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ORIGINAL RESEARCH

Twice-Daily vs. Once-Daily Dosing with 0.075% Bromfenac in DuraSite: Outcomes from a 14-Day Phase 2 Study

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ABSTRACT

Introduction: Bromfenac is a well-known topical ophthalmic nonsteroidal anti-inflammatory drug (NSAID) that is commercialized in the USA and other regions of the world. A new formulation, 0.075% bromfenac in DuraSite®, was developed to treat postoperative inflammation and reduce pain in patients who have undergone cataract surgery. We hypothesized that efficacy and safety would be enhanced with twice-daily (BID) dosing compared to once-daily (QD) dosing.

Methods: This was a multicenter, double-masked, comparative study in which 40 and 45 subjects were randomized to groups receiving BID dosing and QD dosing, respectively. Subjects self-instilled the study drug for 14 days postoperative and were followed for an additional 2-week evaluation phase. The primary efficacy endpoint was the proportion of subjects with an anterior chamber cell (ACC) grade of 0 at day 15.

Results: A total of 45 subjects had cleared ACC (grade "0") at day 15, of whom 21 were in the BID group (52.5%) and 24 were in the QD group (53.5%). A secondary analysis found 7/40 (17.5%) subjects in the BID group and 10/45 (22.2%) subjects in the QD group achieved an ACC grade of 0 at day 8. There were more adverse events in the QD group ($n = 16$) than in the BID group ($n = 12$).

Conclusion: Similar outcomes were observed for subjects using Bromfenac 0.075% in DuraSite® in the BID and QD dosing regimens for the treatment of post-cataract surgery inflammation.

Trial registration: ClinicalTrials.gov identifier, NCT01190878.

Funding: InSite Vision (now a division of Sun Pharma).

Keywords: Bromfenac; Cataract surgery; Cyclooxygenase inhibitor; DuraSite®; Nonsteroidal anti-inflammatory drugs

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a well-accepted treatment to reduce postoperative pain after ocular surgery and to control inflammation [1–5]. There are numerous NSAIDs approved for ophthalmic use in the USA, including bromfenac. Bromfenac is a potent cyclooxygenase inhibitor with a long

history of use in various strengths for ophthalmic indications dating back to 2006 [1, 2, 6–9]. DuraSite® (InSite Vision, Alameda, CA) is a synthetic polymer-based formulation designed to improve solubility, absorption, bioavailability and residence time. Both clinical and nonclinical studies have shown the DuraSite® drug delivery system to be safe and non-toxic [10]. DuraSite® is commercially available in the USA in two antibiotic formulations (one with 1% azithromycin and the other with 0.6% besifloxacin), and DuraSite® technology has also been used in a formulation of loteprednol gel.

In 2016, the Food and Drug Administration approved bromfenac 0.075% administered twice daily (BID) for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery. The on-label indication recommends that BID dosing begin 1 day before surgery and continue on the day of surgery and for 14 days post-surgery [11].

The purpose of this analysis was to compare two dosing regimens of bromfenac 0.075%: once-daily (QD) and BID in post-cataract surgery patients to assess safety, tolerability and efficacy.

METHODS

Study Design

This was a multicenter, randomized, double-masked, parallel-group, comparative subgroup analysis of a larger overall study. Subjects were randomly assigned in a 1:1 ratio to receive 0.075% bromfenac in DuraSite® BID or 0.075% bromfenac in DuraSite® QD according to a validated computer-generated central randomization schedule. There were a total of 85 subjects enrolled: 40 subjects received 0.075% bromfenac BID ("BID group"), 45 subjects received 0.075% bromfenac QD ("QD group"). Subjects were enrolled post-cataract surgery into a 14-day dosing phase, followed by a 2-week evaluation phase. Four visits were required for the study, with two visits taking place during the dosing phase (days 1 and 8) and two during the evaluation phase (days 15 and Day 29). In addition, there was a telephone call on day 3 to obtain visual analog scale (VAS) values for pain/discomfort and photophobia. The subject self-instilled the study medication, not the investigator or his/her study staff.

Key entry criteria included an anterior chamber cell (ACC) grade of $\geq$2 and anterior chamber flare of $\geq$2 in the study eye at the baseline examination on the day after surgery (day 1); uneventful phacoemulsification surgery and intraocular lens implantation; avoidance of topical, systemic or inhaled salicylates or NSAIDs within 1 week before cataract surgery, with the exception of oral doses of aspirin at 165 mg/day or lower; avoidance of topical, inhaled or oral corticosteroid within 15 days before cataract surgery and any depot-corticosteroid within 45 days before cataract surgery; no concurrent use of ocular or systemic antihistamines or mast cell stabilizers within 1 week before surgery, a best-corrected visual acuity (BCVA) of at least +1.0 logMAR (Snellen equivalent of 20/200) in the fellow eye (non-study eye) and an intraocular pressure range of >8 and $\leq$22 mmHg in the study eye.

Key exclusion criteria for the study eye included: a history of severe dry eye, active corneal pathology, Fuchs dystrophy, diabetic retinopathy, previous vitrectomy or epiretinal membrane; any sign of iritis or scleritis; previous glaucoma or refractive surgery in the previous 2 years; chronic or recurrent ocular or systemic disease that may affect wound healing (e.g. diabetes mellitus, systemic connective tissue disease, severe atopic disease); use of any medication that could interfere with normal lacrimation within the week prior to cataract surgery (including, but not limited to, NSAIDs/aspirin, antihistamines or mast cell stabilizers).

Protocol and informed consent forms for this study were reviewed and approved by an Institutional Review Board (IRB) (New England IRB, Needham, MA) and were provided to the contract research organization (ClinOps LLC, San Francisco, CA) before subjects were screened for entry. The study is registered with ClinicalTrials.gov. ID NCT01190878.

Study Drug

The drug 0.075% bromfenac in DuraSite® is preserved with benzalkonium chloride (0.005%). The drug was administered as topical drops in the postoperative eye either QD or BID for 14 days (those in the QD arm were given vehicle drops for the second administration).

DuraSite® is a mucoadhesive material long used to enhance the residence time of a pharmaceutical on the ocular surface, has been evaluated in several other topical ophthalmic formulations, and its efficacy and safety data is well known [12–16].

Subject compliance with instillation frequency was assessed by subject diary.

Primary Efficacy Outcome

The primary efficacy outcome was the proportion of subjects with an ACC grade of 0 at day 15 (see Table 1 for grading). The proportions of subjects with an ACC grade of 0 for the study eye at days 8, 15 and 29, respectively, were summarized using the last observation carried forward (LOCF) method for the intent-to-treat (ITT) population and per protocol (PP) population.

Table 1 Anterior chamber cell and flare grading

Anterior chamber cells		Anterior chamber flare	
Grade	**Cell count**	**Grade**	**Flare count**
0	0	0	None: no haze is detected
1	1–10	1	Mild: a faint haze is detected
2	11–20	2	Moderate: haze is easy to detect, but iris details are not obscured
3	21–50	3	Marked: haze is prominent, and iris details are somewhat obscured
4	>50	4	Severe: haze is dramatic, and iris details are very obscured and/or the aqueous is fibrinoid or plastic

Secondary Outcome: Efficacy

Secondary efficacy endpoints included slit lamp biomicroscopy results at days 8, 15 and 29, respectively, and VAS results (pain or discomfort and photophobia) at days 3, 8, 15 and 29, respectively.

Statistical Analysis

The frequency of subjects with an ACC grade of 0 was compared between the BID and the QD groups at days 8, 15 and 29 using the standard Chi-square test and Fisher's exact test. To supplement the hypothesis tests, confidence intervals for the difference between the BID and the QD groups at each visit in the proportion of subjects with an ACC grade of 0 were computed using Wald's (asymptotic) method and the Clopper–Pearson (exact) method.

Mean VAS scores for pain were compared between the BID and the QD groups at days 8, 15 and 29 using an analysis of covariance model with baseline VAS pain score and study site as covariates. Using the same statistical model as the clinical study report, linear contrasts were used to test for equal mean pain scores at each measurement day and to construct confidence intervals (CI) for the difference. A similar analysis was performed to compare mean VAS scores for photophobia between the BID and the QD groups.

RESULTS

The subject disposition for the two study groups is shown in Table 2.

Table 3 shows that there were no major differences between groups at study entry. The majority of subjects were Caucasian in both groups, and the mean age was 71.3 years in the BID group and 70.9 years in the QD group. A similar percentage of subjects were taking at least one medication in addition to the study drug: 39/40 (97.5%) in the BID group and 44/45 (97.8%) in the QD group.

The number of subjects with cleared ACC (grade 0) at day 15 were similar in the two group: 21/40 (52.5%) in the BID group and 24/45 (53.3%) in the QD group (two-sided

Table 2 Subject disposition

All randomized subjects	0.075% bromfenac in DuraSite® BID ($n = 40$)	0.075% bromfenac in DuraSite® QD ($n = 45$)
Number of subjects in ITT group	40 (100%)	45 (100%)
Number of subjects in the safety population	40 (100%)	45 (100%)
Number of subjects in the per-protocol population	37 (92.5%)	43 (95.6%)
Subjects who withdrew early	3 (7.5%)	3 (6.7%)
Reasons for withdrawal		
Adverse event	1 (2.5%)	0
Lack of efficacy	2 (5.0%)	3 (6.7%)

Values in table are presented as the number with the percentage in parenthesis
BID Twice-daily, *QD* once-daily, *ITT* intention to treat

Fisher's exact test $P = 1.000$). The proportion of subjects with an ACC grade of 0 at days 8 and 29 was seven (17.5%) in BID group and ten (22.2%) in the QD group (two-sided Fisher's exact test $P = 0.7866$), and 27 (67.5%) in BID group and 27 (60%) in the QD group (two-sided Fisher's exact test $P = 0.5062$), respectively. The treatment differences for the proportion of patients with an ACC grade of 0 were computed twice, once with 95% CI (not reported here), and once with 90% CI.

Table 4 shows the VAS results detailing pain or discomfort and photophobia. The difference between the BID and QD groups was not statistically significant.

Safety Evaluation

At least one treatment-emergent adverse event (TEAE) was reported in each group: 11/40 (27.5%) subjects in the BID group and 11/45 (24.4%) subjects in the QD group. Of the 11 subjects with any TEAE, 6/11 (54.5%) in the BID group and 11/11 (100% in the QD group were eye disorders. In the BID group there was one incidence each of the following TEAEs (occurring in 9.1% of subjects): conjunctival cysts, cystoid macular edema (CME), eye

Table 3 Summary of demographics for all randomized subjects

Demographic data for all randomized subjects	0.075% bromfenac in DuraSite® BID ($n = 40$)	0.075% bromfenac in DuraSite® QD ($n = 45$)
Mean age (years)	71.3 ± 7.70	70.9 ± 9.75
Age distribution of study population (years)		
51–70	22 (55%)	22 (48.9%)
>70	198 (45%)	23 (51.1%)
Gender		
Male	16 (40%)	24 (53.3)
Female	24 (60%)	21 (46.7%)
Race		
Asian	1 (2.5%)	0 (0%)
African American or Black	3 (7.5%)	6 (13.3%)
Caucasian or White	35 (87.5%)	39 (86.7%)
Native Hawaiian or other Pacific Islander	1 (2.5%)	0 (0%)
Ethnicity		
Not Hispanic or Latino	36 (90%)	41 (91.1%)
Hispanic	4 (10%)	4 (8.9%)
Iris color		
Blue	11 (27.5%)	13 (28.9%)
Brown	14 (35.0%)	26 (57.8%)
Green	5 (12.5%)	3 (6.7%)
Hazel	10 (25%)	3 (6.7%)

Values in table are presented as the mean ± standard deviation (SD) or as a number with the percentage in parenthesis, as appropriate

Table 4 Visual analog scale outcomes according to the LOCF method

Visual analog scale	Visual analog scale outcomes		
	0.075% bromfenac in DuraSite® BID ($n = 40$)	0.075% bromfenac in DuraSite® QD ($n = 45$)	Difference [90% confidence intervals]
VAS: pain or discomfort			
Pain or discomfort at day 3	9.10 ± 15.84	6.40 ± 13.8)	1.77 [−4.52, 8.05]
Pain or discomfort at day 8	5.88 ± 15.62	1.67 ± 5.12	3.17 [−3.69, 10.03]
Pain or discomfort at day 15	2.20 ± 8.22	3.53 ± 11.93	−2.24 [−8.82, 4.33]
Pain or discomfort at day 29	3.53 ± 10.01	2.29 ± 8.08	0.63 [−5.86, 7.14]
VAS: photophobia			
Photophobia at day 3	8.55 ± 18.35	13.76 ± 21.75	−4.68 [−11.68, 2.32]
Photophobia at day 8	7.80 ± 17.40	6.73 ± 17.24	1.62 [−5.66, 8.90]
Photophobia at day 15	5.53 ± 14.78	6.53 ± 16.66	−0.89 [−7.31, 5.33]
Photophobia at day 29	5.98 ± 16.95	8.71 ± 16.50	−2.61 [−9.16, 3.95]

P values were computed from an analysis of covariance model with terms for baseline pain and site identification. The difference between the BID and QD groups was not statistically significant
VAS outcomes are presented as the score (n) ± SD
LOCF last observation carried forward, *VAS* Visual analog scale

inflammation, eye irritation, eye pain, posterior capsule opacification, trichiasis, hernia, cellulitis, foreign body in eye and nephrolithiasis. In the QD group there was one incidence each of the following TEAEs (occurring in 9.1% of subjects): eyelid margin crusting, meibomian gland dysfunction, ocular hypertension, posterior capsule opacification, bronchitis, hordeolum and pulmonary congestion. In the QD group there were two incidences (occurring in 18.2% of subjects) of eye inflammation and eye pruritis. There were four incidences in the QD group (occurring in 36.4%) of iritis. Only one serious TEAE (fecaloma, in the BID group) was reported, but that was deemed not to be related to the study drug.

Only eye inflammation was deemed to be definitely related to the study drug. CME, eye irritation, eyelid margin crusting, eye pruritis and iritis were considered to be possibly related to the study medication. Moderate eye pain in one subject in the BID group led to the subject's study withdrawal. No other subjects withdrew from the study as a result of AEs.

Best Corrected Visual Acuity

Best corrected visual scuity was assessed in both the study eye and the non-study eye using an Early Treatment Diabetic Retinopathy Study chart (see Table 5). At day 8, one subject in the

Table 5 Summary of study eye best-corrected visual acuity scores

Visual acuity scores	0.075% bromfenac in DuraSite® BID ($n = 40$)	0.075% bromfenac in DuraSite® QD ($n = 45$)
Day 1 n, mean logMAR (SD)	40, 0.26 (0.48)	45, 0.24 (0.25)
Day 8, n, mean logMAR (SD)	39, 0.18 (0.48)	45, 0.13 (0.21)
Day 15, n, mean logMAR (SD)	38, 0.17 (0.49)	44, 0.12 (0.21)
Day 29, n, mean logMAR (SD)	36, 0.15 (0.51)	42, 0.11 (0.23)

QD group (2.2%) had a worsening of 4 lines of vision, but that effect had dissipated at day 15. There were no significant changes in intraocular pressure (IOP) between the two groups at day 8, nor were there any statistically significant differences between the study and non-study eye in either group at any time point, with one exception: one subject in the QD group (1/45; 2.2%) reported ocular hypertension, with an increase in IOP from 18 mmHg at day 1 to 35 mmHg at day 29; the issue was resolved with the use of topical medications.

DISCUSSION

This study compared two different dosing regimens (QD and BID) of 0.075% bromfenac in DuraSite® as part of a phase II study and found that the efficacy and safety outcomes were generally similar between the two dosing regimens.

There has been a recent trend to reduce the number of topical medications, especially in an older population likely to be on concomitant medications and in those with chronic diseases where long-term exposure can be deleterious to the ocular surface. However, those concerns are mitigated somewhat by the evidence that non-high risk cataract surgery patients are likely to be on postoperative topical medication for the treatment of inflammation and pain for a shorter amount of time [17].

Noncompliance with dosing regimens is a common complaint in this older patient group [18, 19]. Missed doses may adversely impact a drug's profile—while the chances for missing a dose with once-daily is smaller than with twice-daily medications, the impact of those missed doses are not equivalent [20]. Comte et al. noted "the pharmacokinetic equivalent of a single missed once-daily dose is 2–3 sequentially omitted twice-daily doses" [20]. Another benefit of twice-daily dosing is that the duration of effect is not diminished as much if/when a patient misses a dose, which may be potentially more relevant when patients are using short-term topical medications. Outside of ophthalmology, twice-daily dosing can have a protective effect against relapse [21] and may provide a greater treatment effect [20, 22–25] In some cases, QD dosing has shown the greatest fluctuation in pharmacokinetic/pharmacodynamics compared with twice- or even thrice-daily dosing [26].

Anecdotal evidence (later verified through physician interviews, data on file, InSite Vision) determined a challenge deemed difficult to overcome with current topical ophthalmic NSAID preparations—namely, bottle size and volume of medication per prescription. It is not uncommon for anterior segment surgeons to recommend dosing ophthalmic NSAIDs for up to 8 weeks (or longer) in post-cataract patients deemed at higher risk for developing CME (e.g. patients with concurrent diabetes) [17, 27, 28]. However, economic restrictions and/or limitations in coverage by insurance plans pose challenges to many patients in terms of a prescription refill (a second bottle) that would allow longer duration of the therapy, which is much needed for these patients [17]. In this context, Insite Vision designed a patient "use" study to study and track patient's experience in using ophthalmic eye drops as part of its phase III trial on 0.075% bromfenac. Based on these data and the outcomes from this current subgroup analysis, the compound BromSite was approved for twice-daily dosing in a 5 mL bottle.

CONCLUSION

In this trial, outcomes from dosing with 0.075% bromfenac BID were equivalent to those from dosing with 0.075% bromfenac QD for the treatment of inflammation and prevention of pain in a uncomplicated postoperative cataract population, and in the ability to achieve ACC grade 0 at day 15.

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The named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Disclosures. Kamran Hosseini: Sun Pharma: employee. William Trattler: Sun Pharma: consultant.

Compliance with Ethics Guidelines. This study received approval from an institutional review board (New England IRB, Needham, MA) and conformed with the Helsinki Declaration as revised in 2013. Informed consent was obtained from all patients before being included in the study.

Data Availability. The datasets generated during and/or analyzed during the study are available from the corresponding author on reasonable request.

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