=168)	Vehicle (N=85)	ISV-303 vs. Vehicle Difference (95% CI)[a]	ISV-303 (N=168)	Vehicle (N=85)	ISV-303 vs. Vehicle Difference (95% CI)[a]
Day 1	129 (76.8%)	41 (48.2%)	28.6 (16.2%, 40.9%)	138 (82.1%)	53 (62.4%)	19.8 (8.0%, 31.6%)
Day 8	152 (90.5%)	33 (38.8%)	51.7 (40.4%, 62.9%)	145 (86.3%)	43 (50.6%)	35.7 (23.9%, 47.6%)
Day 15	156 (92.9%)	36 (42.4%)	50.5 (39.3%, 61.7%)	146 (86.9%)	49 (57.6%)	29.3 (17.6%, 40.9%)
Day 29	143 (85.1%)	40 (47.1%)	38.1 (26.2%, 50.0%)	140 (83.3%)	51 (60.0%)	23.3 (11.5%, 35.2%)

[a] 95% CI were calculated by the statistical reviewer and based on normal approximation to binomial data.
Source: Tables 14.2.1.1 and 17 of Study 003 Report; and Tables 14.2.1.1 and 17 of Study 004 Report..

In both studies, the majority of ISV-303-treated subjects (~80%) had no VAS assessed pain (VAS pain score of 0) starting from post-surgery Day 1 and these proportions were much greater compared with vehicle (about 50% to 60%). Consequently, the applicant argued that these results indicated that in most subjects treatment with ISV-303 prevented pain from occurring. Therefore, the applicant proposed the indication of ISV-303 as "treatment of postoperative inflammation and the **prevention** of ocular pain in patients [redacted] (b) (4) cataract surgery" instead of "treatment of postoperative inflammation and the **reduction** of ocular pain in patients who have undergone cataract surgery", which was the approved indication for all previous bromfenac ophthalmic solutions in different strengths.

PROLENSA™ (Bromfenac ophthalmic solution, 0.07%; Bausch & Lomb, Inc.) was approved in 2013 for the treatment of postoperative inflammation and the **reduction** of ocular pain in patients who have undergone cataract surgery for once a day (QD) dosing of 16 days: the day before surgery, the day of surgery, and 14 days after cataract surgery. The following study results (**Table 2**) were summarized in the statistical review of PROLENSA™. It is noted that the majority of PROLENSA-treated subjects (~80% or more) also had no VAS assessed pain (VAS pain score of 0) starting from post-surgery Day 1 and these proportions were much greater compared with vehicle.

Table 2: Proportion of Subjects Who Were Pain Free (VAS Score of 0) for PROLENSA™

	Study 1			Study 2		
Visit	PROLENSA (N=112)	Vehicle (N=108)	PROLENSA vs. Vehicle Difference (95% CI)	PROLENSA (N=110)	Vehicle (N=110)	PROLENSA vs. Vehicle Difference (95% CI)
Day 1	91 (81.3%)	47 (43.5%)	37.7% (25.9%, 49.6%)	84 (76.4%)	61 (55.5%)	20.9% (8.7%, 33.1%)

Day 3	97 (86.6%)	57 (52.8%)	33.8% (22.5%, 45.2%)	95 (86.4%)	58 (52.7%)	33.6% (22.3%, 45.0%)
Day 8	105 (93.8%)	64 (59.3%)	34.5% (24.2%, 44.8%)	99 (90.0%)	68 (61.8%)	28.2% (17.5%, 38.9%)
Day 15	104 (92.9%)	73 (67.6%)	25.3% (15.2%, 35.3%)	100 (90.9%)	74 (67.3%)	23.6% (13.3%, 33.9%)

Source: Page 49 to 50 of the statistical review for PROLENSA™
(http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203168Orig1s000StatR.pdf)

The statistical reviewer considered the applicant's argument for "**prevention** of ocular pain" reasonable; however, with similar results for pain as a previously approved bromfenac ophthalmic solution which was also dosed one day before the surgery as ISV-303 and approved for "**reduction** of ocular pain in patients (b) (4) cataract surgery", there did not appear to be any strong justification for using the phrase "prevention of ocular pain" either. Furthermore, the statistical reviewer also considered "**treatment** of ocular pain" would be acceptable since this could indicate both prevention and reduction of ocular pain. The statistical reviewer defers the final decision regarding the indication to the clinical review team.

2 INTRODUCTION

2.1 Overview

2.1.1 Drug Class and Indication

ISV-303 is a topical ophthalmic formulation consisting of bromfenac (0.075%), a nonsteroidal anti-inflammatory drug (NSAID), and the applicant's drug delivery system, DuraSite®.

According to the applicant, a cataract is an opacity or clouding of the lens that results in loss of vision, and is considered visually significant when greater than 3 mm and centrally located in the ocular lens. The applicant stated that although the etiology of cataract development is varied, the most frequent factor is the natural aging process. The applicant also mentioned that other etiological factors of cataractogenesis include injury, chronic eye disease and other systemic diseases, such as diabetes. Surgery to remove the opacified lens is the only effective treatment for cataracts. The applicant believed that neither diet, nor medications have been effective in preventing cataract formation. Based on the applicant's research, cataract surgery is the most frequently performed surgical procedure worldwide with over 3 million surgeries performed in the US each year. During cataract surgery the lens is usually replaced with an intraocular lens (IOL) implant.

The applicant stated that cataract surgery is often accompanied by inflammation characterized by redness, swelling, and/or pain associated with irritation or trauma to the eye. According to the applicant, anterior chamber ocular inflammation is clinically assessed as anterior chamber cell (ACC) counts and anterior chamber flare (ACF) following cataract surgery. Thus, the slit lamp is commonly used to assess the degree of inflammation, most often characterized by the presence of white cells and protein in the anterior chamber. However, the applicant believed that postoperative inflammation is frequently viewed as an acceptable risk that is largely outweighed by the numerous benefits of cataract surgery. The applicant also mentioned that topical anti-inflammatory drugs, of different functional classes, such as NSAIDs and/or corticosteroids are used post cataract surgery to mitigate this inflammatory response, and related consequences, such as pain and postsurgical breakdown of the blood-aqueous-barrier, by inhibiting the production of PGs.

2.1.2 History of Drug Development

Diclofenac, ketorolac, bromfenac, and nepafenac are the approved topical NSAIDS for the treatment of inflammation and pain following cataract surgery. The following table summarizes the products containing bromfenac for the treatment of inflammation and/or pain post cataract surgery, by regulatory region, and approved indication.

Table 3: Approved Formulations of Bromfenac by Brand, Region, and Indication

Brand (Manufacture) /Formulation/Posology	Approval Region/Date/NDA Number	Indication
Bronuck® (Senju Pharmaceutical Co., Japan) Bromfenac sodium hydrate ophthalmic solution, 0.1% BID	Japan 2000	Symptomatic treatment of inflammatory disorders of the external eye and the anterior eye (blepharitis, conjunctivitis, scleritis (including episcleritis), postsurgical inflammation).
Xibrom® (ISTA Pharmaceuticals Inc., US) Bromfenac ophthalmic solution 0.09% BID for 2 weeks postsurgery	US 2005; 2006 NDA 021664	Treatment of postoperative inflammation in patients who have undergone cataract extraction. Indication expanded to include reduction of ocular pain in patients who have undergone cataract extraction
Bromday® (Bausch & Lomb, Inc., US) Bromfenac ophthalmic solution, 0.09% QD for 16 days - day before surgery, day of surgery and 14 days after surgery	US 2010 NDA 021664	Treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction
Yellox® (CROMA-PHARMA GmbH, Austria) Yellox 0.9 mg/ml eye drops, solution, Bromfenac BID for 2 weeks postsurgery	Europe 2011	Treatment of postoperative ocular inflammation following cataract extraction in adults.
Prolensa™ (Bausch & Lomb, Inc., US) Bromfenac ophthalmic solution, 0.07% QD for 16 days - day before surgery, day of surgery and 14 days after surgery	USA 2013 NDA 203168	Treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.

BID = twice a day; QD = once a day
Source: Table 2.5-1 of the applicant's clinical overview.

Bromfenac Ophthalmic Solution 0.09% dosed twice per day (BID) was approved in the US by FDA in March, 2005 as Xibrom™ (ISTA Pharmaceuticals, Inc.) for the treatment of postoperative inflammation and later for the reduction of ocular pain in patients who have undergone cataract surgery. The same formulation under the trade name Bromday™ was approved in 2010 for the treatment of postoperative inflammation and the reduction of ocular pain in patients who have undergone cataract surgery for once a day (QD) dosing of 16 days: the day before surgery, the day of surgery, and 14 days after cataract surgery. Prolensa™ (Bromfenac ophthalmic solution, 0.07%; Bausch & Lomb, Inc.) was approved in 2013 for the same indication for QD dosing of 16 days as Bromday™. Additionally, as of August 2014, five generic 0.09% bromfenac ophthalmic formulations have also been approved.

2.1.3 Studies Reviewed

ISV-303 clinical development plan included four clinical studies: one Phase 2 clinical pharmacology study (Study No. C-11-303-002); one Phase 2 efficacy and safety study (Study No. C-10-303-001); and two phase 3 pivotal efficacy and safety studies (Studies C-11-303-003 and C-12-303-004).

C-11-303-002 was a multicenter, double-masked clinical pharmacology study to determine the aqueous humor concentration of bromfenac sodium in subjects administered multiple topical ocular doses of ISV-303 (0.075% bromfenac in DuraSite®) or Bromday™ (0.09% bromfenac) QD prior to cataract surgery. Since this study was conducted mainly for a clinical pharmacology evaluation of a different dosing regimen, the statistical review will not include this study.

C-10-303-001 (also referred to as Study 001 throughout this review) was a multi-center, multiple dose, randomized, vehicle and active controlled to evaluate the ocular safety, tolerability, and efficacy of differing dosing regimens of intraocular ISV-303, administered QD and BID for 14 days, compared to vehicle and Xibrom dosed BID for 14 days post cataract surgery.

Two identical designed phase 3 studies (C-11-303-003 and C-11-303-004) were conducted. Both studies were prospective, multicenter, randomized, double-masked, vehicle-controlled, parallel-group studies to evaluate the ocular safety, tolerability, and efficacy of topical administration of ISV-303 (0.075% bromfenac in DuraSite® ophthalmic solution) compared with DuraSite vehicle when dosed twice daily (BID) for 1 day prior to surgery, the day of surgery, and 14 days after surgery.

This statistical review focused on the two pivotal safety and efficacy studies: Studies C-11-303-003 and C-11-303-004 (also referred to as Study 003 and Study 004 throughout this review); and briefly summarized the primary efficacy results of Study 001 in the Appendix since its dosing schedule was different from the label-proposed dosing schedule. Key information of these three studies is presented in the following table.

Table 4: Key Information for Studies 001, 003, and 004

Study No Phase	Design	Objective	Treatment Groups	Study Population
C-10-303-001 Phase 1/2	Multi-center, randomized, double masked, 4-arm	to compare the ocular safety, tolerability, and efficacy of differing dosing regimens of ISV-303 (0.075% bromfenac in DuraSite) to vehicle and Xibrom in post cataract surgery volunteers	ISV-303 BID: 40 ISV-303 QD: 45 Xibrom BID: 42 Vehicle BID: 42 For 14 days post-surgery	Adult patients who have undergone uncomplicated unilateral cataract surgery
C-11-303-003 Phase 3	Double masked, randomized, multi-center, 2-arm	to compare the ocular safety, tolerability, and efficacy of ISV-303 (0.075% bromfenac in DuraSite) to DuraSite vehicle in cataract surgery subjects	ISV-303 (0.075%): 180 DuraSite Vehicle: 88 BID for 16 days – the day prior to surgery, the day of surgery and 14 days post-surgery	Adult undergoing uncomplicated unilateral cataract surgery
C-11-303-004 Phase 3	Double masked, randomized, multi-center, 2-arm	to compare the ocular safety, tolerability, and efficacy of ISV-303 (0.075% bromfenac in DuraSite) to DuraSite vehicle in cataract surgery subjects	ISV-303 (0.075%): 174 DuraSite Vehicle: 94 BID for 16 days – the day prior to surgery, the day of surgery and 14 days post-surgery	Adult undergoing uncomplicated unilateral cataract surgery

Source: Table 2.7.3.1-1 of Summary of Clinical Efficacy.

2.2 Data Sources

The data sources for this review mainly came from the applicant's study reports for studies 001, 003, and 004. The study reports are available at: \\Cdsesub1\evsprod\NDA206911\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\cat-pain-inflam\5351-stud-rep-contr.

The applicant submitted SAS datasets electronically; the datasets for Study 003 are available at: \\Cdsesub1\evsprod\NDA206911\0000\m5\datasets\c-11-303-003\analysis\legacy\datasets; and for Study 004 are available at: \\Cdsesub1\evsprod\NDA206911\0000\m5\datasets\c-12-303-004\analysis\legacy\datasets.

The SAS program codes that were used to generate the results in the study reports are available at: \\Cdsesub1\evsprod\NDA206911\0000\m5\datasets\c-11-303-003\analysis\legacy\programs and \\Cdsesub1\evsprod\NDA206911\0000\m5\datasets\c-12-303-004\analysis\legacy\programs for Study 003 and Study 004 respectively.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Overall, the submitted data were of good quality with definitions provided for each variable. Results of the primary and key secondary efficacy endpoints can be reproduced by the statistical reviewer with minor data manipulation. The final statistical analysis plans (SAPs) for the two pivotal studies were submitted.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Studies 003 and 004 were two identically designed pivotal studies. Both studies were prospective, multicenter, randomized, double-masked, vehicle-controlled, parallel-group studies to evaluate the ocular safety, tolerability, and efficacy of topical administration of ISV-303 (0.075% bromfenac in DuraSite® ophthalmic solution) compared with DuraSite vehicle when dosed twice daily (BID) for 1 day prior to surgery, the day of surgery, and 14 days after surgery.

For both studies, adult patients scheduled for unilateral cataract surgery (phacoemulsification or extracapsular extraction) with posterior chamber intraocular lens implantation on the day prior to study enrollment were enrolled. Specifically, the protocol-defined key inclusion criteria were:

- Willing to avoid disallowed medication for the duration of the study. Disallowed medications included:

- Topical, systemic, or inhaled salicylates or NSAIDs within 1 week before cataract surgery, except oral doses of aspirin at 165 mg/day or lower
- Any topical, inhaled, or oral corticosteroid within 15 days before cataract surgery and any depot-corticosteroid within 45 days before cataract surgery
- Any concurrent use of ocular or systemic antihistamines, or mast celltabilizers within 1 week before surgery

- A BCVA of at least +1.0 log of the minimum angle of resolution (logMAR [Snellen equivalent of 20/200]) in the fellow eye (non-study eye)
- An IOP of >8 mmHg and ≤22 mmHg in the study eye

The protocol-defined key exclusion criteria were:

- Any history of liver disease within the last 5 years
- History of Fuchs' dystrophy in the study eye
- History of diabetic retinopathy and/or previous vitrectomy in the study eye within the last 2 years
- Any sign of iritis or scleritis in the study eye
- History of glaucoma surgery in the study eye within the last 2 years
- History of epiretinal membrane in the study eye
- Existing diagnosis of severe dry eye in the study eye

Enrolled patients were randomized at Visit 1 (Day -14 to Day -2) in a 2:1 ratio to receive ISV-303 or Vehicle administered one drop in the study eye twice daily (BID) beginning 1 day prior to cataract surgery, the day of surgery, and then continuing for 14 days after surgery. The randomization was stratified by study site. Patients were evaluated for safety and efficacy at Visit 1 (Day -14 to Day -2), Visit 2 (Day 0, the day of surgery), Visit 3 (Day 1 + 1), Visit 4 (Day 8 +1), Visit 5 (Day 15 + 1), and Visit 6 (Day 29 ± 2 days).

Table 5: Schedule of Assessment

Evaluation[a]	**Visit 1** Day -14 to Day -2	**Telephone Call** Day -2	**Visit 2** Day 0	**Visit 3** Day 1 (+1)	**Visit 4** Day 8 (±1)	**Visit 5** Day 15 (+1)	**Visit 6** Day 29 (±2)
Administer informed consent	X						
Record demographics	X						
Review entry criteria	X						
Record medical/ medication history	X						
Administer urine pregnancy test (females only)	X						X
Randomization	X						
Dispense study drug and dosing diary	X						
Dosing reminder call		X					
Surgery			X				
Slit lamp biomicroscopy	X			X	X	X	X
ACC count	X			X	X	X	X

ACF evaluation	X			X	X	X	X
Chemosis	X			X	X	X	X
Bulbar conjunctival injection	X			X	X	X	X
Ciliary injection	X			X	X	X	X
Corneal edema	X			X	X	X	X
Keratic precipitates	X			X	X	X	X
VAS[b]	X			X	X	X	X
Measure IOP	X			X	X	X	X
Measure BCVA	X			X[c]	X	X	X
Ophthalmoscopy	X					X	
Assess AEs	X	X	X	X	X	X	X
Record concomitant medications			X	X	X	X	X
Review dosing diary/pain assessment diary			X	X	X	X	X[d]
Study drug collection and dosing diary						X	X[d]
Exit subject from study							X[d]

ACC = anterior chamber cell; ACF = anterior chamber flare; AE = adverse events; BCVA = best corrected visual acuity; eCRF = electronic Case Report Form; IOP = intraocular pressure; VAS = visual analog scale

[a] All ophthalmic examinations were conducted in the study eye only. The other eye could have been examined at the Investigators' discretion.

[b] Visual Analog Scale (VAS) assessment for pain/discomfort and photophobia

[c] A pinhole test may have been employed at this visit.

[d] If not completed at Visit 5.

Note: Unscheduled visits could have occurred during the study period. All assessments could have been recorded on the eCRF for unscheduled visits, but it was up to the investigator which assessments to conduct. If the subject exited the study at an unscheduled visit, all assessments should have been conducted, including ophthalmoscopy if not obtained at Visit 5.

Source: Table 4 of studies 003 and 004 Reports.

For both studies, the primary endpoint was the proportion of subjects with anterior chamber cell grade of 0 without any rescue therapy by Day 15. Anterior chamber cells was counted and graded according to the following chart:

Table 6: Grading for Anterior Chamber Cell Counts

Anterior Chamber Cells	
Grade[a]	Cell Count
0	0
1	1-10
2	11-20
3	21-50
4	>50

[a] Grade 1 includes cell count 1-5 and cell count 6-10.

Source: Table 5 of Studies 003 and 004 Report.

Rescue therapy was identified by the applicant's clinical team using the following criteria:

- Steroids, NSAIDS, or analgesics for ocular indications were considered. This ruled out systemic indications such as gout, cardiac prophylaxis, headache, etc. It also ruled out medications such as ocular anti-infectives or glaucoma medications. Since oral doses of ≤ 165 mg aspirin per day were allowed, these occurrences were not considered as "rescue."

- Subjects who started these medications during the planned dosing period (16 days, between Day -1 to Day 15) were identified. This ruled out any subject who took a steroid, NSAID, or analgesic after completing the full study drug dosing period.

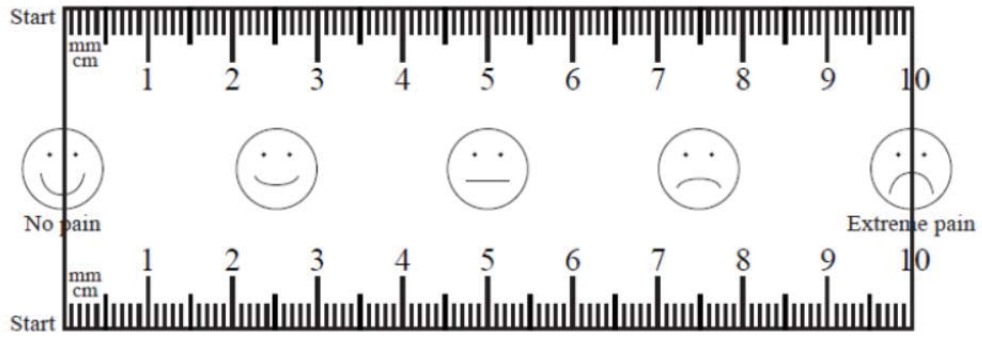
It should be noted that the applicant defined in the study protocol that use of the following medications was prohibited during the study:

- Topical, inhaled, or oral corticosteroids within 15 days before surgery and throughout the duration of the study with the exception of topical corticosteroid administration in the fellow eye, which was allowed after study dosing period (i.e., after Day 15)
- Depot-corticosteroids within 45 days before surgery and throughout the duration of the study
- Topical, systemic, or inhaled NSAIDs (none within 1 week before surgery and throughout the duration of the study, with the exception of aspirin, where oral doses of 165 mg/day or lower were allowed and with the exception of topical NSAID administration in the fellow eye, which was allowed after study dosing period [i.e., after Day 15])
- Ocular or systemic antihistamines or mast cell stabilizers within 1 week before surgery and throughout the dosing period
- Any medication that could have interfered with the study parameters in the opinion of the investigator or sponsor, including pain medication and use of acetaminophen (Tylenol®).

The applicant stated that a prohibited medication could have been administered in an emergency situation if the subject's safety was in jeopardy. If possible, the sponsor was to be consulted prior to administration of the prohibited drug (if not feasible, then as soon as possible afterwards) to determine whether the subject could have continued in the study.

For both studies, the secondary endpoint was the proportion of subjects with a pain grade of 0 without rescue therapy in the study eye at each post-surgical Visual Analog Scale (VAS) assessment time point. Pain/discomfort and photophobia was assessed in the study eye using the VAS according to the time points outlined in the study schedule of assessment table. Subjects were asked to rate their discomfort or pain in the study eye by using a slide on the VAS to align with the images of the descriptive faces (see figure below). The investigator or study staff turned the scale over and recorded the associated measurement (0 mm = absent to 100 mm = maximum).

Figure 1: Visual Analog Scale



In addition, per EU's recommendation (not required by FDA), the applicant also defined an additional secondary efficacy endpoint of the proportion of subjects with an anterior chamber flare (ACF) grade of 0 at Day 15. Based on a single determination, the flare analysis was converted to a grade as defined in Table 7.

Table 7: Grading for Anterior Chamber Flare Evaluation

Grade	Findings
0	None: No haze is detected
1	Mild: A faint haze is detected
2	Moderate: Haze is easy to detect, but iris details are not obscured
3	Marked: Haze is prominent, and iris details are somewhat obscured
4	Severe: Haze is dramatic, and iris details are very obscured and/or the aqueous is fibrinoid or plastic

Source: Table 6 of Study 003 Report.

The sample size estimation of 240 subjects (160 in the ISV-303 arm and 80 in the placebo arm) for both studies was based on the following assumptions proposed by the applicant to support the primary efficacy endpoint:

- Chi-square test at the 0.05 two-sided level of significance.
- The proportion of responders at Day 15 was 0.370 in the Vehicle group.
- The proportion of responders at Day 15 was 0.613 in the ISV-303 group.
- 95% power.

According to the applicant, the above responders' rate for the ISV-303 treatment and placebo groups were derived from a previous study.

3.2.2 Statistical Methodologies

Both studies 003 and 004 intended to demonstrate the superiority of ISV-303 to vehicle based on the proportion of subjects with an ACC grade of 0 at Day 15. The difference between treatment with ISV-303 and Vehicle was tested using the chi-square test. For the primary efficacy analyses, the last observation carried forward (LOCF) was used to impute missing data.

The secondary efficacy endpoint was the proportion of subjects who achieved a pain score of 0 at each postsurgical VAS assessment. The proportion of subjects who achieved a pain score of 0 on the VAS at each postsurgical assessment was calculated for each treatment group. The difference in proportions between the treatment groups was tested using the chi-square test. For the secondary efficacy analyses, the last observation carried forward (LOCF) was used to impute missing data.

The EU-recommended secondary efficacy endpoint of proportion of subjects with an ACF grade of 0 at Day 15 was analyzed as the same fashion as the primary and secondary efficacy endpoint.

To control the overall Type I error rate of testing primary and secondary efficacy endpoints, the following serial gatekeeping procedure was utilized by the applicant in the statistical analysis plan for the US regulatory agency:

- The gatekeeper family F1 consisted of the primary hypothesis (H_{01}: there is no difference between treatment groups in the proportion of subjects who achieved an ACC grade of 0 at Day 15) and the family F2 consisted of the secondary hypothesis (H_{02}: there is no difference between treatment groups in the proportion of subjects who achieved a pain score of 0 at each postsurgical assessment [using VAS]).
- The null hypothesis H_{01} in family F1 was tested at the $\alpha = 0.05$ level. If the H_{01} was accepted, then the testing procedure was to be stopped; otherwise the procedure was to go to the next gate.
- The null hypothesis H_{02} in family F2 was tested at the $\alpha = 0.05$ level.

The applicant also specified the following serial gatekeeping procedure for the EU regulatory agency, who was also interested in the proportion of subjects with an ACF grade of 0 at Day 15. The procedure is included here (b) (4).

A. Define the gatekeeper families.
   The gatekeeper family F1 comprises the primary hypothesis
   H_{01}: there is no difference between treatment groups in the proportion of subjects who achieved an ACC grade of 0 at Day 15.
   The family F2 comprises the secondary hypothesis
   H_{021}: there is no difference in the proportion of subjects with ACF grade of 0 at Day 15 between the ISV-303 and the DuraSite Vehicle groups.
   And the family F3 comprises the secondary hypothesis
   H_{022}: there is no difference in the proportion of subjects who achieve a pain score of 0 at each post-surgical assessment on a VAS between ISV-303 group and DuraSite Vehicle group.
B. Test the null hypothesis H_{01} in family F1 at $\alpha = 0.05$ level. If the H_{01} is accepted, then stop the testing procedure; otherwise go to the next gate C.
C. Test the null hypothesis H_{021} in family F2 at $\alpha = 0.05$ level.
   If the H_{021} is accepted, then stop the testing procedure; otherwise go to the next gate D.
D. Test the null hypothesis H_{022} in family F3 at $\alpha = 0.05$ level.

For both studies, there were three different analysis populations (also known as analysis sets) defined by the applicant:

- **Intent-to-Treat (ITT) analysis set**, which included all randomized patients.
- **Modified Intent-to-Treat (mITT),** which included all subjects who:
  - Were randomized into the trial, and
  - Underwent cataract surgery, and
  - Received at least one dose of study treatment
- **Safety analysis set**, which included all randomized subjects who received at least one dose of study drug.

To assess the sensitivity of the primary analysis result to the LOCF imputations, the first sensitivity analysis of the primary endpoint was performed by the applicant based on worst observation carried forward (WOCF) imputations and the mITT Population following the gatekeeping procedure described above. A second sensitivity analysis of the primary endpoint was performed by the applicant based on the mITT Population and observed cases (OC) (i.e., ACC data with no imputation for missing values).

In addition, in response to a request from FDA statistical reviewers, the applicant added additional sensitivity analyses of the primary and secondary endpoints with missing data imputed by a multiple imputation method. For each treatment group and each single imputation replicate, the following single-imputation procedure was used. First a response parameter θ was selected at random from the predictive posterior Beta distribution for the given treatment group, based on a Jeffries Beta (0.5, 0.5) prior distribution. Then, imputed data for the individual missing values were selected as independent Bernoulli (θ) random variables. The full data set including imputed values was then analyzed by SAS PROC LOGISTIC with a logistic model that included only an effect for treatment group. Parameter estimates from the logistic regression step were analyzed by SAS PROC MIANALYZE to find multiple imputation (MI) estimates of the treatment effect, its standard error, and of the p-value comparing the percent of subjects responding between treatment groups.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Study C-11-303-003

Two hundred and sixty-eight patients were randomized into the study, including 180 in the ISV-303 group and 88 in the Vehicle group. Among these 268 subjects, 14 (12 in the ISV-303 group and 2 in the Vehicle group) did not have cataract surgery; one additional subject (321-009, randomized to Vehicle) who had cataract surgery was withdrawn from the study before receiving any study drug and was not included in the safety population or the mITT Population. Thus, the mITT population included 253 subjects or 94.4% of those randomized (93.3%, [168/180] in the ISV-303 and 96.6%, [85/88] in the Vehicle group) who received at least 1 dose of study drug and had cataract surgery.

The proportions of subjects completing the study (Visit 6, Day 29) differed between groups: 77.2% (139/180) of ISV-303-treated subjects, compared with 37.5% (33/88) of vehicle-treated. Proportionally, many more subjects in the Vehicle group discontinued the study (62.5%, 55/88) compared with subjects in the ISV-303 group (22.8%, 41/180). Most of the subjects discontinuing the study in either group were due to lack of efficacy, and there were more subjects in the Vehicle group, 39.8% (35/88), compared with the ISV-303 group, 8.3% (15/180). The next most frequent reason for study discontinuation was for AEs, and also more frequent in the Vehicle group compared with the ISV-303 group.

Table 8: Study C-11-303-003 Subjects' Disposition

	ISV-303 n (%)	Vehicle n (%)	Overall n (%)
Number of Subjects Randomized	180	88	268
mITT Population[b]	168 (93.3%)	85 (96.6%)[c]	253 (94.4%)
Completed the Study	139 (77.2%)	33 (37.5%)	172 (64.2%)
Discontinued the Study Early	41 (22.8%)	55 (62.5%)	96 (35.8%)
Reasons for Early Discontinuation			
Adverse Event	7 (3.9%)	8 (9.1%)	15 (5.6%)
Investigator decision	2 (1.1%)	1 (1.1%)	3 (1.1%)
Lack of efficacy	15 (8.3%)	35 (39.8%)	50 (18.7%)
Subject withdrew consent	8 (4.4%)	1 (1.1%)	9 (3.4%)
Protocol deviation	5 (2.8%)	7 (8.0%)	12 (4.5%)
Other	4 (2.2%)	3 (3.4%)	7 (2.6%)
Completion by Study Visit			
Visit 1 (Day -14 to Day -2)	180	88	279[a]
Visit 2 (Day 0)	168 (93.3%)	86 (97.7%)	254 (94.8%)
Visit 3 (Day 1)	167 (92.8%)	84 (95.5%)	251 (93.7%)
Visit 4 (Day 8)	159 (88.3%)	59 (67.0%)	218 (81.3%)
Visit 5 (Day 15)	154 (85.6%)	38 (43.2%)	192 (71.6%)
Visit 6 (Day 29)	139 (77.2%)	33 (37.5%)	172 (64.2%)

[a] Eleven of the 279 subjects who were screened were screen failures.
[b] Fourteen subjects did not undergo cataract surgery as planned; 1 of these subjects (Subject 079-004, randomized to ISV-303) received study drug.
[c] One subject (321-009, randomized to Vehicle) had cataract surgery but was withdrawn from the study before receiving any study drug and is not counted in the Safety Population or the mITT Population
Source: Table 9 of Study C-11-303-003 report.

As presented in the following table, except that ISV-303 group had more subjects (21, 12.5%) with green iris color than the vehicle group (1, 1.2%); there were no noted differences in demographic and baseline characteristics between the treatment groups for all the three populations.

Table 9: Study 003 Demographic and Baseline Characteristics (mITT)

Characteristics	ISV-303 (N=168)	Vehicle (N=85)	Total (N=253)
	n (%)	**n (%)**	**n (%)**
Gender			
Male	60 (35.7%)	35 (41.2%)	95 (37.5%)
Female	108 (64.3%)	50 (58.8%)	158 (62.5%)
Age			
Mean (Std)	68.9 (10.1)	68.4 (10.3)	68.7 (10.2)
Min, Max	24, 87	33, 87	24, 87
Median	70.0	69.0	70.0
< 65 Years	47 (28.0)	25 (29.4)	72 (28.5)
≥ 65 Years	121 (70.0)	60 (70.6)	181 (71.5)

Characteristics	ISV-303 (N=168)	Vehicle (N=85)	Total (N=253)
	n (%)	n (%)	n (%)
Race			
White/Caucasian	145 (86.3)	71 (83.5)	216 (85.4)
Black/African American	13 (7.7)	10 (11.8)	23 (9.1)
Asian	9 (5.4)	3 (3.5)	12 (4.7)
American Indian	1 (0.6)	0	1 (0.4)
Native Hawaiian or other Pacific Islander	0	1 (1.2)	1 (0.4)
Ethnicity			
Hispanic or Latino	22 (13.1)	7 (8.2)	29 (11.5)
Non-Hispanic or Latino	146 (86.9)	78 (81.9)	224 (88.5)
Iris Color			
Blue	47 (28.0)	27 (31.8)	74 (29.2)
Brown	79 (47.0)	42 (49.4)	121 (47.8)
Green	21 (12.5)	1 (1.2)	22 (8.7)
Hazel	21 (12.5)	15 (17.6)	36 (14.2)

Source: Tables 11 of Study C-11-303-003 report.

3.2.3.2 Study C-12-303-004

Two hundred and sixty-eight patients were randomized into the study, including 174 to the ISV-303 group and 94 to the Vehicle group. Among these patients, 15 (6 in the ISV-303 group and 9 in the Vehicle group) did not have cataract surgery, thus the mITT population included 253 subjects or 94.4% of those randomized (96.6%, [168/174] in the ISV-303 and 90.4%, [85/94] in the Vehicle group) who received at least 1 dose of study drug and had cataract surgery.

Of 268 randomized subjects, 69.0% (185/268)) completed the study; more ISV-303-treated subjects completed, 78.7% (137/174), compared to vehicle-treated subjects, 51.1% (48/94). The majority of subjects (~ 80% or more), completed through Day 8 of the study, overall and within each treatment group. The proportions of subjects completing the subsequent study visits (Day 15 and Day 29) were lower in the vehicle-treated subjects (55.3% and 51.1%, respectively) compared with ISV-303-treated subjects (87.9% and 79.9%, respectively). More subjects in the Vehicle group, 48.9% (46/94), discontinued the study early compared with the ISV-303 group, 21.3% (37/174). The primary reason for early discontinuation in the Vehicle group was lack of efficacy, reported in 30.9% (29/94) subjects, much higher than reported for the ISV-303 group, 4.0% (7/174).

Table 10: Study 004 Subjects' Disposition

	ISV-303 n (%)	Vehicle n (%)	Overall n (%)
Number of Subjects Randomized	174	94	268[a]
mITT Population[b]	168 (96.6%)[b]	85 (90.4%)[c]	253 (94.4%)[b]

Completed the Study	137 (78.7%)[c]	48 (51.1%)	185 (69.0%)[c]
Discontinued the Study Early	37 (21.3%)	46 (48.9%)	83 (31.0%)
Reasons for Early Discontinuation			
Adverse Event	12 (6.9%)	2 (2.1%)	14 (5.2%)
Investigator decision	5 (2.9%)	0 (0.0%)	5 (1.9%)
Lack of efficacy	7 (4.0%)	29 (30.9%)	36 (13.4%)
Subject withdrew consent	5 (2.9%)	8 (8.5%)	13 (4.9%)
Protocol deviation	5 (2.9%)	4 (4.3%)	9 (3.4%)
Lost to follow-up	1 (0.6)	0 (0.0)	1 (0.4)
Other	4 (2.2%)	3 (3.4%)	7 (2.6%)
Completion by Study Visit			
Visit 1 (Day -14 to Day -2)	174	94	277
Visit 2 (Day 0)	168 (96.6%)	85 (90.4%)	253 (94.4%)
Visit 3 (Day 1)	165 (94.8%)	85 (90.4%)	250 (93.3%)
Visit 4 (Day 8)	159 (91.4%)	75 (79.8%)	234 (87.3%)
Visit 5 (Day 15)	153 (87.9%)	52 (55.3%)	205 (76.5%)
Visit 6 (Day 29)	139 (79.9%)[c]	48 (51.1%)	187 (69.8%)[c]

[a] Nine subjects were screen failures.
[b] Fifteen subject did not undergo cataract surgery as planned; 3 of these subjects (Subjects 264-010, 264-012, and 159-022, all randomized to the ISV-303 group), received study drug prior to study withdrawal. The first 2 subjects were included in the Safety Population but not the mITT Population. Subject 159-022 was not included in either the mITT or Safety Populations.
[c] Two subjects in the ISV-303 group discontinued the same day as Day 29 (Visit 6): Subjects 314-04 and 314-010.
Source: Tables 9 of Study C-12-303-004 report.

As presented in the following table, there were no marked differences in demographic and baseline characteristics between the treatment groups for all the three populations.

Table 11: Study 004 Demographic and Baseline Characteristics (ITT)

Characteristics	**ISV-303 (N=168)**	**Vehicle (N=85)**	**Total (N=253)**
	n (%)	**n (%)**	**n (%)**
Gender			
Male	63 (37.5)	37 (43.5)	100 (39.5)
Female	105 (62.5)	48 (56.5)	153 (60.5)
Age			
Mean (Std)	69.6 (8.9)	72.0 (9.1)	70.4 (9.0)
Min, Max	47, 91	45, 89	45, 91
Median	69.0	72.0	70.0
< 65 Years	44 (26.2)	16 (18.8)	60 (23.7)
≥ 65 Years	124 (73.8)	69 (81.2)	193 (76.3)
Race			
White/Caucasian	129 (76.8)	70 (82.4)	199 (78.7)
Black/African American	28 (16.7)	10 (11.8)	38 (15.0)
Asian	8 (4.8)	3 (3.5)	11 (4.3)
Other	3 (1.8)	2 (2.4)	9 (1.6)
Ethnicity			

Characteristics	ISV-303 (N=168)	Vehicle (N=85)	Total (N=253)
	n (%)	n (%)	n (%)
Hispanic or Latino	22 (13.1)	7 (8.2)	29 (11.5)
Non-Hispanic or Latino	146 (86.9)	78 (81.9)	224 (88.5)
Iris Color			
Blue	50 (29.8)	25 (29.4)	75 (29.6)
Brown	80 (47.6)	39 (45.9)	119 (47.0)
Green	11 (6.5)	4 (4.7)	15 (5.9)
Hazel	25 (14.9)	17 (20.0)	42 (16.6)
Grey	2 (1.2)	0	2 (0.8)

Source: Tables 11 of Study C-12-303-004 report.

3.2.4 Results and Conclusions

3.2.4.1 Anterior Chamber Cell (ACC)

For both studies, the applicant defined primary endpoint was the proportion of subjects with anterior chamber cell (ACC) grade of 0 without rescue therapy by Day 15.

For Study 003, at Day 1 (first day post-surgery) visit, the proportion of patients with ACC grade of 0 was similar between the ISV-303 group and the Vehicle group. By Day 8 visit, there were more subjects in ISV-303 group had ACC grade of 0 compared to Vehicle group. At Day 15 visit, for the mITT population, 57.1% (96/168) of the patients in the ISV-303 group had an ACC grade of 0 compared with 18.8% (16/85) of the patients in the Vehicle group; the treatment difference 38.3% was statistically significant ($p<0.001$) with a 95% CI of (27.1%, 49.5%).

For Study 004, similar trends in the proportion of patients with ACC grade of 0 for Day 1 and Day 8 visits as in Study 003 were observed. However, at the Day 15 visit, the response rate for ISV-303 group was lower than in Study 003; for the mITT population, 38.1% (64/168) of the patients in the ISV-303 group had an ACC grade of 0 compared with 22.4% (19/85) of the patients in the Vehicle group; the treatment difference 15.7% was statistically significant ($p=0.035$) with a 95% CI of (4.2%, 27.3%).

Table 12: Proportion of Subjects with ACC Grade of 0 Without Rescue Therapy over Time for Studies 003 and 004 (mITT, LOCF)

	Study 003			Study 004		
Visit	ISV-303 (N=168)	Vehicle (N=85)	ISV-303 vs. Vehicle Difference (95% CI)[a]	ISV-303 (N=168)	Vehicle (N=85)	ISV-303 vs. Vehicle Difference (95% CI)[a]
Day 1	3 (1.8%)	2 (2.4%)	-0.6% (-4.4%, 3.2%)	5 (3.0%)	1 (1.2%)	1.8% (-1.6%, 5.2%)
Day 8	54 (32.1%)	7 (8.2%)	23.9% (14.7%, 33.1%)	40 (23.8%)	8 (9.4%)	14.4% (5.5%, 23.3%)
Day 15	**96 (57.1%)**	**16 (18.8%)**	**38.3% (27.1%, 49.5%)**	**64 (38.1%)**	**19 (22.4%)**	**15.7% (4.2%, 27.3%)**
Day 29	108 (64.3%)	23 (27.1%)	37.2% (25.3%, 49.1%)	95 (56.5%)	36 (42.4%)	14.2% (1.3%, 27.1%)

[a] 95% CI were calculated by the statistical reviewer and based on normal approximation to binomial data.
Source: Table 14.2.1.1 of Study C-11-303-003 report and Table 14.2.1.1 of Study C-12-303-004 report.

For the analysis of the primary efficacy endpoint, the outcome of ACC grade at Day 15 was imputed using the last observation carried forward (LOCF) method for any patient who had missing values. In Study 003, for the mITT population, 17.3% (29/168) subjects in the ISV-303 group had their ACC grade imputed at Day 15 visit; and 61.2% (52/85) subjects in the Vehicle group had their ACC scores imputed at Day 15 visit. In Study 004, the rates of subjects who had ACC grade missing on Day 15 visit were 18.5% (31/168) and 43.5% (37/85) for ISV-303 and Vehicle respectively (Table 13).

For majority of these patients, the reason for missing ACC scores was lack of efficacy. In Study 003, the percentages of subjects who had ACC scores missing due to lack of efficacy were 8.9% (15/168) for the ISV-303 group and 67.3% (35/52) in the Vehicle group; in Study 004, these percentages were 22.6% (7/31) and 78.4% (29/37) for ISV-303 and Vehicle respectively (Table 13). Therefore imputing "failure" for lack of efficacy patients with missing data was considered by the statistical reviewer as appropriate.

Among subjects who has missing ACC scores due to AE:

- In Study 003, one subject in ISV-303 group had a "success" outcome at Day 15 visit due to LOCF imputation. For the rest of the 14 subjects who had missing ACC scores due to AE, their missing outcome at Day 15 visit were imputed as "failure" due to LOCF imputation.
- In Study 004, one subject in ISV-303 group and one subject in Vehicle group had "success" outcome at Day 15 visit due to LOCF imputation. For the rest of the 12 subjects who had missing ACC scores due to AE, their missing outcome at Day 15 visit were imputed as "failure" due to LOCF imputation.

As part of sensitivity analyses, for subjects who had missing scores of ACC for reasons other than treatment failure (adverse events, protocol violation, etc.), additional analyses were performed by the statistical reviewer where ISV-303-treated patients with missing data had their ACC outcomes imputed as failures at Day 15 and Vehicle-treated patients with missing data had their ACC outcomes imputed as successes at Day 15 (this could be considered as a worst case scenario analysis). The results of this analysis were consistent with the primary analysis results (Table 14). Additional sensitivity analyses conducted by the applicant based on observed data only were also supportive of the primary efficacy results (Table 14).

Table 13: Reasons for Having Missing ACC Scores (mITT)

	Study 003		Study 004	
	ISV-303 (N=168)	**Vehicle (N=85)**	**ISV-303 (N=168)**	**Vehicle (N=85)**
Number of Subjects Who Had Missing ACC Scores at Day 15 Visit	29 (17.3%)	52 (61.2%)	31 (18.5%)	37 (43.5%)
Lack of Efficacy	15 (8.9%)	35 (41.2%)	7 (4.2%)	29 (34.1%)
Adverse Event	7 (4.2%)	8 (9.4%)	12 (7.1%)	2 (2.4%)
Protocol Violation	2 (1.2%)	7 (8.2%)	5 (3.0%)	3 (3.5%)
Physician Decision	2 (1.2%)	1 (1.2%)	5 (3.0%)	0
Other	3 (1.8%)	1 (1.2%)	2 (1.2%)	3 (3.5%)

Source: Statistical reviewer's calculation.

Table 14: Sensitivity Analyses of Proportion of Subjects with ACC Grade of 0 for Studies 003 and 004 (mITT)

	Study 003			Study 004		
	ISV-303	Vehicle	ISV-303 vs. Vehicle Difference (95% CI)[a]	ISV-303	Vehicle	ISV-303 vs. Vehicle Difference (95% CI)[a]
Worst Case	54.8% (92/168)	36.5% (31/85)	18.3% (5.6%, 31.0%)	35.1% (59/168)	28.2% (24/85)	6.9% (-5.1%, 18.9%)
Observed Only	61.7% (95/154)	34.1% (14/41)	27.5% (11.1%, 44.0%)	40.5% (62/153)	30.9 (17/55)	9.6% (4.9%, 24.1%)

[a] 95% CI were calculated by the statistical reviewer and based on normal approximation to binomial data.
Source: Statistical reviewer's calculation.

In conclusion, ISV-303 was superior to Vehicle in regard to the percentage of patients who achieved ACC score of 0 at post-surgical Day 15.

3.2.4.2 VAS Pain Assessment

Pain/discomfort and photophobia was assessed in the study eye using the Visual Analog Scale (VAS) on Study Visit Day 1, Day 8, Day 15, and Day 29. Subjects were asked to rate their discomfort or pain in the study eye by using a slide on the VAS to align with the images of the descriptive faces (see the figure below). The investigator or study staff turned the scale over and recorded the associated measurement (0 mm = absent to 100 mm = maximum, as shown below.).

For both studies 003 and 004, the majority of ISV-303-treated subjects (~80%) had no VAS assessed pain (VAS pain score of 0) starting from post-surgery Day 1 and until the end of study on Day 29; and these proportions were statistically significantly greater compared with vehicle for all the post-surgical visits.

Table 15: Proportion of Subjects Who Achieved a Pain Score of 0 at Each Postsurgical VAS Assessment without Using of Rescue Therapy (mITT, LOCF)

	Study 003			Study 004		
Visit	ISV-303 (N=168)	Vehicle (N=85)	ISV-303 vs. Vehicle Difference (95% CI)[a]	ISV-303 (N=168)	Vehicle (N=85)	ISV-303 vs. Vehicle Difference (95% CI)[a]
Day 1	129 (76.8%)	41 (48.2%)	28.6 (16.2%, 40.9%)	138 (82.1%)	53 (62.4%)	19.8 (8.0%, 31.6%)
Day 8	152 (90.5%)	33 (38.8%)	51.7 (40.4%, 62.9%)	145 (86.3%)	43 (50.6%)	35.7 (23.9%, 47.6%)
Day 15	156 (92.9%)	36 (42.4%)	50.5 (39.3%, 61.7%)	146 (86.9%)	49 (57.6%)	29.3 (17.6%, 40.9%)
Day 29	143 (85.1%)	40 (47.1%)	38.1 (26.2%, 50.0%)	140 (83.3%)	51 (60.0%)	23.3 (11.5%, 35.2%)

[a] 95% CI were calculated by the statistical reviewer and based on normal approximation to binomial data.
Source: Table 17 of Study 003 Report and Table 17 of Study 004 Report.

Similar to the primary efficacy analysis, for the majority of patients with missing VAS missing assessment, the reason for not completing the study was treatment failure; therefore imputing "failure" for these treatment failure patients with missing data was considered by the statistical reviewer as appropriate. For the subjects who had missing scores of VAS assessment for reasons other than treatment failure (adverse events, lost to follow-up, etc.), additional sensitivity analyses were performed by the statistical reviewer using the same worst case scenario analysis

as the primary efficacy endpoint. The results of this analysis were consistent with the applicant's analysis results presented in the above table.

Additional sensitivity analyses conducted by the applicant based on observed data only were also supportive of the results presented in the above table.

Furthermore, the applicant also analyzed the mean VAS pain scores by study visits; and the results (see **Table 16**) were supportive of the results presents in **Table 15** as well.

In conclusion, ISV-303 was superior to Vehicle in regard to the percentage of patients who achieved pain score of 0 at each post-surgical VAS assessment.

Table 16: Mean VAS Pain Scores by Study Visits (mITT, LOCF)

	Study 003			Study 004		
Visit	ISV-303 (N=168) Mean (SD) mm	Vehicle (N=85) Mean (SD) mm	ISV-303 vs. Vehicle Difference (95% CI)[a]	ISV-303 (N=168) Mean (SD) mm	Vehicle (N=85) Mean (SD) mm	ISV-303 vs. Vehicle Difference (95% CI)[a]
Day 1	4.3 (11.5)	15.4 (21.8)	-11.1 (-16.1, -6.1)	4.3 (12.4)	10.1 (17.6)	-5.9 (-10.1, -1.7)
Day 8	2.2 (9.1)	18.1 (24.6)	-16.0 (-21.5, -10.5)	2.9 (11.0)	9.2 (20.1)	-6.3 (-11.0, -1.7)
Day 15	1.9 (9.5)	16.9 (24.2)	-15.0 (-20.4, -9.6)	2.3 (8.8)	6.8 (17.4)	-4.5 (-8.5, -0.5)
Day 29	3.4 (11.9)	16.1 (24.4)	-12.7 (-18.3, -7.2)	4.1 (13.9)	6.8 (18.2)	-2.6 (-7.0, 1.9)

[a] 95% CIs were calculated by the statistical reviewer.
Source: Table 17 of Study 003 Report and Table 17 of Study 004 Report.

3.2.4.3 Rescue Medications

The applicant also summarized and compared the proportion of subjects who received rescue medications. According to the applicant, subjects who started rescue medications during the planned dosing period (16 days, between Day -1 to Day 15) were identified. For both Studies 003 and 004, the proportion of ISV-303-treated subjects who received rescue medications was less than for vehicle-treated subjects: 4.8% (8/168) versus 36.5% (31/85) in Study 003; and 4.8% (8/168), versus 32.9% (28/85) in Study 004 (**Table 17**). These results were supportive of the primary and secondary efficacy results as well. All these subjects who received rescue medications were considered as treatment failures for the primary and secondary efficacy endpoints analyses.

A detailed summary of the reasons for using rescue medications by the statistical reviewer showed that ocular inflammation was the primary reason that subjects received rescue medications (3.0% (5/168) for ISV-303 versus 24.7% (21/85) for Vehicle in Study 003; and 4.8% (8/168) for ISV-303 versus 29.4% (25/85) for Vehicle in Study 004, **Table 18**). The majority of the subjects received both a topical steroid and a topical NSAID simultaneously as rescue medications: 1.8% (3/168) for ISV-303 versus 24.7% (21/85) for Vehicle in Study 003; and 4.2% (7/168) for ISV-303 versus 22.4% (19/85) for Vehicle in Study 004.

Table 17: Proportion of Subjects Who Received Rescue Therapy for Studies 003 and 004 (mITT)

	Study 003			Study 004		
Received Rescue Medication	**ISV-303 (N=168)**	**Vehicle (N=85)**	**ISV-303 vs. Vehicle Difference (95% CI)[a]**	**ISV-303 (N=168)**	**Vehicle (N=85)**	**ISV-303 vs. Vehicle Difference (95% CI)[a]**
Yes	8 (4.8%)	31 (36.5%)	-31.7% (-42.4%, -21.0%)	8 (4.8%)	28 (32.9%)	-28.2% (-38.7%, -17.7%)

[a] 95% CI were calculated by the statistical reviewer and based on normal approximation to binomial data.
Source: Table 14 and Listing 16.2.3.1 of Study 003 Report and Table 14 and Listing 16.2.3.1 of Study 004 Report.

Table 18: Reasons for Receiving Rescue Therapy for Studies 003 and 004 (mITT)

	Study 003		Study 004	
	ISV-303 (N=168)	**Vehicle (N=85)**	**ISV-303 (N=168)**	**Vehicle (N=85)**
Reasons				
Double Vision	1	0	0	0
Hyperemia	1	1	0	0
Ocular Inflammation	5	21	8	25
Uveitis	1	0	0	0
Ocular Pain	0	3	0	1
Endophthalmitis	0	1	0	0
Iritis	0	5	0	1
Increase in Ciliary Injection	0	0	0	1

Source: Statistical Reviewer's Summarization Based on Listing 16.2.3.1 of Study 003 Report and Listing 16.2.3.1 of Study 004 Report.

Table 19: Summary of Rescue Therapy Received for Studies 003 and 004 (mITT)

	Study 003		Study 004	
Medications	**ISV-303* (N=168)**	**Vehicle* (N=85)**	**ISV-303* (N=168)**	**Vehicle* (N=85)**
Topical NSAIDS				
Bromfenac	1	6	1	1
Diclofenac	0	1	2	9
Ketorolac	1	7	4	8
Nevanac	1	7	0	1
Topical Steroids				
Difluprednate	3	10	1	2
Prednisolone	5	20	7	26
Oral Anti-Inflammatory Medications				
Acetaminophen	0	2	n/a	n/a

* Majority of the subjects received both a topical steroid and a topical NSIAD simultaneously as rescue medications.
Source: Statistical Reviewer's Summarization Based on Listing 16.2.3.1 of Study 003 Report and Listing 16.2.3.1 of Study 004 Report.

3.2.4.4 Anterior Chamber Flare (ACF)

Per the EU's recommendation, the applicant included another secondary efficacy endpoint of proportion of subjects with an ACF grade of 0 at Day 15 as part of their EU regulatory application. This endpoint was analyzed as the same fashion as the primary and secondary

efficacy endpoint. Based on these results, ISV-303 was superior to Vehicle in regard to the percentage of patients who achieved ACF score of 0 at post-surgical Day 15.

Table 20: Proportion of Subjects with ACF Grade of 0 over Time for Studies 003 and 004 (mITT, LOCF)

	Study 003			Study 004		
Visit	**ISV-303 (N=168)**	**Vehicle (N=85)**	**ISV-303 vs. Vehicle Difference (95% CI)[a]**	**ISV-303 (N=168)**	**Vehicle (N=85)**	**ISV-303 vs. Vehicle Difference (95% CI)[a]**
Day 1	38 (22.6)	22 (25.9)	-3.3% (-14.5%, 8.0%)	64 (38.1%)	33 (38.8%)	-0.7% (-13.4%, 12.0%)
Day 8	111 (66.1%)	19 (22.4%)	43.7% (32.2%, 55.1%)	110 (65.5%)	30 (35.3%)	30.2% (17.7%, 42.6%)
Day 15	**135 (80.4%)**	**30 (35.3%)**	**45.1% (33.3%, 56.9%)**	**147 (87.5%)**	**45 (52.9%)**	**34.6% (22.8%, 46.3%)**
Day 29	142 (84.5%)	34 (40.0%)	44.5% (32.8%, 56.3%)	144 (85.7%)	50 (58.8%)	26.9% (15.2%, 38.6%)

[a] 95% CI were calculated by the statistical reviewer and based on normal approximation to binomial data.
Source: Table 14.2.2.1 of Study C-11-303-003 report and Table 14.2.2.1 of Study C-12-303-004 report.

Since the proportion of subjects with both ACC Grade of 0 and ACF Grade of 0 was used as the primary efficacy endpoint for PROLENSA™, the statistical reviewer analyzed the proportion of subjects with both ACC Grade of 0 and ACF Grade of 0 without rescue therapy to further investigate the treatment effect of ISV-303, the results demonstrated that ISV-303 was superior to Vehicle as well. In addition, the treatment differences in terms of this proportion were consistent across the two pivotal studies at all post-surgery study visits (Table 21).

Table 21: Proportion of Subjects with Both ACC and ACF Grade of 0 without Rescue Therapy over Time for Studies 003 and 004 (mITT, LOCF)

	Study 003			Study 004		
Visit	**ISV-303 (N=168)**	**Vehicle (N=85)**	**ISV-303 vs. Vehicle Difference (95% CI)[a]**	**ISV-303 (N=168)**	**Vehicle (N=85)**	**ISV-303 vs. Vehicle Difference (95% CI)[a]**
Day 1	5 (3.0%)	1 (1.2%)	1.8% (-5.2%, 1.6%)	3 (1.8%)	1 (1.2%)	0.6% (-2.4%, 3.7%)
Day 8	40 (23.8%)	8 (9.4%)	14.4% (5.5%, 23.3%)	37 (22.0%)	7 (8.2%)	13.8% (5.2%, 22.4%)
Day 15	64 (38.1%)	19 (22.4%)	15.7% (4.2%, 27.3%)	48 (28.6%)	10 (11.8%)	16.8% (7.1%, 26.5%)
Day 29	95 (56.6%)	36 (42.4%)	14.2% (1.3%, 27.1%)	93 (55.4%)	32 (37.7%)	17.7% (5.0%, 30.5%)

[a] 95% CIs were based on normal approximation to binomial data.
Source: Statistical Reviewer's Analysis.


(b) (4)

3.3 Evaluation of Safety

For Study 003, all 254 subjects who were exposed to the study treatment were included in the safety analysis set. For Study 004, 255 subjects were exposed to study drug; however, the dosing diary data indicated that 251 subjects were exposed to study drug, since there were 4 subjects (Subjects 092-027, 321-014, 321-025, and 321-032) who either did not return or did not complete their dosing diaries at the end of study, thus were not included in the exposure summary statistics. The following tables present the treatment-emergent adverse events for both studies.

Table 22: Summary of Treatment-Emergent Adverse Events of Studies 003 and 004 (Safety Analysis Set)

	Study 003		Study 004	
	ISV-303 (N=169)	**Vehicle (N=85)**	**ISV-303 (N=170)**	**Vehicle (N=85)**
Patients discontinued due to an adverse event	**7 (4.1%)**	**13 (15.2%)**	**12 (7.1%)**	**4 (4.7%)**
Discontinued due to nonfatal serious adverse events	0	1 (1.2%)	0	0
Discontinued due to nonserious adverse events	7 (4.1%)	12 (14.1%)	12 (7.1%)	4 (4.7%)
Treatment-related	4 (2.4%)	9 (10.6%)	1 (0.6%)	1 (1.2%)
Not related to treatment	3 (1.8%)	3 (3.5%)	11 (6.5%)	3 (3.5%)
Patients with at least 1 treatment-emergent adverse event (related and not related combined)	**52 (30.8%)**	**37 (43.5%)**	**49 (28.8%)**	**25 (29.4%)**
Most frequent treatment-emergent adverse events (reported by 1% or more of the patients in either Treatment group)				
Eye Disorders				
Anterior Chamber Inflammation	0	0	5 (2.9%)	3 (3.5%)
Conjunctival Haemorrhage	0	0	3 (1.8%)	0
Conjunctival Hyperaemia	0	1 (1.2%)	0	1 (1.2%)
Corneal Disorder	0	0	0	1 (1.2%)
Corneal Oedema	2 (1.2%)	0	1 (0.6%)	1 (1.2%)
Corneal Opacity	0	1 (1.2%)	4 (2.4%)	2 (2.4%)
Corneal Striae	0	1 (1.2%)	4 (2.4%)	2 (2.4%)
Cystoid Macular Oedema	1 (0.6%)	1 (1.2%)	1 (0.6%)	1 (1.2%)
Dry Eye	1 (0.6%)	0	0	1 (1.2%)
Eye Inflammation	0	2 (2.4%)	0	0
Eye Irritation	0	0	1 (0.6%)	1 (1.2%)
Eye Pain	8 (4.7%)	11 (12.9%)	4 (2.4%)	2 (2.4%)
Eyelid Ptosis	0	0	0	1 (1.2%)
Foreign Body Sensation in Eyes	3 (1.8%)	1 (1.2%)	0	1 (1.2%)
Iritis	3 (1.8%)	5 (5.9%)	5 (2.9%)	2 (2.4%)
Lacrimation Increased	1 (0.6%)	1 (1.2%)		
Ocular Discomfort	2 (1.2%)	3 (3.5%)		
Ocular Hyperaemia	0	1 (1.2%)	1 (0.6%)	1 (1.2%)
Ocular Hypertension	***16 (9.5%)***	***3 (3.5%)***	***17 (10.0%)***	***5 (5.9%)***
Photophobia	1 (0.6%)	4 (4.7%)	1 (0.6%)	0
Punctate keratitis	0	0	3 (1.8%)	1 (1.2%)
Retinal Haemorrhage	0	1 (1.2%)	1 (0.6%)	0
Vision blurred	0	0	1 (0.6%)	1 (1.2%)
Visual acuity reduced	0	0	0	1 (1.2%)
Vitreous detachment	0	0	0	1 (1.2%)
Vitreous floaters	4 (2.4%)	0	2 (1.2%)	0
Gastrointestinal Disorders				
Colitis	0	0	0	1 (1.2%)
Dyspepsia	0	0	0	1 (1.2%)
General Disorders and Administration Site Conditions				
Instillation Site Pain	2 (1.2%)	1 (1.2%)	0	0
Pain	0	1 (1.2%)	0	1 (1.2%)

Infections and Infestations				
Bronchitis	0	1 (1.2%)	0	0
Endophthalmitis	0	1 (1.2%)	0	0
Sepsis	0	0	0	1 (1.2%)
Upper Respiratory Tract Infection	1 (0.6%)	1 (1.2%)	0	0
Urinary Tract Infection	0	0	0	1 (1.2%)
Injury, Poisoning and Procedural Complications				
Incision Site Complication	0	1 (1.2%)	0	0
Foreign body in eye	0	0	3 (1.8%)	1 (1.2%)
Posterior capsule opacification	0	0	2 (1.2%)	1 (1.2%)
Metabolism and Nutrition Disorders				
Dehydration	0	0	0	1 (1.2%)
Gout	0	1 (1.2%)	0	0
Hyperkalaemia	0	0	1 (0.6%)	1 (1.2%)
Neoplasms Benign, Malignant and Unspecified				
Blepharal papilloma	0	0	0	1 (1.2%)
Nervous System Disorders				
Dizziness	0	0	2 (1.2%)	0
Headache	4 (2.4%)	5 (5.9%)	1 (0.6%)	0
Migraine with aura	0	0	0	1 (1.2%)
Renal and Urinary Disorders				
Renal Failure Acute	0	0	0	1 (1.2%)
Vascular Disorder				
Hyperaemia	1 (0.6%)	3 (3.5%)	0	0
Hypertension	2 (1.2%)	0	0	0

Source: Table 14.3.1.2 of Study 003 report and Table 14.3.1.2 of Study 004 report.

For both studies 003 and 004, there were more subjects that had ocular hypertension as treatment-emergent adverse events in the ISV-303-treated group (9.5% [16/168] in Study 003, and 10% [17/168] in Study 004) than in the Vehicle-treated group (3.5% [3/85] in Study 003, and 5.9% [5/85] in Study 004). A clinically significant increase in IOP was defined by the applicant as a $\geqslant$ 10 mmHg increase from baseline (or any proceeding visit) or an IOP of > 22 mmHg at any time point. The applicant summarized the number of subjects who had an increase in IOP of $\geqslant$ 10 mmHg from baseline (or any proceeding visit), who had an IOP of > 22 mmHg separately by treatment groups and study visits (Table 23). Based on this detailed summary by study visits, the applicant concluded that the greatest proportion of subjects with clinically notable changes in IOP occurred at Day 1 and diminished at subsequent study visits. The statistical reviewer concurred with this conclusion; however, the statistical reviewer would like to defer to the clinical review team regarding the clinical significance of more subjects in the ISV-303-treated group having sudden increase in IOP on the first day post-surgery.

Table 23: Percentage of Subjects with Significant IOP Changes by Study Visit (Study Eye, Safety Population)

		Study 003		Study 004	
Visit	**IOP Change**	**ISV-303 N=169**	**Vehicle N=85**	**ISV-303 (N=168)**	**Vehicle N=85**
Day 1	n	167	84	166	85
	IOP Change $\geqslant$ 10 mmHg from Baseline	13 (7.8%)	3 (3.6%)	12 (7.2%)	2 (2.4%)
	IOP Change $\geqslant$ 10 mmHg from any preceding post-treatment visit	1 (0.6%)	0	0	0
	IOP > 22 mmHg at visit	17 (10.2%)	4 (4.8)	20 (12.0%)	5 (5.9%)
Day 8	n	161	76	161	81

	IOP Change ⩾ 10 mmHg from Baseline	0	0	3 (1.9%)	0
	IOP Change ⩾ 10 mmHg from any preceding post-treatment visit	0	0	2 (1.2%)	2 (2.5%)
	IOP > 22 mmHg at visit	2 (1.2%)	1 (1.3%)	4 (2.5%)	1 (1.2%)
Day 15	n	155	43	154	55
	IOP Change ⩾ 10 mmHg from Baseline	0	0	1 (0.6%)	0
	IOP Change ⩾ 10 mmHg from any preceding post-treatment visit	1 (0.6%)	0	1 (0.6%)	0
	IOP > 22 mmHg at visit	0	0	3 (1.9%)	0
Day 28	n	144	34	146	50
	IOP Change ⩾ 10 mmHg from Baseline	0	0	0	0
	IOP Change ⩾ 10 mmHg from any preceding post-treatment visit	0	0	1 (0.7%)	0
	IOP > 22 mmHg at visit	0	0	2 (1.4%)	0

Source: Table 30 of Study 003 report and Table 31 of Study 004 report.

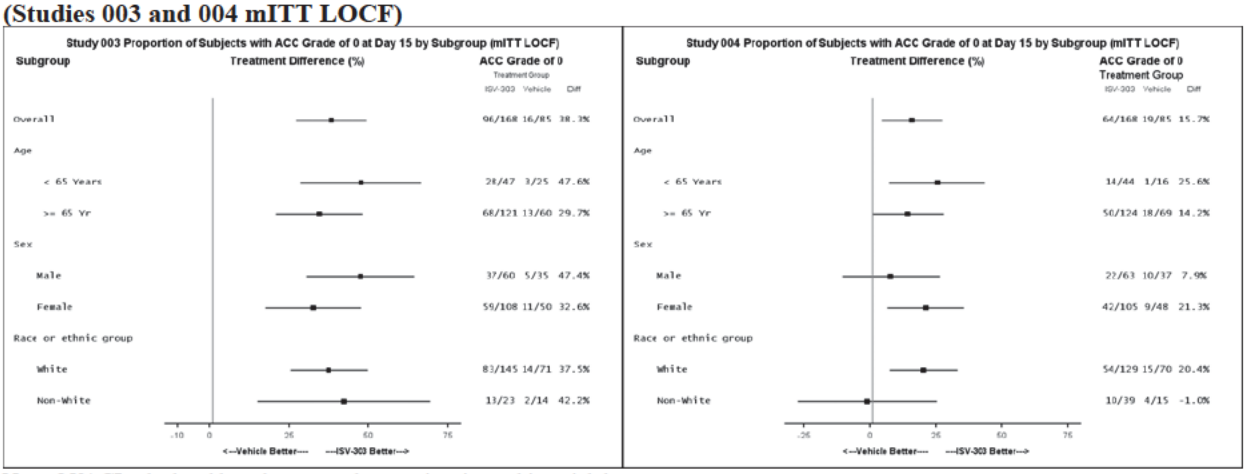
Other than ocular hypertension, overall, ISV-303 had similar adverse events rates as Vehicle-treated groups. Please see the review of the medical reviewer for details of the safety evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, Baseline Otowick Use, and Duration of Current Episode

Subgroup analyses based on gender, race, and age were performed. In Study 004, Vehicle had slightly higher proportion of subjects with ACC score of 0 at Day 15 compared to ISV-303 in non-white subjects. Other than this sub-group in Study 004, in general, there were no marked differences in the efficacy results among the various subpopulations.

Figure 2: Forest Plots of Subgroup Analyses for Proportion of Subjects with ACC Grades of 0 at Day 15 (Studies 003 and 004 mITT LOCF)



Note: 95% CI calculated based on normal approximation to binomial data.
Source: Statistical reviewer's analyses

Figure 3: Forest Plots of Subgroup Analyses for Proportion of Subjects with No Pain at Day 1 (Studies 003 and 004 mITT LOCF)

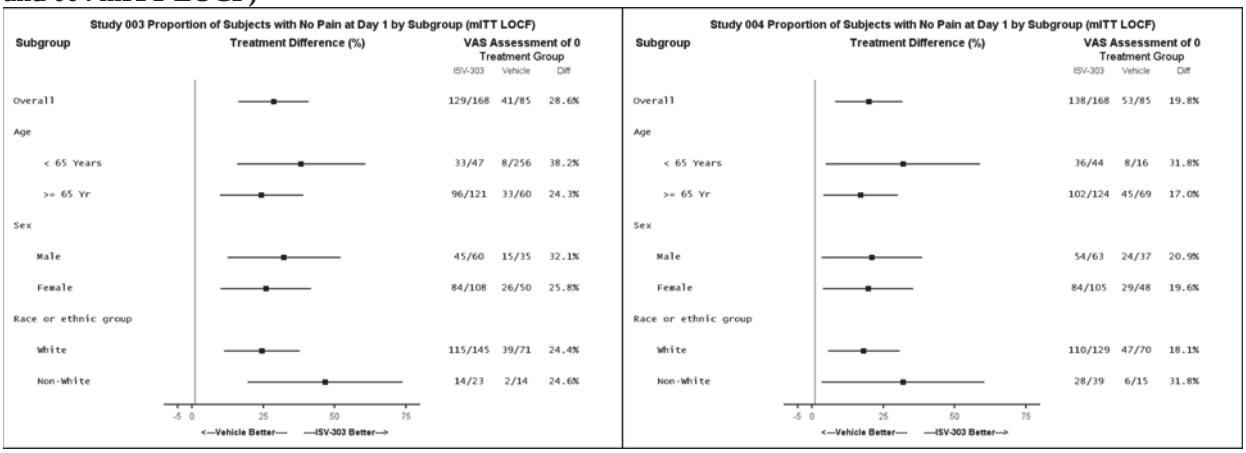
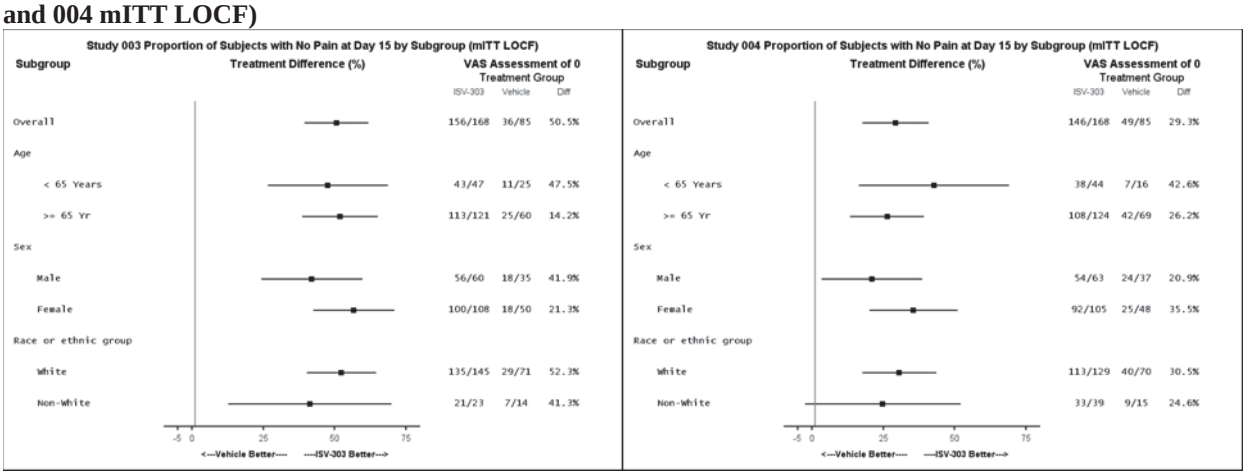


Figure 4: Forest Plots of Subgroup Analyses for Proportion of Subjects with No Pain at Day 15 (Studies 003 and 004 mITT LOCF)



5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no major statistical issues identified for the two pivotal studies submitted.

For the analysis of the primary efficacy endpoint, the outcome of ACC grade at Day 15 was imputed using the last observation carried forward (LOCF) method for any patient who had missing values. In Study 003, for the mITT population, 17.3% (29/168) subjects in the ISV-303 group had their ACC grade imputed at Day 15 visit; and 61.2% (52/85) subjects in the Vehicle group had their ACC scores imputed at Day 15 visit. In Study 004, the rates of subjects who had

ACC grade missing on Day 15 visit were 18.5% (31/168) and 43.5% (37/85) for ISV-303 and Vehicle respectively. For majority of these patients, the reason for them not completing the study treatment and therefore having missing ACC scores was lack of efficacy. In Study 003, the percentages of subjects who had ACC scores missing due to lack of efficacy were 51.7% (15/29) for the ISV-303 group and 67.3% (35/52) in the Vehicle group; in Study 004, these percentages were 22.6% (7/31) and 78.4% (29/37) for ISV-303 and Vehicle respectively. Therefore imputing "failure" for lack of efficacy patients with missing data was considered by the statistical reviewer as appropriate.

For the remaining subjects who had missing scores of ACC for reasons other than lack of efficacy (adverse events, protocol violation, etc.), additional sensitivity analyses were performed by the statistical reviewer where ISV-303-treated patients with missing data had their ACC outcomes imputed as failures at Day 15 and Vehicle-treated patients with missing data had their ACC outcomes imputed as successes at Day 15 (this could be considered as a worst case scenario analysis). The results of this analysis were consistent with the primary analysis results. Additional sensitivity analyses conducted by the applicant based on observed data only, and multiple imputations method were also supportive of the primary efficacy results.

5.2 Collective Evidence

Proportion of Subjects with an ACC Score of 0 without Rescue Therapy at Day 15 Visit – Primary Efficacy Endpoint

For Study 003, at Day 15 visit, in the mITT population, 57.1% (96/168) of the patients in the ISV-303 group had an ACC grade of 0 without rescue therapy compared with 18.8% (16/85) of the patients in the Vehicle group; the treatment difference 38.3% was statistically significant ($p<0.001$) with a 95% CI of (27.1%, 49.5%).

For Study 004, at the Day 15 visit, for the mITT population, 38.1% (64/168) of the patients in the ISV-303 group had an ACC grade of 0 without rescue therapy compared with 22.4% (19/85) of the patients in the Vehicle group; the treatment difference 15.7% was statistically significant ($p=0.035$) with a 95% CI of (4.2%, 27.3%).

Proportion of Subjects Who Were Pain Free Without Rescue Therapy at Each Postsurgical VAS Assessment – Secondary Efficacy Endpoint

In Study 003, at each of the postsurgical time points (Days 1, 8, 15, and 29), proportionally more ISV-303-treated subjects (76.8%, 90.5%, 92.9% and 85.1%, respectively) had no pain (VAS score of 0), compared with vehicle-treated subjects (48.2%, 38.8%, 42.4% and 47.1%, respectively), and at each time point these differences in proportions (28.6%, 51.7%, 50.5%, and 38.1%, respectively) were statistically significant ($p < 0.001$) with 95% CI of (16.2%, 40.9%), (40.4%, 62.9%), (39.3%, 61.7%), and (26.2%, 50.0%), respectively.

In Study 004, proportionally more ISV-303-treated subjects (82.1%, 86.3%, 86.9% and 83.3%, respectively) were pain free (VAS score of 0) compared with vehicle-treated subjects (62.4%, 50.6%, 57.6% and 60.0%, respectively). At each of these time points the differences in proportions (19.8%, 35.7%, 29.3%, and 23.3%, respectively) were statistically significant ($p < 0.001$) with 95% CI of (8.0%, 31.6%), (23.9%, 47.6%), (17.6%, 40.9%), and (11.5%, 35.2%), respectively.

Table 24: Summary of the Primary and Secondary Efficacy Results (mITT)

Proportion of Subjects with an ACC Score of 0 Without Rescue Therapy						
	Study 003			**Study 004**		
Visit	**ISV-303 (N=168)**	**Vehicle (N=85)**	**ISV-303 vs. Vehicle Difference (95% CI)[a]**	**ISV-303 (N=168)**	**Vehicle (N=85)**	**ISV-303 vs. Vehicle Difference (95% CI)[a]**
Day 1	3 (1.8%)	2 (2.4%)	-0.6% (-4.4%, 3.2%)	5 (3.0%)	1 (1.2%)	1.8% (-1.6%, 5.2%)
Day 8	54 (32.1%)	7 (8.2%)	23.9% (14.7%, 33.1%)	40 (23.8%)	8 (9.4%)	14.4% (5.5%, 23.3%)
Day 15	**96 (57.1%)**	**16 (18.8%)**	**38.3% (27.1%, 49.5%)**	**64 (38.1%)**	**19 (22.4%)**	**15.7% (4.2%, 27.3%)**
Day 29	108 (64.3%)	23 (27.1%)	37.2% (25.3%, 49.1%)	95 (56.5%)	36 (42.4%)	14.2% (1.3%, 27.1%)
Proportion of Subjects Who Were Pain Free (VAS Score of 0) Without Rescue Therapy						
	Study 003			**Study 004**		
Visit	**ISV-303 (N=168)**	**Vehicle (N=85)**	**ISV-303 vs. Vehicle Difference (95% CI)[a]**	**ISV-303 (N=168)**	**Vehicle (N=85)**	**ISV-303 vs. Vehicle Difference (95% CI)[a]**
Day 1	129 (76.8%)	41 (48.2%)	28.6 (16.2%, 40.9%)	138 (82.1%)	53 (62.4%)	19.8 (8.0%, 31.6%)
Day 8	152 (90.5%)	33 (38.8%)	51.7 (40.4%, 62.9%)	145 (86.3%)	43 (50.6%)	35.7 (23.9%, 47.6%)
Day 15	156 (92.9%)	36 (42.4%)	50.5 (39.3%, 61.7%)	146 (86.9%)	49 (57.6%)	29.3 (17.6%, 40.9%)
Day 29	143 (85.1%)	40 (47.1%)	38.1 (26.2%, 50.0%)	140 (83.3%)	51 (60.0%)	23.3 (11.5%, 35.2%)

[a] 95% CI calculated based on normal approximation to binomial data.
Source: Tables 14.2.1.1 and 17 of Study 003 Report; and Tables 14.2.1.1 and 17 of Study 004 Report; difference and 95% CI were calculated by the statistical reviewer.

5.3 Conclusions and Recommendations

In conclusion, ISV-303 (BromSite™ (bromfenac ophthalmic solution) 0.075%) is superior to Vehicle in terms of:

- The percentage of patients who achieved an ACC score of 0 at Day 15;
- And the percentage of patients who achieved a pain score of 0 at VAS assessment for each post-surgical visit time point (Days 1, 8, 15, and 29).

Therefore, the statistical reviewer found evidence of efficacy for BromSite™ (bromfenac ophthalmic solution) 0.075%.

5.4 Labeling Recommendations

The applicant proposed the indication of ISV-303 as "treatment of postoperative inflammation and the **prevention** of ocular pain in patients (b) (4) cataract surgery" instead of "treatment of postoperative inflammation and the **reduction** of ocular pain in patients who have undergone cataract surgery", which was the approved indication for all previous bromfenac

ophthalmic solutions in different strengths. The applicant's argument for changing the indication is that the majority of ISV-303-treated subjects (~80%) had no VAS assessed pain starting from post-surgery Day 1 and these proportions were much greater compared with vehicle (about 50% to 60%) in both studies, these results indicated that in most subjects treatment with ISV-303 prevented pain from occurring.

The following study results were summarized in the statistical review of PROLENSA™ (bromfenac ophthalmic solution) 0.07%, which was approved for treatment of postoperative inflammation and the **reduction** of ocular pain in patients who have undergone cataract surgery. It is noted that the majority of PROLENSA-treated subjects (~80% or more) also had no VAS assessed pain (VAS pain score of 0) starting from post-surgery Day 1 and these proportions were much greater compared with vehicle.

Table 25: Proportion of Subjects Who Were Pain Free (VAS Score of 0) for PROLENSA™

	Study 1			Study 2		
Visit	**PROLENSA (N=112)**	**Vehicle (N=108)**	**PROLENSA vs. Vehicle Difference (95% CI)**	**PROLENSA (N=110)**	**Vehicle (N=110)**	**PROLENSA vs. Vehicle Difference (95% CI)**
Day 1	91 (81.3%)	47 (43.5%)	37.7% (25.9%, 49.6%)	84 (76.4%)	61 (55.5%)	20.9% (8.7%, 33.1%)
Day 3	97 (86.6%)	57 (52.8%)	33.8% (22.5%, 45.2%)	95 (86.4%)	58 (52.7%)	33.6% (22.3%, 45.0%)
Day 8	105 (93.8%)	64 (59.3%)	34.5% (24.2%, 44.8%)	99 (90.0%)	68 (61.8%)	28.2% (17.5%, 38.9%)
Day 15	104 (92.9%)	73 (67.6%)	25.3% (15.2%, 35.3%)	100 (90.9%)	74 (67.3%)	23.6% (13.3%, 33.9%)

Source: Page 49 to 50 of the statistical review for PROLENSA™
(http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203168Orig1s000StatR.pdf)

The statistical reviewer considered the applicant's argument for "**prevention** of ocular pain" reasonable; however, with similar results for pain as a previously approved bromfenac ophthalmic solution which was also dosed one day before the surgery as ISV-303 and approved for "**reduction** of ocular pain in patients (b) (4) cataract surgery", there did not appear to be any strong justification for using the phrase "prevention of ocular pain" either. Furthermore, the statistical reviewer also considered "**treatment** of ocular pain" would be acceptable since this could indicate both prevention and reduction of ocular pain. The statistical reviewer defers the final decision regarding the indication to the clinical review team.

The statistical reviewer recommended that studies' results be presented as follows for Section 14 CLINICAL STUDIES of the labeling, which replaces p-value with treatment difference and its corresponding 95% confidence interval (CI):

Proportion of Subjects with Cleared Ocular Inflammation, ACC Grade 0				
	Visit	*BromSite*	*Vehicle*	*Difference (95% CI)*
Study 1	*Day 8*	*54/168 (32.1%)*	*7/85 (8.2%)*	*23.9% (14.7%, 33.1%)*
	Day 15	*96/168 (57.1%)*	*16/85 (18.8%)*	*38.3% (27.1%, 49.5%)*
Study 2	*Day 8*	*40/168 (23.8%)*	*8/85 (9.4%)*	*14.4% (5.5%, 23.3%)*
	Day 15	*64/168 (38.1%)*	*19/85 (22.4%)*	*15.7% (4.2%, 27.3%)*
Proportion of Subjects with Cleared Ocular Inflammation, ACF Grade 0				
Study 1	*Day 8*	*111/168 (66.1%)*	*19/85 (22.4%)*	*43.7% (32.2%, 55.1%)*
	Day 15	*135/168 (80.4%)*	*30/85 (35.3%)*	*45.1% (33.3%, 56.9%)*

Study 2	*Day 8*	*110/168 (65.5%)*	*30/85 (35.3%)*	*30.2% (17.7%, 42.6%)*
	Day 15	*147/168 (87.5%)*	*45/85 (52.9%)*	*34.6% (22.8%, 46.3%)*
Proportion of Subjects who were Pain Free				
Study 1	*At Day 1*	*129/168 (76.8%)*	*41/85 (48.2%)*	*28.6% (16.2%, 40.9%)*
Study 2	*At Day 1*	*138/168 (82.1%)*	*53/85 (62.4%)*	*19.8% (8.0%, 31.6%)*

(b) (4)

Appendix 1: Brief Summary of Study C-10-303-001

C-10-303-001 was a multi-center, multiple dose, randomized, vehicle and active controlled to evaluate the ocular safety, tolerability, and efficacy of differing dosing regimens of intraocular ISV-303, administered QD and BID for 14 days, compared to vehicle and Xibrom dosed BID for 14 days post cataract surgery.

Eligible subjects were randomly assigned to one of the 4 groups (ISV-303 BID, ISV-303 QD, Xibrom BID, or Vehicle BID) at Day 1 after surgery in a 1:1:1:1 ratio. The randomization was stratified by study site. The study consisted of 4 visits for evaluation safety and efficacy:

- Visit 1, Screening/Baseline/Treatment (Day 1: 16 to 32 hours after surgery)
- Visit 2 (Day 8 ± 1)
- Visit 3 (Day 15 [within 12-48 hours after last dose on Day 14])
- Visit 4 (Day 29 ± 2)

The procedures and measurements evaluated at each study visit are shown in the following table.

Table 26: Study C-10-303-001 Schedule of Visits and Measurements

Evaluation	Day 0	Screening/ Baseline/Treatment Day 1 (16 to 32 hours after surgery) Visit 1	Day 3 (or 4) Call	Day 8 ± 1 Visit 2	Day 15 (12-48 hours after last dose) Visit 3	Day 29 ± 2 Visit 4
Surgery	X					
Informed Consent[1]		X				
Entry Criteria		X				
Medical/Ocular History[1]		X				
Pregnancy Test		X[1]				X
Randomization		X				
Slit Lamp Exam (signs)		X		X	X	X
Anterior chamber cell		X		X	X	X
Anterior chamber flare		X		X	X	X
Chemosis		X		X	X	X
Bulbar conjunctival injection		X		X	X	X
Ciliary injection		X		X	X	X
Corneal edema		X		X	X	X
Keratic precipitates		X		X	X	X
VAS (symptoms)		X	X	X	X	X
Eye pain/discomfort		X	X	X	X	X
Photophobia		X	X	X	X	X
Intraocular Pressure		X		X	X	X
Best Corrected Visual Acuity		X		X	X	X
Ophthalmoscopy		X				X
Dispense Study Drug and Dosing Diary		X				
AE Assessment		X		X	X	X
Record Concomitant Medications		X		X	X	X
Review Dosing Diary				X	X	
Collect Study Medication and Dosing Diary					X	X[2]

[1] Could be done prior to Visit 1 before any protocol-specific procedures were conducted, at investigator's option

[2] If not collected at Visit 3

Source: Table 3 of Study C-10-303-001 Report

The primary efficacy outcome for this study was the proportion of subjects with an anterior chamber cell grade of 0 using the following grading scale at Day 15 for the study eye.

Table 27: Study C-10-303-001 Grading for Anterior Chamber Cell Counts

Anterior Chamber Cells	
Grade[a]	Cell Count
0	0
1	1-10
2	11-20
3	21-50
4	>50

[a] Grade 1 includes cell count 1-5 and cell count 6-10.
Source: Table 4 of Study C-10-303-001 Report

There were no clearly defined secondary endpoints for this study.

The primary efficacy analysis was carried out on the ITT population, which included all randomized subjects regardless whether post-baseline measures were collected. Missing data were imputed using LOCF (last-observation-carried-forward) method.! The proportion of subjects with anterior chamber cell grade of 0 at Visit 3 (Day 15) for the following four paired groups were evaluated and compared:

1. Group 1: 0.075% bromfenac in DuraSite dosed BID vs. Group 4: vehicle
2. Group 2: 0.075% bromfenac in DuraSite dosed QD vs. Group 4: vehicle
3. Group 1: 0.075% bromfenac in DuraSite dosed BID vs. Group 3: Xibrom BID
4. Group 2: 0.075% bromfenac in DuraSite dosed QD vs. Group 3: Xibrom BID

All these 4 comparisons were analyzed using a 2-sided Fisher's Exact Test at significance level of 0.05.

One hundred and sixty-nine (169) patients across 14 centers in the US were randomized into the study: 40 subjects were randomized to receive treatment with ISV-303 BID, 45 subjects were randomized to receive treatment with ISV-303 QD, 42 subjects were randomized to receive treatment with Xibrom BID, and 42 subjects were randomized to receive treatment with Vehicle BID.

Results for the primary efficacy endpoint of anterior chamber cell grade of 0 at Day 15 for the ITT population are summarized in the following table.

Table 28: Efficacy Analysis of Proportion of Subjects with Anterior Chamber Cell Grade of 0 (Study C-10-303-001, ITT, LOCF)

	ISV-303 BID (N=40)	ISV-303 QD (N=45)	Xibrom BID (N=42)	Vehicle BID (N=42)
Day 8	7 (17.5%)	10 (22.2%)	10 (23.8%)	3 (7.1%)
p-value (vs. Xibrom)	0.5892	1.0000		
p-value (vs. Vehicle)	0.1888	0.0706		
Day 15	21 (52.5%)	24 (53.5%)	18 (42.9%)	8 (19.0%)
p-value (vs. Xibrom)	0.51	0.39		
p-value (vs. Vehicle)	0.0024	0.0016		
Day 29	27 (67.5%)	27 (60.0%)	30 (71.4%)	20 (47.6%)

p-value (vs. Xibrom)	0.8115	0.3668		
p-value (vs. Vehicle)	0.0786	0.2860		

Source: Tables 9 and 10 of Study C-10-303-001 Report. ITT population included all randomized subjects.

A statistically significant higher proportion of subjects in ISV-303 BID group had cleared anterior chamber cells at Day 15 compared to Group 4 (Vehicle BID) (52.5% vs. 19.0%, p-value: 0.0024). A statistically significant higher proportion of subjects in ISV-303 QD group had cleared anterior chamber cells at Day 15 compared to Group 4 (Vehicle BID) (53.3% vs. 19.0%, p-value: 0.0016). There was not a statistically significant difference between ISV-303 BID group and Xibrom BID group (52.5% vs. 42.9%, p-value: 0.51) or between ISV-303 QD group and Xibrom BID group (53.3% vs. 42.9%, p-value: 0.39).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YUNFAN DENG
02/09/2016

YAN WANG
02/09/2016
I concur.

Statistics Filing Checklist for NDA - 206911

NDA Number:	206911
NDA Type:	Standard Review
Drug Name:	BromSite™ (bromfenac ophthalmic solution) 0.075%
Indication:	Treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery
Applicant:	InSite Vision Inc.
Stamp Date:	June 10, 2015
Reviewer:	Yunfan Deng

1. Brief Summary of Controlled Clinical Trial(s)

The submission contains four clinical studies; one Phase 2 clinical pharmacology study; one Phase 2 efficacy and safety study, two phase 3 efficacy and safety studies. Brief summary for the efficacy and safety studies are provided in Appendix 1.

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information from Review of the Protocol and the Study Report

Content Parameter	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	☑			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	☑			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			☑	
Appropriate references for novel statistical methodology (if present) are included.			☑	
Safety data organized to permit analyses across clinical trials in the NDA.	☑			
Investigation of effect of missing data and discontinued follow-up on statistical analyses as described by applicant appears adequate.	☑			

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\Cdsesub1\evsprod\NDA206911
Dataset structure (e.g., SDTM or ADaM)	YES
Based on the analysis datasets, can results of the primary endpoint(s) be reproduced? (Yes or No)	YES
List the dataset(s) that contains the primary endpoint(s)	Dataset name **adef.xpt** and primary efficacy variable **anvaln** is the primary efficacy variable**.**
Are there any concerns about site(s) that could lead to inspection? If so, list of site(s) that needs inspection and rationale	NA
Are the define files sufficiently detailed?	YES
Safety data are organized to permit analyses across clinical trials in the NDA.	YES

4. Filing Issues

Table 4: Initial overview of the NDA/BLA application for refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	☑			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	☑			• ISE and ISS datasets were included in the submission. • Complete study reports were available for individual studies.
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	☑			
Data sets in EDR are accessible and conform to applicable guidance (e.g., existence of define.pdf file for data sets).	☑			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? YES

Based on our preliminary review, the NDA is fileable. However, issues are noted. We have the following review issue to be forwarded to the Applicant for the 74-day letter.

- We cannot locate in your NDA submission the SAS programs used to generate the secondary efficacy analyses results and safety results for the three efficacy studies (C-10-303-001, C-11-303-003, and C-11-303-004). Please submit all the SAS program codes used to produce the efficacy and safety analysis results presented in the study reports of each study (C-10-303-001, C-11-303-003, and C-11-303-004). Please also provide define documents to explain the purpose of the submitted SAS codes. These documents and the SAS codes will help us in reviewing your NDA.

Appendix 1: Brief Summary of NDA 206911

Submission Background

This NDA seeks approval of BromSite™ (bromfenac ophthalmic solution) 0.075% (also known as ISV-303 throughout this Appendix) for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery. This is a standard 10-month review NDA.

Bromfenac Ophthalmic Solution 0.09% dosed twice per day (BID) was approved in the US by FDA in March, 2005 as Xibrom™ (ISTA Pharmaceuticals, Inc.) for the treatment of postoperative inflammation and later for the reduction of ocular pain in patients who have undergone cataract surgery. The same formulation under the trade name Bromday™ was approved in 2010 for the treatment of postoperative inflammation and the reduction of ocular pain in patients who have undergone cataract surgery for once a day (QD) dosing of 16 days: the day before surgery, the day of surgery, and 14 days after cataract surgery. Prolensa™ (Bromfenac ophthalmic solution, 0.07%;! Bausch & Lomb, Inc.) was approved in 2013 for the same indication for QD dosing of 16 days: the day before surgery, the day of surgery, and 14 days after cataract surgery. Additionally, as of August 2014, five generic 0.09% bromfenac ophthalmic formulations have also been approved.

The Sponsor is now developing ISV-303 with 0.075% bromfenac formulated in the sponsor's patented drug delivery system, DuraSite® as a (b) (4) topical eye drop that can be dosed BID for 16 days: the day prior to surgery, the day of surgery, and postoperatively for 14 days for treating postsurgical inflammation. The proposed indication is also slightly different from previously approved indication – for the treatment of postoperative inflammation and **prevention** of ocular pain in patients undergoing cataract surgery.

The Sponsor has conducted four clinical trials to support the safety and efficacy of their product: one Phase 1/2 study (Study No. C-10-303-001), one Phase 2 study (Study No. C-11-303-002), and two Phase 3 studies (Studies C-11-303-003 and C-12-303-004). The following table briefly summarized key design factors of each study.

Summary of Clinical Studies Conducted

Study No Phase	Design	Objective	Treatment Groups	Study Population
C-10-303-001 Phase 1/2	Multi-center, randomized, double masked, 4-arm	to compare the ocular safety, tolerability, and efficacy of differing dosing regimens of ISV-303 (0.075% bromfenac in DuraSite) to vehicle and Xibrom in post cataract surgery volunteers	ISV-303 BID: 40 ISV-303 QD: 45 Xibrom BID: 42 Vehicle BID: 42 For 14 days post-surgery	Adult patients who have undergone uncomplicated unilateral cataract surgery
C-11-303-002 Phase 2	Double masked, multi-center, randomized, 2-arm	To determine the AH concentration of bromfenac sodium in subjects administered multiple topical ocular doses of ISV-303 (0.075% bromfenac in DuraSite) or Bromday (0.09% bromfenac) QD prior to cataract surgery	ISV-303: 30 Bromday: 30 QD for 2 days prior to surgery and the morning of surgery.	Adult undergoing uncomplicated unilateral cataract surgery

C-11-303-003 Phase 3	Double masked, randomized, multi-center, 2-arm	to compare the ocular safety, tolerability, and efficacy of ISV-303 (0.075% bromfenac in DuraSite) to DuraSite vehicle in cataract surgery subjects	ISV-303 (0.075%): 180 DuraSite Vehicle: 88 BID for 16 days – the day prior to surgery, the day of surgery and 14 days post-surgery	Adult undergoing uncomplicated unilateral cataract surgery
C-11-303-004 Phase 3	Double masked, randomized, multi-center, 2-arm	to compare the ocular safety, tolerability, and efficacy of ISV-303 (0.075% bromfenac in DuraSite) to DuraSite vehicle in cataract surgery subjects	ISV-303 (0.075%): 174 DuraSite Vehicle: 94 BID for 16 days – the day prior to surgery, the day of surgery and 14 days post-surgery	Adult undergoing uncomplicated unilateral cataract surgery

Study C-11-303-002

C-11-303-002 was a multicenter, double-masked clinical study to determine the aqueous humor concentration of bromfenac Sodium in subjects administered multiple topical ocular doses of ISV-303 (0.075% bromfenac in DuraSite®) or Bromday™ (0.09% bromfenac) QD prior to cataract surgery. Subjects administered 1 drop of either ISV-303 or Bromday once daily into the study eye, at approximately 24 hour intervals, for 3 days; with the last instillation to occur 3 hours prior to the subject's scheduled cataract surgery. Aqueous humor samples were collected during surgery for analysis of bromfenac levels. Since this study was conducted mainly for clinical pharmacology evaluation purpose with a different dosing regimen, the NDA review will not include this study.

Study C-10-303-001

C-10-303-001 was a multi-center, multiple dose, randomized, vehicle and active controlled to evaluate the ocular safety, tolerability, and efficacy of differing dosing regimens of intraocular ISV-303, administered QD and BID for 14 days, compared to vehicle and Xibrom dosed BID for 14 days post cataract surgery.

Eligible subjects were randomly assigned to one of the 4 groups (ISV-303 BID, ISV-303 QD, Xibrom BID, or Vehicle BID) in a 1:1:1:1 ratio. The study consisted of 4 visits for evaluation safety and efficay:

- Visit 1, Screening/Baseline/Treatment (Day 1: 16 to 32 hours after surgery)
- Visit 2 (Day 8 ± 1)
- Visit 3 (Day 15 [within 12-48 hours after last dose on Day 14])
- Visit 4 (Day 29 ± 2)

The procedures and measurements evaluated at each study visit are shown in the following table.

Schedule of Visits and Measurements

Evaluation	Day 0	Screening/ Baseline/Treatment Day 1 (16 to 32 hours after surgery) Visit 1	Day 3 (or 4) Call	Day 8 ± 1 Visit 2	Day 15 (12-48 hours after last dose) Visit 3	Day 29 ± 2 Visit 4
Surgery	X					
Informed Consent[1]		X				
Entry Criteria		X				
Medical/Ocular History[1]		X				
Pregnancy Test		X[1]				X
Randomization		X				
Slit Lamp Exam (signs)		X		X	X	X
Anterior chamber cell		X		X	X	X
Anterior chamber flare		X		X	X	X
Chemosis		X		X	X	X
Bulbar conjunctival injection		X		X	X	X
Ciliary injection		X		X	X	X
Corneal edema		X		X	X	X
Keratic precipitates		X		X	X	X
VAS (symptoms)		X	X	X	X	X
Eye pain/discomfort		X	X	X	X	X
Photophobia		X	X	X	X	X
Intraocular Pressure		X		X	X	X
Best Corrected Visual Acuity		X		X	X	X
Ophthalmoscopy		X				X
Dispense Study Drug and Dosing Diary		X				
AE Assessment		X		X	X	X
Record Concomitant Medications		X		X	X	X
Review Dosing Diary				X	X	
Collect Study Medication and Dosing Diary					X	X[2]

[1] Could be done prior to Visit 1 before any protocol-specific procedures were conducted, at investigator's option
[2] If not collected at Visit 3

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The primary efficacy outcome for this study was the proportion of subjects with an anterior chamber cell grade of 0 using the following grading scale at Day 15 for the study eye.

Anterior Chamber Cells	
Grade	**Cell Count**
0	0
1	1-10
2	11-20
3	21-50
4	>50

There were no clearly defined secondary endpoints for this study.

The primary efficacy analysis was carried out on the ITT population, which included all randomized subjects regardless whether post-baseline measures were collected. Missing data were imputed using LOCF (last-observation-carried-forward) method.! The proportion of subjects with

anterior chamber cell grade of 0 at Visit 3 (Day 15) for the following four paired groups were evaluated and compared:

1. Group 1: 0.075% bromfenac in DuraSite dosed BID vs. Group 4: vehicle
2. Group 2: 0.075% bromfenac in DuraSite dosed QD vs. Group 4: vehicle
3. Group 1: 0.075% bromfenac in DuraSite dosed BID vs. Group 3: Xibrom BID
4. Group 2: 0.075% bromfenac in DuraSite dosed QD vs. Group 3: Xibrom BID

All these 4 comparisons were analyzed using a 2-sided Fisher's Exact Test at significance level of 0.05.

One hundred and sixty-nine (169) patients across 14 centers in the US were randomized into the study: 40 subjects were randomized to receive treatment with ISV-303 BID, 45 subjects were randomized to receive treatment with ISV-303 QD, 42 subjects were randomized to receive treatment with Xibrom BID, and 42 subjects were randomized to receive treatment with Vehicle BID.

Results for the primary efficacy endpoint of anterior chamber cell grade of 0 at Day 15 for the ITT population are summarized in the following table.

Primary Efficacy Analysis: Anterior Chamber Cell Grade of 0 at Day 15 – ITT Population, LOCF

	ISV-303 BID (n=40)	ISV-303 QD (n=45)	Xibrom BID (n=42)	Vehicle BID (n=42)
Anterior Chamber Cell Grade of 0 at Day 15	21 (52.5%)	24 (53.5%)	18 (42.9%)	8 (19.0%)
p-value (vs. Xibrom)	0.51	0.39		
p-value (vs. Vehicle)	0.0024	0.0016		

Source: Table 9 of Study C-10-303-001 Report.

A statistically significant higher proportion of subjects in ISV-303 BID group had cleared anterior chamber cells at Day 15 compared to Group 4 (Vehicle BID) (52.5% vs. 19.0%, p-value: 0.0024). A statistically significant higher proportion of subjects in ISV-303 QD group had cleared anterior chamber cells at Day 15 compared to Group 4 (Vehicle BID) (53.3% vs. 19.0%, p-value: 0.0016). There was not a statistically significant difference between ISV-303 BID group and Xibrom BID group (52.5% vs. 42.9%, p-value: 0.51) or between ISV-303 QD group and Xibrom BID group (53.3% vs. 42.9%, p-value: 0.39).

Studies C-11-303-003 and C-11-303-004

Two identical designed phase 3 studies (C-11-303-003 and C-11-303-004) were conducted. Both studies were prospective, multicenter, randomized, double-masked, vehicle-controlled, parallel-group studies to evaluate the ocular safety, tolerability, and efficacy of topical administration of ISV-303 (0.075% bromfenac in DuraSite® ophthalmic solution) compared with DuraSite vehicle when dosed twice daily (BID) for 1 day prior to surgery, the day of surgery, and 14 days after surgery.

Enrolled patients were randomized at 2:1 ratio to receive either ISV-303 or Vehicle administered twice daily for 16 days (1 day prior to surgery, the day of surgery, and 14 days after surgery). There were 6 visits scheduled during the study: Screening (between 2 and 14 days prior to surgery (Visit 1); 3 visits during the dosing phase, Day 0 (surgery day; Visit 2), Day 1 (Visit 3), and Day 8 (Visit 4); and 2 visits during the evaluation phase, Day 15 (Visit 5) and Day 29 (Visit 6). In addition, a

telephone call was made by the site on Day -2 to remind subjects to begin dosing the day before cataract surgery. Subjects were to instill 32 doses of study drug in total: 3 prior to surgery (2 on Day -1, and 1 on Day 0 prior to surgery), and 1 dose the evening after surgery, and were to continue dosing BID for 14 days after surgery.

The primary efficacy endpoint was the proportion of subjects with an anterior chamber cell (ACC) grade of 0 (using the same grading scale of Study C-10-303-001) at Day 15. Subjects with an ACC grade of > 0 at Day 15 or who received rescue medication were considered treatment failures.

The secondary efficacy endpoint was the proportion of subjects who achieved a pain score of 0 at each postsurgical Visual Analog Scale (VAS, 0 = absent to 100 = maximum) assessment (Day 1, Day 8, Day 15, and Day 29).

Primary and secondary analyses were conducted with modified intent-to-treat (mITT) population, which included all patients who were randomized, underwent cataract surgery, and received at least one dose of study treatment. LOCF was used to impute missing data. The difference between treatment with ISV-303 and Vehicle was tested using the chi-square test. Gatekeeping procedure was used to control the overall Type I error rate for testing of primary and secondary endpoints – confirmatory statistical tests on the secondary endpoint were to be performed only if the null hypothesis for the primary endpoint was rejected. Furthermore, for the analysis of the proportion of subjects with a pain score of 0 at Day 1, Day 8, Day 15, and Day 29, adjustments for multiple comparisons at different visits were made using Hochberg's step-up method.

According to the sponsor, to assess the sensitivity of the primary analysis result to the LOCF imputations, the first sensitivity analysis of the primary endpoint was performed, based on worst observation carried forward (WOCF) imputations and the mITT Population. A second sensitivity analysis of the primary endpoint was performed based on the mITT Population and observed cases (OC) (i.e., ACC data with no imputation for missing values). For the integrated data analyses of both studies C-11-303-003 and C-11-303-004, a sensitivity analysis with multiple imputation was conducted for the primary endpoint, the proportion of subjects with an ACC grade of 0 at Day 15, with missing values imputed using predictive posterior distributions for the treatment groups defined by observed cases (OC) and the Jeffries Beta (½, ½) prior distribution.

For Study C-11-303-003, 268 patients from 15 centers across US were randomized, including 180 in the ISV-303 group and 88 in the Vehicle group. Of the 268 randomized subjects, 14 (12 in the ISV-303 group and 2 in the Vehicle group) did not have cataract surgery. One additional subject (321-009, randomized to Vehicle) who had cataract surgery was withdrawn from the study before receiving any study drug and was not counted in the mITT Population. Thus, 253 subjects or 94.4% of those randomized (93.3%, [168/180] in the ISV-303 and 96.6%, [85/88] in the Vehicle group) received at least 1 dose of study drug and had cataract surgery; these subjects comprised the mITT Population.

For Study C-11-303-004, 268 patients from 14 centers across US were randomized, including 174 in the ISV-303 group and 94 in the Vehicle group. Of the 268 randomized subjects, 15 (6 in the ISV-303 group and 9 in the Vehicle group) did not have cataract surgery, thus 253 (94.4%) subjects comprised the mITT Population

For both studies, as shown in the following tables (based on the applicant's reported study results for studies C-11-303-003 and C-11-303-004):

- ISV-303 was superior to Vehicle in regard to the percentage of patients who achieved clearance of anterior chamber cells at Day 15 post cataract surgery;
- ISV-303 was superior to Vehicle in regard to the percentage of patients who were free of ocular pain at Days 1, 8, 15, and 29 post cataract surgery.

Proportion of Subjects with ACC Grade of 0 at Visit 5 (Day 15) and Who Did not Receive Any Rescue Therapy on or Before the Assessment Day (mITT, LOCF)

Study C-11-303-003					
	ISV-303 (N=168) n (%)	**Vehicle (N=85) n (%)**	**Difference (%)**	**95% CI[1] (%)**	**p-value[2]**
	96 (57.1)	16 (18.8)	38.3	(27.1, 49.5)	<0.0001
Study C-11-303-004					
	ISV-303 (N=168) n (%)	**Vehicle (N=85) n (%)**	**Difference (%)**	**95% CI[1] (%)**	**p-value[2]**
	64 (38.1)	19 (22.4)	15.7	(4.2, 27.3)	0.016

Source: Table 16 of Study 003 Report and Table 16 of Study 004 Report; difference and 95% CI were calculated by the statistical reviewer.
[1] 95% Confidence Interval (CI) calculated based on normal approximation to binomial data.
[2] p-value was from chi-square test.

Proportion of Subjects Who Achieved a Pain Score of 0 at Each Postsurgical VAS Assessment without Using of Rescue Therapy (mITT, LOCF)

Study C-11-303-003					
Visit (Study Day)	**ISV-303 (N=168) n (%)**	**Vehicle (N=85) n (%)**	**Difference (%)**	**95% CI[1] (%)**	**p-value[2]**
Visit 3 (Day 1)	129 (76.8)	41 (48.2)	28.6	(16.2, 40.9)	<.0001
Visit 4 (Day 8)	152 (90.5)	33 (38.8)	51.7	(40.4, 62.9)	<.0001
Visit 5 (Day 15)	156 (92.9)	36 (42.4)	50.5	(39.3, 61.7)	<.0001
Visit 6 (Day 29)	143 (85.1)	40 (47.1)	38.1	(26.2, 50.0)	<.0001
Study C-11-303-004					
Visit (Study Day)	**ISV-303 (N=168) n (%)**	**Vehicle (N=85) n (%)**	**Difference (%)**	**95% CI[1] (%)**	**p-value[2]**
Visit 3 (Day 1)	138 (82.1)	53 (62.4)	19.8	(8.0, 31.6)	0.0005
Visit 4 (Day 8)	145 (86.3)	43 (50.6)	35.7	(23.9, 47.6)	<.0001
Visit 5 (Day 15)	146 (86.9)	49 (57.6)	29.3	(17.6, 40.9)	<.0001
Visit 6 (Day 29)	140 (83.3)	51 (60.0)	23.3	(11.5, 35.2)	<.0001

Source: Table 17 of Study 003 Report and Table 17 of Study 004 Report; difference and 95% CI were calculated by the statistical reviewer.
[1] 95% Confidence Interval (CI) calculated based on normal approximation to binomial data.
[2] p-value was from chi-square test.

Because in both studies, majority of ISV-303-treated subjects (~80%) had no VAS assessed pain (VAS pain score of 0) starting from post-surgery Day 1 and these proportions were statistically significantly greater compared with vehicle; the sponsor argues that these results indicated that in most subjects treatment with ISV-303 prevented pain from occurring. Therefore, the sponsor proposes the indication of ISV-303 as "treatment of postoperative inflammation and the **prevention**

of ocular pain in patients [redacted] cataract surgery" instead of "treatment of postoperative inflammation and the [redacted] of ocular pain in patients [redacted] cataract surgery".

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/s/

YUNFAN DENG
07/28/2015

YAN WANG
07/28/2015