

# Difluprednate ophthalmic emulsion 0.05% (Durezol<sup>®</sup>) administered two times daily for managing ocular inflammation and pain following cataract surgery

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ST601-004 Study Group

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**Objective:** To evaluate the efficacy and safety of twice-daily difluprednate ophthalmic emulsion 0.05% (Durezol<sup>®</sup>) versus placebo administered before surgery for managing inflammation and pain following cataract extraction.

**Methods:** Eligible subjects (N = 121) were randomized 2:1 to topical treatment with 1 drop difluprednate or placebo administered twice daily for 16 days, followed by a 14-day tapering period. Dosing was initiated 24 hours before unilateral ocular surgery. Clinical signs of inflammation (anterior chamber [AC] cell and flare grade, bulbar conjunctival injection, ciliary injection, corneal edema, and chemosis), ocular pain/discomfort, intraocular pressure (IOP), and adverse events were assessed.

**Results:** Clearing of inflammation on day 14 (primary endpoint), defined as an AC cell grade of 0 ( $\leq 5$  cells) and a flare grade of 0 (complete absence), was achieved in a significantly greater percentage of subjects treated with difluprednate, compared with placebo (74.7% vs 42.5%;  $P = 0.0006$ ). A significantly greater percentage of difluprednate-treated subjects were free of ocular pain/discomfort on day 14 than placebo-treated subjects (64.6% vs 30.0%;  $P = 0.0004$ ). Three subjects (3.7%) in the difluprednate group had a clinically significant IOP rise (defined as  $\geq 21$  mmHg and a change from baseline  $\geq 10$  mmHg at same visit).

**Conclusions:** Difluprednate, administered 2 times daily starting 24 hours before cataract surgery, was highly effective for managing ocular inflammation and relieving pain and discomfort postoperatively. Difluprednate was well tolerated and provides a convenient twice-daily option for managing postoperative ocular inflammation.

**Keywords:** difluprednate, safety, efficacy, twice daily, postoperative ocular inflammation, corticosteroids

## Introduction

Although recent advances in cataract extraction (CE) surgery have decreased the physical trauma associated with ocular surgery, disruption of the blood–aqueous barrier during surgery can lead to postoperative ocular inflammation, increasing the risk of secondary ocular complications, consisting of mild iritis with increased cells and protein in the anterior chamber (AC). This condition is often self-limiting, but untreated inflammation can interfere with the patient's visual rehabilitation, and in rare cases can result in complications such as cystoid macular edema, posterior capsule fibrosis, keratopathy, fibrin reaction, or chronic uveitis.<sup>1–3</sup> Anti-inflammatory agents

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are routinely prescribed to resolve signs and symptoms more rapidly and to improve patient comfort.

Topical corticosteroids are a very effective treatment for postoperative ocular inflammation since they efficiently block the initial release of inflammatory mediators. In June 2008 the US Food and Drug Administration approved difluprednate ophthalmic emulsion 0.05% (Durezol<sup>®</sup>; Alcon Laboratories, Fort Worth, Texas, USA), a strong topical steroid, for the treatment of postoperative ocular inflammation and pain – the first steroid to be indicated for pain associated with ocular surgery. The approved dosing for difluprednate is 1 drop in the affected eye(s) 4 times daily beginning 24 hours after surgery and continuing for 2 weeks, followed by twice-daily dosing for a week, and then tapering based on the patient's response.

Two multicenter, randomized, placebo-controlled phase 3 (registration) trials in 438 subjects with significant postoperative ocular inflammation (defined as more than 11 AC cells) demonstrated that both 4-times-daily and 2-times-daily difluprednate, beginning 24 hours after surgery, effectively reduced inflammation and pain compared with placebo.<sup>4</sup> A subsequent phase 3B study in 124 subjects has recently shown that difluprednate dosed 4 times daily and started 24 hours before surgery was highly effective for the management of postoperative ocular inflammation and pain associated with CE (Sirion Therapeutics, Tampa, Florida, USA. ST-601-003. Nov 15, 2007. Data on file).

The phase 3B study reported here followed a similar design to evaluate the efficacy and safety of a twice-daily regimen of difluprednate versus placebo 24 hours before surgery for the management of postoperative ocular inflammation and pain in subjects undergoing CE with or without intraocular lens (IOL) implantation. The comparison to placebo (vehicle) allows the results obtained in this study to be compared with the results from the phase 3 studies, in which treatment with twice-daily difluprednate was begun 24 hours after surgery in patients who presented with significant inflammation.

## Patients and methods

This was a multicenter, randomized, double-masked, placebo-controlled, phase 3B trial conducted in accordance with the International Conference on Harmonisation (ICH) guidelines and Good Clinical Practice. The study protocol was approved by a central Institutional Review Board (RCRC IRB, Austin, Texas, USA) utilized by all study sites. Before beginning any study-related procedures, informed written consent

was obtained from all subjects (or parent or guardian if the subject was a minor).

Male and female subjects aged 2 years or older scheduled to have unilateral ocular surgery were included (all were CE with or without IOL implantation). Subjects were excluded if they had a history of glaucoma or ocular hypertension in the study eye, had previously experienced steroid-related intraocular pressure (IOP) rise, or at the time of screening had an IOP  $\geq$  24 mmHg in the study eye. Patients were also excluded if they showed evidence of endogenous uveitis or any current corneal abrasion or ulceration in the study eye, or were pregnant or nursing. Prohibited medications included topical ocular corticosteroids or topical nonsteroidal anti-inflammatory drugs (NSAIDs) in the study eye within 24 hours before instillation of the test agent and throughout the duration of the study (although preoperative administration of a topical NSAID to prevent miosis was permitted); anti-coagulants, systemic corticosteroids, or immunosuppressive drugs within 2 weeks before enrollment; periocular injection of any corticosteroid solution in the study eye within 4 weeks before instillation of the test agent; and depot corticosteroids within 2 months before instillation of the test agent.

Subjects were screened for eligibility from 1 to 7 days prior to surgery on day 0 (ie, days  $-7$  to  $-1$ ) and informed consent was obtained. Those who met all eligibility criteria were randomized according to a computer-generated list in a 2:1 ratio to receive either difluprednate or its vehicle (placebo). The 2 test agents were identical in appearance. Dosing was initiated on day  $-1$ , 24 hours before ocular surgery. After screening, each subject received the test agent with instructions for self-administration. Subjects instilled 1 drop 2 times daily. The treatment period was 16 days, followed by a tapering period of 14 days. If the investigator judged that treatment response was inadequate at any time point, subjects were withdrawn from the trial and switched to another medication.

Safety and efficacy assessments were conducted on days 1, 3 or 4, 7, 14, 28, and 35. Efficacy assessments included AC cell grade, AC flare, chemosis, bulbar conjunctival injection, ciliary injection, and corneal edema. Ocular pain/discomfort was assessed using a visual analogue scale (VAS, scale 0–100) (Table 1). The primary efficacy endpoint was the percentage of subjects with cleared ocular inflammation, defined as an AC cell grade of 0 ( $\leq$ 5 cells) and a flare grade of 0 (complete absence) on day 14. Secondary efficacy endpoints included (1) percentage of subjects with an AC cell grade of 0 and a flare grade of 0 on day 7; (2) percentage of subjects with a pain/discomfort score of 0 on

**Table 1** Study design and criteria

Study design	A phase 3B, multicenter, randomized, double-masked, placebo-controlled, parallel-group trial
Primary efficacy endpoint	On day 14, the percentage of patients having both an anterior chamber (AC) cell grade of 0 (count of $\leq 5$ cells) and an AC flare grade of 0 (complete absence of flare)
Efficacy endpoint grading criteria	<p>AC cell count<sup>a</sup>:</p> <p>Grade 0      <math>\leq 5</math> cells</p> <p>Grade 1      6–15 cells</p> <p>Grade 2      16–25 cells</p> <p>Grade 3      26–50 cells</p> <p>Grade 4      <math>&gt; 50</math> cells</p> <p>AC flare:</p> <p>Grade 0      Complete absence</p> <p>Grade 1      Very slight</p> <p>Grade 2      Moderate</p> <p>Grade 3      Marked</p> <p>Grade 4      Intense</p> <p>Chemosis, bulbar conjunctival injection, ciliary injection, corneal edema:</p> <p>Grade 0      Absent</p> <p>Grade 1      Mild</p> <p>Grade 2      Moderate</p> <p>Grade 3      Severe</p> <p>Ocular pain/discomfort:</p> <p>Visual analog scale (VAS) 0–100 mm (0 = absent, 100 = maximal)</p>
Secondary endpoint	Symptom assessment: On day 14, the percentage of patients having an ocular pain/discomfort score of 0 based on the VAS
Inclusion criteria	<p>Unilateral ocular surgery</p> <p>Age 2 years or older on day of consent</p> <p>Negative urine pregnancy test, administered as deemed necessary</p> <p>Provide signed, written consent</p>
Methods	All subjects ( $n = 121$ ) were randomized 2:1 to topical treatment with either difluprednate ( $n = 81$ ) or placebo ( $n = 40$ )
Dosing regimen	1 drop of difluprednate or placebo administered 2 times daily for 16 days (initiated 24 hours before surgery), followed by a 14-day tapering period

<sup>a</sup>AC cell count recorded as exact number of cells observed if  $\leq 15$ .

day 14; (3) percentage of subjects with a pain/discomfort score of 0 on day 7; (4) percentage of subjects with a pain/discomfort score of 0 on day 3 or 4; and (5) percentage of subjects with an AC cell grade of 0 and a flare grade of 0 on day 3 or 4. Safety assessments included corneal endothelial cell density, IOP, best-corrected visual acuity, slit lamp examination, ophthalmoscopy, comfort and tolerability assessment, and recording of adverse events (AEs). MedDRA terms are used to describe AEs.

## Statistical analysis

Based on the prior results of published studies using the endpoints in this trial, a sample of 120 subjects allocated to treatment in the ratio of 2 (active):1 (placebo) provides 90% power to detect a difference between groups of 30%. Results from this study were reported using descriptive statistics – number of subjects (N); mean, standard deviation or standard error of the mean, median, maximum, and minimum for continuous

outcomes; and frequency and percentage for categorical variables – at each assessment time point. Differences between treatment groups on multiple endpoints were compared in a hierarchical manner to control for family-wise type 1 error. Specifically, these endpoints were tested in a specified order (as mentioned previously) with a two-sided alpha of 0.05, and testing continued until a  $P$  value  $> 0.05$  was obtained.<sup>5</sup> The analysis of a set of 2 (active, placebo)  $\times$  2 (responder, nonresponder) contingency tables stratified by investigative site was performed using the Mantel – Haenszel method.<sup>6</sup> The analysis of continuous and ordinal variables used the applicable parametric methods ( $t$ -test, ANOVA, ANCOVA).<sup>7</sup> The last (post-baseline) observation carried forward (LOCF) method was adopted for measures repeated over visits; screening values, however, were not carried forward. The intent-to-treat (ITT) population was defined as all randomized patients receiving the study drug who underwent surgery and returned for at least one postsurgical visit. The safety popula-

tion was defined as all randomized subjects who received at least 1 dose of the study drug. Efficacy results are reported for the ITT population (LOCF). Statistical analyses were conducted using SAS version 9.1 (DATA, Inc., Bayou La Batre, AL, USA).

## Results

Subjects were enrolled at 6 sites in the United States between January and April 2008. A total of 129 subjects were screened. Five were screen failures and 3 were excluded from the ITT

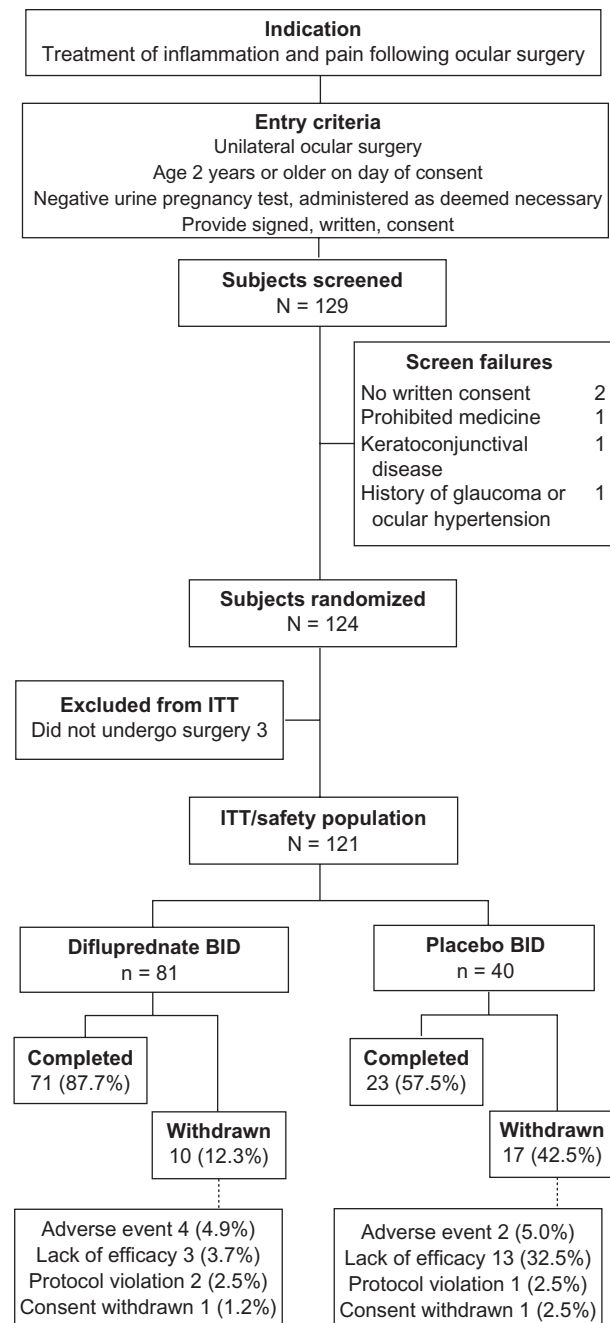


Figure 1 Subject disposition.

Table 2 Subject demographics by treatment group, safety ITT/safety population

Subject characteristic	Difluprednate (n = 81)	Placebo (n = 40)
<b>Mean age, years (standard deviation)</b>	69.4 (9.44)	71.3 (6.62)
Range	44–86	55–87
<b>Gender, n (%)</b>		
Female	51 (63.0%)	14 (35.0%)
<b>Race, n (%)</b>		
White	68 (84.0%)	32 (80.0%)
Black/African-American	9 (11.1%)	7 (17.5%)
Asian	4 (4.9%)	0 (0.0%)
Native Hawaiian/other Pacific Islander	0 (0.0%)	1 (2.5%)
<b>Iris color, n (%)</b>		
Blue	24 (29.6%)	9 (22.5%)
Green	5 (6.2%)	3 (7.5%)
Gray	2 (2.5%)	0 (0.0%)
Brown	42 (51.9%)	18 (45.0%)
Hazel	8 (9.9%)	10 (25.0%)
<b>Surgery type, n (%)</b>		
Cataract extraction with intraocular lens implantation	81 (100%)	40 (100%)

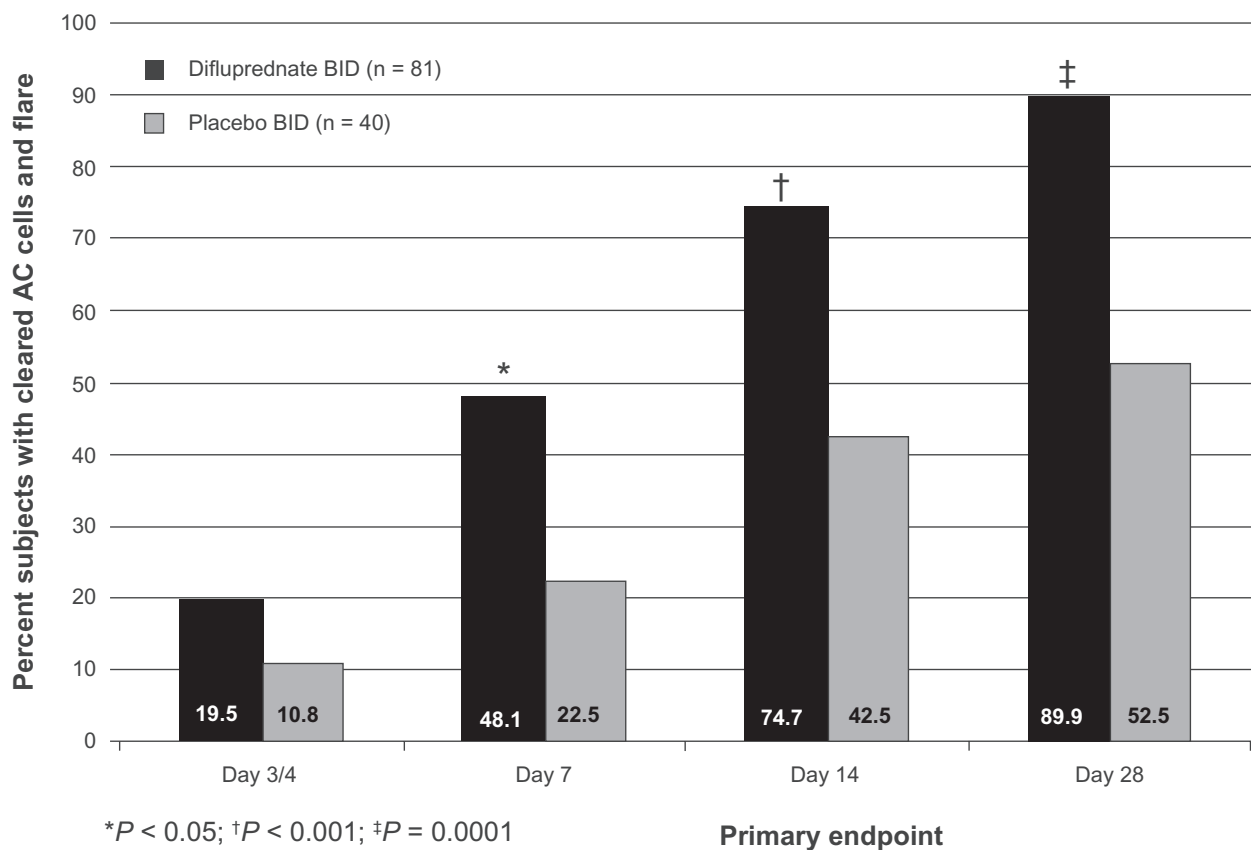
because they did not undergo ocular surgery and weren't dosed with the study drug. The remaining 121 subjects were randomized 2:1 for treatment with difluprednate twice daily (n = 81) or with placebo twice daily (n = 40) (Figure 1). Baseline demographics for the ITT population are summarized in Table 2.

Demographics were comparable between treatment groups with respect to age, ethnicity, race, iris color, and type of surgery received (CE with or without IOL implantation). The difluprednate group had a preponderance of female subjects and the placebo group a preponderance of male subjects.

As seen in Figure 1, the majority of subjects (87.7%) in the difluprednate group completed the study compared with only 57.5% of subjects in the placebo group. Of the subjects withdrawn from the study, significantly more subjects in the placebo group (32.5%) discontinued because of lack of efficacy compared with only 3.7% of subjects in the difluprednate group (13/40 patients vs 3/81 patients, respectively,  $P < 0.0001$ ). An additional 4 subjects (4.9%) in the difluprednate group were withdrawn because of AEs, as were 2 patients (5%) in the placebo group. The remaining reasons for withdrawal (protocol violations, consent withdrawal) did not differ significantly between treatment groups (3 in the difluprednate group; 2 in the placebo group).

## Efficacy results

The percentage of subjects with cleared AC inflammation, defined as an AC cell grade of 0 ( $\leq 5$  cells) and a flare grade



**Figure 2** Percent of subjects with cleared anterior chamber (AC) inflammation – AC cell grade of 0 ( $\leq 5$  cells) and a flare grade of 0 (complete absence) – at each time point.

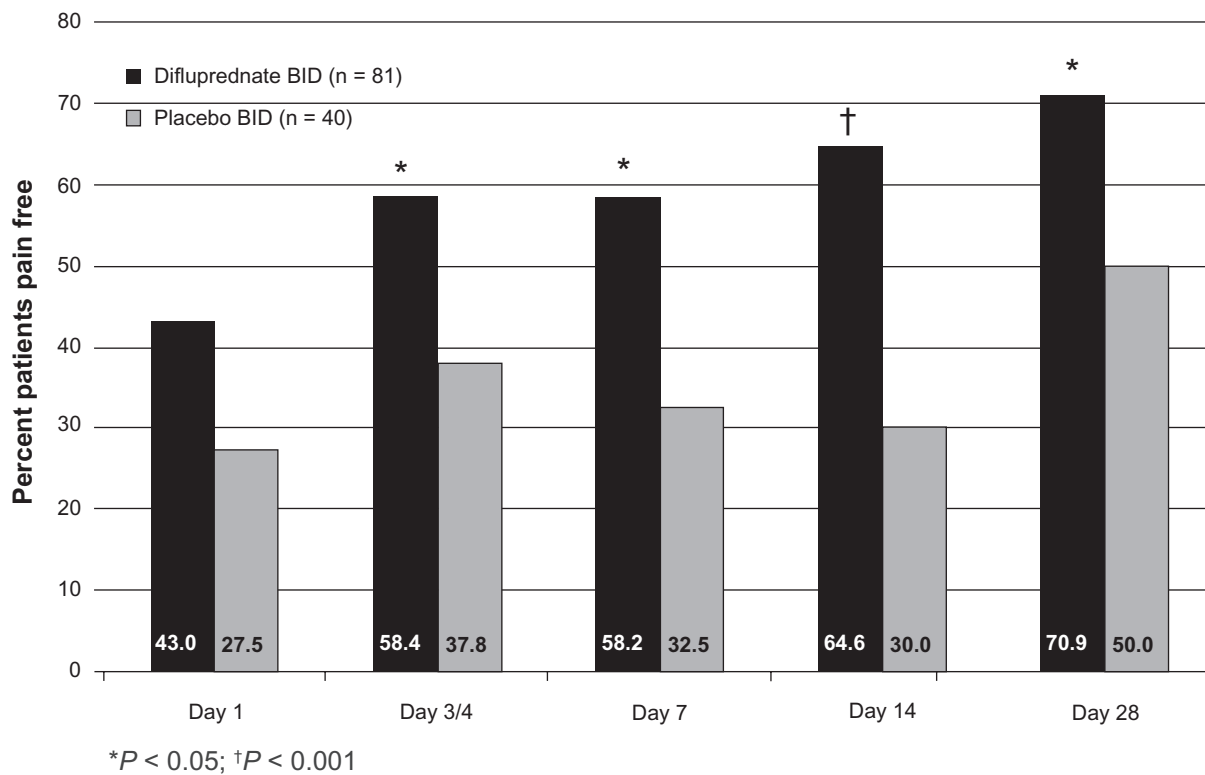
of 0 (complete absence), at each time point is shown in Figure 2. From day 7 through day 28, significantly more subjects in the difluprednate group had cleared AC inflammation compared with the placebo group. On day 14 (the defined primary endpoint), 59 subjects (74.7%) in the difluprednate group compared with 17 subjects (42.5%) in the placebo group had cleared AC inflammation ( $P = 0.0006$ ). At that time, the actual AC cell count was 0 in 44 subjects (55.7%) in the difluprednate group compared with 14 subjects (35%) in the placebo group ( $P = 0.0329$ ). Analysis of the mean change from baseline of AC cell grade – a sensitive measure of improvement – showed a statistically significant response to treatment beginning on day 3/4 ( $P = 0.0073$ ) and continuing through day 28 ( $P \leq 0.0001$ ).

Compared with the placebo group, a significantly greater percentage of difluprednate-treated subjects reported that they were free from ocular pain/discomfort (defined as a VAS score of 0) on day 14 compared with those on placebo (64.6% vs 30.0%;  $P = 0.0004$ ). This benefit was clinically and statistically significant by day 3/4, and was sustained through day 28 (Figure 3). Improvements in the mean grades of bulbar conjunctival injection and of ciliary injection were significantly greater in the difluprednate group compared

with the placebo group as early as day 3/4, and continuing through day 28 (Figure 4). Similar results were shown for corneal edema (Figure 5). The mean score showed notably greater improvement for the difluprednate twice-daily treatment group compared with the placebo group at days 7, 14, and 28. Interestingly, improvement in chemosis grade was also significantly greater in the difluprednate group on day 28 ( $P = 0.0343$ ). However, baseline chemosis levels were low, and the clinical significance of the change seen with difluprednate treatment remains to be determined.

## Safety

A clinically significant IOP increase (defined as an observed value  $\geq 21$  mmHg that was also a change from baseline  $\geq 10$  mmHg at the same visit) occurred in 3 difluprednate-treated subjects (3.7%); only 1 received medication to reduce IOP. Two other difluprednate-treated subjects were withdrawn from study treatment because of an IOP increase. Among the 9 subjects (11.1%) in the difluprednate group reported to have an increased IOP, 5 (6.2%) were considered related to the study drug, and 3 (3.7%) of these were considered clinically significant. No placebo-treated subjects experienced elevated IOP.



**Figure 3** Percent of subjects with an ocular pain/discomfort score of 0 on the visual analogue scale.

Fifteen subjects (18.5%) in the difluprednate group and 19 subjects (47.5%) in the placebo group experienced ocular AEs considered by the investigator to be related to the test article (Table 3). The most frequent of these were reduced visual acuity, conjunctival hyperemia, ocular hyperemia, ciliary hyperemia, and eye pain. Although all were considered related to the study drug, each (except for IOP increase) occurred more frequently in the placebo group, suggesting that the vast majority were the result of either surgical or postoperative inflammation.

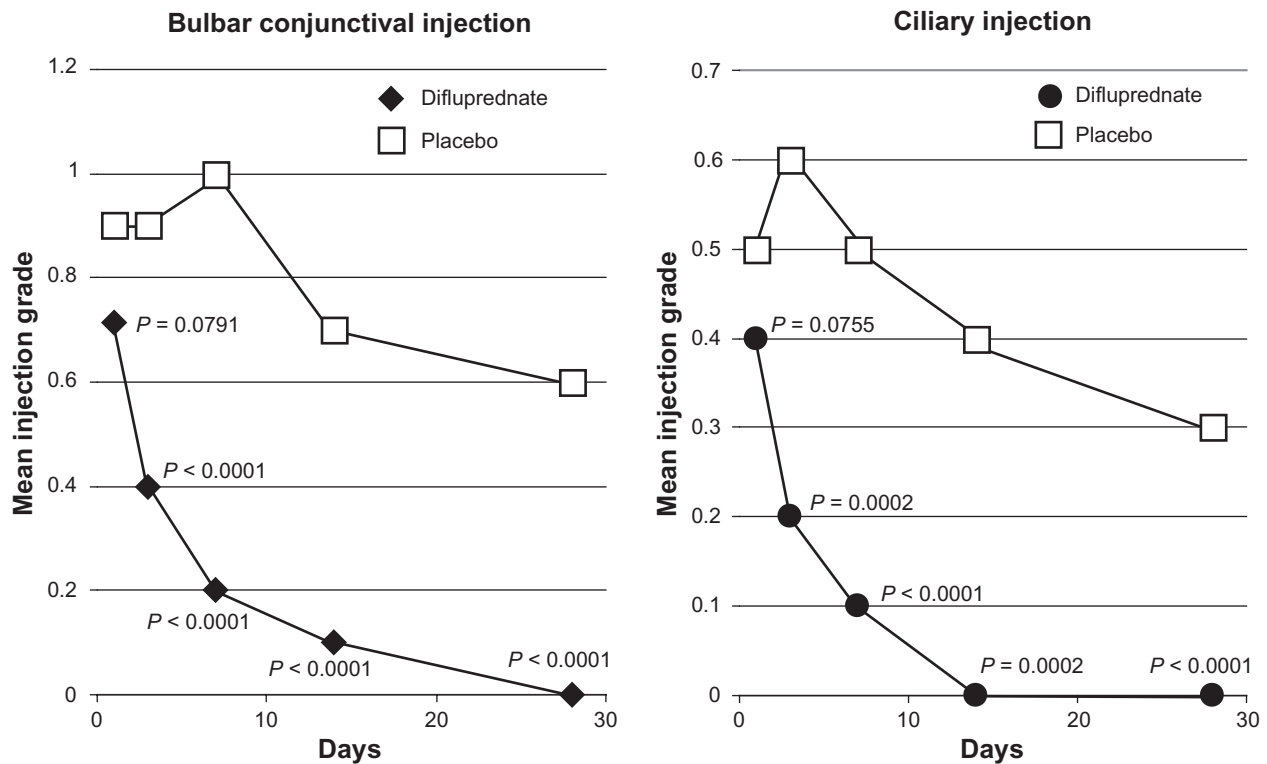
No deaths or serious ocular AEs were reported in either treatment group. Nonocular AEs associated with any particular system organ class were observed in  $\leq 2.5\%$  of subjects in either treatment group. These events were mostly mild and transient, and gave no indication of systemic toxicity. One subject in the difluprednate group had a serious nonocular AE (gastric ulcer hemorrhage) that resulted in permanent study discontinuation. This event was not considered to be related to the study drug.

## Discussion

Using a wide range of clinical indicators, this study showed that administration of difluprednate 2 times daily starting 24 hours before surgery was highly effective for the management of postoperative ocular inflammation and pain. Clinical

resolution of AC inflammation (based on cells and flare) on day 14 was demonstrated, a difference both clinically meaningful and highly statistically significant ( $P = 0.0006$ ). Moreover, this treatment benefit was observed as early as day 7 and was sustained through day 28. Ocular pain and discomfort was also significantly reduced in the difluprednate group ( $P < 0.001$  on day 14); this treatment benefit was observed early (day 3/4) and sustained through day 28. This is particularly impressive, since no other anti-inflammatory agents were used in this trial.

Based on the randomized phase 3 trials of difluprednate administered 2 times daily and 4 times daily starting 24 hours after ocular surgery in patients with significant inflammation at baseline,<sup>4</sup> it was expected that twice-daily dosing beginning 24 hours before surgery would be somewhat more effective. Despite the possibility that accepting subjects without regard to degree of inflammation could have diluted the efficacy results, the hypothesis was validated by this study. The percentage of patients in the present study using twice-daily dosing starting 24 hours before surgery with cleared ocular inflammation at day 14 was comparable to that achieved in the phase 3 studies: predosing (24 hours before surgery) with difluprednate = 74.7% versus postdosing (24 hours after surgery) with difluprednate = 72.7%. Patients in the present study had a lower mean AC cell count (18.0 cells) on day 1



**Figure 4** Mean bulbar conjunctival injection and ciliary injection grades in the difluprednate-treated and placebo-treated subjects.

compared with the baseline value (day after surgery) reported for the pooled phase 3 studies (24.1 cells), in which a grade 2 or higher was required on the day after surgery. Probably as a consequence of this, 30.4% of difluprednate-treated subjects in the current study had AC cell counts of 0 on day 7, compared with 17.3% of difluprednate-treated subjects on the same day in the twice-daily dosing arm of the phase 3 trial.

Comparing the efficacy results from this study to those of the identically designed phase 3B study of 4-times-daily dosing suggests that the overall benefit of twice-daily difluprednate, with respect to reducing ocular inflammation and pain, is similar to that achieved with 4-times-daily dosing. The percentage of patients with cleared ocular inflammation at day 14 in the 4-times-daily dosing study was 81.3%, compared with 74.7% in this study. Since twice-daily dosing is more convenient and shows similar efficacy, this may improve compliance and expose patients to a lower total steroid dose compared with 4-times-daily treatment.

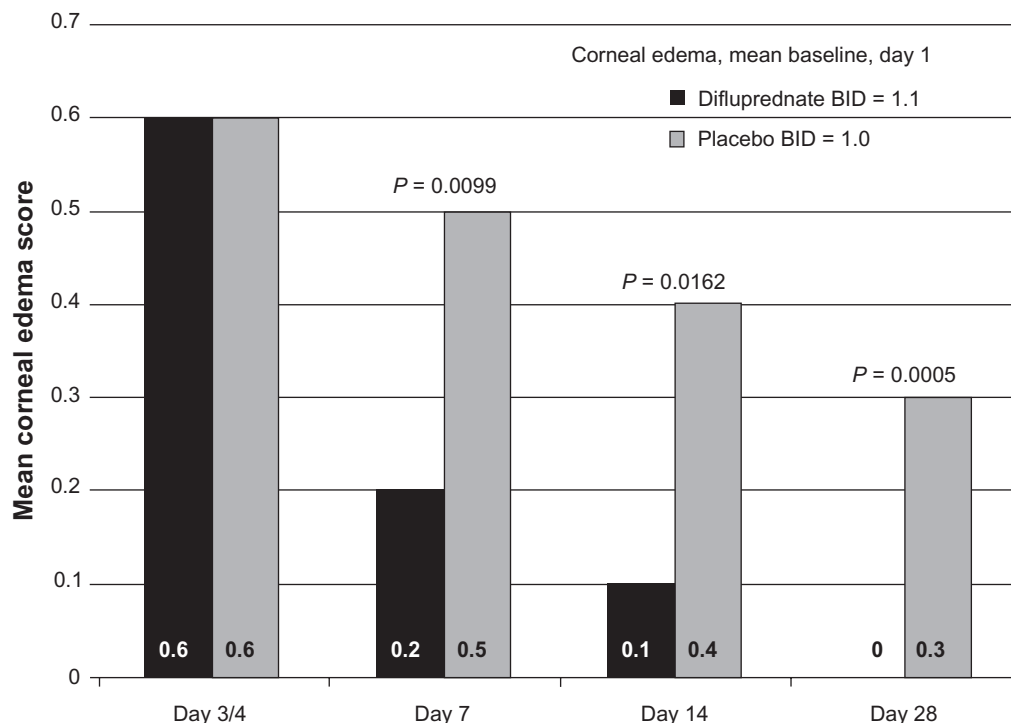
This study used vehicle of difluprednate as a comparator to allow comparison with the results from the phase 3 trial, which also used a vehicle comparator (control group). This study design has been widely adopted to provide evidence of anti-inflammatory efficacy in phase 3.<sup>8</sup> This does not answer any questions about comparative efficacy compared with

current therapy, except by comparison between similarly designed vehicle controlled studies.

Three (3.7%) subjects in the difluprednate group had a clinically significant increase in IOP that resolved either spontaneously or with appropriate medical treatment. This rate of IOP increase is similar to that observed when difluprednate is dosed 4 times daily<sup>4</sup> and similar to other topical steroids, including prednisolone and rimexolone, in similar clinical settings.<sup>9-11</sup>

With the exception of reversible IOP increase, the incidence of AEs was substantially higher in the placebo group compared with the difluprednate group. This was expected since subjects in the placebo group received no anti-inflammatory medication and also had more postoperative complications related to ocular inflammation and its associated pain and discomfort. No deaths and only 1 serious AE occurred during the study period: One subject in the difluprednate group was hospitalized with a bleeding gastric ulcer and was discontinued from study; this event was not considered to be related to difluprednate.

In conclusion, twice-daily difluprednate, dosed alone (without an NSAID) beginning 24 hours before surgery, was well tolerated and effective for the management of postoperative ocular inflammation and relief of ocular pain and discomfort in subjects undergoing CE when compared with placebo. This study indicates that twice-daily



**Figure 5** Corneal edema, mean score (last observation carried forward).

difluprednate begun 24 hours before surgery is a convenient and effective approach to managing ocular inflammation associated with CE.

**Table 3** Treatment-related ocular adverse events (AEs) occurring in  $\geq 5\%$  of subjects in either treatment group: safety population

System organ class and preferred term (MedDRA 10.0)	Number of subjects reporting treatment-related ocular AEs, n (%)	
	Difluprednate n = 81	Placebo n = 40
Eye disorders <sup>a</sup>	15 (18.5%)	19 (47.5%)
Visual acuity reduced	6 (7.4%)	7 (17.5%)
Conjunctival hyperemia	4 (4.9%)	12 (30.0%)
Eye pain	2 (2.5%)	6 (15.0%)
Ocular hyperemia	2 (2.5%)	4 (10.0%)
Ciliary hyperemia	2 (2.5%)	4 (10.0%)
Anterior chamber inflammation	1 (1.2%)	2 (5.0%)
Macular edema	1 (1.2%)	2 (5.0%)
Photophobia	1 (1.2%)	2 (5.0%)
Vision blurred	1 (1.2%)	2 (5.0%)
Anterior chamber cell	0 (0.0%)	4 (10.0%)
Anterior chamber flare	0 (0.0%)	3 (7.5%)
Corneal edema	0 (0.0%)	2 (5.0%)

<sup>a</sup>The categories of "possibly" and "probably" related comprise the relationship summarized. At each level of summarization, subjects reporting the same AE more than once were counted only once. Within system organ class, preferred terms are presented by descending incidence in the difluprednate group. Ocular AEs in the fellow eye are excluded from the AE summary tables.

## Acknowledgments

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## Disclosure

The study was supported by Sirion Therapeutics, Tampa, Florida, USA. Drs Smith, Lorenz, and Peace were investigators in this study; Dr Peace has a consulting agreement with Sirion Therapeutics; Dr Vogel and Kimberly McLeod are former employees and shareholders of Sirion Therapeutics.

## Conference presentation

Presented at the ASCRS Symposium on Cataract, IOL, and Refractive Surgery, San Francisco, California, USA, April 3–8, 2009.

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