CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206911Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	206,911
Submission Date(s):	June 10, 2015
Proposed Brand Name	BromSite
Generic Name; Code Name	Bromfenac; ISV-303
Primary Reviewer	Yongheng Zhang, Ph.D.
Team Leader	Philip M. Colangelo, Pharm.D., Ph.D.
OCP Division	DCP4
OND Division	DTOP
Applicant	Insite Vision Inc.
Submission Type; Code	5S (New formulation ; Standard review)
Formulation; Strength(s)	Bromfenac 0.075%
Indication	Treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery
Dosage and Administration	Instill 1 drop in the eye(s) twice daily (morning and evening) 1 day prior to surgery, the day of surgery, and 14 days post-surgery.

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1. EXECUTIVE SUMMARY

ISV-303 is a topical ophthalmic solution of a 0.075% concentration of the nonsteroidal anti-inflamatory drug (NSAID), Bromfenac. ISV-303 is formulated in InSite Vision's drug delivery system, DuraSite, which contains (b) (4) a polyacrylic acid polymer that increases the drug residence time on the ocular surface to facilitate better ocular bioavailability and drug penetration. ISV-303 is manufactured as a sterile-preserved, multidose eye drop intended for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

At present, there are three FDA-approved bromfenac-containing ophthalmic products for the treatment of inflammation and pain post cataract surgery, including Xibrom (bromfenac 0.09%; BID; under NDA 21664), Bromday (bromfenac 0.09%; QD; under NDA 21664/SE2-013), and Proclensa (bromfenac 0.07%; QD; under NDA 203168). Refer to the Clinical Pharmacology Reviews of the original NDA 21,664 (*by Dr. Lei Zhang dated March 8, 2005*), of NDA 21664/SE2-013 (*by Dr. Kimberly L. Bergman dated July 12, 2010*), and of NDA 203168 (*by Dr, Yoriko Harigaya dated Feb 19, 2013*). In addition, six generic 0.09% bromfenac ophthalmic formulations have been approved as of 01/04/2016.

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

- One Phase I/II study (C-10-303-001) to evaluate the comparative safety and efficacy in post cataract surgery patiens between ISV-303 (BID and QD), Xibrom BID (standard treatment at the time of study initiation) and vehicle, over 14 days.

- One Phase II study (C-11-303-002) in subjects scheduled to undergo cataract surgery and to compare the **aqueous humor (AH) concentrations** of bromfenac when ISV-303 or Bromday were each administered QD, for 3 days.

- Two Phase III 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 utilized in each study group: BID administration for 16 days, starting the day before surgery.

    - **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.

1.1. Recommendation

The Clinical Pharmacology information provided by the Applicant in the NDA submission is acceptable, and the Clinical Pharmacology review team recommends approval of ISV-303 (Bromfenac 0.075% ophthalmic solution).

The reviewer's proposed label changes in *Appendix 4.1* are to be forwarded to the sponsor.

1.2. Phase IV Commitments

None.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Following bilateral topical ocular twice-daily dosing of IV-303 (Bromfenac 0.075% ophthalmic solution), 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.

2. QUESTION BASED REVIEW

There are multiple FDA-approved bromfenac-containing ophthalmic products, including Xibrom (bromfenac 0.09%; BID; under NDA 21664), Bromday (bromfenac 0.09%; QD; under NDA 21664/SE2-013), and Proclensa (bromfenac 0.07%; QD; under NDA 203168). Therefore, no review in the OCP question-based review (QBR) format is warranted. Please refer to the Clinical Pharmacology Reviews of the original NDA 21,664 (by Dr. Lei Zhang dated March 8, 2005), of NDA 21664/SE2-013 (by Dr. Kimberly L. Bergman dated July 12, 2010), and of NDA 203168 (by Dr, Yoriko Harigaya dated Feb 19, 2013) for additional information.

3. LABELING RECOMMENDATIONS

See Appendix 4.1. for details.

4. APPENDICES

4.1. Proposed Package Insert (Original and Annotated) with Clinical Pharmacology edits (noted as underline and strikethrough) as of 22December 2015

12.3 Pharmacokinetics

(b) (4)

Following bilateral topical ocular twice-daily dosing of Bromfenac 0.075% ophthalmic solution, the plasma concentrations of bromfenac ranged from below the limit of quantification (LOQ = 0.20 ng/mL) to 2.42 ng/mL at 30 to 60 minutes post-dose.

4.2. Individual Study Reviews

4.2.1. Pharmacokinetics of Bromfenac in cataract surgery subjects: PK substudy from Study C-12-303-004

Study Number: C-12-303-004
Determination of Bromefenac Concentration in Human Plasma for Study C-12-303-004: 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

Dates: 7 May, 2013 to 12 December, 2014
Study Sponsor: InSite Vision, Inc.
Analytical site: (b) (4)

OBJECTIVES:

The objective was to determine plasma bromfenac concentrations at 2 timepoints after topical ocular dosing of bromfenac in order to assess the extent of systemic bromfenac absorption in subjects who underwent routine cataract surgery.

FORMULATION & ADMINISTRATION

Subjects were randomly assigned at 2:1 ratio to receive either ISV-303 or vehicle for 16 days BID beginning 1 day prior to cataract surgery, the day of surgery, and then continuing for 14 days after surgery.

Treatment	Formulation Control Number	Batch Number
ISV-303 (0.075% bromfenac in DuraSite)	303P20075D1	00313B
DuraSite vehicle	303P20000D1	00313G

STUDY DESIGN:

During the conduct of Protocol C-12-303-004 whole blood samples were collected from a subset of subjects, in both randomly assigned treatment groups, after ocular dosing of 5 doses (BID on Day -1, BID on Day 0 and 1 dose the morning of Day 1) and 32 doses of ISV-303.

Blood samples for pharmacokinetic analysis:

- Collected between 30-60 minutes post dose on Day 1 (after administration of 5 ocular doses), and
- Collected between 12-48 hours after the last dose on Day 14.

The subjects evaluated in this study were a subset of 268 subjects (174 in the ISV-303 and 94 in the vehicle group). A resulting subset (36 subjects) had both Day 1 and Day 15 blood samples collected. Of these 36 subjects, 29 were from the ISV-303 treatment group and 7 were from the vehicle treatment group. One subject in the ISV-303 group had sample collection on Day 15, but the sample was not separated into plasma and therefore was not analyzed. This resulted in a total

of 35 subjects (28 in the ISV-303 group and 7 in the Vehicle group) who had samples analyzed on Day 15.

Day 1 blood samples were collected from a total of 43 subjects (30 in the ISV-303 and 13 in the vehicle group). Of the 30 blood samples collected in the ISV-303 group, 27 blood samples were collected within 30-60 minutes of the Day 1 morning dose of ISV-303. Blood samples from 2 subjects (Subjects 324-001 and Subject 325-002) were collected prior to the recommended 30-60 minute window, at 24 and 28 minutes post-dose, respectively. One blood sample (Subject 264-003) was collected on Day 2. This subject received 2 additional doses of study drug, the evening of Day 1 and the morning of Day 2 for a total of 7 doses; however; the blood sample was collected 34 minutes after the Day 2 morning dose.

Day 15 blood samples were collected from a total of 36 subjects (29 in the ISV-303 and 7 in the Vehicle group). One of the blood samples (Subject 325-005) was not separated into plasma, and therefore not analyzed. Of the remaining 28 samples collected in the ISV-303 group, 21 samples were collected within 12-48 hours of the last dose of ISV-303 on Day 14. Four (4) samples were collected between approximately 9-12 hours post-dose. The remaining 3 subjects (Subjects 092-003, 325-002, and 325-006) had an extra dose of ISV-303 administered on the morning of Day 15, with blood samples collected following the last dose at 2 hours and 13 minutes, 30 minutes, and 36 minutes, respectively.

ASSAY METHODOLOGY:
Plasma concentrations for bromfenac were determined using validated HPLC/MS/MS methods. The method was validated with respect to accuracy, precision, and sample stability consistent with the sample collection and storage procedures.

The analyte and internal standard (Amfenac) were extracted from human plasma by solid phase extraction. After evaporation to dryness and reconstitution, the extracts were analyzed by LC-MS/MS. Run times (time between injections) were approximately six minutes.

This assay was calibrated using a standard curve generated from nine non-zero bromfenac (0.200, 0.500, 1.00, 2.00, 5.00, 20.0, 45.0, and 50.0). In addition, QCs prepared in plasma at concentrations of 0.200, 0.600, 20.0, and 40.0 ng/mL of bromfenac were included in each analysis.

Criterion	Nepafenac	Comments
Conc. range, ng/mL	0.20-50.0	satisfactory
LLOQ, ng/mL	0.20	satisfactory
Linearity, r^2	>0.99	satisfactory
QC Accuracy , % RE	Intra-assay (-5.08%-1.92%) Inter-assay (0.792% - 3.59%)	Satisfactory
QC Precision, % CV	Intra-assay (<6.33%) Inter-assay (<8.11%)	Satisfactory
Selectivity	Control plasma from six different individual lots	Satisfactory
Stability	Short-term matix, Freeze/thaw (-20ºC and -70ºC), refrigerator, extract, antoinjector stability, et al.	Satisfactory

From Document [redacted] (b) (4)

DATA ANALYSIS

Descriptive statistics were used to summarize the systemic pharmacokinetic parameters of nepafenac and amfenac including C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, t1/2, kel, and CL/F (nepafenac only).

RESULTS:

The rationale for collecting samples between 30-60 minutes on Day 1 was based on nonclinical pharmacokinetic results which indicated that maximal plasma bromfenac concentrations (Cmax) were achieved at approximately 0.5 hours (Tmax) after instillation of ISV-303. As the Phase 3 study design required a safety assessment 12-48 hours post the last dose of study drug on Day 14, the whole blood samples for determining bromfenac levels were collected at that visit.

Day 1
Bromfenac was measurable in 29 out of 30 samples from subjects in the ISV-303 treatment group and bromfenac levels ranged from 0.10-2.42 ng/mL. Bromfenac levels for 1 subject (Subject 324-001) were BQL.

Bromfenac was below the quantitation limit of 0.20 ng/mL in all of the 13 samples obtained from the Vehicle group at Day 1 or Day 2.

Day 15
Bromfenac was detectable in 6 out of the 28 samples from subjects in the ISV-303 treatment group. Three (3) of these samples (Subjects 092-005, 236-017 and 304-006) were collected within 12-14 hours after the last dose, with resulting plasma bromfenac concentrations of 0.206 ng/mL, 0.225 ng/mL and 0.287 ng/mL, respectively. The other 3 samples were from Subjects 092-003, 325-002, and 325-006, who had 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 ng/mL, 0.482 ng/mL and 1.66 ng/mL, respectively.

Bromfenac was below the quantitation limit of 0.20 ng/mL in all of the 7 subject samples obtained from the Vehicle group at Day 15.

Reviewer's note*: Acocrding to the protocol, two timepionts were planned to assess bromfenac systemic exposure following repeated topical ocular administration of ISV-303: 30-60 min following the 5th dose (n=30) and 12-48 hours post the last dose of ISV-303 on Day 14. However, it turned out that bromfenac systemic exposure following repeated topical ocular administration of ISV-303 was assessed at three timepoints:*
1) 30-60 min following the 5th dose (n=30),
2) within 12-48 hours post the last dose of ISV-303 on Day 14 (n=25), and
3) 30 min – ~2 hour following the morning dose on Day 15 (n=3, due to protocol deviation).

Table 1: Mean Human Plasma Bromfenac Concentrations in Subjects Dosed Topically with ISV-303 or Vehicle at Day 1 (5 Doses) and Day 15 (32 Doses)

Study Visit	ISV-303 (N=174)
Day 1 (Visit 3)	
N	30[1,2]
BQL samples [n (%)]	1 (3.3)
Mean (± SD) ng/mL	1.12 (0.65)
Median	1.09
Min, Max	0.10[3], 2.42
Day 15 (Visit 5)	
N	28[4,5]
BQL samples [n (%)]	22 (78.6)
Mean (± SD) ng/mL	0.19 (0.30)
Median	0.10
Min, Max	0.10, 1.66

[1] One subject (Subject 264-003) received 2 extra doses: evening of Day 1 and morning of Day 2 and the blood sample was collected on Day 2.

[2] One subject (Subject 264-002) received 2 extra doses on separate days, and the blood sample was collected on Day 2.

[3] Assay results reported below quantitation limit (BQL) were analyzed as 0.10 ng/mL which is one-half the BQL.

[4] Three subjects (Subjects 092-003, 325-002, and 325-006) received an extra dose of ISV-303 on Day 15.

[5] Two subjects (Subject 325-001 and Subject 325-007) received an extra dose of vehicle on Day 15.

SPONSORS CONCLUSIONS:

In this study, plasma bromfenac concentrations were found to be very low after administration of both 5 doses (BID for 2.5 days) and 32 total doses (BID for 16 days) of topical ocular ISV-303 (0.075% bromfenac). The maximum plasma concentration of bromfenac at Day 1 was 2.42 ng/mL, and after 16 days of dosing, 1.66 ng/mL, indicating a lack of systemic accumulation. These results confirm that systemic exposure of bromfenac is negligible after 16 days of BID ocular ISV-303 dosing.

REVIEWER'S ASSESSMENT & RECOMMENDATION:

The analytical method utilized in this study (LOQ of 0.20 ng/mL) is 250-fold more sensitive than that reported (LOQ of 50 ng/mL) for the currently marketed product, Prolensa™ (0.07% bromfenac). The method was validated and deemed acceptable. Based on the reviewer's assessment, bromfenac plasma levels following repeated topical ocular administration of ISV-303 were assessed at three timepoints – See Table below:

Time Frame Assessed	Concentration range
30-60 min following the 5th dose (n=30)	BLQ - 2.42 ng/mL
within 12-48 hours post the last dose on Day 14 (n=25)	BLQ – 0.287 ng/mL
30 min – ~2 hour following the morning dose on Day 15 (n=3, due to protocol deviation)	0.246-1.66 ng/mL

The reviewer's conclusions are as follows:

Following bilateral topical ocular twice-daily dosing of ISV-303 ophthalmic solution, the plasma concentrations of bromfenac ranged from below the limit of quantification (LOQ = 0.20 ng/mL) to 2.42 ng/mL at 30 to 60 minutes post-dose.

4.2.2. Study to determine aqueous humor concentration of bromfenac

Study Number: C-11-303-002
Report Date: October 26, 2011
Study Location: (b) (4)
Title: A Double-Masked Clinical Study to Determine the Aqueous Humor Concentration of Bromfenac Sodium in Subjects Administered Multiple Topical Ocular Doses of ISV-303 (0.075% bromfenac in DuraSite®) or Bromday™ (0.09% bromfenac) QD Prior to Cataract Surgery

Objectives:
To evaluate the aqueous humor concentration of bromfenac sodium after administration of 3 topical ocular doses of either ISV-303 (0.075% bromfenac in DuraSite), or Bromday (0.09% bromfenac) QD prior to routine cataract surgery.

Methodology:

In this multi-center, randomized, double-masked, 2-arm, parallel-group, comparative clinical trial, 60 subjects were randomly assigned to 2 treatment groups (ISV-303 or Bromday, n=30 for each group) in a 1:1 ratio. Both medications contained bromfenac in different concentrations.

Subjects administered 1 drop of either ISV-303 or Bromday once daily into the study eye, at approximately 24 hour intervals, for 3 days; with the last instillation to occur 3 hours prior to the subject's scheduled cataract surgery. ISV-303 and Bromday were packaged in identical study bottles. Aqueous humor samples were collected during surgery (Visit 2) for analysis of bromfenac levels.

Sponsor's conclusions:
Although ISV-303 contains a lower concentration of bromfenac (0.075%) than Bromday (0.09%), the commercially available product, mean bromfenac aqueous humor concentration in subjects receiving ISV-303 were significantly (more than 2-fold) higher compared with those who received Bromday after 3 days of dosing. Additionally, no adverse events were observed and the study treatment was well tolerated. The study confirmed superior tissue penetrat ion of ISV-303 against Bromday in patients who underwent routine cataract surgery.

Reviewer's assessment and Recommendations:

According to the method validation report (b) (4) *rabbit aqueous humor was used as a surrogate matrix for the analysis of human aqueous humor samples. In addition, there was no claim with respect to aqueous humor concentration of bromfenac following topical ocular administration of ISV-303 in the proposed label.* **Therefore*, no substantial review is warranted for this study report.***

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/s/

YONGHENG ZHANG
02/09/2016

PHILIP M COLANGELO
02/09/2016

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	206911	**SDN**	001
Applicant	Insite Vision Inc.	**Submission Date**	06/10/2015
Generic Name	Bromfenac 0.075%	**Brand Name**	BromSite
Drug Class	Nonsteroidal anti-inflammatory drug		
Indication	Treatment of postoperative inflammation and prevention of ocular pain		
Dosage Regimen	Instill 1 drop in the eye(s) twice daily (morning and evening) 1 day prior to surgery, the day of surgery, and 14 days post-surgery.		
Dosage Form	Ophthalmic eye drop solution	**Route of Administration**	Topical ocular
OCP Division	IV	**OND Division**	DTOP

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Yongheng Zhang, Ph.D.	Philip Colangelo Pharm. D., Ph.D.
Pharmacometrics	-	
Genomics	-	

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	8/9/2015	**74-Day Letter Date**	8/23/2015
Review Due Date	2/10/2016	**PDUFA Goal Date**	4/10/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		
☐ Distribution		
☐ Drug-Drug Interaction		

In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☑ Multiple Dose	2	Phase 2 Study C-11-303-002; Phase 3 Study C-12-303-004
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
☐ QT			
Pharmacometrics			
☐ Population Pharmacokinetics			
☐ Exposure-Efficacy			
☐ Exposure-Safety			

Total Number of Studies	**In Vitro**		**In Vivo**	2
Total Number of Studies to be Reviewed				2

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	Phase 2 Study C-11-303-002, aqueous humor exposure; Phase 3 Study C-12-303-004, systemic exposure (See **Table 1**)
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	Report # (b) (4) for aqueous humor; Report # (b) (4) for human plasma
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☐Yes ☐No ☑N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Table 1: Tabular Listing of Clinical Pharmacology Studies

Study No. (Country)	Study Objective	Study Design	No. Subjects Entered/ Completed	Age (Years) Mean (Range)	Treatments (Sample Collection Time)	Bromfenac Concentration Data		
						Mean (SD) ng/mL	Median ng/mL	Min, Max ng/mL
C-11-303-002 (USA)	Compare aqueous humor concentration of ISV-303 with commercially available bromfenac product	Randomized, Double-masked, QD for 3 days	Total: 60/58 ISV-303: 30/29 Bromday: 30/29	69.4 (47-90)	ISV-303 (During surgery, after 3 QD doses)	49.33 (41.87)	34.8	3.4, 161.0
					Bromday (During surgery, after 3 QD doses)	23.65 (16.31)	20.6	0.3, 83.0
C-12-303-004 Plasma Substudy (USA)	Determine plasma bromfenac levels after ocular instillation of ISV-303	Randomized, Double-masked, BID for 16 days	Total: 43/36[a] ISV-303: 30/29 Vehicle: 13[b]/7	70.4 (45-91)	ISV-303 (Day following surgery, after 5 BID doses)	1.12 (0.65)	1.09	0.10, 2.42
					ISV-303 (12-48 hours post last dose on Day 14, after 32 BID doses)	0.19 (0.30)	0.10	0.10, 1.66

QD = once daily; BID = twice daily; SD = standard deviation

[a]Although 58 subjects entered the study, only 43 subjects had blood samples collected.

[b] Vehicle data not shown as all vehicle subjects (n=13) were Below Quantitation Limit (BQL).

Note: Assay results BQL utilized 0.10 ng/mL (one-half the BQL) to calculate the mean, median and range.

From 2.7.2 Summary of Clinical Pharmacology Studies.

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/s/

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07/27/2015

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07/27/2015