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Randomized, Placebo-Controlled, Integrated Phase III Clinical Trials of a Once Daily, Low-Concentration, Modified Bromfenac Ophthalmic Solution Following Cataract Surgery: Focus on Zero to Trace Anterior Chamber Inflammation

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Abstract

Purpose: To evaluate in a *post-hoc* analysis the reduction of ocular inflammation to 0 or trace anterior chamber inflammation of low-concentration, modified bromfenac ophthalmic solution dosed once daily compared to placebo following cataract surgery in 2 integrated clinical trials.

Methods: Subjects undergoing unilateral cataract surgery (phacoemulsification or extracapsular cataract extraction) with posterior chamber IOL implantation were randomized to either low-concentration, modified bromfenac ophthalmic solution (n=222) or placebo (n=218). Once daily dosing began 1 day before cataract surgery, continued on the day of surgery, and through post-surgery Day 14. The proportion of subjects with trace anterior chamber inflammation, defined as a Summed Ocular Inflammation Score (SOIS) of 0-0.5 (0-5 cells in the anterior chamber and flare grade of 0), was assessed at Days 1, 3, 8, and 15. Safety was assessed by the incidence and frequency of ocular and systemic adverse events, and ophthalmological evaluations (visual acuity, slit lamp examination, intraocular pressure, and dilated funduscopic examination). Statistical significance was determined using a Fisher's exact test.

Results: In the intent-to-treat population, subjects had a mean age of 68.0 years, were predominantly Caucasian (74.8%), and included a higher percentage of female subjects (65.2%). Baseline characteristics were similar across treatment groups. A significantly higher proportion of subjects achieved trace ocular inflammation in the bromfenac group compared to placebo as early as Day 3 (27.9% vs. 13.8%, p=0.0008), continued on Day 8 (55.4% vs. 24.3%, p < 0.0001), and through Day 15 (71.2% vs. 39.4%, p < 0.0001). Compared to placebo, low-concentration, modified bromfenac ophthalmic solution dosed once daily produced a lower overall incidence of ocular adverse events.

Conclusion: Low concentration, modified bromfenac ophthalmic solution dosed once daily effectively and safely reduced ocular inflammation 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 [5]
- Based on extensive post-marketing experience and data from clinical trials, bromfenac ophthalmic solution has demonstrated a favorable safety profile
- The advanced formulation of bromfenac facilitates intraocular penetration, thereby allowing a lower medication load while maintaining clinical efficacy with once daily dosing

Purpose

- To evaluate in a *post-hoc* analysis the reduction of ocular inflammation to 0 or trace anterior chamber inflammation of advanced formulation, low-concentration, bromfenac ophthalmic solution dosed once daily compared to placebo following cataract surgery in 2 integrated clinical trials.

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 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 with trace inflammation (SOIS= 0-0.5)**

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**

Table 1: Schedule of Clinical Visit and Procedures

Table 2: 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

Table 3: Anterior Inflammation Counts at Day 15

Anterior Chamber Cells		Anterior Chamber Flare	
Grade	Cell Count	Grade	Flare Count
0	0	0	Complete absence
1	1-5 cells (trace)	-	-
2	6-15	1	Very slight (barely visible)
3	16-25	2	Moderate (iris and lens clear)
4	26-50	3	Marked (iris and lens hazy)
5	> 50	4	Intense (fibrin clot)

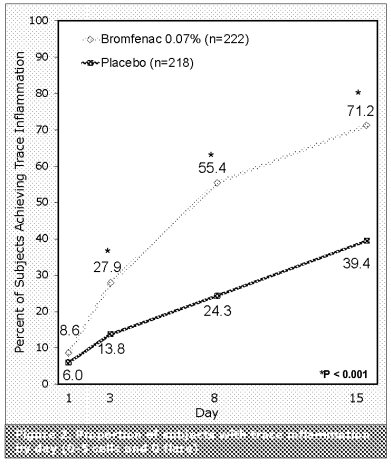

Figure 2: Subjects Achieving Trace Inflammation

Compliance and Early Discontinuation

Table 4: Treatment Compliance and Early Discontinuation

Percent Compliance	Bromfenac (n = 222)	Placebo (n = 218)
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 5: Incidence of Adverse Events Reported by ≥ 2% of Subjects in Any Treatment Group (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.

Conclusions

- **Advanced formulation, low-concentration bromfenac ophthalmic solution dosed once daily effectively and safely reduced ocular inflammation associated with cataract surgery.**
- **Once daily bromfenac ophthalmic solution 0.07% was approved on April 5th, 2013 by the U.S. Food and Drug Administration (FDA) as PROLENSA™[6]**

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