CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206911Orig1s000

MEDICAL REVIEW(S)

Deputy Division Director Review for NDA 206-911

Date	April 8, 2016
From	Wiley A. Chambers, M.D.
NDA #	206-911
Applicant	InSite Vision Incorporated
Date of Submission	June 10, 2015
Type of Application	505(b)(2)
Name	BromSite (bromfenac ophthalmic solution) 0.075%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery
Recommended:	Recommended for Approval

1. Introduction

BromSite is a topical ophthalmic solution of bromfenac, a nonsteroidal anti-inflammatory drug (NSAID). It 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 proposed to be administered twice a day for 16 days (the day before surgery, the day of surgery, and 14 days after cataract surgery). BromSite (bromfenac ophthalmic solution) 0.075% was called ISV-303 during its drug development.

This is a 505(b)(2) application. NDA 206911 (BromSite) relies on FDA's previous finding of nonclinical safety from the listed drug Xibrom/Bromday (NDA 21-664). The application does not rely on information from any other NDAs. The applicant conducted a nonclinical ocular toxicity study in rabbits, but did not conduct any nonclinical studies to evaluate carcinogenicity, mutagenicity, use in pregnancy or the potential for the drug product to impair fertility. In the rabbit ocular toxicity study and in human clinical studies, the applicant measured plasma levels of bromfenac following topical administration and demonstrated that the systemic absorption was well below the level evaluated by the Agency for the labeling of NDA 21-664. The measured levels of bromfenac following administration of BromSite support reliance on the nonclinical data used to support approval of Xibrom and described in the labeling of Xibrom.

2. Background

Currently Available Treatments (Approved Drugs) for Proposed Indication

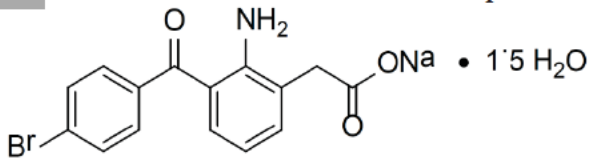
NDA	Drug	Indication
22-212	Difluprednate ophthalmic emulsion 0.05% (Durezol)	DUREZOL is a topical corticosteroid that is indicated for the treatment of inflammation and pain associated with ocular surgery. DUREZOL is also indicated for the treatment of endogenous anterior uveitis.
202-872	Loteprednol etabonate ophthalmic gel 0.5% (Lotemax)	LOTEMAX is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.
20-474	Rimexolone ophthalmic suspension 1% (Vexol)	VEXOL 1% (rimexolone ophthalmic suspension) is indicated for the treatment of post-operative inflammation following ocular surgery and in the treatment of anterior uveitis.
203-168	Bromfenac ophthalmic solution 0.07% (Prolensa)	PROLENSA is a NSAID indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.
21-664*	Bromfenac sodium ophthalmic solution 0.09% (Xibrom)	XIBROM is a NSAID indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.
21-664 201-211 202-030 203-395	Bromfenac sodium ophthalmic solution 0.09% (Bromday)	BROMDAY is a NSAID indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.
21-862	Nepafenac ophthalmic suspension 0.1% (Nevanac)	NEVANAC ophthalmic suspension is a NSAID indicated for the treatment of pain and inflammation associated with cataract surgery.
203-491	Nepafenac ophthalmic suspension 0.3% (Ilevro)	ILEVRO (nepafenac ophthalmic suspension), 0.3% is a NSAID indicated for the treatment of pain and inflammation associated with cataract surgery.
19-700	Ketorolac tromethamine ophthalmic solution 0.5% (Acular)	ACULAR ophthalmic solution is a NSAID indicated for: • The treatment of inflammation following cataract surgery • The temporary relief of ocular itching due to seasonal allergic conjunctivitis
22-427	Ketorolac tromethamine ophthalmic solution 0.45% (Acuvail)	ACUVAIL ophthalmic solution is a NSAID indicated for the treatment of pain and inflammation following cataract surgery.
20-037	Diclofenac sodium ophthalmic solution 0.1% (Voltaren Ophthalmic)	VOLTAREN ophthalmic is indicated for the treatment of post-operative inflammation in patients who have undergone cataract extraction and for the temporary relief of pain and photophobia in patients undergoing corneal refractive surgery.

*NDA 21-664 is the reference listed drug for this 505(b) (2) application.

3. CMC

DRUG SUBSTANCE:

The applicant cross-referenced DMF (b) (4) to provide drug substance CMC information for bromfenac sodium. DMF (b) (4) was reviewed and was found adequate to support NDA 206911.



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). This drug substance is a bright orange to yellow powder of a (b) (4). Bromfenac is adequately soluble (≥ 0.5% w/w) over the pH range of (b) (4) to achieve the target drug product concentration of 0.075%. Stability data from the DMF holder support a retest period of (b) (4) months for bromfenac sodium drug substance manufactured at (b) (4) and stored at (b) (4)

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

Bromfenac ophthalmic solution, 0.075% drug product is a sterile, preserved, (b) (4) viscous, multidose eye drop in 7.5 mL white low density polyethylene (LDPE) bottles (5 mL fill) with clear LDPE dropper tips, gray high density polyethylene (HDPE) dropper caps and white LDPE tamper-evident overseal. Additionally, each bottle is enclosed in a (b) (4) sealed laminated (b) (4) foil pouch.

The active ingredient is bromfenac. Each mL of the drug product contains 0.76 mg of bromfenac as free acid, which is equivalent to 0.81 mg of bromfenac sodium. . DuraSite, InSite Vision's drug delivery system, is composed of (b) (4). DuraSite has been used in several approved drug products including AzaSite NDA# 50810.

Ingredient	Concentration (%w/w)	Function
Bromfenac sodium sesquihydrate	0.075	Active
Boric Acid, NF Sodium Borate, NF Citric Acid Anhydrous, USP Sodium Citrate Dihydrate, USP Poloxamer 407, NF	(b) (4)	
Benzalkonium Chloride, NF	0.005	(b) (4) preservative
Polycarbophil, USP Sodium Chloride Edetate Disodium Dihydrate, USP	(b) (4)	
(b) (4) Sodium Hydroxide, NF	Adjust to pH 8.3	pH adjustor
Water for Injection, USP	(b) (4)	

CONTAINER CLOSURE SYSTEM:

The proposed drug product is packaging in a 7.5 mL white LDPE bottle with a clear LDPE dropper tip

and a gray HDPE cap. The components of the container/closure system used are summarized in the table below. The 7.5 mL bottle is manufactured [redacted] The dropper tip is made from [redacted] the specification for the [redacted] is provided. The cap is a gray colored eyedropper cap made from HDPE [redacted]

Table 3.2.P.7-1: Container Closure System Components

Components Description	Material	Material Supplier	Component Manufacturer
White 7.5 mL bottle and tamper-evident overwrap	[redacted]		
[redacted] dropper tip			
[redacted] gray HDPE cap			
Bottle Label			
Secondary Laminated Foil Pouch			
Tertiary Packaging			

The average and range of drop sizes measured were very similar from the studied 3 batches with 2 fill volumes (2.5 mL and 5 mL). The average drop size is [redacted] mg.

PROPOSED REGULATORY SPECIFICATIONS:
Regulatory Specifications

Attribute	Acceptance Criterion
Bromfenac Identification HPLC Retention Time	Pass
Bromfenac Identification UV/Vis	Pass
Bromfenac concentration	(b) (4)%
Chromatographic Purity	(b) (4) (RRT (b) (4)) NMT (b) (4)%
	(b) (4) (RRT (b) (4)) NMT (b) (4)%
	Unspecified NMT (b) (4)%
	Total impurities NMT (b) (4)%
Appearance	Greenish-yellow to yellow
	(b) (4) translucent liquid
pH	(b) (4)
Osmolality	(b) (4) mOsm/Kg
Viscosity	(b) (4) cps
Benzalkonium Chloride	(b) (4)%
Particulates	(b) (4) NMT
	(b) (4) NMT
	(b) (4) NMT
Sterility	Sterile

It is noted that the specification for unspecified peaks in the chromatographic purity ((b) (4)%) is higher than usually accepted for ophthalmic products (i.e., 0.1%).

FACILITIES INSPECTIONS:
The facilities supporting manufacturing of drug substance and drug product for BromSite (bromfenac ophthalmic solution) 0.075%, NDA 206911, are assessed to be acceptable as of 2/27/2016.

The results of stability studies for 3 lots have been submitted with data through 30 months. In one lot, the appearance changed from yellow to orange at month 30. The applicant is investigating this change, but at present does not have a definitive explanation. (b) (4) Expiration dating will therefore be set at 24 months (the last time point within specifications for all three lots).

4. Nonclinical Pharmacology/Toxicology

Nonclinical data submitted to support approval of ISV-303 include comparative ocular distribution, pharmacokinetic and ocular toxicity assessment. Compared to BromDay/Xibrom, administration of ISV-303 resulted in approximately 4-fold higher levels in the sclera, choroid and aqueous humor and approximately 1.4-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.

The applicant proposed drug substance impurity specifications for stability which exceed those recommended in ICH guidance. 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 levels which exceed those proposed.

5. Clinical Pharmacology/Biopharmaceutics

The systemic exposure to bromfenac was assessed in a subgroup of patients enrolled in Study C-12-303-004 following topical ocular BID dosing of ISV-303. 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.

6. Sterility Assurance

The proposed expiration date is (b) (4) months (based on the 12 month stability results). Stability studies were conducted under long-term (25°C/40% RH) conditions. Sterility testing is performed initially and then annually through 36 months. The registration batch numbers 00313-B, -C, and –D were sterile under long-term conditions up to 12 months. The applicant has provided successful results verifying release and stability sterility testing per USP<71>. AET (per USP<51>) will be performed routinely for post-approval stability testing due to AET failures of multiple dose topical ophthalmic products preserved with benzalkonium chloride.

The applicant states that the first three commercial production batches will be placed on a long-term stability program. Every year thereafter, one production batch will be added to the program.

The applicant has provided sufficient results demonstrating the integrity of the container-closure as a microbial barrier.

The Division of Microbiology Assessment has reviewed NDA 206911 for BromSite (bromfenac ophthalmic solution) 0.075%, and found the microbiology information adequate. From a microbiology perspective, NDA 206911 is recommended for **APPROVAL.**

7. Clinical/Statistical - Efficacy

Study	Title	Treatment Groups	Population
C-11-303-003 Phase 3	A randomized double-masked study 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 BID (88) For 16 days (the day prior to surgery, the day of surgery and 14 days post-surgery).	Cataract surgical candidates ≥ 18 y/o
C-12-303-004 Phase 3	A randomized double-masked study 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 BID (94) For 16 days (the day prior to surgery, the day of surgery and 14 days post-surgery).	Cataract surgical candidates ≥ 18 y/o

The protocols for Study C-11-303-003 and C-12-303-004 were identical, with the following exceptions incorporated into Protocol C-12-303-004.

- The primary efficacy endpoint was changed from "the proportion of subjects with anterior chamber cell (ACC) Grade of 0 by Day 15" to "the proportion of subjects with ACC Grade of 0 at Day 15." It is important to note both studies were analyzed the same way; the language was prospectively clarified in this second Phase 3 study protocol.
- In order to assess the systemic exposure to bromfenac, a whole blood sample was collected from a subgroup of about 40 subjects on Days 1 and 15, and the bromfenac levels measured in the resultant plasma.
- A second pain measurement instrument was added by having subjects assess pain levels via the subject diary prior to administration of ISV-303.
- Subjects with a history of diabetic retinopathy were allowed if there was no visual impairment.
- Use of triamcinolone was prohibited within 90 days before surgery and throughout the dosing period.

Primary Efficacy Endpoint (US and EU)

- Proportion of subjects with an ACC grade of 0 at Day 15, was based on the mITT Population; the last observation carried forward (LOCF) was used to impute missing data. The difference between treatment with ISV-303 and Vehicle was tested using the chi-square test.

Secondary Efficacy Endpoint (VAS Pain Assessment)

- Proportion of subjects who achieve a pain score of 0 on the VAS (0 to 100 mm scale) at each postsurgical assessment.

Analysis of Primary Endpoint(s)

Study C-11-303-003: Proportion of Subjects with an ACC Grade of 0 in the Study Eye (mITT Population)

ACC Grade	ISV-303 N=168	Vehicle N=85	Adjusted p-value
Visit 3 (Day 1)			
0 (Did not receive rescue therapy)	3 (1.8%)	2 (2.4%)	1.000
0 (Received rescue therapy)	1 (0.6%)	0	
>0	164 (97.6%)	83 (97.6%)	
Visit 4 (Day 8)			
0 (Did not receive rescue therapy)	54 (32.1%)	7 (8.2%)	<0.001
0 (Received rescue therapy)	1 (0.6%)	2 (2.4%)	
>0	113 (67.3%)	76 (89.4%)	
Visit 5 (Day 15) Primary Endpoint			
0 (Did not receive rescue therapy)	96 (57.1%)	16 (18.8%)	<0.001
0 (Received rescue therapy)	2 (1.2%)	3 (3.5%)	
>0	70 (41.7%)	66 (77.6%)	
Visit 6 (Day 29)			
0 (Did not receive rescue therapy)	108 (64.3%)	23 (27.1%)	<0.001
0 (Received rescue therapy)	2 (1.2%)	3 (3.5%)	
>0	58 (34.5%)	59 (69.4%)	

Study C-12-303-004: Proportion of Subjects with an ACC Grade of 0 in the Study Eye (mITT Population)

ACC Grade	ISV-303 N=168	Vehicle N=85	Adjusted p-value
Visit 3 (Day 1)			
0 (Did not receive rescue therapy)	5 (3.0%)	1 (1.2%)	0.374
0 (Received rescue therapy)	0	0	
>0	163 (97.0%)	84 (98.8%)	
Visit 4 (Day 8)			
0 (Did not receive rescue therapy)	40 (23.8%)	8 (9.4%)	0.023
0 (Received rescue therapy)	0	0	
>0	128 (76.2%)	77 (90.6%)	
Visit 5 (Day 15) Primary Endpoint			
0 (Did not receive rescue therapy)	64 (38.1%)	19 (22.4%)	0.035
0 (Received rescue therapy)	0	0	
>0	104 (61.9%)	66 (77.6%)	
Visit 6 (Day 29)			
0 (Did not receive rescue therapy)	95 (56.5%)	36 (42.4%)	
0 (Received rescue therapy)	0	0	
>0	73 (43.5%)	49 (57.6%)	

Analysis of Secondary Endpoint(s)

Study C-11-303-003: Proportion of Subjects Who Achieved a Pain Score of 0 at Each Post-surgical VAS Assessment

Visit (Study Day) Pain Score of 0 (No rescue therapy)	ISV-303 N=168	Vehicle N=85	Adjusted p-value
Visit 3 (Day 1)	129 (76.8%)	41 (48.2%)	<0.001
Visit 4 (Day 8)	152 (90.5%)	33 (38.8%)	<0.001
Visit 5 (Day 15)	156 (92.9%)	37 (42.4%)	<0.001
Visit 6 (Day 29)	143 (85.1%)	40 (47.1%)	<0.001

Study C-12-303-004: Proportion of Subjects Who Achieved a Pain Score of 0 at Each Post-surgical VAS Assessment

Visit (Study Day) Pain Score of 0 (No rescue therapy)	ISV-303 N=168	Vehicle N=85	Adjusted p-value
Visit 3 (Day 1)	138 (82.1%)	53 (62.4%)	<0.001
Visit 4 (Day 8)	145 (86.3%)	43 (50.6%)	<0.001
Visit 5 (Day 15)	146 (86.9%)	49 (57.6%)	<0.001
Visit 6 (Day 29)	140 (83.3%)	51 (60.0%)	<0.001

Both clinical trials demonstrate statistical significance in the proportion of subjects who achieved reduction in inflammation and a pain score of 0 at each postsurgical VAS assessment. Analysis of the secondary efficacy endpoint was based on the mITT Population; the LOCF method was used to impute missing data.

Study C-11-303-003: Mean ACC Grade at Each Postsurgical Assessment by Visit (mITT Population)

ACC Grade	ISV-303 N=168	Vehicle N=85	Adjusted p-value
Visit 3 (Day 1) Mean (sd)	1.5 (0.7)	1.6 (0.8)	0.551
Visit 4 (Day 8) Mean (sd)	0.8 (0.7)	1.4 (0.9)	<0.001
Visit 5 (Day 15) Mean (sd)	0.5 (0.7)	1.2 (1.0)	<0.001
Visit 6 (Day 29) Mean (sd)	0.4 (0.7)	1.1 (1.0)	<0.001

Study C-12-303-004: Mean ACC Grade at Each Postsurgical Assessment by Visit (mITT Population)

ACC Grade	ISV-303 N=168	Vehicle N=85	Adjusted p-value
Visit 3 (Day 1) Mean (sd)	1.9 (1.0)	2.1 (0.9)	0.200
Visit 4 (Day 8) Mean (sd)	1.0 (0.8)	1.7 (1.0)	<0.001
Visit 5 (Day 15) Mean (sd)	0.8 (0.8)	1.3 (1.0)	<0.001
Visit 6 (Day 29) Mean (sd)	0.6 (0.8)	1.0 (1.1)	0.002

Two adequate and well controlled studies demonstrate the efficacy of BromSite (bromfenac ophthalmic solution) 0.075% for treatment of post-operative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

Common Adverse Events

Study C-11-303-003: Summary of All Treatment Emergent AEs by System Organ Class (Safety Population)

	Bromfenac Study 3 N=169	Bromfenac Study 4 N=170	Vehicle Study 3 N=85	Vehicle Study 4 N=85
Number of Treatment Emergent AEs	90	49	53	25
Number of Subjects with TEAEs	52		37	
Cardiac Disorders				
Coronary artery occlusion	1			
Bradycardia		1		
Eye disorders				
AC cells		1		
Anterior Chamber inflammation		5		3
Blepharitis	1			
Ciliary hyperemia	1			
Conjunctival hemorrhage		3		
Conjunctival hyperemia			1	1
Corneal deposit		1		
Corneal edema	2	1		1
Corneal opacity			1	
Corneal striae			1	
Corneal dystrophy		1		
CME	1	1	1	1
Diplopia	1			
Dry eye	1			1
Eye inflammation			2	
Eye irritation		1		1
Eye pain	8	4	11	2
Eyelid margin crusting	1			
Eyelid Ptosis				1
Foreign body sensation	3		1	1
Iritis	3	5	5	2
Lacrimation increased	1		1	
Lens dislocation		1		
Meibomian gland dysfunction	1			
Ocular discomfort	2		3	
Ocular hyperemia	0		1	
Ocular hypertension	16	17	3	5
Photophobia	1		4	
Photopsia		1		
Posterior capsular rupture	1			
Posterior capsule opacification		2		1
Punctate keratitis		3		1
Retinal hemorrhage		1	1	
Retinal tear	1			
Retinal vein occlusion		1		
Trichiasis	1			
Uveitis	1			
Visual acuity reduced				1
Visual impairment	1			
Vision blurred		1		

Vitreous floaters	4			
Vitreous adhesions		1		
Vitreous detachment				1
Vitreous loss		1		
GI disorders				
Abdominal distention	1			
Abdominal pain upper	1			
Colitis				1
Diarrhea	1			
Dyspepsia				1
Nausea	1	1	2	
Vomiting		1		
General Disorders				
Chest pain	1	1		
Instillation site pain	2		1	
Pain	0		1	1
Infections				
Bronchitis	0		1	
Endopthalmitis	0		1	
Influenza	1			
Nasopharyngitis		1		
Sepsis				1
Sinusitis	1	1		
Upper respiratory tract infection	1		1	
Urinary Tract Infection				1
Injury				
Corneal abrasion	1			1
Foreign body in eye		3		1
Incision site complication	0		1	
Ligament sprain	1			
Spinal compression fracture	1			
Investigations				
Pancreatic enzymes increased	1			
Metabolism disorders				
Dehydration				
Gout	0		1	
Hyperglycemia				
Hyperkalemia				
Musculoskeletal disorders				
Arthralgia	1			
Musculoskeletal stiffness	1			
Nervous system disorders				
Dizziness		2		
HA	4	1	5	
Migraine				1

Psychiatric disorders				
Bipolar disorders	1			
Depression	1			
Panic attack	1			
Respiratory disorders				
Cough	1			
Dyspnea		1		
Epistaxis	1			
Nasal congestion	1	1		
Pleurisy	1			
Skin disorders				
Contact dermatitis		1		
Hyperhidrosis		1		
Pruritis	1			
Pruritis generalized	1			
Rash	1	1		
Rosacea	1			
Skin wrinkling	1			
Vascular disorders				
Hyperemia	1		3	
HTN	2			

The most commonly reported adverse events following use of BromSite after cataract surgery include: anterior chamber inflammation (iritis), headache, vitreous floaters, eye pain and elevated intraocular pressure (ocular hypertension). These reactions were reported in roughly 1.2% to 8.1 % of patients.

8. Advisory Committee Meeting

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

9. Pediatrics

Safety and effectiveness of BromSite in pediatric patients below the age of 18 years has not been established. This application did not trigger PREA and was not presented at PERC.

10. Other Relevant Regulatory Issues

OSI
An Office of Scientific Investigations (OSI) audit was requested. The sites of Drs. Berdy, Walters, DaVanzo, and McLaurin were chosen because of their relatively large enrollment numbers.

Name of CI, Location	Protocol #/ Site #/ # of Subjects (enrolled)	Inspection Dates	Final Classification
Gregg Jonathan Berdy, M.D. Ophthalmology Associates 12990 Manchester Road, Suite 200 St. Louis, MO 63131	C-11-303-003/ 105/ 22	9-10 Sep 2015	NAI
Thomas R. Walters, M.D. Texan Eye, PA / Keystone Research, Ltd. 5717 Balcones Drive Austin, TX 78731	C-11-303-003/ 6/ 30	30 Oct-3 Nov 2015	NAI
Robert J. DaVanzo, M.D. Cornerstone Health Care 307 North Lindsay Street High Point, NC 27262	C-12-303-004/ 321/ 34	27 Jul-3 Aug 2015	NAI
Eugene B. McLaurin, M.D. Total Eye Care, P.A. 6060 Primacy Parkway, Suite 200 Memphis, TN 38119	C-12-303-004/ 264/ 21	21-23 Sep 2015	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

None of these sites were issued a Form FDA 483.The final classification of each of these inspections was No Action Indicated (NAI). The studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

FINANCIAL DISCLOSURE
The applicant has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity information as provided by the investigators, as defined in 21 CFR 54.2. There were no disclosed financial interests/arrangements. There is no evidence to suggest that the results of the study were impacted by any financial payments.

DIVISION OF MEDICATION ERROR PREVENTION AND ANALYSIS (DMEPA)
In a review finalized 9/14/2015, DMEPA has reviewed the proposed carton labeling, bottle label and prescribing information. DMEPA provided recommendations on the packaging configuration and the package insert labeling. These are incorporated into the Medical Officer's labeling where appropriate.

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

OFFICE OF PRESCRIPTION DRUG PROMOTION (OPDP)
In a review finalized 3/1/2016, OPDP has reviewed the proposed product labeling (i.e., package insert). These are incorporated into the Medical Officer's labeling where appropriate.

DIVISION OF MEDICAL POLICY PROGRAMS (DMPP)
In a review finalized 3/4/2016, DMPP has reviewed the proposed Instructions for Use. DMPP provided track changes and clean versions of the revised Instructions for Use. Two sentences, (b) (4) were deleted from the DMPP revision since this information was also removed from the package insert labeling.

11. Labeling

Listed below is the applicant's revised labeling:

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

12. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 206911, BromSite (bromfenac ophthalmic solution) 0.075%, is recommended for approval for treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

The most commonly reported adverse events following use of BromSite after cataract surgery include: anterior chamber inflammation (iritis), headache, vitreous floaters, eye pain and ocular hypertension. These reactions were reported in roughly 1% to 8% of patients.

RISK BENEFIT ASSESSMENT:
The benefits of using this drug product outweigh the risks for the above indication. Pharmacology/Toxicology, CMC, Biostatistics, Clinical, Clinical Pharmacology, and Product Quality Microbiology have recommended approval for this application.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:
There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events. There are no recommended Postmarketing Requirements or Phase 4 Commitments.

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/s/

WILEY A CHAMBERS
04/08/2016

CLINICAL REVIEW

Application Type	NDA
Submission Number	206-911
Submission Code	000
Letter Date	6/10/15
Stamp Date	6/10/15
PDUFA Goal Date	4/10/16
Reviewer Name	Sonal D. Wadhwa, MD
Review Completion Date	2/8/15
Established Name	bromfenac ophthalmic solution 0.075%
(Proposed) Trade Name	BromSite
Therapeutic Class	NSAID
Applicant	InSite Vision
Priority Designation	S
Formulation	ophthalmic solution
Dosing Regimen	Instill one drop to the affected eye twice daily (morning and evening) 1 day prior to surgery, the day of surgery, and 14 days post-surgery.
Indication	Treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery
Intended Population	Patients with post-operative inflammation and pain

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 206-911 is recommended for approval with the revised labeling identified in this review. The clinical studies contained in this submission support the use of BromSite for treatment of post-operative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

1.2 Risk Benefit Assessment

The benefits of using this drug product outweigh the risks for the above indication.

1.3 Recommendations for Post-marketing Risk Management Activities

There are no proposed risk management actions except the usual post-marketing collection and reporting of adverse experiences associated with the use of drug product.

1.4 Recommendations for other Post-Marketing Study Commitments

There are no recommended Phase 4 clinical study commitments.

2 Introduction and Regulatory Background

2.1 Product Information

BromSite (bromfenac ophthalmic solution) 0.075% was called ISV-303 during its drug development.

BromSite is a topical ophthalmic solution of 0.075% bromfenac, a nonsteroidal anti-inflammatory drug (NSAID), formulated in DuraSite®, InSite Vision's drug delivery vehicle. It 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 administered twice a day for 16 days (the day before surgery, the day of surgery, and 14 days after cataract surgery).

2.2 Tables of Currently Available Treatments for Proposed Indications

NDA	Drug	Indication
22-212	Difluprednate ophthalmic emulsion 0.05% (Durezol)	DUREZOL is a topical corticosteroid that is indicated for the treatment of inflammation and pain associated with ocular surgery. DUREZOL is also indicated for the treatment of endogenous anterior uveitis.
202-872	Loteprednol etabonate ophthalmic gel 0.5% (Lotemax)	LOTEMAX is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.
20-474	Rimexolone ophthalmic suspension 1% (Vexol)	VEXOL 1% (rimexolone ophthalmic suspension) is indicated for the treatment of post-operative inflammation following ocular surgery and in the treatment of anterior uveitis.
203-168	Bromfenac ophthalmic solution 0.07% (Prolensa)	PROLENSA is a NSAID indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.
21-664*	Bromfenac sodium ophthalmic solution 0.09% (Xibrom)	XIBROM is a NSAID indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.
21-664 201-211 202-030 203-395	Bromfenac sodium ophthalmic solution 0.09% (Bromday)	BROMDAY is a NSAID indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.
21-862	Nepafenac ophthalmic suspension 0.1% (Nevanac)	NEVANAC ophthalmic suspension is a NSAID indicated for the treatment of pain and inflammation associated with cataract surgery.
203-491	Nepafenac ophthalmic suspension 0.3% (Ilevro)	ILEVRO (nepafenac ophthalmic suspension), 0.3% is a NSAID indicated for the treatment of pain and inflammation associated with cataract surgery.
19-700	Ketorolac tromethamine ophthalmic solution 0.5% (Acular)	ACULAR ophthalmic solution is a NSAID indicated for: • The treatment of inflammation following cataract surgery • The temporary relief of ocular itching due to seasonal allergic conjunctivitis
22-427	Ketorolac tromethamine ophthalmic solution 0.45% (Acuvail)	ACUVAIL ophthalmic solution is a NSAID indicated for the treatment of pain and inflammation following cataract surgery.
20-037	Diclofenac sodium ophthalmic solution 0.1% (Voltaren Ophthalmic)	VOLTAREN ophthalmic is indicated for the treatment of post-operative inflammation in patients who have undergone cataract extraction and for the temporary relief of pain and photophobia in patients undergoing corneal refractive surgery.

*NDA 21-664 is the referenced drug for this 505(b) (2) application.

2.3 Availability of Proposed Active Ingredient in the United States

NDA 21-664: Xibrom (bromfenac ophthalmic solution) 0.09%

Bromday (bromfenac ophthalmic solution) 0.09%

NDA 203-168: Prolensa (bromfenac ophthalmic solution) 0.07%

As of August 2014, five (5) generic bromfenac ophthalmic solutions 0.09% have been approved:

ANDA 201-211
ANDA 202-030
ANDA 202-435
ANDA 202-620
ANDA 203-395

2.4 Important Safety Issues With Consideration to Related Drugs

Several AEs have been identified as specifically NSAID-related and are frequently observed with the use of ophthalmic NSAIDs including: transient burning, stinging, hyperaemia of the conjunctiva and hypersensitivity reactions. Other characteristic NSAID-related ocular AEs include increased bleeding time (including hyphemas), delayed healing, keratitis, and corneal changes (Ilevro, Nevanac, Xibrom, Bromday and Prolensa label).

2.5 Summary of Pre-Submission Regulatory Activity Related to Submission

PIND 107723 meeting	4/26/10
EOP2 meeting	2/17/12
Pre-NDA meeting	1/13/14
Pre-NDA meeting	4/15/14

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

DSI was consulted for routine inspections. The clinical sites of Drs. Berdy, Walters, DaVanzo, and McLaurin were inspected in support of this NDA. None of these sites were issued a Form FDA 483. The final classification of each of these inspections was No Action Indicated (NAI). The studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

3.2 Compliance with Good Clinical Practices

There is no evidence to suggest that the clinical trials were not conducted in compliance with good clinical practices.

3.3 Financial Disclosures

See Attachment 1 for Financial Disclosures template.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

BromSite is a topical ophthalmic solution of 0.075% bromfenac, a NSAID, formulated in DuraSite®, InSite Vision's drug delivery vehicle. It 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 administered twice a day for 16 days (the day before surgery, the day of surgery, and 14 days after cataract surgery).

BromSite is formulated with the drug substance bromfenac sodium sesquihydrate (equivalent to 0.075% bromfenac free acid) in the (b) (4) is comprised of polycarbophil, edetate disodium (EDTA) dihydrate, sodium chloride, water for injection, and sodium hydroxide to adjust pH (b) (4) boric acid, sodium borate, citric acid anhydrous, sodium citrate dihydrate, benzalkonium chloride (0.005%), and poloxamer 407. ISV-303 has target parameters for pH and osmolality of approximately 8.3 and 290 mOsm/kg, respectively.

BromSite is filled in white low density polyethylene (LDPE) bottles (5 mL capacity) with clear LDPE dropper tips, gray high density polyethylene (HDPE) dropper caps and white LDPE tamper-evident overseal. Additionally, each bottle is enclosed in a (b) (4) sealed laminated (b) (4) foil pouch. ISV-303 is to be stored at room temperature (15° – 25°C). Long term stability data (25°C ± 2°C/40% Relative Humidity (RH) ± 5%RH) of 12-month duration on the pouched drug product is provided with this submission. ISV-303 has also been shown to be stable for 30 days after the bottle is removed from its foil laminate pouch when used by the patient for a standard 16-day course of therapy.

4.2 Clinical Microbiology

This product is not an anti-infective.

4.3 Pre-clinical Pharmacology/Toxicology

Ocular toxicity study was performed for BromSite. Rabbit (Dutch Belted or New Zealand White) was selected as the species for assessing topical ocular pharmacokinetics and toxicity of ISV-303 due to the historical use of this species in assessment of ocular toxicity, the ocular structural similarity to humans, as well as pharmacodynamic data indicating activity of bromfenac in this species. See Pharm/Tox review for more details.

This application is a 505(b)(2) referencing NDA 21-664 (BromDay) for additional support for the Pharm/Tox. The non-clinical testing plan for ISV-303 was designed to supplement the existing published data on bromfenac following oral and intravenous administration with data on ocular administration of ISV-303. For pharmacology and studies such as carcinogenicity, genotoxicity, reproductive toxicology, drug interaction, excretion, and metabolism, InSite will rely on the FDA general findings of safety and effectiveness of the listed drug Bromday/Xibrom (NDA 21-664). InSite Vision conducted a non-clinical study in rabbits which demonstrated that the plasma levels of bromfenac following topical ocular administration of BromSite were comparable to those obtained with the listed drug Bromday (Study No. S11135).

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Nonsteroidal anti-inflammatory agents, including bromfenac, have been demonstrated to inhibit cyclooxygenase (COX), also known as prostaglandin (PG) H2 synthase. Cyclooxygenase enzymes are present in many organs and body tissues, and are key enzymes that convert arachidonic acid to PGs. Prostaglandins are lipid compounds that regulate a number of physiologic processes, including trauma-, or injury-induced inflammation. There are two major isoforms of COX: COX-1 and COX-2.1 COX-1 is a ubiquitous protein found constitutively in many body tissues and has a key role in many physiologic functions, such as gastric protection and platelet aggregation. COX-2 is an inducible enzyme that is released during, and contributes to, the inflammatory process. Prostaglandins are major mediators of inflammation that can lead to pain and photophobia, in a majority of patients.

4.4.2 Pharmacodynamics

No human pharmacodynamic or drug-drug interaction studies were conducted by InSite Vision for ISV-303.

4.4.3 Pharmacokinetics

Two human pharmacokinetic (PK) studies were conducted during the ISV-303 drug development program. The Phase 2 clinical study, Study No. C-11-303-002, was conducted to determine the AH (aqueous humor) concentration of bromfenac after ocular dosing of either

ISV-303 or Bromday, and a substudy to the Phase 3 study, Study No. C-12-303-004, was conducted to determine the systemic concentration of bromfenac after ocular dosing of ISV-303.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Study	Title	Study Design	Treatment Groups	Population
C-10-303-001 Phase 1/2	A randomized double-masked 14-day study 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	Multi-center, randomized, double-masked, 4- arm	ISV-303 BID (40) ISV-303 QD (45) Xibrom BID (42) Vehicle BID (42) All for 14 days post-surgery	Subjects ≥ 18 y/o who have Undergone uncomplicated unilateral cataract surgery
C-11-303-002 Phase 2	A double-masked clinical study 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	Double-masked, multi-center, randomized, 2-arm	ISV-303 (30) Bromday QD (30) For 2 days prior to surgery and the morning of surgery.	Subjects ≥ 18 y/o who have undergone uncomplicated unilateral cataract surgery
C-11-303-003 Phase 3	A randomized double-masked study to compare the ocular safety, tolerability, and efficacy of ISV-303 (0.075% bromfenac in DuraSite) to DuraSite vehicle in cataract surgery subjects	Double-masked, randomized, multi-center, 2-arm	ISV-303 (0.075%) (180) DuraSite Vehicle BID (88) For 16 days (the day prior to surgery, the day of surgery and 14 days post-surgery).	Subjects ≥ 18 y/o who have undergone uncomplicated unilateral cataract surgery
C-11-303-004 Phase 3	A randomized double-masked study to compare the ocular safety, tolerability, and efficacy of ISV-303 (0.075% bromfenac in DuraSite) to DuraSite vehicle in cataract surgery subjects	Double-masked, randomized, multi-center, 2-arm	ISV-303 (0.075%) (174) DuraSite Vehicle BID (94) For 16 days (the day prior to surgery, the day of surgery and 14 days post-surgery).	Subjects ≥ 18 y/o who have undergone uncomplicated unilateral cataract surgery

5.2 Review Strategy

The sources of clinical data utilized in this review include the studies listed in section 5.1.

5.3 Discussion of Individual Studies

Study C-11-303-003

The objective of this study was 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 BID beginning 1 day prior to cataract surgery, the day of surgery, and then continuing for 14 days after surgery.

This study was a multicenter, randomized, double-masked, vehicle-controlled, parallel-group clinical trial designed to evaluate the ocular safety, tolerability, and efficacy of topical administration of ISV-303 compared with DuraSite vehicle when dosed BID beginning 1 day prior to cataract surgery, the day of surgery, and then continuing for 14 days after surgery. The study consisted of 3 phases:

- Screening/Randomization Phase: Up to 2 weeks before surgery/start of treatment
- Dosing Phase: 16 days of treatment, BID
- Evaluation Phase: 14 ± 2 days after treatment end

Six visits were required for full study participation, including the dosing phase and the evaluation phase. Subjects were to exit the study on Visit 6 (Day 29).

Inclusion Criteria

- Male or female subjects age 18 or older, scheduled for unilateral cataract surgery (phacoemulsification or extracapsular extraction) with posterior chamber intraocular lens implantation
- If female of childbearing potential, she must have agreed to and submitted to a negative pregnancy test before any protocol-specific procedures were conducted. The subject must have used effective contraception for the duration of the study. Suitable methods were defined as spermicide with barrier, oral contraceptive, transdermal contraceptive, injectable or implantable contraceptive, intrauterine device (specified in medical history), abstinence, or surgical sterilization of partner. Female subjects who were not of childbearing potential included those who had undergone a hysterectomy, bilateral oophorectomy, or a bilateral tubal ligation; those who had been postmenopausal for at least 12 months; or those who were premenarchal.
- Had signed the ICF
- 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)
- Were willing to avoid disallowed medications for the duration of the study

- Were willing and able to follow all instructions and attend all study visits
- Were able to self-administer study drug, or had a caregiver available to instill all doses of the study drug, as instructed
- IOP of > 8 mmHg and ≤ 22 mmHg in the study eye

Exclusion Criteria

- Had any history of liver disease within the last 5 years
- Had a history of Fuchs' dystrophy in the study eye
- Had a history of diabetic retinopathy and/or previous vitrectomy in the study eye within the last 2 years
- Had any sign of iritis or scleritis in the study eye
- Had a history of glaucoma surgery in the study eye within the last 2 years
- Had an existing diagnosis of severe dry eye in the study eye
- Had a known hypersensitivity or poor tolerance to bromfenac sodium or any component of the study drug or any of the procedural medications such as anesthetic and/or fluorescein drops, dilating drops, etc.
- Had a known hypersensitivity to salicylates (aspirin) or other NSAIDs
- Had any active or chronic/recurrent ocular or systemic disease that was uncontrolled and likely to have affected wound healing (ie. diabetes mellitus, systemic connective tissue disease, severe atopic disease)
- Had a known blood dyscrasia or bone marrow suppression
- Had any active corneal pathology noted in the study eye
- Had any extraocular/intraocular inflammation in the study eye noted prior to surgery (blepharitis was allowed if scurf only without any concurrent conjunctivitis or lid erythema/edema) or ongoing, unresolved uveitis
- Had any intraocular inflammation (cells or flare in anterior chamber) or ocular pain (greater than 0) on the pain scale in either eye
- Had undergone radial keratotomy, corneal transplant, or LASIK in the study eye within the last 2 years
- If female, were currently pregnant or nursing, were planning a pregnancy, or had a positive pregnancy test
- Were suffering from alcohol and/or drug abuse
- Had prior participation in this study protocol
- Had prior (within 30 days of beginning study treatment) or anticipated having concurrent use of an investigational drug or device
- Had a condition or a situation which, in the investigator's opinion, might have put the subject at increased risk, confounded study data, or interfered significantly with the subject's study participation
- Would be wearing contact lens during the dosing period on Days -1 to Day 15
- Had used any medication the investigator thought might have interfered with the study parameters

Subjects were randomly assigned to receive either ISV-303 or DuraSite vehicle for 16 days BID beginning 1 day prior to cataract surgery, the day of surgery, and then continuing for 14 days after surgery. Subjects were instructed to store study drug at room temperature and to administer 2 doses on Day -1 in the study eye; 1 dose on Day 0 prior to cataract surgery, 1 dose the evening after surgery; and to continue dosing BID at approximately 12-hour intervals for 14 days after surgery. Subjects were given a dosing diary to record study drug application dates and times.

The following study formulations were used in this study:

- ISV-303 (0.075% bromfenac in DuraSite) contains bromfenac sodium sesquihydrate (equivalent to 0.075% bromfenac free acid), boric acid, sodium borate, citric acid anhydrous, sodium citrate dihydrate, poloxamer 407, sodium hydroxide (b) (4) (polycarbophil, sodium chloride, edetate disodium dihydrate), and water for injection. The formulation is preserved with benzalkonium chloride (0.005%).
- (b) (4) contains boric acid, sodium borate, citric acid anhydrous, sodium citrate dihydrate, poloxamer 407, sodium hydroxide (b) (4) polycarbophil, sodium chloride, edetate disodium dihydrate), and water for injection. The formulation is preserved with benzalkonium chloride (0.005%).

Study Plan

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) (12 to 48 hours after last dose)	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				

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) (12 to 48 hours after last dose)	Visit 6 Day 29 (± 2)
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

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.

Efficacy Measurements

Grading for AC Cell Counts (ACC)

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

Grading for AC Flare (ACF)

Grade	Finding
0	None: No haze detected
1	Mild: A faint haze 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

VAS Pain Assessment

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. The investigator or study staff turned the scale over and recorded the associated measurement (0 mm = absent to 100 mm = maximum).

Primary Efficacy Endpoint (US and EU)

- Proportion of subjects with an ACC grade of 0 at Day 15, was based on the mITT Population; the last observation carried forward (LOCF) was used to impute missing data. The difference between treatment with ISV-303 and Vehicle was tested using the chi-square test.

Secondary Endpoint (US)

- The proportion of subjects who achieved a pain score of 0 at each postsurgical VAS assessment. Analysis of the secondary efficacy endpoint was based on the mITT Population; the LOCF method was used to impute missing data. 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.

Secondary Endpoints (EU)

- The proportion of subjects who achieved a pain score of 0 at each postsurgical VAS assessment. Analysis of the secondary efficacy endpoint was based on the mITT Population; the LOCF method was used to impute missing data.

- The proportion of subjects with an ACF grade of 0 at Day 15 (note: this is also a US secondary analysis). The proportion of subjects with an ACF grade of 0 at Day 15 was calculated for each treatment group. Analysis of the secondary efficacy endpoint was based on the mITT Population; LOCF method was used to impute missing data. The difference in proportions between the treatment groups was calculated using the chi-square.

Investigators for Study C-12-303-003

Table 1: Investigators and Study Sites

Site #	Principal Investigator	Study Location	Number of Subjects Enrolled
006	Thomas Walters, MD	Texan Eye, PA/Keystone Research, Ltd. 5717 Balcones Dr. Austin, TX 78731	30
008	Daniel Long, MD	120 Meadowcrest Street, Suite 330 Gretna, LA 70056	11
053	Leonard Cacioppo, MD	Hernando Eye Institute 14543 Cortez Blvd. Brooksville, FL 34613	8
079	Michael H Rotberg, MD	Charlotte Eye Ear Nose and Throat 6035 Fairview Road Charlotte, NC 28210	2
102	Harvey Reiser, MD	Eye Care Specialists 703 Rutter Avenue Kingston, PA 18704	20
104	Jason Bacharach, MD	North Bay Eye Associates, Inc. 104 Lynch Creek Way, Suite 12 Petaluma, CA 94954	10
105	Gregg Berdy, MD	Ophthalmology Associates 12990 Manchester Road, #200 St. Louis, MO 63131	22
144	Steven M Silverstein, MD	Silverstein Eye Centers Independence Office 4240 Blue Ridge Blvd., Suite 1000 Kansas City, MO 64133	10
159	Jung Dao, MD	Cornea Consultants of Arizona 3815 E. Bell Road, Suite 2500 Phoenix, AZ 85032	24
236	David L Cooke, MD	Great Lakes Eye Care 2848 Niles Road St. Joseph, MI 49085	28
273	Mark Bergmann, MD	Eye Care Associates of Greater Cincinnati, Inc. Western Hills Location 2859 Boudinot Avenue, Suite 301 Cincinnati, OH 45238	23
298	Bernard Perez, MD	International Research Center 4506 Wishart Place Tampa, FL 33603	24
299	Robert Smyth-Medina, MD	North Valley Eye Medical Group, Inc. 11550 Indian Hills Road, Suite 341 Mission Hills, CA 91345	16
301	Jodi Luchs, MD	South Shore Eye Care, LLP 2185 Wantagh Avenue Wantagh, NY 11793	10
321	Robert J DaVanzo, MD	Cornerstone Health Care 307 North Lindsay Street High Point, NC 27262	30

Study C-12-303-004

The protocols for Study C-11-303-003 and C-12-303-004 were identical, with the following exceptions incorporated into Protocol C-12-303-004.

- The primary efficacy endpoint was changed from "the proportion of subjects with anterior chamber cell (ACC) Grade of 0 by Day 15" to "the proportion of subjects with ACC Grade of 0 at Day 15." It is important to note both studies were analyzed the same; the language was prospectively clarified in this second Phase 3 study protocol.
- In order to assess the systemic exposure to bromfenac, a whole blood sample was collected from a subgroup of about 40 subjects on Days 1 and 15, and the bromfenac levels measured in the resultant plasma.
- A second pain measurement instrument was added by having subjects assess pain levels via the subject diary prior to administration of ISV-303.
- Subjects with a history of diabetic retinopathy were allowed if there was no visual impairment.
- Use of triamcinolone was prohibited within 90 days before surgery and throughout the dosing period.

Investigators for Study C-12-303-003

Site No.	Principal Investigator	Study Location	Number of Subjects Enrolled
092	James D Branch, MD	224 Town Run Lane Winston-Salem, NC 27101	31
096	Barry Katzman, MD	West Coast Eyecare Associates 6945 El Cajon Blvd. San Diego, CA 92115	8
104	Jason Bacharach, MD	North Bay Eye Associates, Inc. 104 Lynch Creek Way, Ste. 12 Petaluma, CA 94954	4
105	Gregg J Berdy, MD	Ophthalmology Associates 12990 Manchester Road, Ste. 200 St. Louis, MO 63131	24
143	David G Shulman, MD	999 E. Basse Road, Ste. 127 San Antonio, TX 78209	0
159	Jung T Dao, MD	Cornea Consultants of Arizona 3815 E. Bell Road, Ste. 2500 Phoenix, AZ 85032	26
236	David L Cooke, MD	Great Lakes Eye Care 2848 Niles Road St. Joseph, MI 49085	33
264	Eugene B McLaurin, MD	Total Eye Care, P.A. 6060 Primacy Parkway, Ste. 200 Memphis, TN 38119	21
304	Michael J Depenbusch, MD	Arizona Eye Center 604 W. Warner Road, Ste. B-6 Chandler, AZ 85225	16
305	Joseph Tauber, MD	Tauber Eye Center 4400 Broadway, Ste. 202 Kansas City, MO 64111	0
314	David Louis Wirta, MD	Eye Research Foundation 520 Superior Ave., Ste. 235 Newport Beach, CA 92663	10
316	Joseph R Martel, MD	Martel Eye Medical Group 11216 Trinity River Drive Rancho Cordova, CA 95670	19
321	Robert J DaVanzo, MD	Cornerstone Health Care 307 North Lindsay Street High Point, NC 27262	34

Site No.	Principal Investigator	Study Location	Number of Subjects Enrolled
324	Sanjiv Ramesh Kumar, MD	DCT Kumar, LLC DBA: Discovery Clinical Trials 927 East Main Street Uvalde, TX 78801	5
325	Andrew Gardner Logan, MD	Andrew Gardner Logan DBA: Logan Ophthalmic Research, LLC 7401 N. University Dr., Ste. 201 Tamarac, FL 33321	19
326	Navin Tekwani, MD	Tekwani Vision Center 9911 Kennerly Road, Ste. A St. Louis, MO 63128	18

6 Review of Efficacy

Efficacy Summary

6.1 Indication

6.1.1 Methods

The support for efficacy is from 2 clinical studies (Studies C-11-303-003 and C-11-303-004).

6.1.2 Demographics

Study C-11-303-003: Subject Demographics (mITT Population)

Demographic	**ISV-303 N=168**	**Vehicle N=85**
Age		
Mean	68.9	68.4
Min, max	24, 87	33, 87
<65 years	47	25
>=65 years	121	60
Gender		
Male	60	35
Female	108	50
Ethnicity		
Hispanic or Latino	22	7
Non-Hispanic or Latino	146	78
Race		
American Indian or Alaskan Native	1	0
African American	13	10
Asian	9	3
Caucasian	145	71
Native Hawaiian	0	1
Iris Color		
Blue	47	27
Brown	79	42
Green	21	1
Hazel	21	15

Study C-11-303-004: Subject Demographics (mITT Population)

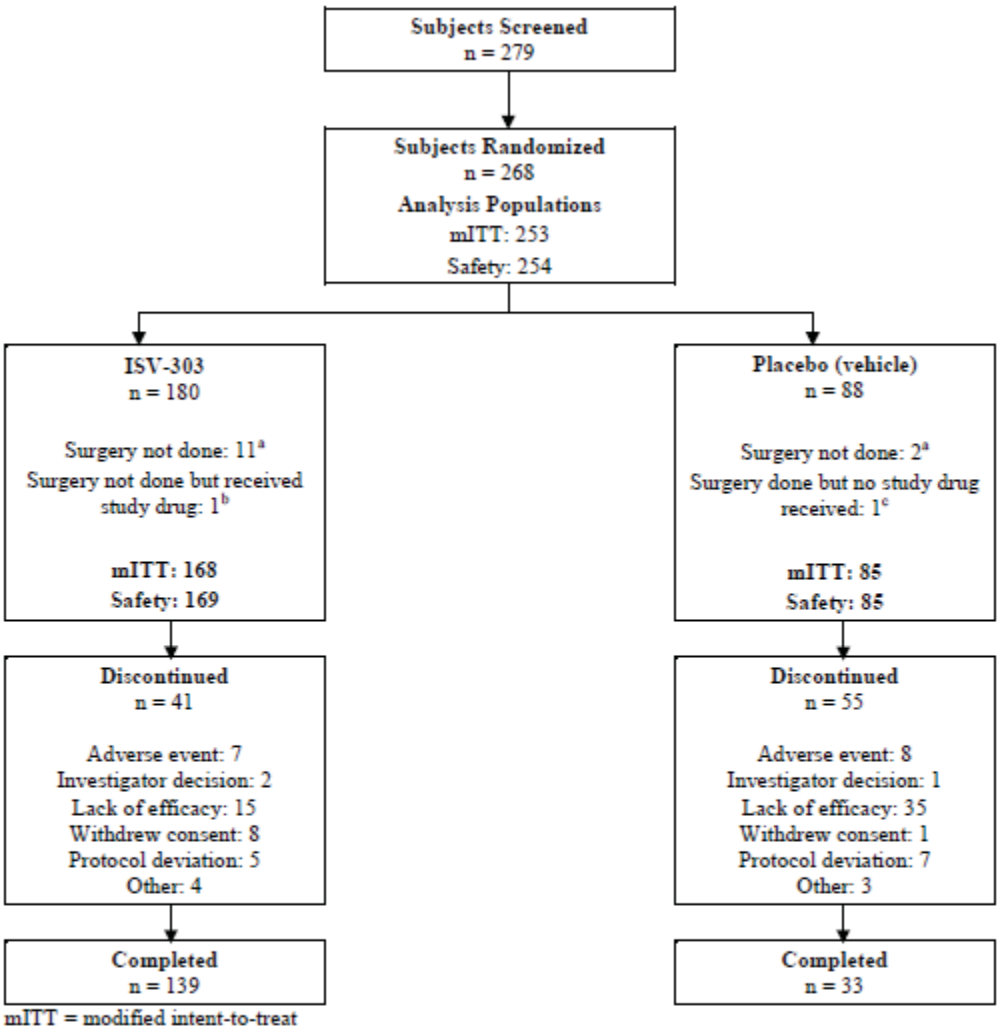
Demographic	ISV-303 N=168	Vehicle N=85
Age		
Mean	69.6	72.0
Min, max	47, 91	45, 89
<65 years	44	16
>=65 years	124	69
Gender		
Male	63	37
Female	105	48
Ethnicity		
Hispanic or Latino	20	11
Non-Hispanic or Latino	148	74
Race		
African American	28	10
Asian	8	3
Caucasian	129	70
Other	3	2
Iris Color		
Blue	50	25
Brown	80	39
Grey	2	0
Green	11	4
Hazel	25	17

6.1.3 Patient Disposition

Study C-11-303-003: Subject Disposition (All Screened Subjects)

Subject disposition	ISV-303	Vehicle
Randomized	180	88
mITT Population	168	85
Safety Population	169	85
Completed the Study	139	33
Discontinued the Study Early	41	55
Reasons for Early Discontinuation		
AE	7	8
Investigator decision	2	1
Lack of Efficacy	15	35
Subject Withdrew Consent	8	1
Protocol Deviation	5	7
Other	4	3

Figure 2: Subject Disposition



mITT = modified intent-to-treat

[a] Fourteen subjects did not undergo cataract surgery as planned (Table 8).

[b] Subject 079-004 was randomized to the ISV-303 group but did not have cataract surgery performed. He received one dose of study drug prior to the intended surgery and then withdrew from study, and thus is included in the Safety Population.

[c] Subject 321-009 was randomized to the Vehicle group and had cataract surgery, but was withdrawn from the study before receiving any study drug and is not included in either the Safety Population or the mITT Population.

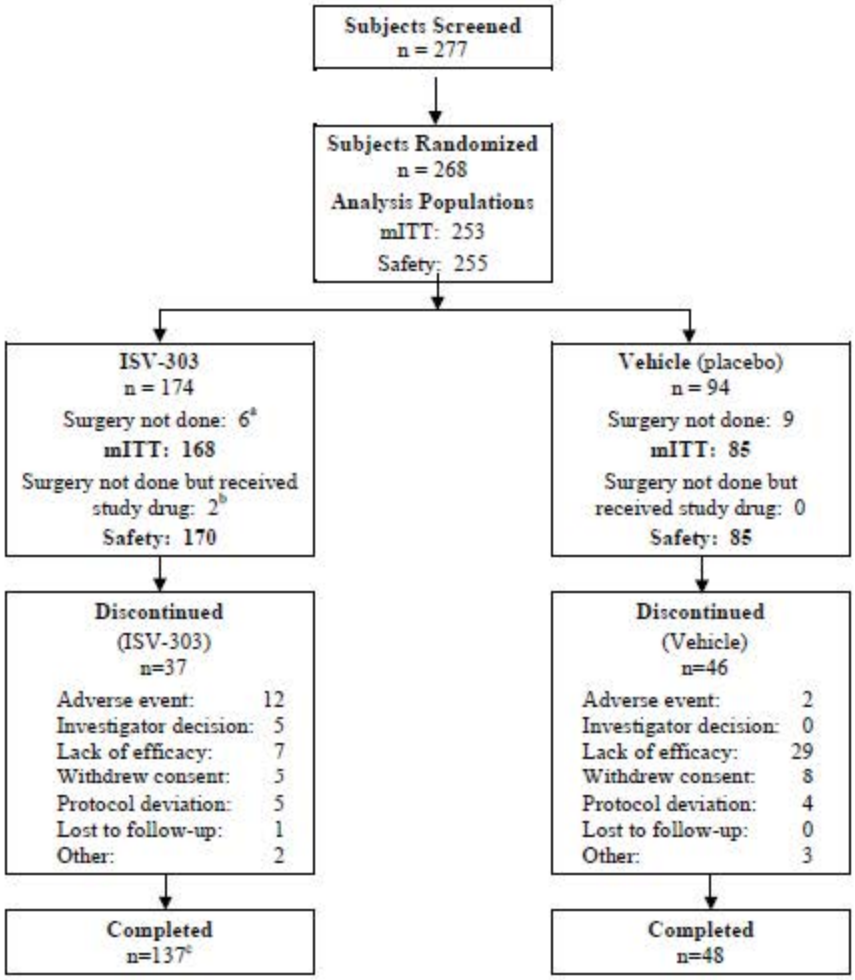
Data Sources: Table 14.1.1; Listing 16.2.1.1, and Listing 16.2.1.2

Study C-11-303-004: Subject Disposition (All Screened Subjects)

Subject disposition	ISV-303	Vehicle
Randomized	174	94
mITT Population	168	85
Safety Population	170	85
Completed the Study	137	48
Discontinued the Study Early	37	46
Reasons for Early Discontinuation		
AE	12	2
Investigator decision	5	0

Lack of Efficacy	7	29
Subject Withdrew Consent	5	8
Protocol Deviation	5	4
Lost to f/u	1	0
Other	2	3

Figure 2: Subject Disposition



mITT = modified intent-to-treat.

[a]Includes Subject 159-022 who did not have surgery performed and was initially reported not to have received study drug and was not included in either the mITT or Safety Populations. However, post database lock, the subject was found to have received 2 doses of study drug prior to the intended surgery.

[b]Subjects 264-010 and 264-012 were randomized to the ISV-303 group, did not have surgery performed, but did receive study drug prior to the intended surgery and study withdrawal; thus, they were included in the Safety Population but not the mITT.

[c]Two subjects in the ISV-303 group (Subjects 314-04 and 314-010) discontinued the same day as Day 29 (Visit 6).

Data Source: Table 14.1.1; Listings 16.2.1.1, 16.2.1.2

6.1.4 Analysis of Primary Endpoint(s)

Definition of Study Populations:
Safety Population: subjects who were randomized into the study and took at least 1 dose of study drug, regardless of cataract surgery having been performed or not.

Intent-to-Treat (ITT): all randomized subjects

Modified Intent-to-Treat (mITT): all subjects who:

- were randomized into the trial, and
- underwent cataract surgery, and
- received at least one dose of study drug

Study C-11-303-003: Primary Efficacy Endpoint Results-Proportion of Subjects with an ACC Grade of 0 in the Study Eye at Day 15 (mITT)

ACC Grade	ISV-303 N=168	Vehicle N=85	Adjusted p-value
0 (Did not receive rescue therapy)	96 (57.1%)	16 (18.8%)	<0.001
0 (Received rescue therapy)	2 (1.2%)	3 (3.5%)	
>0	70 (41.7%)	66 (77.6%)	

Study C-11-303-004: Primary Efficacy Endpoint Results-Proportion of Subjects with an ACC Grade of 0 in the Study Eye at Day 15 (mITT)

ACC Grade	ISV-303 N=168	Vehicle N=85	Adjusted p-value
0 (Did not receive rescue therapy)	64 (38.1%)	19 (22.4%)	0.035
0 (Received rescue therapy)	0	0	
>0	104 (61.9%)	66 (77.6%)	

Reviewer Comments: *Both clinical trials demonstrate statistical significance for the primary efficacy endpoint in the specified mITT population.*

6.1.5 Analysis of Secondary Endpoints(s)

Study C-11-303-003: Proportion of Subjects Who Achieved a Pain Score of 0 at Each Post-surgical VAS Assessment

Visit (Study Day) Pain Score of 0 (No rescue therapy)	ISV-303 N=168	Vehicle N=85	Adjusted p-value
Visit 3 (Day 1)	129 (76.8%)	41 (48.2%)	<0.001
Visit 4 (Day 8)	152 (90.5%)	33 (38.8%)	<0.001
Visit 5 (Day 15)	156 (92.9%)	37 (42.4%)	<0.001
Visit 6 (Day 29)	143 (85.1%)	40 (47.1%)	<0.001

Study C-11-303-004: Proportion of Subjects Who Achieved a Pain Score of 0 at Each Post-surgical VAS Assessment

Visit (Study Day) Pain Score of 0 (No rescue therapy)	ISV-303 N=168	Vehicle N=85	Adjusted p-value
Visit 3 (Day 1)	138 (82.1%)	53 (62.4%)	<0.001
Visit 4 (Day 8)	145 (86.3%)	43 (50.6%)	<0.001
Visit 5 (Day 15)	146 (86.9%)	49 (57.6%)	<0.001
Visit 6 (Day 29)	140 (83.3%)	51 (60.0%)	<0.001

Reviewer Comments: *Both clinical trials demonstrate statistical significance in the proportion of subjects who achieved a pain score of 0 at each postsurgical VAS assessment. Analysis of the secondary efficacy endpoint was based on the mITT Population; the LOCF method was used to impute missing data.*

6.1.6 Other Endpoints

Study C-11-303-003: Proportion of Subjects with an ACF (Anterior Chamber Flare) Grade of 0 at Day 15 (mITT Population)

ACF Grade	ISV-303 N=168	Vehicle N=85	Adjusted p-value
0 (Did not receive rescue therapy)	135 (80.4%)	30 (35.3%)	<0.001
0 (Received rescue therapy)	3 (1.8%)	11 (12.9%)	<0.001
>0	30 (17.9%)	44 (51.8%)	<0.001

Study C-11-303-004: Proportion of Subjects with an ACF (Anterior Chamber Flare) Grade of 0 at Day 15 (mITT Population)

ACF Grade	ISV-303 N=168	Vehicle N=85	Adjusted p-value
0 (Did not receive rescue therapy)	147 (87.5%)	45 (52.9%)	<0.001
0 (Received rescue therapy)	1 (0.6%)	7 (8.2%)	<0.001
>0	20 (11.9%)	33 (38.8%)	<0.001

Study C-11-303-003: Proportion of Subjects with an ACC Grade of 0 in the Study Eye at Day 1, Day 8, and Day 29 (mITT Population)

ACC Grade	ISV-303 N=168	Vehicle N=85	Adjusted p-value
Visit 3 (Day 1)			
0 (Did not receive rescue therapy)	3 (1.8%)	2 (2.4%)	1.000
0 (Received rescue therapy)	1 (0.6%)	0	

>0	164 (97.6%)	83 (97.6%)	
Visit 4 (Day 8)			
0 (Did not receive rescue therapy)	54 (32.1%)	7 (8.2%)	<0.001
0 (Received rescue therapy)	1 (0.6%)	2 (2.4%)	
>0	113 (67.3%)	76 (89.4%)	
Visit 6 (Day 29)			
0 (Did not receive rescue therapy)	108 (64.3%)	23 (27.1%)	<0.001
0 (Received rescue therapy)	2 (1.2%)	3 (3.5%)	
>0	58 (34.5%)	59 (69.4%)	

Study C-11-303-004: Proportion of Subjects with an ACC Grade of 0 in the Study Eye at Day 1, Day 8, and Day 29 (mITT Population)

ACC Grade	**ISV-303 N=168**	**Vehicle N=85**	**Adjusted p-value**
Visit 3 (Day 1)			
0 (Did not receive rescue therapy)	5 (3.0%)	1 (1.2%)	0.374
0 (Received rescue therapy)	0	0	
>0	163 (97.0%)	84 (98.8%)	
Visit 4 (Day 8)			
0 (Did not receive rescue therapy)	40 (23.8%)	8 (9.4%)	0.023
0 (Received rescue therapy)	0	0	
>0	128 (76.2%)	77 (90.6%)	
Visit 6 (Day 29)			
0 (Did not receive rescue therapy)	95 (56.5%)	36 (42.4%)	
0 (Received rescue therapy)	0	0	
>0	73 (43.5%)	49 (57.6%)	

Study C-11-303-003: Proportion of Subjects with an ACF Grade of 0 in the Study Eye at Day 1, Day 8, and Day 29 (mITT Population)

ACC Grade	**ISV-303 N=168**	**Vehicle N=85**	**Adjusted p-value**
Visit 3 (Day 1)			
0 (Did not receive rescue therapy)	38 (22.6%)	22 (25.9%)	0.564
0 (Received rescue therapy)	2 (1.2%)	0	

>0	128 (76.2%)	63 (74.1%)	
Visit 4 (Day 8)			
0 (Did not receive rescue therapy)	111 (66.1%)	19 (22.4%)	<0.001
0 (Received rescue therapy)	3 (1.8%)	8 (9.4%)	
>0	54 (32.1%)	58 (68.2%)	
Visit 6 (Day 29)			
0 (Did not receive rescue therapy)	142 (84.5%)	34 (40.0%)	<0.001
0 (Received rescue therapy)	3 (1.8%)	11 (12.9%)	
>0	23 (13.7%)	40 (47.1%)	

Study C-11-303-004: Proportion of Subjects with an ACF Grade of 0 in the Study Eye at Day 1, Day 8, and Day 29 (mITT Population)

ACC Grade	**ISV-303 N=168**	**Vehicle N=85**	**Adjusted p-value**
Visit 3 (Day 1)			
0 (Did not receive rescue therapy)	64 (38.1%)	33 (38.8%)	0.910
0 (Received rescue therapy)	0	0	
>0	104 (61.9%)	52 (61.2%)	
Visit 4 (Day 8)			
0 (Did not receive rescue therapy)	110 (65.5%)	30 (35.3%)	<0.001
0 (Received rescue therapy)	1 (0.6%)	3 (3.5%)	
>0	57 (34.0%)	52 (61.2%)	
Visit 6 (Day 29)			
0 (Did not receive rescue therapy)	144 (85.7%)	50 (58.8%)	<0.001
0 (Received rescue therapy)	2 (1.2%)	7 (8.2%)	
>0	22 (13.1%)	28 (32.9%)	

Study C-11-303-003: Mean ACC Grade at Each Postsurgical Assessment by Visit and Treatment Group (mITT Population)

ACC Grade	**ISV-303 N=168**	**Vehicle N=85**	**Adjusted p-value**
Visit 3 (Day 1) Mean (sd)	1.5 (0.7)	1.6 (0.8)	0.551
Visit 4 (Day 8) Mean (sd)	0.8 (0.7)	1.4 (0.9)	<0.001
Visit 5 (Day 15)	0.5 (0.7)	1.2 (1.0)	<0.001

Mean (sd)			
Visit 6 (Day 29) Mean (sd)	0.4 (0.7)	1.1 (1.0)	<0.001

Study C-11-303-004: Mean ACC Grade at Each Postsurgical Assessment by Visit and Treatment Group (mITT Population)

ACC Grade	ISV-303 N=168	Vehicle N=85	Adjusted p-value
Visit 3 (Day 1) Mean (sd)	1.9 (1.0)	2.1 (0.9)	0.200
Visit 4 (Day 8) Mean (sd)	1.0 (0.8)	1.7 (1.0)	<0.001
Visit 5 (Day 15) Mean (sd)	0.8 (0.8)	1.3 (1.0)	<0.001
Visit 6 (Day 29) Mean (sd)	0.6 (0.8)	1.0 (1.1)	0.002

6.1.7 Subpopulations

Demographic subgroup results were generally consistent with the overall results; there were proportionally more ISV-303-treated subjects than vehicle-treated subjects with an ACC grade of 0 at Day 15 across the demographic subgroup categories, and some of these between treatment-group differences were statistically significant. Some categories within each subgroup were larger than others (ie. there were more females than males, more ≥ 65 years than < 65 years, and more whites than other racial groups), hence there would have been greater statistical power to detect differences in the categories with more subjects.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Only one dosing regimen was studied in both Studies C-11-303-003 and C-11-303-004**.**

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Long-term effectiveness was not evaluated for the clinical studies.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

Two clinical studies (C-11-303-003 and C-11-303-004) were used to evaluate safety. (b) (4) [redacted].

7.1.2 Adequacy of Data

Between the 2 studies there were 336 patients in the safety database who received ISV-303.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Two studies are used to support the safety of BromSite. See Section 7.4.1 of this review.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Study C-11-303-003: Exposure to Study Drug: Study Eye by Treatment Group (Safety Population)

Exposure	ISV-303 N=169	Vehicle N=85
Subjects exposed to study drug	169	85
Subjects completed all doses	135	66
Exposure (doses)		
N	168	84
Mean (sd)	30.0 (6.3)	21.4 (10.3)
Min, Max	1, 39	2, 34

Study C-11-303-004: Exposure to Study Drug: Study Eye by Treatment Group (Safety Population)

Exposure	ISV-303 N=170	Vehicle N=85
Subjects exposed to study drug	170	85
Subjects completed all doses	140	75
Exposure (doses)		
N	166	85
Mean (sd)	29.5 (7.4)	25.1 (9.2)
Min, Max	2, 34	4, 35

7.2.2 Explorations for Dose Response

Only one dosing regimen was studied.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was performed.

7.2.4 Routine Clinical Testing

Not applicable.

7.2.5 Metabolic, Clearance, and Interaction Workup

Studies to evaluate metabolism, clearance, and interaction were not performed due to the negligible systemic absorption of IVS-303 given by the topical route of administration.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

See section 2.4.

7.3 Major Safety Results

7.3.1 Deaths

Study C-11-303-003 and C-11-303-004: No deaths.

7.3.2 Nonfatal Serious Adverse Events

Study C-11-303-003: SAEs

Subject	Group	Description
105-022	Vehicle	The SAE of endophthalmitis began 4 days after surgery, and the subject was withdrawn from the study at that point. The same day treatment was initiated with prednisolone (1 drop, hourly), ketorolac (QID), homatropine (TID), vancomycin (q2h), moxifloxacin (400 mg po QD), vancomycin (1 mg single ocular injection), and ceftazidime (2.25 mg single ocular injection); difluprednate (q2h) was added 10 days subsequent to withdrawal. The SAE was indicated to have resolved after 38 days.

Study C-11-303-004: SAEs

Subject	Group	Description
264-009	ISV-303	A 71 yo caucasian male whose first dose of study drug was administered on (b) (6) and was stopped on (b) (6). His cataract surgery took place on (b) (6). An episode of severe chest pain occurred the same day as surgery and resolved

		on (b) (6) with no action taken.
316-004	Vehicle	A 77 yo cCaucasian female whose first dose of study drug was administered on (b) (6) and stopped on (b) (6) Cataract surgery took place on (b) (6). An episode of colitis of moderate intensity started on (b) (6) and the subject was hospitalized, but not withdrawn from the study. The colitis resolved on (b) (6)

Reviewer's Comments: *These types of adverse events are consistent with the age of the population of enrolled patients, and they do not appear directly attributable to the drug product. Two of the three events are related to use of vehicle.*

7.3.3 Dropouts and/or Discontinuations

Study C-11-303-003: List of Subjects with TEAEs Leading To Discontinuation From the Study

Subject Number	Event
ISV-303	
105-015	Posterior capsule rupture
159-002	Headache
273-006	Pruritis generalized Musculoskeletal stiffness
273-008	Iritis
273-017	Iritis
298-019	Diplopia
321-019	Hyperemia
Vehicle	
006-013	Ocular discomfort
006-020	Eye pain
008-008	Corneal opacity
053-003	Conjunctival hyperemia Photophobia Pain Headache
079-001	Eye inflammation
105-017	Eye pain Photophobia
105-022	Endophthalmitis
159-004	Eye pain Photophobia Iritis
273-011	Iritis
273-015	Iritis
301-003	Eye inflammation
321-024	Hyperemia

Study C-11-303-004: List of Subjects with TEAEs Leading To Discontinuation From the Study

Subject Number	Event
ISV-303	
105-011	Eye irritation Ocular hyperemia

159-013	Headache Ocular hypertension
236-023	Dermatitis contact
264-009	Foreign body sensation
304-001	AC inflammation
304-002	Eye pain AC inflammation
304-003	Eye pain AC inflammation
304-007	AC rebound inflammation
304-015	CME
314-010	Iritis
316-003	Drug hypersensitivity
325-005	Oreign body sensation Lens dislocation
Vehicle	
264-007	FBS
314-002	Iritis
321-022	Corneal disorder (Descemet's fold)
325-013	Punctate keratitis

7.3.4 Significant Adverse Events

See section 7.3.2.

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study C-11-303-003: Summary of All Treatment Emergent AEs by System Organ Class (Safety Population)

	ISV-303 N=169	Vehicle N=85
Number of Treatment Emergent AEs	90	53
Number of Subjects with TEAEs	52	37
Cardiac Disorders		
Coronary artery occlusion	1	0
Eye disorders		
Blepharitis	1	0
Ciliary hyperemia	1	0
Conjunctival hyperemia	0	1

Corneal edema	2	0
Corneal opacity	0	1
Corneal striae	0	1
CME	1	1
Diplopia	1	0
Dry eye	1	0
Eye inflammation	0	2
Eye pain	8	11
Foreign body sensation	3	1
Iritis	3	5
Lacrimation increased	1	1
Meibomian gland dysfunction	1	0
Ocular discomfort	2	3
Ocular hyperemia	0	1
Ocular hypertension	16	3
Photophobia	1	4
Posterior capsular rupture	1	0
Retinal hemorrhage	0	1
Retinal tear	1	0
Trichiasis	1	0
Uveitis	1	0
Visual impairment	1	0
Vitreous floaters	4	0
GI disorders		
Abdominal distention	1	0
Abdominal pain upper	1	0
Diarrhea	1	0
Nausea	1	2
General Disorders		
Chest pain	1	0
Instillation site pain	2	1
Pain	0	1
Infections		
Bronchitis	0	1
Endopthalmitis	0	1
Influenza	1	0
Sinusitis	1	0
Upper respiratory tract infection	1	1
Injury		
Corneal abrasion	1	0
Incision site complication	0	1
Ligament sprain	1	0
Spinal compression fracture	1	0
Investigations		
Pancreatic enzymes increased	1	0
Metabolism disorders		

Gout	0	1
Musculoskeletal disorders		
Arthralgia	1	0
Musculoskeletal stiffness	1	0
Nervous system disorders		
HA	4	5
Psychiatric disorders		
Bipolar disorders	1	0
Depression	1	0
Panic attack	1	0
Respiratory disorders		
Cough	1	0
Epistaxis	1	0
Nasal congestion	1	0
Pleurisy	1	0
Skin disorders		
Pruritis	1	0
Pruritis generalized	1	0
Rash	1	0
Rosacea	1	0
Skin wrinkling	1	0
Vascular disorders		
Hyperemia	1	3
HTN	2	0

Study C-11-303-004: Summary of All Treatment Emergent AEs by System Organ Class (Safety Population)

	ISV-303 N=170	Vehicle N=85
Number of Subjects with TEAEs	49	25
Cardiac Disorders		
Bradycardia	1	0
Congenital and genetic disorders		
Corneal dystrophy	1	0
Eye disorders		
AC cell	1	0
AC inflammation	5	3
Conjunctival hemorrhage	3	0
Conjunctival hyperemia	0	1
Corneal deposits	1	0
Corneal disorder	0	1
Corneal edema	1	1
Cystoid macular edema	1	1

Deposit eye	1	0
Dry eye	0	1
Eye irritation	1	1
Eye pain	4	2
Eyelid margin crusting	1	0
Eyelid ptosis	0	1
Foreign body sensation	0	1
Iritis	5	2
Lens dislocation	1	0
Ocular hyperemia	1	1
Ocular hypertension	17	5
Photopsia	1	0
Punctate keratitis	3	1
Retinal hemorrhage	1	0
Retinal vein occlusion	1	0
Vision blurred	1	1
Visual acuity reduced	0	1
Vitreous adhesions	1	0
Vitreous detachment	0	1
Vitreous loss	1	0
GI disorders		
Colitis	0	1
Dyspepsia	0	1
Nausea	1	0
Vomiting	1	0
General disorders		
Chest pain	1	0
Pain	0	1
Immune System disorders		
Drug hypersensitivity	1	0
Infections		
Nasophharyngitis	1	0
Sepsis	0	1
Sinusitis	1	0
UTI	0	1
Injury		
Corneal abrasion	0	1
Foreign body in eye	3	1
Post-procedureal discomfort	1	0
Posterior capsule opacification	2	1
Metabolism disorders		
Dehydration	0	1
Hyperglycemia	1	0
Hyperkalemia	1	1
Neoplasms		

Dizziness	2	0
HA	1	0
Migraine with aura	0	1
Renal disorders		
Renal failure acute	0	
Respiratory disorders		
Dysopnea	1	0
Upper respiratory tract congestion	1	0
Skin disorders		
Dermatitis contact	1	0
Hyperhidrosis	1	0
Rash	1	0

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)

SOC Preferred Term	Treatment Group		
	ISV-303 (N = 422) n (%)	Xibrom (N = 42) n (%)	Vehicle (N = 212) n (%)
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.

Reviewer's Comments: *The most commonly reported adverse events following use of BromSite after cataract surgery include: anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain and ocular hypertension. These reactions were reported in roughly 1.2% to 8.1 % of patients.*

7.4.2 Laboratory Findings

Clinical laboratory tests were not performed during this study.

7.4.3 Vital Signs

No vital signs were recorded as part of the study assessments.

7.4.4 Electrocardiograms (ECGs)

ECGs were not performed during this study.

7.4.5 Special Safety Studies

None.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Not performed

7.5.2 Time Dependency for Adverse Events

Not performed

7.5.3 Drug-Demographic Interactions

See section 6.1.17.

7.5.4 Drug-Disease Interactions

BromSite was not studied with any drug-disease interaction analysis.

7.5.5 Drug-Drug Interactions

No studies were conducted to evaluate a drug-drug interaction between BromSite and any of the concomitant medications allowed in those studies.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

Because of the low expected absorption of IVS-303 in topical preparations, no carcinogenicity studies were conducted

7.6.2 Human Reproduction and Pregnancy Data

This drug has not been tested in pregnant women.

7.6.3 Pediatrics and Effect on Growth

Safety and effectiveness of BromSite in pediatric patients below the age of 18 years has not been established. Height and weight data were not collected as part of this protocol.

During the pre-NDA meeting the Agency recommend that InSite submit a Pediatric Study Plan (PSP). (b) (4)

(b) (4)

This application did not trigger PREA and was not presented at PERC.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

BromSite is a non-narcotic and does not have abuse potential.

7.7 Additional Submissions

A 120 day safety update was submitted on 10/7/15 and the Applicant stated, "No new safety information has been learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling."

8 Postmarketing Experience

None.

9 Appendices

9.1 Literature Review/References

A pub med search did not reveal any new information on BromSite.

9.2 Labeling Recommendations

See Attachment 2.

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

Attachment 1

Clinical Investigator Financial Disclosure
Review Template

Application Number: 206-911

Submission Date(s): 6/10/15

Applicant: InSite Vision

Product: BromSite (bromfenac ophthalmic solution 0.075%)

Reviewer: Sonal D. Wadhwa

Date of Review: 11/23/15

Covered Clinical Study (Name and/or Number): C-11-303-003 and C-12-303-004

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: C-11-303-003: 15 investigators and C-12-303-004: 16 investigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		

Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

N/A-There were no disclosed financial interests/arrangements.

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

1 See [web address].

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

/s/

SONAL D WADHWA
03/14/2016

WILLIAM M BOYD
03/15/2016

CLINICAL FILING CHECKLIST FOR NDA 206-911

NDA/BLA Number: 206-911 **Applicant: InSite Vision** **Stamp Date: 6/10/15**

Drug Name: BromSite (bromfenac ophthalmic solution 0.075%) **NDA/BLA Type: 505(b)(2)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505 (b)(2)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?				Bromday (NDA 21664)
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	x			
15.	Describe the scientific bridge (e.g., BA/BE studies)	x			Applicant conducted a non-clinical bridging study in rabbits which demonstrated that the plasma levels of bromfenac following topical ocular administration of ISV-303 were comparable to those obtained with

CLINICAL FILING CHECKLIST FOR NDA 206-911

	Content Parameter	Yes	No	NA	Comment
					the listed drug Bromday (Study No. S11135).
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: C-10-303-001 Study Title: A Randomized Double-Masked 14-Day Study 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 Sample Size: 129 Arms:4	x			Four arms (BromSite BID, BromSite QD, Xibrom BID, and vehicle)
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: C-11-303-003 (268 patients, 180 in Bromsite BID and 88 in vehicle) Indication: Treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery Pivotal Study #: C-12-303-004 (268 patients, 174 in BromSite BID and 94 in vehicle) Indication: Treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery	x			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			x	
23.	Has the applicant presented a safety assessment based on all	x			

	Content Parameter	Yes	No	NA	Comment
	current worldwide knowledge regarding this product?				
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			x	
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	x			
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			(b) (4)
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
37.	Are all datasets to support the critical safety analyses available and complete?	x			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA 206-911

	Content Parameter	Yes	No	NA	Comment
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

N/A.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

Reviewing Medical Officer Date

Clinical Team Leader Date

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

/s/

SONAL D WADHWA
08/10/2015

WILLIAM M BOYD
08/12/2015