

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-664

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoeconomics and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

NDA/Serial Number: 21-664

Drug Name: XIBROM (bromfenac sodium ophthalmic solution) 0.1%

Indication(s): For the treatment of postoperative inflammation .
~~in patients who have undergone cataract extraction~~
in patients who have undergone cataract extraction

Applicant: ISTA Pharmaceuticals, Inc.

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Data from both Study ISTA-BR-CS001-ER and Study ISTA-BR-CS001-WR showed efficacy of bromfenac sodium 0.1% at the Day 15 visit on the treatment of postoperative inflammation in patients who have undergone cataract extraction. The study ISTA-BR-CS001-ER showed statistically significant difference of ocular clearance proportion between bromfenac (62.6%) and placebo (39.8%) in the ITT population ($p=.0002$) and the study ISTA-BR-CS001-WR also showed statistically significant difference of ocular clearance proportion between bromfenac (65.8%) and placebo (48.0%) in the ITT population ($p=.0099$). Sensitivity analyses by the reviewer showed the statistically significant results from both studies, thereby reassuring the sponsor's statistically significant analysis results.

1.2 Brief Overview of Clinical Study

The sponsor submitted the results of studies that document the efficacy and safety of bromfenac sodium 0.1% on the treatment of postoperative inflammation in patients who have undergone cataract extraction with posterior chamber intraocular lens implantation. These were a **1-month**, double-masked, placebo-controlled, multi-center studies to investigate the safety and ocular anti-inflammatory effect of **bromfenac sodium 0.1% ophthalmic solution twice a day** in patients who have undergone cataract extraction. The data for these studies were collected under a common protocol (ISTA-BR-CS001), but analyzed as two studies (ISTA-BR-CS001-ER and ISTA-BR-CS001-WR) based on site of enrollment (i.e., Eastern Region or Western Region, respectively). The sites were apportioned to each study geographically, adhering as closely as possible to sites located west of the Mississippi (ISTA-BR-CS001-WR) in one study and sites located east of the Mississippi (ISTA-BR-CS001-ER) in the second study. This splitting was agreed between the sponsor and FDA as recorded in August 7th email (see the section 1.6 Documentation of FDA Interactions in Vol. 1 of the submission).

In Study ISTA-BR-CS001-ER, 296 patients were randomized to bromfenac sodium 0.1% arm ($n = 198$) and placebo arm ($n = 98$) in 2:1 ratio.

In Study ISTA-BR-CS001-WR, 231 patients were randomized to bromfenac sodium 0.1% arm ($n = 158$) and placebo arm ($n = 73$) in 2:1 ratio.

The primary objective of the studies was to document an efficacy for therapy with bromfenac sodium 0.1% on postoperative ocular inflammation when compared to placebo.

The primary efficacy endpoint for the studies was the proportion of patients with summed ocular inflammation score (anterior chamber cell score plus flare score) equal to zero on Day 15. The anterior chamber cell and flare scores are determined as follows:

Anterior Chamber Cells		Anterior Chamber Flare	
Grade	Cell Count	Grade	Flare
0	None – 5 (trace)	0	Complete absence
1	6 - 15	1	Very slight
2	16 – 25	2	Moderate
3	26 – 50	3	Marked
4	> 50	4	Intense

Pre-planned statistical methods used to evaluate efficacy included the chi-square test or Fisher’s exact test for comparison of proportions; the Cochran-Mantel-Haenszel test for comparison of proportions conditional on covariates; the Zelen test to evaluate treatment-by-site interaction.

1.3 Statistical Issues and Findings

For the efficacy analysis, the sponsor based its inferences on ITT data from Study ISTA-BR-CS001-ER and Study ISTA-BR-CS001-WR with last observation carried forward (LOCF) for missing summed ocular inflammation score data and compared bromfenac sodium 0.1% with placebo in the proportion of patients with summed ocular inflammation score equal to 0 for the statistical significance.

For the primary efficacy analysis, when a subject discontinued test agent treatment early and was given alternative anti-inflammatory medication, the subject’s data were not censored and considered coming from the original randomized treatment. As a secondary analysis of the primary efficacy endpoint, subjects who discontinued masked test agent treatment prior to Day 15 visit and received an alternative anti-inflammatory medication were censored at the visit closest to (on or before) receipt of the alternative medication.

One interim analysis was conducted by the Data Safety Monitoring Board when 50% of the subjects have completed the Day 29 visit or terminated the study. Using the spending function approach with O’Brien-Fleming boundary, an alpha level for the final analysis was adjusted to .049.

Sponsor’s ITT population was defined as all subjects who were randomly assigned to test agent.

Sponsor’s PP population was defined as all patients who met the following criteria:

- All pre-surgery and post-surgery entry criteria must have been satisfied for the subject to be considered protocol compliant

- Subjects must have had a Visit 4 and Visit 6 in the specified study windows. Subjects may have missed one other visit and still have been considered protocol compliant. All other study visits must have occurred within (\pm) one day of the window specified in the protocol.
- Subjects must have had at least one dose of test agent for 14 consecutive days and have been at least 80% compliant overall with regard to dosing (i.e., received a total of at least 22 doses).
- Subjects with documented pre-enrollment approval by the Sponsor of sporadic use of disallowed medications prior to surgery were to be considered protocol compliant as long as the medication was not received within one week of surgery. Subjects without documented pre-enrollment approval of or with continual use of a disallowed medication prior to surgery (topical, inhaled, or oral corticosteroids within 15 days, depo-corticosteroids within 45 days, and all other disallowed medications within seven days) were not to be considered protocol compliant. ‘Sporadic’ use of a medication was defined as up to two days of use based on the start and stop dates of the medication, or medication frequency recorded as “PRN” (as needed).
- Subjects who received a disallowed medication from 48 hours prior to randomization through randomization were not to be included in the protocol compliant population.
- Subjects with sporadic (defined as up to two days of use based on the start and stop dates of the medication or a medication frequency recorded as PRN) use of a disallowed medication from randomization through Visit 4 were to be considered protocol compliant. Subjects with continual use of a disallowed medication from randomization through Visit 4 were not to be considered protocol compliant.
- Subjects receiving disallowed medications after Visit 4 were to be considered protocol compliant.

Based on our review of the data up to 1 month we conclude the following.

Study ISTA-BR-CS001-ER

The statistically significant difference in the proportion of ocular clearance as primary endpoint was shown when comparing bromfenac sodium 0.1% with placebo in ITT LOCF analysis without censoring ($p=.0002$), in ITT LOCF analysis with censoring ($p<.0001$), and in PP analysis ($p=.0058$). Sensitivity analyses on ITT population treating patient with missing data on Day 15 as no cleared ocular inflammation also showed the statistically significant differences ($p<.0001$ without censoring or with censoring) reassuring that the statistical significance is robust against missing data imputation method.

Study ISTA-BR-CS001-WR

The statistically significant difference in the proportion of ocular clearance as primary endpoint was shown when comparing bromfenac sodium 0.1% with placebo in ITT

LOCF analysis without censoring ($p=.0099$) and in ITT LOCF analysis with censoring ($p<.0001$), but not in PP analysis ($p=.0637$). Sensitivity analyses on ITT population treating patient with missing data on Day 15 as no cleared ocular inflammation also showed the statistically significant difference ($p<.0001$ without censoring or with censoring) again reassuring that the statistical significance is robust against missing data imputation method.

2. INTRODUCTION

2.1 Overview

2.1.1 Drug class and regulatory history

Xibrom (bromfenac sodium hydrate ophthalmic solution) 0.1% is a new, highly potent, topical NSAID for the treatment of post-cataract surgery ocular inflammation. In clinical trials conducted outside the United States, Xibrom instilled in a twice daily treatment regimen has a clinical therapeutic potency similar to the other topical NSAIDs that are administered four times daily.

Bromfenac sodium hydrate ophthalmic solution, 0.1% has been manufactured and marketed as BronuckTM by Senju since July 2000 in Japan. Xibrom is the same formulation of bromfenac for the U.S. market.

Per agreement at a pre-NDA teleconference meeting between the sponsor and FDA, the full reports for Senju's clinical studies are included in the Xibrom NDA. Summaries of results from these studies are provided separately from the Phase III studies of Xibrom conducted in the U.S. in the clinical overview and summary.

2.1.2 Proposed Indication for XIBROM (bromfenac sodium ophthalmic solution) 0.1%

XIBROM ophthalmic solution is indicated for the treatment of postoperative inflammation _____ in patients who have undergone cataract extraction.

2.2 Data Sources

The original submission on May 28, 2004 can be found on paper submission with CDER electronic document room (EDR) data.

Final Report:
Paper Submissions

Document Room
9201 CORP

Data set:
\\Cdsesub1\n21664\N_000\2004-05-24\CRT\DATASETS

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Study ISTA-BR-CS001-ER and Study ISTA-BR-CS001-WR were a 1-month, multi-center, double-masked study of the safety and efficacy of bromfenac sodium 0.1% ophthalmic solution twice a day in patients who have undergone cataract extraction. Patients were randomized to bromfenac sodium 0.1% or placebo in 2:1 ratio.

Figure 1 in Appendix shows schematic of study design for Study ISTA-BR-CS001-ER and Study ISTA-BR-CS001-WR, respectively.

Twenty investigators enrolled subjects from US sites and participated in the clinical trial Study ISTA-BR-CS001-ER.

Nineteen investigators enrolled subjects from US sites and participated in the clinical trial Study ISTA-BR-CS001-WR.

As the primary efficacy endpoint, the proportion of patients in each treatment group with clearance of ocular inflammation was calculated at Day 15.

The proportions of ocular clearance were compared between treatment groups using chi-square test.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

As shown in Table 1 in Appendix, about 19% and 20% of the patients discontinued from Study ISTA-BR-CS001-ER and Study ISTA-BR-CS001-WR, respectively.

For the missing data due to discontinuation, LOCF was used in the efficacy analysis on ITT data from two studies.

Table 2 in Appendix shows patient demographics by treatment groups for Study ISTA-BR-CS001-ER and Study ISTA-BR-CS001-WR, respectively. There were no statistically

significant imbalances among treatment groups with respect to demographic variables in Study ISTA-BR-CS001-ER. There were no statistically significant imbalances among treatment groups with respect to demographic variables except for gender ($p=.0499$) and iris color ($p=.0284$) in Study ISTA-BR-CS001-WR.

3.1.3 Statistical Methodologies

To show superiority in Study ISTA-BR-CS001-ER and Study ISTA-BR-CS001-WR, the sponsor employed the chi-square test comparing the proportion of ocular clearance between treatment groups based on ITT with LOCF and PP populations.

3.1.4 Results and Conclusions

Tables 3.1 – 4.2 in Appendix present the statistical analyses done by sponsor and reviewer. Following are review results of the analyses.

Study ISTA-BR-CS001-ER

The statistically significant difference in proportion of ocular clearance was shown when comparing bromfenac sodium 0.1% with placebo in ITT LOCF analysis without censoring ($p=.0002$), in ITT LOCF analysis with censoring ($p<.0001$), and in PP analysis ($p=.0058$). (See Table 3.1 in Appendix.)

Defining missing observation as non-ocular clearance by reviewer, the statistically significant difference in proportion of ocular clearance was shown when comparing bromfenac sodium 0.1% with placebo in ITT analysis ($p<.0001$ without censoring or with censoring). (See Table 4.1 in Appendix.)

Study ISTA-BR-CS001-WR

The statistically significant difference in proportion of ocular clearance was shown when comparing bromfenac sodium 0.1% with placebo in ITT LOCF analysis without censoring ($p=.0099$) and in ITT LOCF analysis with censoring ($p<.0001$), but not in PP analysis ($p=.0637$). (See Table 3.2 in Appendix.)

Defining missing observation as non-ocular clearance by reviewer, the statistically significant difference in proportion of ocular clearance was shown when comparing bromfenac sodium 0.1% with placebo in ITT analysis ($p<.0001$ without censoring or with censoring). (See Table 4.2 in Appendix.)

3.2 Evaluation of Safety

Safety analyses were done by Clinical reviewer, Jennifer Harris, M.D.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The sponsor did not include the subgroup analysis from individual study reports due to the small number of subjects in some subgroup strata.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

5.1.1 Statistical Issues

For the efficacy analysis, the sponsor based its inferences on ITT data from Study ISTA-BR-CS001-ER and Study ISTA-BR-CS001-WR with last observation carried forward (LOCF) for missing summed ocular inflammation score data and compared bromfenac sodium 0.1% with placebo in the proportion of patients with summed ocular inflammation score equal to 0 for the statistical significance.

For the primary efficacy analysis, when a subject discontinued test agent treatment early and was given alternative anti-inflammatory medication, the subject's data were not censored and considered coming from the original randomized treatment. As a secondary analysis of the primary efficacy endpoint, subjects who discontinued masked test agent treatment prior to Day 15 visit and received an alternative anti-inflammatory medication were censored at the visit closest to (on or before) receipt of the alternative medication.

One interim analysis was conducted by the Data Safety Monitoring Board when 50% of the subjects have completed the Day 29 visit or terminated the study. Using the spending function approach with O'Brien-Fleming boundary, an alpha level for the final analysis was adjusted to .049.

5.1.2 Collective Evidence

Based on our review of the data up to 1 month we conclude the following.

Study ISTA-BR-CS001-ER

The statistically significant difference in the proportion of ocular clearance as primary endpoint was shown when comparing bromfenac sodium 0.1% with placebo in ITT

LOCF analysis without censoring ($p=.0002$), in ITT LOCF analysis with censoring ($p<.0001$), and in PP analysis ($p=.0058$). Sensitivity analyses on ITT population treating patient with missing data on Day 15 as no cleared ocular inflammation also showed the statistically significant differences ($p<.0001$ without censoring or with censoring) reassuring that the statistical significance is robust against missing data imputation method.

Study ISTA-BR-CS001-WR

The statistically significant difference in the proportion of ocular clearance as primary endpoint was shown when comparing bromfenac sodium 0.1% with placebo in ITT LOCF analysis without censoring ($p=.0099$) and in ITT LOCF analysis with censoring ($p<.0001$), but not in PP analysis ($p=.0637$). Sensitivity analyses on ITT population treating patient with missing data on Day 15 as no cleared ocular inflammation also showed the statistically significant difference ($p<.0001$ without censoring or with censoring) again reassuring that the statistical significance is robust against missing data imputation method.

5.2 Conclusions and Recommendations

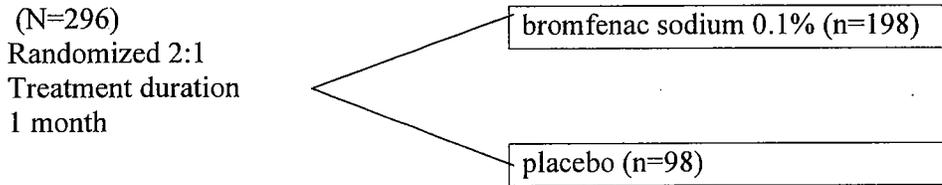
Data from both Study ISTA-BR-CS001-ER and Study ISTA-BR-CS001-WR showed efficacy of bromfenac sodium 0.1% at the Day 15 visit on the treatment of postoperative inflammation in patients who have undergone cataract extraction. The study ISTA-BR-CS001-ER showed statistically significant difference of ocular clearance proportion between bromfenac (62.6%) and placebo (39.8%) in the ITT population ($p=.0002$) and the study ISTA-BR-CS001-WR also showed statistically significant difference of ocular clearance proportion between bromfenac (65.8%) and placebo (48.0%) in the ITT population ($p=.0099$). Sensitivity analyses by the reviewer showed the statistically significant results from both studies, thereby reassuring the sponsor's statistically significant analysis results.

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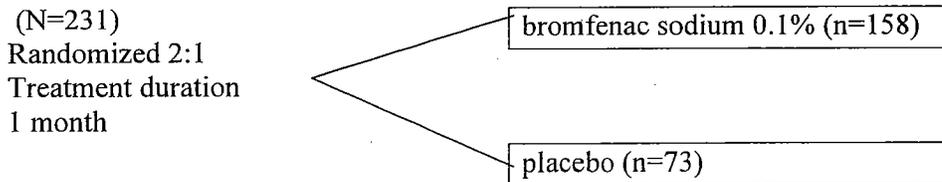
6. APPENDIX

Figure 1. Schematic of Study Design

Study ISTA-BR-CS001-ER:



Study ISTA-BR-CS001-WR:



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Table 1. Patient Disposition

Study ISTA-BR-CS001-ER:

	bromfenac sodium 0.1%	placebo	total
RANDOMIZED:	198	98	296
COMPLETED:	180 (90.9%)	59 (60.2%)	239 (80.7%)
DISCONTINUED:	18 (9.1%)	39 (39.8%)	57 (19.3%)
Adverse Event	6	14	20
Lack of Efficacy	6	21	27
Other	6	4	10

Study ISTA-BR-CS001-WR:

	bromfenac sodium 0.1%	placebo	total
RANDOMIZED:	158	73	231
COMPLETED:	142 (89.9%)	44 (60.3%)	186 (80.5%)
DISCONTINUED:	16 (10.1%)	29 (39.7%)	45 (19.5%)
Adverse Event	4	11	15
Lack of Efficacy	5	16	21
Other	7	2	9

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Table 2. Baseline Demographics and Ocular Characteristics by Treatment Group (ITT Patients)

Study ISTA-BR-CS001-ER:

	total		bromfenac sodium 0.1%		placebo		p-value
	N	%	N	%	N	%	
Total	296	100.0	198	66.9	98	33.1	
Age (years)							
Mean (SD)	69.7 (9.8)		69.3 (10.1)		70.4 (9.2)		.3429
Range	35 - 93		35 - 88		40 - 93		
Gender							
Male	135	45.6	93	47.0	42	42.9	.5038
Female	161	54.4	105	53.0	56	57.1	
Race							
Asian	3	1.0	2	1.0	1	1.0	.5304
Black	34	11.5	20	10.1	14	14.3	
Caucasian	235	79.4	162	81.8	73	74.5	
Hispanic	20	6.8	11	5.6	9	9.2	
American Indian	0	0.0	0	0.0	0	0.0	
Other	4	1.4	3	1.5	1	1.0	
Iris Color							
Brown	130	43.9	85	42.9	45	45.9	.6662
Hazel	43	14.5	33	16.7	10	10.2	
Blue	90	30.4	58	29.3	32	32.7	
Green	28	9.5	19	9.6	9	9.2	
Other	5	1.7	3	1.5	2	2.0	
Cataract Type*							
Nuclear	275	92.9	185	93.4	90	91.8	.6144
Cortical	123	41.6	81	40.9	42	42.9	.7489
Posterior Subcapsular	103	34.8	73	36.9	30	30.6	.2876
Pseudoexfoliation	2	0.7	2	1.0	0	0.0	1.0000

*Subjects could have had more than one type of cataract in the study eye.

Study ISTA-BR-CS001-WR:

	total		bromfenac sodium 0.1%		placebo		p-value
	N	%	N	%	N	%	
Total	231	100.0	158	68.4	73	31.6	
Age (years)							
Mean (SD)	69.9 (10.0)		70.3 (9.4)		68.8 (11.4)		.3183
Range	32 - 93		42 - 93		32 - 91		
Gender							
Male	111	48.1	69	43.7	42	57.5	.0499
Female	120	51.9	89	56.3	31	42.5	
Race							
Asian	5	2.2	3	1.9	2	2.7	.8824
Black	8	3.5	5	3.2	3	4.1	
Caucasian	198	85.7	134	84.8	64	87.7	
Hispanic	18	7.8	14	8.9	4	5.5	
American Indian	1	0.4	1	0.6	0	0.0	
Other	1	0.4	1	0.6	0	0.0	
Iris Color							
Brown	96	41.6	69	43.7	27	37.0	.0284
Hazel	34	14.7	17	10.8	17	23.3	
Blue	77	33.3	57	36.1	20	27.4	
Green	16	6.9	8	5.1	8	11.0	
Other	8	3.5	7	4.4	1	1.4	
Cataract Type*							
Nuclear	224	97.0	154	97.5	70	95.9	.6816
Cortical	147	63.6	99	62.7	48	65.8	.6494
Posterior Subcapsular	73	31.6	49	31.0	24	32.9	.7769
Pseudoexfoliation	2	0.9	1	0.6	1	1.4	.5331

*Subjects could have had more than one type of cataract in the study eye.

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Table 3.1. Analysis Results of Ocular Clearance Comparing bromfenac 0.1% versus placebo: Study ISTA-BR-CS001-ER

	Bromfenac Sodium 0.1% n/N (%)	Placebo n/N (%)	P-value
Primary analysis, ITT with LOCF	124/198 (62.6%)	39/98 (39.8%)	0.0002
Secondary analysis, ITT with LOCF censored	113/198 (57.1%)	23/98 (23.5%)	<0.0001
Secondary analysis, PP	74/117 (63.3%)	12/33 (36.4%)	0.0058

P-values calculated from the chi-square test.

Table 3.2. Analysis Results of Ocular Clearance Comparing bromfenac 0.1% versus placebo: Study ISTA-BR-CS001-WR

	Bromfenac Sodium 0.1% n/N (%)	Placebo n/N (%)	P-value
Primary analysis, ITT with LOCF	104/158 (65.8%)	35/73 (48.0%)	0.0099
Secondary analysis, ITT with LOCF censored	98/158 (62.0%)	23/73 (31.5%)	<0.0001
Secondary analysis, PP	65/90 (72.2%)	18/33 (54.6%)	0.0637

P-values calculated from the chi-square test.

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Table 4.1. Sensitivity Analysis Results of Ocular Clearance Comparing bromfenac 0.1% versus placebo: Study ISTA-BR-CS001-ER

	Bromfenac Sodium 0.1% n/N (%)	Placebo n/N (%)	P-value
Primary analysis, ITT with BOCF	113/198 (57.1%)	22/98 (22.5%)	<0.0001
Secondary analysis, ITT with BOCF censored	112/198 (56.6%)	22/98 (22.5%)	<0.0001

P-values calculated from the chi-square test.

Table 4.2. Sensitivity Analysis Results of Ocular Clearance Comparing bromfenac 0.1% versus placebo: Study ISTA-BR-CS001-WR

	Bromfenac Sodium 0.1% n/N (%)	Placebo n/N (%)	P-value
Primary analysis, ITT with BOCF	96/158 (60.8%)	22/73 (30.1%)	<0.0001
Secondary analysis, ITT with BOCF censored	96/158 (60.8%)	22/73 (30.1%)	<0.0001

P-values calculated from the chi-square test.

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SIGNATURES/DISTRIBUTION LIST

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