BAUSCH + LOMB

AAO 2012 **PO 005**

Integrated Phase III Clinical Trials of Low-Concentration, Modified Bromfenac Ophthalmic Solution Dosed Once Daily for Cataract Surgery

Contact information:
Tim McNamara, Pharm.D.
Clinical Affairs
Bausch & Lomb, Inc.
50 Technology Drive
Irvine, CA 92618
Phone: (949) 788-5388
Email: tim.mcnamara@bausch.com

J.A. Gow,[1] D.F. Goldberg,[2] J.H. Peace,[3] T.R. Walters,[4] J.P. Gira,[5] S.M. Klier,[1] T.R. McNamara[1]
for the Low Concentration Bromfenac Ophthalmic Solution Once Daily Study Group
[1]Bausch & Lomb Inc., Irvine, CA; [2]Wolstan Eye Associates, Torrance, CA; [3]United Medical Research Institute, Inglewood, CA; [4]Texan Eye, Austin, TX; [5]Ophthalmology Consultants, Ltd, St. Louis, MO

Abstract

Purpose: To evaluate the efficacy and safety of low-concentration, modified bromfenac solution dosed QD for cataract surgery.

Methods: Subjects received either bromfenac (n=222) or placebo (n=218) QD. Dosing began 1 day before cataract surgery and continued daily through post-surgery Day 14. Primary efficacy endpoint was no ocular inflammation by Day 15; secondary efficacy endpoint was no ocular pain at Day 1

Results: Bromfenac was superior to placebo for primary and secondary efficacy endpoints (P<0.0001). Compared to placebo, bromfenac had a lower incidence of ocular adverse events (P=0.0001).

Conclusion: Low-concentration, modified bromfenac solution dosed QD is safe and effective to treat the inflammation and pain associated with cataract surgery.

Introduction

- Bromfenac is a non-steroidal anti inflammatory drug (NSAID) with an extensive history of clinical efficacy; it acts by blocking prostaglandin synthesis by inhibiting cyclooxygenase 1 and 2 in the arachidonic acid pathway [1]
- The bromine moiety in bromfenac enhances lipophilicity and facilitates penetration throughout ocular tissues [2-3]
- Bronuck® (bromfenac sodium ophthalmic solution) 0.1% was initially approved in Japan in July 2000 and was subsequently approved for the treatment of blepharitis, conjunctivitis, scleritis (including episcleritis) and post-operative inflammation[4]
- Xibrom™ (bromfenac ophthalmic solution) 0.09%, administered twice daily, was approved by the Food and Drug Administration (FDA) on March 24, 2005 for the treatment of patients with post-cataract ocular inflammation, and in January 2006 for the treatment of ocular pain following cataract surgery[4]
- Bromday™ (bromfenac ophthalmic solution) 0.09% administered once daily, was approved by the FDA on October 16, 2010 for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction[1]
- Based on extensive post-marketing experience and data from clinical trials, bromfenac ophthalmic solution has demonstrated a favorable safety profile
- The modified formulation of bromfenac facilitates intraocular penetration, thereby allowing a lower medication load while maintaining clinical efficacy with once daily dosing

Purpose

- To evaluate the efficacy and safety of low-concentration, modified bromfenac sodium ophthalmic solution dosed once daily for the treatment of ocular inflammation and ocular pain associated with cataract surgery in subjects who have undergone cataract extraction with posterior chamber intraocular lens implantation

Methods

Study Design and Subjects

- Phase 3, placebo-controlled, randomized, double-masked, multi-center study
- 440 subjects randomized (222 in the bromfenac group, 218 in the placebo group)at 39 clinical sites
- Eligible subjects were scheduled for a unilateral cataract surgery (phacoemulsification or extracapsular) with PCIOL implantation

Screening Phase: Days -8 to -1

- **Subjects were assigned to receive either bromfenac sodium ophthalmic solution or placebo dosed QD**
- **Subjects must have met inclusion and exclusion criteria to be eligible for clinical trial**
- **Primary efficacy endpoint was clearance of ocular inflammation [Summed Ocular Inflammation Score (SOIS) = 0] by day 15**
- **Secondary efficacy endpoint was proportion of subjects pain-free at day 1**

Treatment Phase: Day -1 to Day 15

- **Subjects began dosing on Day -1 (~ 24 hours before surgery)**
- **Subjects returned to the office on Day 1 for evaluation of safety and efficacy**
- **Subjects returned to the office on Day 3±1 for evaluation of safety and efficacy**
- **Subjects returned to the office on Day 8±1 for evaluation of safety and efficacy**
- **Discontinued test agent on day 14 and subjects returned to the office on Day 15±1 for evaluation of safety and efficacy**

Follow-up Phase : Day 22+3 or 7+3 Days After Final Dose

- **Subjects returned to the office on Day 22+3 or 7+3 days after discontinuation of test agent for termination evaluation**

Figure 1. Algorithm of Clinical Trial Procedures

Table 1. Subject Demographics (ITT population)

	Bromfenac (n = 222)	Placebo (n = 218)
Age (Years)		
Mean (SD)	68.4 (10.70)	68.5 (9.68)
Sex		
Female	141 (63.5.)	146 (67.0%)

Results

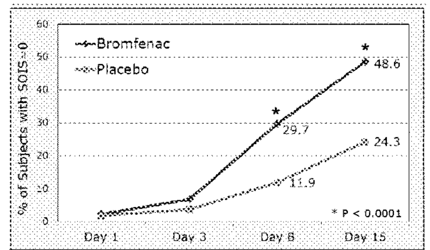

Figure 2. Proportion of Subjects Cleared of Ocular Inflammation

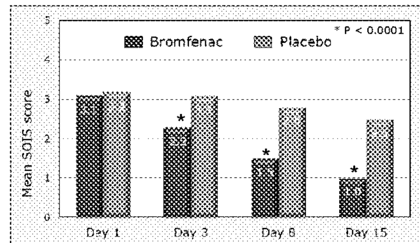

Figure 3. Mean Summed Ocular Inflammation Score (SOIS) at Each Study Day

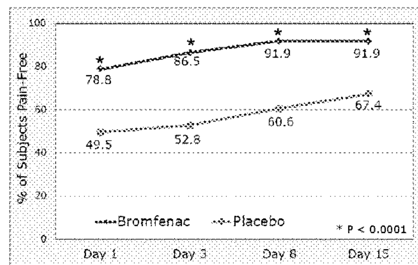

Figure 4. Proportion of Subjects Pain-Free at Each Study Visit

Compliance and Early Discontinuation

Table 2. Treatment Compliance and Discontinuations

Percent Compliance	Bromfenac	Placebo
Mean[1]	91.21%	75.98%
Early Discontinuations		
Subjects who discontinued test agent early	34 (15.3%)	96 (44.0%)
Due to lack of efficacy	7 (3.2%)	52 (23.9%)

[1] % Compliance = 100 x number of doses received / 16

Safety

Table 3. Adverse Events (AE) Affecting the Study Eye (Safety Population)

Adverse Event	Bromfenac (n = 212)	Placebo (n = 204)
Subjects reporting an AE affecting the study eye or both eyes	14 (6.6%)	43 (21.1%)
Eye Pain	6 (2.8%)	16 (7.8%)
Anterior chamber inflammation	5 (2.4%)	11 (5.4%)
Conjunctival hyperemia	2 (0.9%)	8 (3.9%)
Photophobia	1 (0.5%)	8 (3.9%)
Corneal edema	1 (0.5%)	5 (2.5%)
Lacrimation increased	1 (0.5%)	5 (2.5%)
Foreign body sensation	0	5 (2.5%)
Ocular hyperemia	0	4 (2.0%)

Cystoid Macular Edema (CME)/Macular Edema (ME)

- The incidence of CME/ME was 0.5% (1/212) in the bromfenac group compared with 2.0% (4/204) in the placebo group.

Conclusion

Low-concentration, modified bromfenac solution dosed QD is safe and effective to treat the inflammation and pain associated with cataract surgery.

References:

1. Bromday™ [package insert]. Irvine, CA: ISTA Pharmaceuticals, Inc.; 2010.
2. Brown HB, Taylor P. In: Hardman JG, Limbird LE, Molinoff PB, et al eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York: McGraw-Hill;1996:141–60.
3. Baklayan GA, Patterson HM, Song CK, et al. J Ocular Pharmacol Therapeutics 2008;24:392-8.
4. Henderson BA, Gayton JL, Chandler SP et al. Ophthalmology. 2011; 118:2120-7
5. Donnenfeld ED, Donnenfeld A. Int Ophthalmol Clin. 2006;46:21-40.

Financial support: Bausch & Lomb Inc., Irvine, CA, USA
Financial disclosures: JA Gow and TM McNamara are employees of Bausch & Lomb, Inc. SM Klier is a former employee of Bausch & Lomb, Inc. DF Goldberg, JH Peace, and JP Gira are consultants for Bausch & Lomb Inc.

Presented at the 2012 Annual Meeting of the American Academy of Ophthalmology, November 10-13, 2012, Chicago, IL

SENJU EXHIBIT 2227
LUPIN v. SENJU
IPR2015-01097