CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206911Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Renata Albrecht, MD
Subject	Division Director Summary Review
NDA/BLA #	NDA 206991
IND	IND 107723
Applicant	InSite Vision Inc.
Date of Submission	June 10, 2015
PDUFA Goal Date	April 10, 2016
Proprietary Name / Non-Proprietary Name	BromSite Bromfenac ophthalmic solution
Dosage Form(s) / Strength(s)	0.075%
Applicant Proposed Indication(s)/Population(s)	Treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery
Dosage Regimen	Instill one drop 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.
Action	*Approval*
Approved/Indication/Population	*Treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery*

Material Reviewed/Consulted	Names of discipline reviewers
Medical Officer Review	Sonal Wadhwa, William Boyd 3/14/2016
Statistical Review	Yungfan Deng, Yan Wang 2/9/2016
Pharmacology Toxicology Review	Aaron Ruhland, Lori Kotch 3/15/2016
OPQ Review*	Katherine Windsor, Chunchun Zhang, David Anderson, Jonathan Swoboda, Frank Wackes, Om Anand, Paul Perdue, Balajee Shanmugam 3/4/3016 Chunchun Zhang 4/8/2016
Clinical Pharmacology Review	Yongheng Zhang, Phil Colangelo 2/9/2016
OPDP	Meena Ramachandra 3/1/2016
OSI	Roy Blay 1/8/2016
CDTL Review	William Boyd, 4/8/2016
Deputy Director Review	Wiley Chambers, 4/8/2016
OSE/DMEPA label review	Nicole Garrison, 9/14/2015
DMEPA proprietary name review	Karen Townsend 10/15/2015
DMPP patient labeling review	Sharon Williams, Shawna Hutchins, Lashawn Griffiths, 3/4/2016
ADL (acting)	Jin Chen
Project Manager	Diana Willard

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DMPP =Division of Medical Policy Programs
*OPQ review includes drug substance, drug product, manufacturing process, microbiology, facility and biopharmaceutics.

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1. Benefit-Risk Assessment

All disciplines recommend approval of the application. Labeling has been discussed with the applicant and finalized. A number of regulatory and scientific issues were identified. I have addressed these issues in the review that follows, and agree with the reviewers that the application will be approved.

See Benefit –Risk Table summary below

Benefit-Risk Summary and Assessment

BromSite is a topical ophthalmic solution of bromfenac, 0.075%, a nonsteroidal anti-inflammatory drug (NSAID); during development it was called ISV-303 and this name is used in many of the documents and tables in the application and FDA reviews. BromSite is a sterile, preserved, multi-dose eye drop intended for the treatment of post-surgical inflammation and prevention of ocular pain in patients (b) (4) cataract (b) (4) surgery. BromSite is to be administered twice a day for 16 days (the day before surgery, the day of surgery, and 14 days after cataract surgery). The safety and efficacy was evaluated in two Phase 3 clinical trials, both of which showed the product to be effective in the treatment of the inflammation in the anterior chamber of the eye following cataract surgery, and well as in the prevention of pain after surgery. The adverse event profile includes a transient increase in intraocular pressure and other local ocular findings associated with the procedure and product. These risks are acceptable considering the benefits. Risk management strategies are described in the package insert and Instructions for Use. This includes counseling information about maintaining sterility of the dropper tip, avoiding use of contacts because of the preservative in the eye drops, delayed healing with NSAIDs, and waiting 5 minutes when administering other eye drops. The Instructions for Use provide step by step procedures for using the product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Cataracts are opacities or clouding of the lens in the eye. As the cataract progresses, it results in loss of vision, and is considered visually significant when it interferes with activities of daily living. The most frequent etiology is natural aging but other causes include injury, and some systemic diseases, such as diabetes. Surgery to remove the opacified lens is the only effective treatment for cataracts, and over 3 million cataract surgeries are performed in the US each year. Cataract surgery is often associated with inflammation characterized by inflammatory cells in the anterior chamber, and/or pain. Post-operatively, ocular inflammation is assessed by anterior chamber cell (ACC) counts determined by using a slit lamp with magnification; zero cells correspond to grade 0 and >50 cells correspond to the maximum grade 4. Pain can be assessed by the patient using a visual analog scale (VAS) based on emoticon facial expressions which are recorded on a corresponding number scale ranging from 0 (no pain) to 100mm (maximum pain). Topical anti-inflammatory drugs such as NSAIDs and/or corticosteroids are used post cataract surgery to mitigate this inflammatory response, and related pain.	Cataract surgery is the gold standard treatment of cataracts, and an intraocular lens is usually placed in the native lens capsule. The inflammation and any associated pain resulting after surgery are generally managed with topical ophthalmic anti-inflammatory drugs.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	There are multiple topical corticosteroids and NSAIDS approved for post-operative use to treat or reduce pain and inflammation, including two other concentrations of bromfenac ophthalmic solution: Prolensa, 0.07%, and Bromday/Xibrom 0.09%. A tabular list is of approved products is provided in Section 2.	There are multiple approved products, BromSite offers another option.
Benefit	Two controlled clinical trials showed statistically and clinically significant reproducible evidence of resolution of postsurgical inflammation on Day 15 as evaluated on anterior chamber cell (ACC) counts, and prevention of pain on Day 1, as well as thereafter, as reported by patients using a visual analog scale (VAS), shown in Section 8 of this document.	Bromfenac, a non-steroidal anti-inflammatory drug, was effective in treating the post-operative inflammation and pain.
Risk	Complications of surgery include inflammation and pain, but may include injury, bleeding or infection. Post-operative care of the eye includes various medications and other strategies. The most common risks associated with the use of BromSite included increased intraocular pressure (IOP) in about 8% of patients, particularly on the first day, with most patients returning to baseline within the following weeks.	The risks of this topical NSAID were generally not different from the vehicle control, except transient IOP elevations and vitreous floaters.
Risk Management	The labeling for this product included patient labeling which provides instruction on how the bottle should be handled to dispense medications twice daily, and includes precautions about contamination, and avoidance of contact lenses during BromSite use because of the presence to the preservative.	Information on risk management is covered in labeling, including patient labeling.

2. Background

BromSite (bromfenac ophthalmic solution) 0.075% is a NSAID for use post-operatively to treat inflammation and pain after cataract surgery. It was developed under IND 107723 starting in January of 2010. A preIND meeting was held April 26, 2010, an end-of Phase 2 meeting on February 17, 2012, and pre NDA meetings on January 13 and April 15, 2014. During these meetings, guidance was provided on manufacturing, quality microbiology, nonclinical testing, pharmacokinetic testing, clinical trial design (including entry criteria, endpoints, sample size), statistical considerations, regulatory considerations for a 505(b)(2) submission, content and format of the application and labeling.

At present, there are two FDA-approved bromfenac-containing ophthalmic products marketed under three different labels for the treatment of inflammation and pain post cataract surgery: Xibrom (bromfenac 0.09% BID; NDA 21664), Bromday (bromfenac 0.09% QD; NDA 21664/S013), and Prolensa (bromfenac 0.07% QD; NDA 203168). In addition, a number of generic 0.09% bromfenac ophthalmic solutions have been approved. A list of approved products for use post-surgery to manage inflammation and pain are listed below:

NDA	Drug
22-212	Difluprednate ophthalmic emulsion 0.05% (Durezol)
202-872	Loteprednol etabonate ophthalmic gel 0.5% (Lotemax)
20-474	Rimexolone ophthalmic suspension 1% (Vexol)
203-168	Bromfenac ophthalmic solution 0.07% (Prolensa)
21-664	Bromfenac sodium ophthalmic solution 0.09% (Xibrom)
21-664 201-211, 202-030, 202-435, 202-620, 203-395	Bromfenac sodium ophthalmic solution 0.09% (Bromday) generic products
21-862	Nepafenac ophthalmic suspension 0.1% (Nevanac)
203-491	Nepafenac ophthalmic suspension 0.3% (Ilevro)
19-700	Ketorolac tromethamine ophthalmic solution 0.5% (Acular)
22-427	Ketorolac tromethamine ophthalmic solution 0.45% (Acuvail)
20-037	Diclofenac sodium ophthalmic solution 0.1% (Voltaren Ophthalmic)

Source: adapted from Medical Officer Review

3. Product Quality

Drug Substance

The drug substance information is contained in DMF (b) (4). Bromfenac sodium (sodium 2-amino-3-(4-bromobenzoyl)phenylacetate sesquihydrate) is a member of the phenylacetic acid class of non-steroidal anti-inflammatory drugs (NSAIDs) and has been used in other FDA approved ophthalmic solutions (Prolensa, Bromday, and Xibrom). The drug substance is a bright orange to yellow powder of (b) (4).

Drug Product

The active ingredient is bromfenac sodium (b) (4). Each mL contains bromfenac sodium sesquihydrate 0.81 mg, which is equivalent to bromfenac free acid 0.76 mg. BromSite is a

greenish-yellow to dark yellow viscous liquid with an osmolality of approximately 290 mOsmol/kg. The products contains the preservative benzalkonium chloride 0.005%, and inactive ingredients include boric acid, sodium borate, citric acid anhydrous, sodium citrate dihydrate, poloxamer 407, polycarbophil, sodium chloride, edetate disodium dihydrate, sodium hydroxide (to adjust pH to 8.3), and water for injection (USP). All the excipients are compendial.

DuraSite is InSite Vision's drug delivery system and composed of (b) (4) . DuraSite has been used in several approved drug products including AzaSite NDA 50810.

Container Closure
BromSite (bromfenac ophthalmic solution) 0.075% is a sterile, preserved, (b) (4), viscous, multidose eye drop supplied in white, opaque, low density polyethylene (LDPE) plastic bottles and translucent dropper tips, and gray, high density polyethylene (HDPE) eyedropper caps. A white tamper evident overcap is provided. Each bottle is provided in a sealed foil laminated pouch. The 7.5 mL bottle is filled with 5 mL of product. Product should be stored at 15ºC – 25ºC (59º F – 77ºF) and has a 24 month expiration date under these storage conditions.

Inspections
The final recommendation from facilities inspections for the drug substance and drug product was acceptable on 2/27/2016.

The CMC review team recommends approval of the product.

4. Nonclinical Pharmacology/Toxicology

This 505(b)(2) application relied on NDA 21644 (Bromday/Xibrom) for nonclinical information, as listed under Item 20 on Form 356h in the application. In addition, the applicant conducted nonclinical studies to evaluate the comparative ocular distribution, pharmacokinetic and ocular toxicity of their product and the listed drug, Bromday. Bromfenac levels were highest in the sclera followed by similar levels in the choroid and aqueous humor, and lowest levels in the vitreous humor of the Dutch belted rabbit. Compared to Bromday, administration of ISV-303 resulted in about 4-fold higher levels in the sclera, choroid and aqueous humor and approximately1.4-fold higher levels in the vitreous humor. The increased exposure was not associated with ocular toxicity when rabbits were dosed topically BID with up to 0.18% ISV-303 for 14 days. When normalized, the plasma levels of BromSite were similar to Bromday/Xibrom, allowing for a bridging between the present formulation and the NDA 21644 product.

For labeling, the applicant is relying on the Agency's previous finding from NDA 21664. The labeling for NDA 21664 contains sufficient information on general toxicology,

carcinogenicity, reproductive and developmental toxicology for safety margins for BromSite to be calculated.

The drug substance impurity specifications for stability exceed those recommended in the ICH guidance and the applicant included nonclinical studies to qualify the impurity specifications. No toxicity was associated with BromSite which had undergone forced degradation and contained specified impurities at levels which exceed those proposed.

The Pharmacology/Toxicology review team recommends approval.

5. Clinical Pharmacology

The clinical pharmacology review notes that bromfenac (ISV-303 during development) is a topical ophthalmic solution of a 0.075% concentration of the nonsteroidal anti-inflammatory drug (NSAID). The product is formulated in InSite Vision's drug delivery system, DuraSite, which contains (b) (4), a polyacrylic acid polymer – the intent is to increase drug residence time on the ocular surface and improve ocular bioavailability and drug penetration.

The systemic exposure to bromfenac was assessed in a subgroup of patients (out of 268) enrolled in Study C-12-303-004. Blood samples were collected between 30-60 minutes post dose on Day 1 (after administration of 5 ocular doses), and between 12-48 hours after the last dose on Day 14 (after 32 doses).

On Day 1, bromfenac was measurable in 29 out of 30 samples from subjects in the ISV-303 treatment group and bromfenac levels ranged from 0.2 - 2.42 ng/mL. Bromfenac levels for 1 subject were BQL.[1]

On Day 15, bromfenac was detectable in 6 out of the 28 samples from subjects in the bromfenac treatment group. Three samples were collected within 12-14 hours after the last dose, with resulting plasma bromfenac concentrations of 0.206, 0.225 and 0.287 ng/mL. The other 3 samples were from patients who received one extra dose of study drug on Day 15, and whose blood samples were collected 2 hours and 13 minutes, 30 minutes, and 36 minutes post-dose, with resulting plasma bromfenac concentrations of 0.246, 0.482 and 1.66 ng/mL, respectively.

All vehicle control group subjects had levels below the quantitation limit of 0.20 ng/mL

The labeling will reflect that following bilateral topical ocular twice-daily dosing of ISV-303 (bromfenac ophthalmic solution 0.075%), the plasma concentration of bromfenac ranged from below the limit of quantification (LOQ = 0.20 ng/mL) to 2.42 ng/mL at 30-60 min post-dose.

[1] Hogger P and P Rohdewald. Pharmacokinetics of bromfenac in healthy subjects after single oral administration of three different doses . Arzneimittelforschung. 1993 Oct;43(10):1114-8. Bromfenac exhibits a Cmax of approximately 3.5 micrograms/mL following oral dosing.

The Clinical Pharmacology review team recommends approval.

6. Clinical Microbiology

Not Applicable

7. Clinical/Statistical-Efficacy

In support of the present NDA, the Applicant submitted the following randomized, controlled, clinical studies:

- Phase 1/2 study (C-10-303-001) to evaluate the comparative safety and efficacy of QD and BID BromSite dosing regimens to Xibrom BID and vehicle BID over 14 days in post cataract surgery patients.
- Two Phase 3 studies (C-11-303-003 & C-12-303-004) in subjects scheduled to undergo cataract surgery to compare the safety and efficacy of ISV-303 versus vehicle. The same dosing schedule was tested in each study: BID administration for 16 days, starting the day before surgery. The study enrolled patients 18 years of age and older.

The phase 3 studies (also referred to as Study 003 and Study 004) were prospective, multicenter, randomized, double-masked, vehicle-controlled, parallel-group studies.

The primary analysis population 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.

Primary Efficacy Endpoint (US and EU)
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 were counted and graded according to the following chart:

Grading for Anterior Chamber Cell Counts

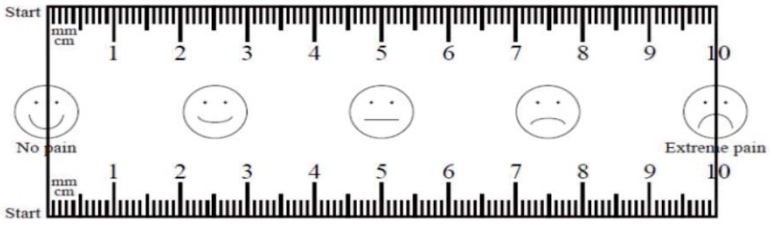
Grade *	Cell Count
0	0
1	1-10
2	11-20
3	21-50
4	>50

* Grade 1 includes cell count 1-5 and cell count 6-10.
Source: Table 5 of Studies 003 and 004 Report. (Statistical Review)

Secondary Efficacy Endpoint (VAS Pain Assessment)
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. 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).

Visual Analog Scale



Patient Disposition

In both studies, a substantially greater proportion of vehicle control patients discontinued from the study early due to lack of efficacy; 40% of patients in Study 003 and 31% of patients in study 004, compared to 4-8% of ISV-303 patients. This is corroborated by the greater use of rescue medication in the vehicle group, primarily to treat ocular inflammation (see tables below).

Study C-11-303-003 Patient 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%)

Source: Statisitical Review

Study C-12-303-004 Patient 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%)

Source: Statistical Review

Reasons Patients Received Rescue Medication

	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
Initis	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.

Efficacy Results

The reviewers concluded that BromSite (bromfenac ophthalmic solution) 0.075% is statistically and clinically superior to vehicle on both the primary and the secondary endpoints:

These results are reflected in Table 1 (below) from the statistical review.

- Study 003:
  - There were 96 (57.1%) BromSite patients vs 16 (18.8%) vehicle patients who achieved an ACC score of 0 on Day 15, 95% CI = 38.3% (27.1%, 49.5%)
  - There were 129 (76.8%) BromSite patients vs 41 (48.2%) vehicle patients who achieved a pain score of 0 on Day 1, 95% CI = 28.6 (16.2%, 40.9%)
- Study 004:
  - There were 64 (38.1%) BromSite patients vs 19 (22.4%) vehicle patients who achieved an ACC score of 0 on Day 15, 95% CI = 15.7% (4.2%, 27.3%)
  - There were 138 (82.1%) BromSite patients vs 53 (62.4%) vehicle patients who achieved a pain score of 0 on Day 1, 95% CI =19.8 (8.0%, 31.6%)

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..

The following table of results derived from the above table will be included in labeling.

Proportion of Subjects with Cleared Ocular Inflammation, ACC Grade 0				
	Visit	BromSite	Vehicle	Treatment 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 who were Pain Free				
Study 1	Day 1	129/168 (76.8%)	41/85 (48.2%)	28.6% (16.2%, 40.9%)
Study 2	Day 1	138/168 (82.1%)	53/85 (62.4%)	19.8% (8.0%, 31.6%)

The clinical reviewers and statistical reviewers recommend approval.

8. Safety

All patients who were enrolled and received drug were evaluated for safety; there were 336 patients who received the to-be-marketed regimen of BromSite versus 170 patients in the vehicle control.

There were no deaths reported. Serious adverse events were reported in two vehicle patients (endophthalmitis, colitis; both events resolved) and one BromSite patient who reported severe chest pain on the day of surgery; the pain resolved. Drop-outs and discontinuations are reported in the Patient Disposition tables in Section 7. Common treatment-emergent adverse events are provided in the tables below:

Table 2.7.4-7: Summary of Common (≥ 1%) Treatment-Emergent Adverse Events (Integrated Safety Population)

SOC Preferred Term	Treatment Group		
	ISV-303 (N = 422) n (%)	Xibrom (N = 42) n (%)	Vehicle (N = 212) n (%)
Subjects with at least 1 TEAE	123 (29.1)	9 (21.4)	72 (34.0)
Subjects with at least one common TEAE	78 (18.5)	9 (21.4)	51 (24.1)
Eye Disorders	68 (16.1)	4 (9.5)	43 (20.3)
Anterior Chamber Inflammation	5 (1.2)	0	3 (1.4)
Eye Inflammation	3 (0.7)	1 (2.4)	4 (1.9)
Eye Pain	13 (3.1)	0	14 (6.6)
Eye Pruritus	2 (0.5)	1 (2.4)	0
Foreign Body Sensation in Eyes	3 (0.7)	2 (4.8)	2 (0.9)
Iritis	12 (2.8)	1 (2.4)	8 (3.8)
Ocular Discomfort	2 (0.5)	0	3 (1.4)
Ocular Hypertension	34 (8.1)	0	8 (3.8)
Photophobia	1 (0.2)	0	4 (1.9)
Visual Acuity Reduced	0	0	3 (1.4)
Vitreous Floaters	6 (1.4)	0	1 (0.5)
Injury, Poison, Procedural Complication	4 (0.9)	1 (2.4)	1 (0.5)
Foreign Body in Eye	4 (0.9)	1 (2.4)	1 (0.5)
Nervous System Disorders	5 (1.2)	1 (2.4)	6 (2.8)
Headache	5 (1.2)	1 (2.4)	6 (2.8)
Respiratory, Thoracic, Mediastinal Disorders	1 (0.2)	2 (4.8)	0
Chronic Obstructive Pulmonary Disease	0	1 (2.4)	0
Epistaxis	1 (0.2)	1 (2.4)	0 (0.0)
Skin and Subcutaneous Tissue Disorders	2 (0.5)	1 (2.4)	0 (0.0)
Rash	2 (0.5)	1 (2.4)	0 (0.0)
Vascular Disorders	1 (0.2)	0	3 (1.4)
Hyperaemia	1 (0.2)	0	3 (1.4)

SOC = system organ class; TEAE = treatment-emergent adverse event
Source: Tables 3.1.2 and 3.1.3.

Source: Medical Officer Review

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.

Subjects with IOP Elevations by Study Visit

Visit	IOP Change	Study 003 ISV-303 N=169	Study 003 Vehicle N=85	Study 004 ISV-303 (N=168)	Study 004 Vehicle N=85
Day 1	n	167	84	166	85
	IOP Change ≥ 10 mmHg from Baseline	13 (7.8%)	3 (3.6%)	12 (7.2%)	2 (2.4%)
	IOP Change ≥ 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.
Source: Statistical Review

In both the statistical review and clinical review, a higher percentage of IOP changes are noted in the bromfenac group compared to the vehicle control group (see Table 2.7.4.-7 from the Medical Officer Review and Table 22 from Statistical Review). As further noted in the table titled **Subjects with IOP Elevations by Study Visit**, the difference is noted on Day 1, and in the majority of patients the elevations resolved in the following weeks.

The explanation of these findings was provided by the clinical reviewer that elevated intraocular pressure occurs as a result of the surgical procedure. Ocular inflammation lowers intraocular pressure. The reason for the higher pressures in the NSAID treated group is because the inflammation is being treated and therefore it is not lowering the elevated intraocular pressure caused by the surgery. These elevations are over a relatively short period of time and have minimal consequences at the level of IOP elevation observed in the trial.

The clinical reviewers and statistical reviewers recommend approval.

9. Advisory Committee Meeting

This application did not raised new scientific issues that needed input from the Advisory Committee.

10. Pediatrics

The application does not trigger the Pediatric Research Equity Act because it is not a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. There are no clinical studies in pediatric patients.

11. Other Relevant Regulatory Issues

This is a 505(b)(2) application that relied on NDA 21664 for nonclinical data to be included in labeling Sections 8 and 13 (See Section 4 of this document for a brief summary). Of note is that both NDA 21664 and NDA 206168 Prolensa were submitted as 505(b)(1) applications and those products are licensed from Senju Pharmaceuticals, Japan, as stated in the B&L labeling.

OSI Inspection Three sites were inspected based on relatively large enrollment and all three were classified as NAI.

Financial Disclosure
As provided under 21 CFR 54.2, there were no disclosed financial interests/arrangements nor evidence to suggest that the results of the study were impacted by any financial payments.

12. Labeling

The **INDICATIONS AND USAGE** section in **HIGHLIGHTS OF PRESCRIBING INFORMATION** will include the established pharmaceutical class for bromfenac: non-steroidal anti-inflammatory drug (NSAID). Link to established pharmaceutical class text page: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM428333.pdf

The **FULL PRESCRIBING INFORMATION** portion of labeling will include the following text in Section 1 and 2.

1 INDICATIONS AND USAGE

BromSite (bromfenac ophthalmic solution) 0.075% is indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

One drop of BromSite should be applied to the affected eye twice daily (morning and evening) 1 day prior to surgery, the day of surgery, and 14 days post-surgery.

2.2 Use with Other Topical Ophthalmic Medications

BromSite should be administered at least 5 minutes after instillation of other topical medications. BromSite may be administered in conjunction with other topical

ophthalmic medications such as alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics.

Regarding the indication: In both studies, the majority of ISV-303-treated subjects (~80%) had a VAS pain score of 0 starting from post-surgery Day 1 compared to vehicle (about 50% to 60%). The applicant noted these results indicated that in most subjects, treatment with ISV-303 prevented pain from occurring and proposed the indication as "treatment of postoperative inflammation and the prevention of ocular pain in patients (b) (4) cataract surgery." It is noted that some ophthalmic NSAID, including bromfenac, are approved for "treatment of postoperative inflammation and the reduction of ocular pain in patients who have undergone cataract surgery." Some products are approved for "treatment of postoperative inflammation and pain." 21 CFR 314.3 provides definitions for various terms, and includes the definition of the following: "Drug substance means an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates use in the synthesis of such ingredient." Therefore, the choice of the term prevention in the context of the current indication is acceptable.

The labeling for this product is in PLR format and includes information from the clinical studies, as well as information on warnings and precautions, adverse events.

The labeling was reviewed by the Office of Prescription Drug Promotion and DMEPA, and their recommendations incorporated as appropriate.

Instructions for Use
The Division of Medical Policy Programs reviewed the Instructions for Use, and agreed upon labeling was finalized with the applicant.

Carton and Container
The Division of Medication Errors Product Assessment reviewed the proposed carton labeling, bottle label and prescribing information. DMEPA provided recommendations that were incorporated as appropriate.

Trade Name
DMEPA concluded that the proposed proprietary name, BromSite, was conditionally acceptable in a letter to the applicant dated 10/15/2015.

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

Not applicable

- Other Postmarketing Requirements and Commitments

Not applicable

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

/s/

RENATA ALBRECHT
04/08/2016