

## A New Paradigm in NSAID Treatment

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## Current Uses of Ophthalmic NSAIDs

- ◆ Intraoperative miosis<sup>1</sup>
- ◆ Relief of:
  - Pain<sup>2\*</sup>
  - Inflammation<sup>2,3,4\*</sup>
  - photophobia<sup>2\*</sup>
- ◆ Ocular allergy<sup>5\*</sup>
- ◆ Reduction of post-cataract cystoid macular edema (CME)<sup>6\*</sup>

Xibrom™ dosed BID is indicated **only** for the treatment of postoperative inflammation and the reduction of ocular pain in patients who have undergone cataract surgery

**\*Conditions for which bromfenac ophthalmic solution has been studied or for which data are available.**

*Note: All topical nonsteroidal anti-inflammatory drugs may slow or delay healing. Topical corticosteroids are also known to slow or delay healing.*

1. Ohara K, et al. Jpn J Clin Ophthalmol. 2004;58:1325-1328. 2. Data on File, ISTA Pharmaceuticals; Xibrom US Phase III Trials  
 3. Kawaguchi T, et al. Folia Ophthalmol Jpn. 2003;54:276. 4. Ohara K, et al. Jpn J Cataract & Refractive Surgery 2004;18:1-12. 5. Miyake-Kashima M, et al. Jpn J Ophthalmol. 2004;48:587.

## Current NSAIDs – Common Issues

- ◆ Dosing Schedule: Compliance & Convenience<sup>1</sup>

BID	TID	QID
Xibrom™	Nevanac™	Acular®; Acular® LS; Voltaren®

- ◆ Patient Tolerability<sup>1</sup>:

Burning & Stinging:	Sticky Sensation:
<ul style="list-style-type: none"> <li>◆ Acular® 40%; Acular® LS 20%</li> <li>◆ Voltaren® 5-15%</li> <li>◆ Xibrom™ 1.4%</li> </ul>	<ul style="list-style-type: none"> <li>◆ Nevanac™ 5-10%</li> </ul>

- ◆ Acular® onset of effect
  - Statistical Significance vs placebo 1<sup>st</sup> demonstrated: <sup>2</sup>
    - Day 14-16 for reduction in anterior chamber cells<sup>2</sup>
    - Day 6-8 for reduction in anterior chamber flare<sup>2</sup>
    - Day 6-8 for ocular pain<sup>2</sup>

1. Physicians' Desk Reference. 2004 & 2006.  
 2. Heier J. Ketorolac Tromethamine 0.5% Ophthalmic Solution in the treatment of Moderate to Severe Ocular Inflammation after cataract Surgery: A Randomized, Vehicle-Controlled Clinical Trial. AJO. Mar 1999; 127: 253-259

## History of Xibrom™

- ◆ Japan Approval, May 2000:
  - blepharitis, conjunctivitis, scleritis and post-operative inflammation
  - 6 Years & approximately 10.3 million patient uses
    - established track record of efficacy & safety<sup>1</sup>
- ◆ US Approval, March 2005:
  - same formulation as used in Japan

1. Data on File, ISTA Pharmaceuticals

## Published Comparative Papers From Trials in Japan

- ◆ Inflammation Post-Surgery
  - Significantly less flare in first 14 days for bromfenac (BID) vs. diclofenac (QID)<sup>1</sup>
  - Significantly less AC cells & protein in first 3 days for bromfenac (BID) than diclofenac (TID)<sup>2</sup>
- ◆ Relief of Seasonal Allergy
  - Bromfenac equal in efficacy to pemirolast<sup>3</sup>
- ◆ Prevention of Miosis in Cataract Surgery
  - Bromfenac equal in efficacy to diclofenac<sup>4</sup>

1. Kawaguchi T, et al. Folia Ophthalmol Jpn. 2003;54:276. 2. Ohara K, et al. Jpn J Cataract Refract Surgery 2004;18:1-12. 3. Miyake-Kashima M, et al. Jpn J Ophthalmology 2004; 48: 587-590. 4. Ohara K et al. Jpn J Clin Ophthalmol 2004; 58: 1325-1328

# Xibrom™

(bromfenac ophthalmic solution) 0.09%

**In The US:**

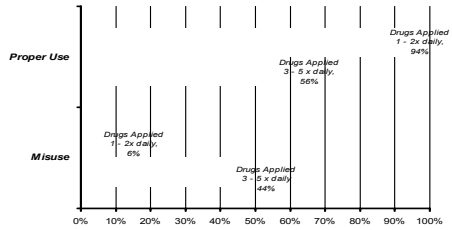
- ◆ Indicated as:
  - the first and only BID dosed NSAID for the treatment of postoperative inflammation and the reduction of ocular pain in patients who have undergone cataract extraction
- ◆ Contraindicated:
  - in patients with known hypersensitivity to any ingredient in the formulation
- ◆ Most commonly reported adverse experiences:
  - Abnormal sensation in eye, conjunctival hyperemia, eye irritation, eye pain, eye pruritus, eye redness, headache and iritis. These events were reported in 2%-7% of patients

# Effect of BID on Compliance

"Evaluation and Multivariate Statistical Analysis of Factors Influencing Patient Adherence to Ophthalmic Solutions"<sup>1</sup>

◆ 71 ophthalmic patients

◆ Ophthalmology Department at Hiroshima University



# Xibrom™ Phase III Trials: Key Points

- ◆ No pre-surgical dosing of an NSAID
- ◆ No anti-inflammatory agent until **ONE DAY** after surgery
- ◆ Summed Ocular Inflammation score *prior to treatment* = 3.7
  - High level of inflammation for routine cataract procedure
- ◆ Xibrom™: Dosed BID

*Data presented in following slides represent patients treated with Xibrom as their only anti-inflammatory (no steroid used)*

# Xibrom™ US Phase III Protocol Review

Number of cataract surgery patients	527 (356 Xibrom, 171 placebo)
Number of US sites	39
Baseline summed cells and flare: (prior to treatment)	<b>3.7</b>
Pre-Surgery Dosing w/NSAID or Steroid	<b>NO</b>
Xibrom (or placebo) Dose	<b>BID</b> for 14 days
Efficacy Endpoint Measures	<ul style="list-style-type: none"> <li>◆ Reduction in Summed Cell &amp; Flare Score                             <ul style="list-style-type: none"> <li>◆ Reduction in AC Cell Score</li> <li>◆ Reduction in AC Flare Score</li> <li>◆ Resolution of Pain</li> </ul> </li> </ul>

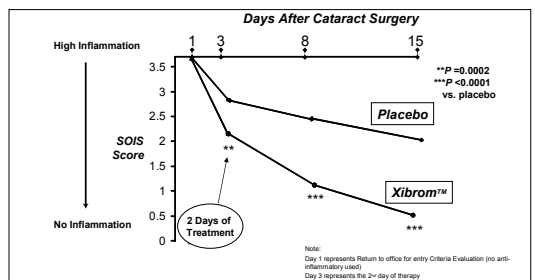
- ◆ Randomized, double masked, placebo-controlled studies
- ◆ Similar protocol to ketorolac 0.5% Phase III
- ◆ **ONLY** NSAID pivotal trial requiring an end-point of **zero**

<sup>1</sup>SOIS = Summed Ocular Inflammation Score: Anterior chamber cell grade added to anterior chamber flare grade

# Visit & Treatment Schedule

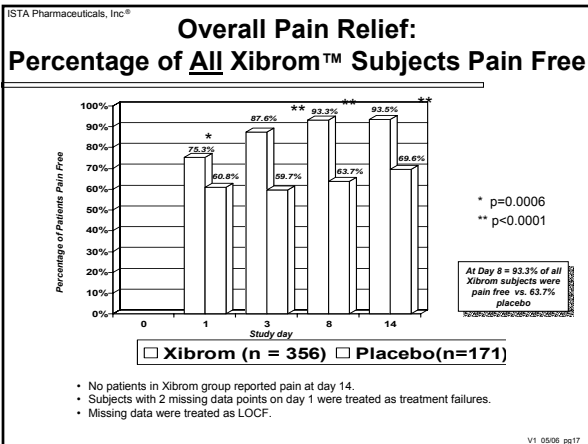
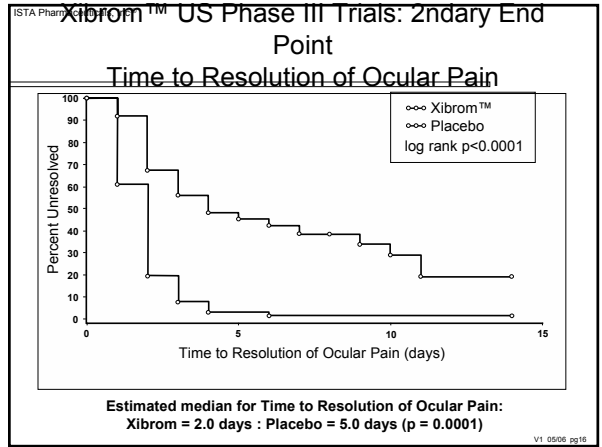
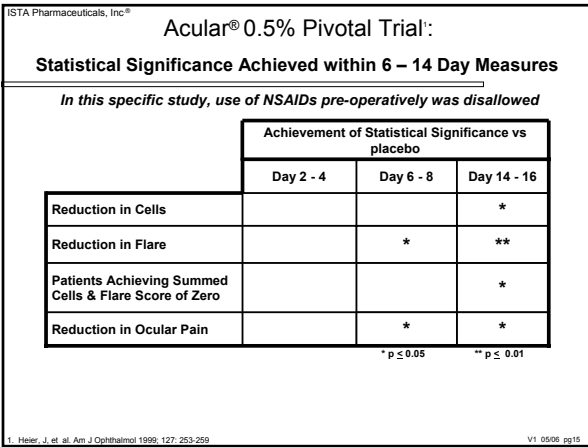
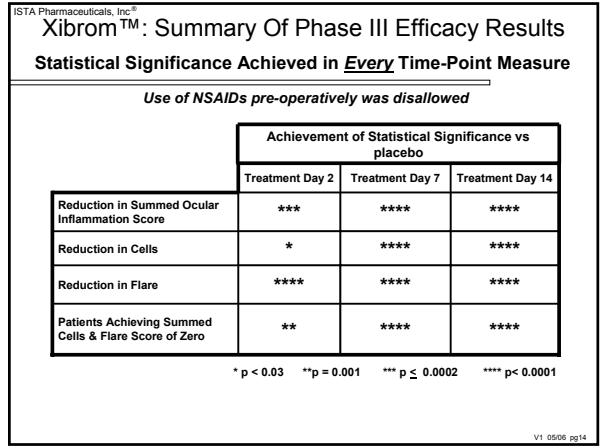
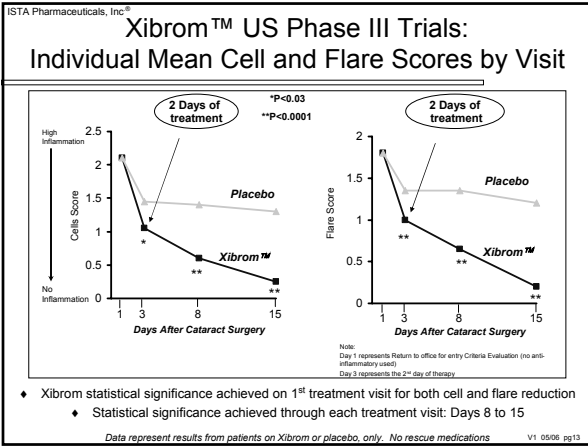
Treatment Evaluation	Days Post-Surgery	Days Post-Treatment Initiation	Approximate Doses of Xibrom
	Day 0 = Day of Surgery		
	Day 1: Return to office for Entry Criteria Evaluation (still no anti-inflammatory used)		
<b>1st</b>	<b>Day 3</b>	<b>2</b>	<b>4-6</b>
2nd	Day 8	7	14-16
3rd	Day 15	14	28
4th	Day 22	21	
5th	Day 29	28	

# Xibrom™ US Phase III Trials: Inflammation Reduction: Summed Ocular Inflammation Score



- ◆ Xibrom achieved statistical significance on 1<sup>st</sup> treatment evaluation (2 treatment days)
- ◆ Xibrom™ achieved statistically significant reduction from baseline at all study visits

Data represent results from patients on Xibrom or placebo, only. No rescue medications



- ISTA Pharmaceuticals, Inc.<sup>®</sup>
- ### Xibrom™ Post-Approval US Trials
- ♦ **Comfort vs. Acular LS**
    - H.D. Perry, MD, T.Y. Chou, MD
  - ♦ **Physician Satisfaction**
    - 589 Ophthalmologists/ 12,033 Patient Experiences
  - ♦ **CME Treatment Post-Cataract Surgery vs. Acular and Voltaren**
    - D.S. Rho, MD, S.M. Soll, MD, B.J. Markovitz, MD
  - ♦ **Macular Edema Treatment Post-Glaucoma Surgery vs. Acular**
    - A.M. Solish, MS, MD
- V1 0506 pg18

## Xibrom™ Post-Approval Trials: Comfort

### A Comparison of Xibrom™ and Acular® LS in a Test of Comfort and Corneal Anesthesia

- Henry D. Perry, MD
- Timothy Y. Chou, MD

**Purpose:**

- Compare comfort of Xibrom and Acular LS
- 20 normal healthy volunteers

**Methods:**

- 20 subjects administered single drop of each test agent to their eyes in a random and masked fashion.
- Burning and stinging on a 0 – 4 scale.

## Results: Subjective Assessment of Comfort Upon Instillation

Level of Burning or Stinging	Number of Patients Reporting None to Severe Burning & Stinging			
	None	Mild	Moderate	Severe
Xibrom	17	3	0	0
Acular LS	7	7	5	1

Xibrom: 17 of 20 (85%) reported no burning or stinging  
 Acular LS: 7 of 20 (35%) reported no burning or stinging

Xibrom: 0 of 20 (0%) reported moderate or severe burning or stinging  
 Acular LS: 6 of 20 (30%) reported moderate or severe burning or stinging

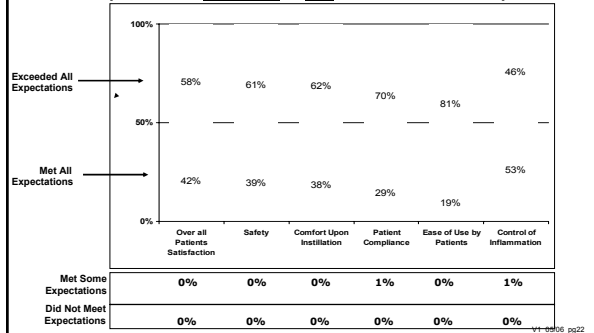
## Xibrom™ Post Marketing Trials: Physician Satisfaction – Xibrom First Experience (XFE) Trial

- ◆ MDs placed a minimum of 10 patients on Xibrom
  - May through June, 2005
  - Jan through Mar, 2006
- ◆ MDs rated Xibrom performance:
  - Very Satisfied: “Exceeded My Expectations”
  - Satisfied: “Met All My Expectations”
  - Dissatisfied: “Met Some of My Expectations”
  - Very Dissatisfied: “Did Not Meet My Expectations”
- ◆ Robust MDs experiences captured:
  - 589 MDs reported to date
  - 12,033 patients experiences reported

## Xibrom™: Early Experience Program

589 ophthalmologists: 12,033 patient experiences

### MD Expectations: Exceeded or Met in 99% to 100% of Reports



## Xibrom™ Phase 4 Trials: Cystoid Macular Edema (CME)<sup>1</sup>

### A Comparison of Bromfenac, Ketorolac, and Diclofenac for Treatment of Acute Pseudophakic Cystoid Macular Edema (Preliminary Data)

- David S. Rho, MD, Stephen M. Soll, MD, Bruce J. Markovitz, MD

**Purpose:**

- Comparison of Xibrom, Acular, and Voltaren for treatment of acute CME post-cataract surgery

**Methods:**

- 64 post-cataract patients with acute CME randomized to one of three regimens: Xibrom BID, Acular QID, or Voltaren QID, in the affected eye
- Visual acuities measured; Snellen VA charts and ETDRS charts

## Xibrom™ Phase 4 Trials: Cystoid Macular Edema (CME)<sup>1</sup>

	Bromfenac	Diclofenac	Ketorolac
Initial VA	20/150 ± 28.9	20/175 ± 45.6	20/162 ± 45.0
Initial VA (ETDRS letters)	19.6 ± 13.7	9.0 ± 5.0	10.6 ± 7.1
Final VA	20/58.4 ± 44.6	20/107 ± 47.0	20/102 ± 47.6
Final VA (ETDRS letters)	34.6 ± 11.6	20.6 ± 9.9	22.2 ± 10.9
ETDRS Letters gained	15.0 ± 11.2	11.5 ± 7.5	11.6 ± 8.6

P-values for ETDRS letters gained within treatment groups: Bromfenac p < 0.00005, Diclofenac p < 0.0005, Ketorolac p < 0.0005  
 P-values for ETDRS letters gained between treatment groups: Bromfenac vs Diclofenac p = 0.28, Bromfenac vs Ketorolac p = 0.25, Ketorolac vs Diclofenac p = 0.96

## Xibrom™ Phase 4 Trials: Macular Edema Treatment Post-Glaucoma Surgery<sup>1</sup>

### A Prospective, Randomized Comparison of Bromfenac with Ketorolac for the Treatment of Patients with Reduced Visual Acuity Following Glaucoma Surgery

• Alfred M. Solish, MS, MD

#### Purpose:

- Comparison of Xibrom and Acular for treatment of macular edema post-glaucoma surgery

#### Methods:

- 20 post-glaucoma surgery patients with decreased corrected visual acuity (VA), whose vision had not improved with topical steroids, were randomized to either Xibrom BID or Acular QID
- Corrected visual acuities were compared following 4-6 weeks of treatment

## Xibrom™ Phase 4 Trials: Macular Edema Treatment Post-Glaucoma Surgery<sup>1</sup>

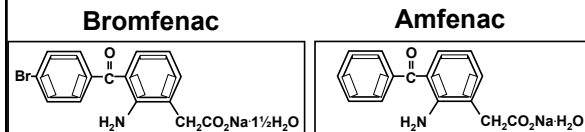
	Bromfenac	Ketorolac	P (t-test)
Initial IOP (mmHg)	9.7±5.6	6.7±4.2	0.048
Follow-up IOP (mmHg)	11.8±8.2	8.3±6.3	0.093
Follow-up (days)	46.3±23	34.7±21.7	0.071
Change in VA (lines corrected)	+1.5±2.6	+0.3±1.6	0.073
Patients gaining VA (≥2 lines)	6/16 (37.5%)	4/19 (21%)	
Patients losing VA (≥1 line)	2/16 (12.5%)	5/19 (26.3%)	

More patients had VA improvement with Xibrom than with Acular, though the difference was not statistically significant

## Penetration & Potency Data

Helps answer the question:  
*How and why is Xibrom BID?*

## Chemical Structures and Related Activities



Chemical structure of bromfenac is similar to amfenac, shown above

- Substitution of the benzoyl ring has pronounced effects on *in-vivo* and *in-vitro* potency and absorption (B > 2x more potent than A in this study)<sup>1</sup>

- In general, compounds that contain a halogen, are more potent (I ~ Br > Cl > F > H).

## Octanol/Water (O/W) Partition Coefficients

The octanol/water partition coefficient for bromfenac compared to other NSAIDs and Steroids at physiological pH 7.4\*

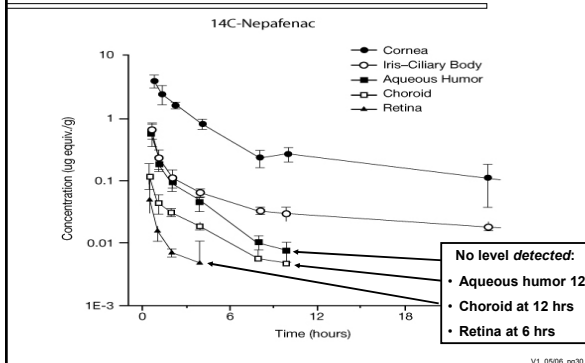
Drug	O/W Partition Coefficients
Bromfenac <sup>1</sup>	2.23
Amfenac <sup>1</sup>	1.23
Ketorolac <sup>2</sup>	1.88

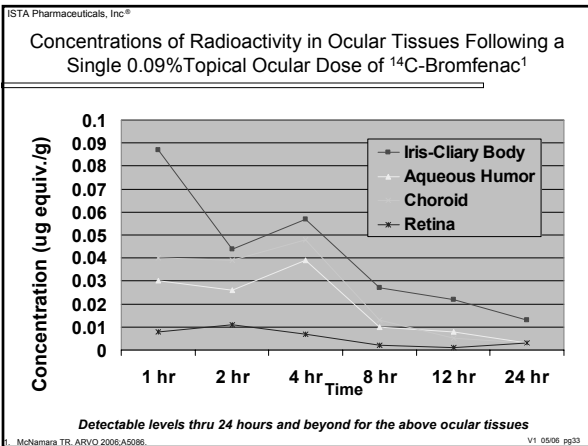
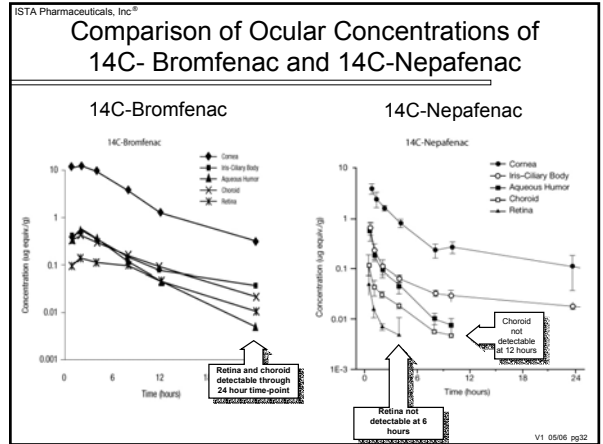
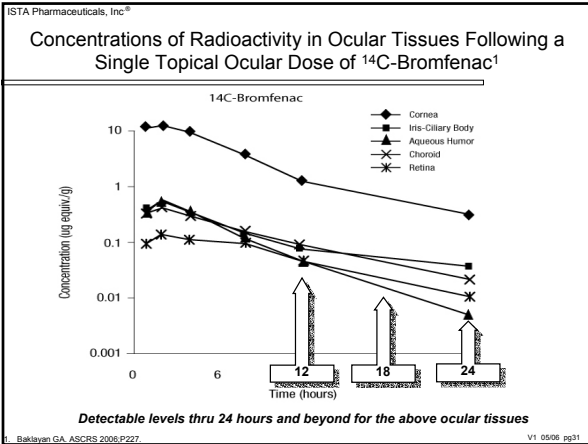
\*The higher the coefficient, the higher the penetration across membranes. 1.0 unit difference = 10 fold difference

1. Ruiz J et al. Journal of Computer-Aided Molecular Des. 1993. 183-198

2. QSAR tables

## Amfenac Penetration: Data From Amfenac Patent 6,646,001 B2





ISTA Pharmaceuticals, Inc.<sup>®</sup>

### PK Profile of a Single 0.09% Topical Ocular Dose of Bromfenac in Subjects Undergoing Cataract Surgery<sup>1</sup>

Time of instillation before surgery (min)	No. of cases	BF conc. in aqueous humor (ng/ml) (mean + SD)
t ≤ 30	1	9.8
30 < t ≤ 60	5	11.5 ± 6.6
60 < t ≤ 90	11	36.4 ± 43.8
90 < t ≤ 120	7	59.6 ± 45.2
120 < t ≤ 150	7	65.5 ± 69.8
150 < t ≤ 180	5	78.7 ± 68.1
180 < t ≤ 210	3	63.1 ± 44.4
210 < t ≤ 240	5	42.1 ± 14.3
240 < t ≤ 270	4	40.0 ± 42.1
270 < t ≤ 300	3	23.3 ± 15.3
300 < t ≤ 330	2	22.3 ± 13.5
t > 330	1	52

Bromfenac concentrations in aqueous humor at grouped 30-min intervals

1. Ogawa T, ARVO 2006.A687 V1 05/06 pg34

ISTA Pharmaceuticals, Inc.<sup>®</sup>

### PK Profile of a Single 0.09% Topical Ocular Dose of Bromfenac in Subjects Undergoing Cataract Surgery<sup>1</sup>

	IC50
Human recombinant prostaglandin G/H synthase	4.0 nM, 1.5 ng/mL
Rabbit alveolar macrophages	23 nM, 8.8 ng/mL

IC50 value of bromfenac in human and rabbit COX-2 inhibitory activity

1. Ogawa T, ARVO 2006.A687 V1 05/06 pg35

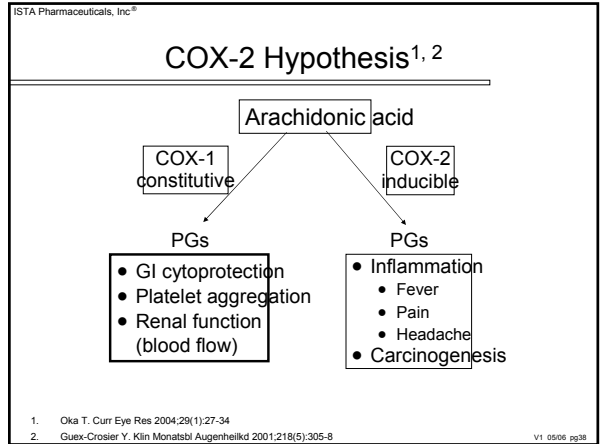
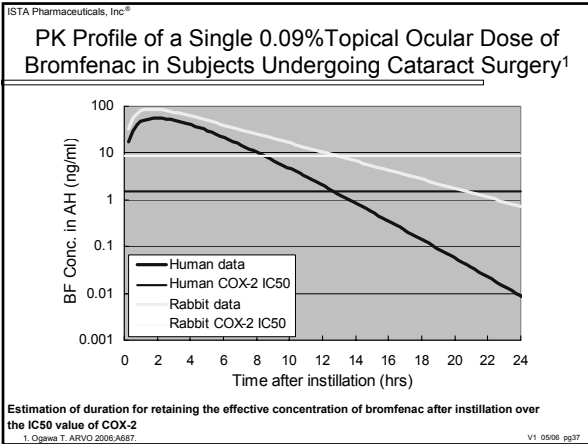
ISTA Pharmaceuticals, Inc.<sup>®</sup>

### PK Profile of a Single 0.09% Topical Ocular Dose of Bromfenac in Subjects Undergoing Cataract Surgery<sup>1</sup>

	Tmax (hr)	Cmax (ng/mL)	T <sub>1/2</sub> (hr)
Human	2.0	55.8	1.4
Rabbit	1.7	86.5	3.1

PK parameters of bromfenac in aqueous humor of human and rabbit

1. Ogawa T, ARVO 2006.A687 V1 05/06 pg36



ISTA Pharmaceuticals, Inc.<sup>®</sup>

### Potency Measurement: IC<sub>50</sub>

- ◆ Drug concentration required to inhibit enzyme activity by 50%
- ◆ The smaller the number, the more potent the molecule

V1 0506 pg39

ISTA Pharmaceuticals, Inc.<sup>®</sup>

### Relative Potency of NSAIDs In Vitro: IC<sub>50</sub> vs COX-1 and COX-2\* enzymes

Lower IC<sub>50</sub> = Greater Potency

	IC <sub>50</sub> , COX -1	IC <sub>50</sub> , COX -2
<b>Bromfenac</b>	0.53 μM	0.023 μM
<b>Diclofenac<sub>1</sub></b>	0.95 μM	0.085 μM
<b>Amfenac<sub>2</sub></b>	0.250 μM	0.150 μM

3.7X (Bromfenac COX-2 vs Diclofenac COX-2)  
6.5X (Amfenac COX-2 vs Bromfenac COX-2)

\*COX II Enzyme most responsible for pain and inflammation  
IC<sub>50</sub> of bromfenac for COX-2 is 18 fold greater than ketorolac<sup>3</sup>

The clinical significance of these data is unknown. The Cox-1 and Cox-2 *in vitro* assay is highly variable between laboratories and types of assays used.

1. Data on file B2003R0504. ISTA Pharmaceuticals; 2. Gamahe et al Inflammation LS:307  
3. Waterbury et al. Curr Med Res Opin 2006;22(6):1133-1140

V1 0506 pg40

ISTA Pharmaceuticals, Inc.<sup>®</sup>

### Xibrom™ Safety

- ◆ Extensive testing from Phase I – Phase III
- ◆ 6 years of ophthalmic use
- ◆ Over 10.3 million ophthalmic uses
- ◆ 3,425 patients officially tracked by 703 institutions

A very safe drug:  
No reported drug related serious systemic side effects

V1 0506 pg41

ISTA Pharmaceuticals, Inc.<sup>®</sup>

### Xibrom™ US Phase III Trials: Common Treatment-Emergent Ocular Adverse Events (≥ 2% incidence rate)

Clinical studies demonstrated a minimal incidence of adverse events

Adverse Event	n (% of Subjects)	
	Xibrom™ (n = 356)	Placebo (n = 171)
Iritis	25 (7.0%)	31 (18.1%)
Ocular pain	15 (4.2%)	20 (11.7%)
Abnormal sensation in eye	23 (6.5%)	14 (8.2%)
Eye pruritus	14 (3.9%)	5 (2.9%)
Eye irritation	9 (2.5%)	8 (4.7%)
Eye redness	8 (2.2%)	13 (7.6%)
Photophobia	7 (2.0%)	19 (11.1%)

Other Reported Adverse Events:  
• ONLY 1.4% incidence of burning and stinging in Xibrom patients  
• CME reported: Xibrom 1.4% ; Placebo 4.7% (p < 0.05)

Note: Xibrom is not indicated for the treatment of CME nor Photophobia

V1 0506 pg42

## Experience with Bromfenac Sodium Ophthalmic Solution in Japan (2000-2006)

### Well established "6 Year" safety profile

- ◆ **10.3 million** uses & in over **7.8 million** patients in Japan<sup>1</sup>
  - **Zero** drug related serious systemic events reported
  - Serious ocular adverse events
    - Reported in 0.0002% of patients (16)
- ◆ 14 corneal events reported in the Japanese post-marketing surveillance program involving 3,425 patients observed from May 2000 to January 2004 (0.41%).
- ◆ Dosing schedules, length of therapy, and indications may vary between Xibrom and bromfenac ophthalmic solution used in Japan
- ◆ Products in Japan and U.S. are identical

1. Data on file: ISTA Pharmaceuticals

2. Kitao N, Shimoi H, Fukuda M, Atarashi Ganka 2005;22:1299-1308.

## Xibrom™ (Bronuck) Post Marketing Safety Report (Japan) Filed with Minister of Health, Labour and Welfare 3/2005

**Marketed since 7/2000: There have been no drug related serious systemic adverse events reported with use of bromfenac sodium ophthalmic solution**

Patients or Usage of Xibrom (Bronuck)	Number of patients
Total Patients Surveyed (7/2000 – 1/2006)	3,425
Patient Age: 1 Month to 15 Years	249
Patient Age: 65 Years or Older	1,772
Patients with known <b>pre-existing</b> liver disorders	39
Patients with known <b>pre-existing</b> kidney disorders	20
More than 2 times per day	358
More than 4 times per day	88
Between 50-99 drops of drug	1,516
Between 100-149 drops of drug	692
Between 150-199 drops of drug	254
Over 200 drops of drug	145

*Xibrom, in the US, is indicated for BID dosing for 14 days of treatment*

## Summary of Xibrom™

- ◆ A Very Potent NSAID
  - IC<sub>50</sub> data for bromfenac & diclofenac & amfenac in similar models
- ◆ Rapidly Treats Significant Inflammation
  - Excellent penetration
- ◆ BID dose
  - Compliance & Convenience
- ◆ Comfortable
  - 1.4% burning/stinging
- ◆ Safe
  - 6 years experience & 10.3 million uses

## HIDDEN/BACK-UP SLIDES

## Xibrom™ US Phase III Trials: Grading Scale for Cells & Flare

Grade	Cells (Count)	Grade	Flare
0	0-5 (trace)	0	Complete Absence
1	6 – 15	1	Very Slight
2	16 – 25	2	Moderate
3	26 – 50	3	Marked
4	> 50	4	Intense

### Inclusion Criteria:

Patients were required to have a Summed Ocular Inflammation Score (cell score + flare score)  $\geq 3$  at 16 to 32 hours, **after surgery – PRIOR to Treatment**

\*SOIS = Summed Ocular Inflammation Score:

Anterior chamber cell grade added to anterior chamber flare grade

## Xibrom™ : US Phase III Trials

Patients with **EXISTING** significant inflammation were treated with Xibrom, or placebo, BID

- Treatment started **AFTER** inflammation had developed
- Cells & flare graded each visit
- 1<sup>st</sup> treatment visit: 2 days of Xibrom treatment

Safety Issues have occurred with all **ORAL** NSAIDs

- ◆ Diclofenac (Voltaren<sup>®</sup>)
  - Gastrointestinal perforations, ulcerations, and bleeding
- ◆ Ketorolac (Toradol<sup>®</sup>)
  - Gastrointestinal perforations, ulcerations, and bleeding
  - Black box warning in U.S.<sup>2</sup>, withdrawn from market in France and Germany
  - 143 deaths from 1990-1993<sup>1</sup>
- ◆ Bromfenac (Duract<sup>™</sup>)
  - Hepatotoxicity, acute hepatic failures, when used outside of labeled dosage
  - Manufacturer *voluntarily* withdrew from US market
  - 4 deaths in 1997-1998

1. Macario A, et al Pain Medicine Vol.2, 2001  
 2. Physicians' Desk Reference, 2004.

Xibrom<sup>™</sup> US Phase III Trials:  
 Liver Function Tests Show *No Effect on Liver*

Liver Function Test	n (% of Patients) With Toxicity Grade = 1 at Study Termination	
	Xibrom <sup>™</sup> (n = 340)	Placebo (n = 157)
Aspartate aminotransferase (AST)	3 (0.9%)	2 (1.3%)
Alanine transaminase (ALT)	4 (1.2%)	2 (1.3%)
γ-glutamyl transpeptidase (GGT)	8 (2.3%)	3 (1.9%)
Total bilirubin	2 (0.6%)	0
Direct bilirubin	0	0
Alkaline phosphatase	0	0

- ◆ No significant differences between treatment groups
- ◆ No subjects with results > CTC grade 1

CTC = common toxicity criteria

5

5

gnto document safety and efficacy

5