ARTICLE

Multicenter randomized phase 3 study of a sustained-release intracanalicular dexamethasone insert for treatment of ocular inflammation and pain after cataract surgery

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Purpose: To assess the efficacy and safety of a sustained-release intracanalicular dexamethasone insert for the treatment of postoperative ocular inflammation and pain in patients having cataract surgery.

Setting: Twenty-one United States sites.

Design: Prospective multicenter randomized parallel-arm double-masked vehicle-controlled phase 3 study.

Methods: Patients with planned clear corneal cataract surgery were randomized (1:1) to receive dexamethasone insert or placebo, and the treatment was placed in the canaliculus of the eye immediately after surgery (Day 1). The primary efficacy endpoints were complete absence of anterior chamber cells at Day 14 and complete absence of pain at Day 8.

Results: The study comprised 438 adult patients (216 in the treatment arm and 222 in the placebo arm). At Day 14, significantly more patients had an absence of anterior chamber cells in the dexamethasone insert arm compared with placebo (52.3% versus 31.1%; $P < .0001$). At Day 8, significantly more patients had an absence of ocular pain in the dexamethasone insert arm compared with placebo (79.6% versus 61.3%; $P < .0001$). The dexamethasone insert arm showed no increase compared with placebo in incidence of all adverse events or ocular adverse events. Twice as many placebo patients required rescue therapy, compared with treated patients at Day 14.

Conclusions: Both primary endpoints were successfully met. In addition, patients receiving the dexamethasone insert experienced a decrease in inflammation after surgery as early as Day 4 through Day 45, and a decrease in pain as early as one day after surgery (Day 2) through Day 45. The dexamethasone insert was well-tolerated, and the adverse events profile was similar to placebo.

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Corticosteroids are routinely prescribed for the postoperative management of inflammation and pain related to cataract surgery as part of a prophylactic perioperative regimen in conjunction with a nonsteroidal antiinflammatory drop. Persistent ocular inflammation can increase the risk for secondary ocular complications,

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such as increased intraocular pressure (IOP), cystoid macular edema (CME), posterior synechiae formation, posterior capsule opacification, secondary glaucoma, delayed recovery, ocular pain, and reduced visual outcomes, whereas untreated pain can affect overall patient surgical satisfaction.[1–3]

Despite the widespread use of topical eyedrop preparations, this means of drug delivery is suboptimal and might be associated with poor patient compliance.[4] Largely across preparations, there is poor bioavailability from eyedrops; experts estimate less than 5% of the applied dose of topical preparations reaches the intraocular tissues.[A] Studies show wide variations in patients' ability to successfully administer drops to the ocular surface; in a study conducted by An et al.,[5] 92.6% of post-cataract patients exhibited improper drop administration, characterized by missing their eye, instilling the incorrect amount of drops, contaminating the bottle tip by touching the ocular surface, and failing to wash their hands before administration. Researchers commented that most patients in this population have not regularly used eyedrops before their surgery. In a different study,[6] researchers observed an elderly ($\geq$80 years) population with chronic ophthalmic pathologies exhibiting similar difficulties: 61% scratched the eyedrop container along the conjunctiva or cornea upon administration, and 11% of patients in this cohort failed to successfully apply a drop to the corneoconjunctival surface.

Several explanations are attributed to the clinical reality of noncompliance, including the burden of regimen frequency and complexity associated with obligate tapering, forgetfulness, and physical difficulty instilling drops, in particular among elderly patients who have limited dexterity.[7] As expected, this lack of compliance adversely affects drug efficacy. Moreover, improper execution or abrupt discontinuation of topical corticosteroids can result in ocular rebound inflammation in which the signs and symptoms of inflammation return after starting to resolve.[8] Topical eyedrop administration, by nature of its intermittent application, also results in variable drug concentration over time, with peak concentrations (immediately after instillation) potentially increasing the risk for side effects and trough concentrations (before the next instillation) potentially producing insufficient pharmacologic effect.

To optimize the delivery of a corticosteroid after cataract surgery, a sustained-release intracanalicular dexamethasone insert (Dextenza, Ocular Therapeutix, Inc.) has been developed. The insert, containing 0.4 mg of active pharmaceutical product, is placed within the canaliculus to provide a sustained and tapered delivery of drug to the ocular surface over 30 days after a one-time insertion. The attributes of the insert reduce the risks for improper corticosteroid tapering and unwanted peaks and troughs in drug concentration.[9] The amount of corticosteroid contained in the insert represents a fraction of the total dose of corticosteroid delivered in a typical topical monthly course, which might minimize untoward side effects while maintaining sufficient corticosteroid concentrations because of its direct proximity to the ocular surface. Based on a preclinical model, it is estimated that this modality has the potential to increase bioavailability from less than 5% to over 70%.[B] Because the insert is placed by a physician, patient compliance concerns are removed, and the patient burden of complex corticosteroid instillation is eliminated. Over time, the insert softens and is cleared through the inferior nasolacrimal canaliculus, obviating the requirement for removal by a physician. If necessary, however, during the course of treatment, the insert can be expressed. In addition, the insert is manufactured preservative-free to eliminate ocular surface toxicity.

Two multicenter randomized double-masked placebo-controlled phase 3 registration trials in 488 adult patients undergoing cataract surgery demonstrated efficacy for inflammation and pain control.[10] A statistically significantly greater proportion of patients receiving the dexamethasone insert in both studies were found to have an absence of pain at Day 8, compared with patients receiving placebo (Study 1: 80.4% versus 43.4%, $P < .0001$, difference: 37.0%; Study 2: 77.5% versus 58.8%, $P = .0025$%, difference: 18.7%). Similarly, a greater proportion of patients receiving the dexamethasone insert had an absence of anterior chamber cells at Day 14 in both studies. This difference was statistically significant in the first study but not the second one (Study 1: 33.1% versus 14.5%, $P = .0018$, difference: 18.7%; Study 2: 39.4% versus 31.3%, $P = .2182$, difference: 8.1%).

The dexamethasone insert had a favorable safety profile in both studies,[10] with the most common adverse events across the studies being anterior chamber inflammation (dexamethasone insert, 5.9%; placebo, 7.3%), increased IOP (dexamethasone insert, 5.6%; placebo, 4.3%), iritis (dexamethasone insert, 4.0%; placebo, 9.1%), and corneal edema (dexamethasone insert, 1.6%; placebo, 5.5%). Given the results from the first two phase 3 trials with the dexamethasone insert, this third phase 3 study was designed to further evaluate the effect of the dexamethasone insert on inflammation and pain in patients undergoing cataract surgery. The phase 3C study reported here followed a similar study design to the previous 2 registration trials to assess the efficacy and safety of a sustained-release dexamethasone insert as a new method to deliver a corticosteroid as part of a treatment regimen for postoperative ocular inflammation and pain in adult patients undergoing cataract extraction with intraocular lens (IOL) implantation. Although the trials differed somewhat with respect to randomization, study visit schedule, and the guidance provided to investigators regarding the use of rescue medication, the coprimary endpoints evaluating the absence of anterior chamber cells and pain were the same.

PATIENTS AND METHODS

Institutional Review Board (Salus IRB, Austin, TX) approval was obtained and the trial was registered on Clinicaltrials.gov (NCT02736175). Before beginning any study-related procedures,

written informed consent was obtained from all patients. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice, and it was compliant with the U.S. Health Insurance Portability and Accountability Act. This study was sponsored by Ocular Therapeutix, Inc.

Study Design

This was a prospective multicenter randomized parallel-arm double-masked vehicle-controlled phase 3 study to evaluate the safety and efficacy of a sustained-release dexamethasone insert compared with placebo for the treatment of ocular inflammation and pain in patients planning to undergo clear corneal cataract extraction with IOL implantation. At the screening visit, patients were assessed for eligibility, and demographic data, significant medical/ophthalmic history, and previous and concomitant medication use were collected from eligible patients.

Patients were randomized in a 1:1 ratio. Once it was determined that the patient was eligible for the study, he/she was randomized into the study and provided with the assigned treatment, dexamethasone insert or placebo. The investigational product or placebo was inserted into the inferior vertical canaliculus of the operated eye within minutes after the completion of cataract surgery. Patients returned for 6 additional visits over approximately 6 weeks (at Days 2, 4, 8, 14, 30, and 45), in which the following assessments were performed: ocular pain assessment (using a numerical rating scale from 0 to 10, where 0 = no pain and 10 = severe pain [disabling; unable to perform activities of daily living]), slitlamp biomicroscopy (inflammation—cells and flare—were graded from 0 to 4 + using the Standardization of Uveitis Nomenclature [SUN] Working Group grading scheme[11]), Snellen pinhole corrected distance visual acuity (CDVA) examination, punctum evaluation (using a slitlamp with a blue light and yellow filter)/visualization of intracanalicular insert, Goldmann tonometry, and adverse event collection (Figure 1).

Treatment

Patients were randomly assigned to receive implantation of either the dexamethasone insert or placebo into the canaliculus of the study eye during cataract surgery. The dexamethasone insert is a polyethylene glycol (PEG)-based hydrogel intracanalicular insert containing 0.4 mg of the active ingredient, dexamethasone. The rod-shaped insert expands upon contact with fluid, securing it within the canaliculus and allowing sustained and tapered release of preservative-free dexamethasone to the ocular surface for up to 30 days. Through gradual hydrolysis of the PEG hydrogel, the insert slowly softens over time and is eventually cleared through the nasolacrimal duct without the need for removal once the drug product is exhausted. The PEG hydrogel in the insert is conjugated with fluorescein dye so that the insert illuminates when excited with a blue light source and yellow filter, enabling visualization to provide a means to confirm its presence within the canaliculus. The placebo insert consisted of the same fluorescent PEG hydrogel as the dexamethasone insert without the active ingredient. Topical antibiotics were prescribed preoperatively and postoperatively at the discretion of the investigator; intraocular antibiotic, and antiinflammatory treatments were not permitted preoperatively, intraoperatively, or postoperatively.

At Days 2, 4, 8, and 14, the need for antiinflammatory rescue medication was assessed and administered to patients.

Inclusion/Exclusion Criteria

Inclusion criteria included age 18 years and older, presence of a cataract and plans to undergo clear corneal cataract surgery with phacoemulsification and implantation of a posterior chamber IOL, and potential postoperative Snellen pinhole CDVA of at least 20/200 in both eyes. Key exclusion criteria at the screening visit included the presence of any intraocular inflammation (cells and flare) in the study eye, a score greater than "0" on the ocular pain assessment in the study eye, active or chronic or recurrent uncontrolled ocular or systemic disease, active or history of chronic or recurrent inflammatory eye disease, acute external ocular infections, proliferative diabetic retinopathy, significant macular pathology, and certain ocular surgeries or procedures during the study period (specifically, corneal or retinal procedures—both laser or incisional—during the study period and 6 months prior in either eye, intraoperative complications were also exclusionary). Patients were also excluded from the study if they had a history of glaucoma or ocular hypertension or were taking medications to treat either of those conditions, or a history of IOP spikes in either eye, including corticosteroid-related IOP increases. Although topical nonsteroidal antiinflammatory drug (NSAID) use was specifically prohibited, systemic NSAID usage of 375 mg or less per day was allowed.

Study Endpoints

The coprimary efficacy endpoints of this study were:

- Absence of anterior chamber cells (score of 0) in the study eye at Day 14
- Absence of pain (score of 0) in the study eye at Day 8

The secondary efficacy endpoints, measured at Days 2, 4, 8, 14, and 30 in the study eye, were absence of anterior chamber cells and

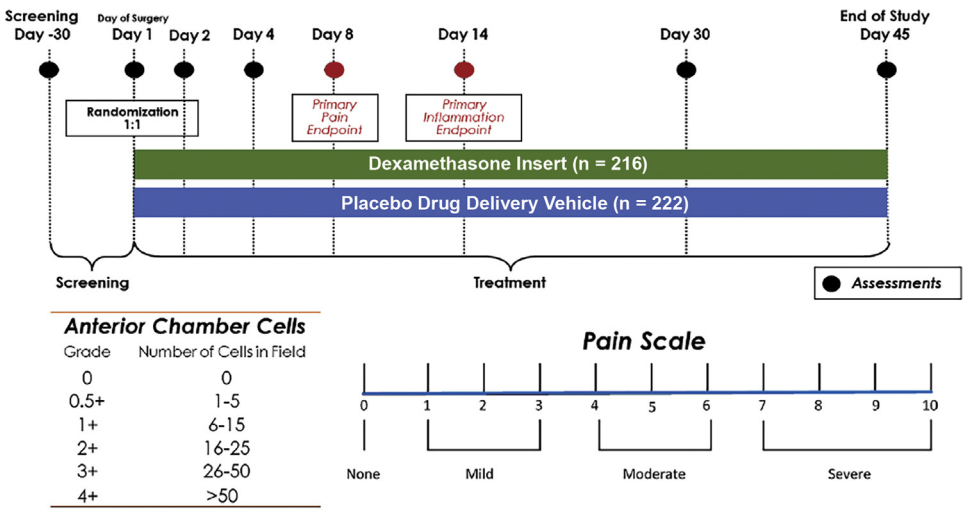

Figure 1. Study design and inflammation and pain evaluation scales.

mean anterior chamber cell score, absence of anterior chamber flare and mean anterior chamber flare score, and absence of pain and mean pain score. The other endpoints were ease of intracanalicular insert placement and subsequent visualization at all timepoints as judged by the investigators. Patient satisfaction questionnaires were also completed. Safety assessments were comprised of (1) adverse events collected at each visit, (2) slitlamp evaluation, (3) IOP, (4) CDVA, and (5) dilated fundus examination. Rescue medication (topical NSAID and/or a corticosteroid at the discretion of the physician) was prescribed for patients who exhibited grade 3+ ($\geq$26) or in higher anterior chamber cells, grade 3+ or higher (marked: iris and lens details hazy) in flare, and/or grade 4 or higher (moderate to severe) in ocular pain.

Statistical Analysis

All efficacy analyses were performed using the intent-to-treat population (all randomized patients). All safety analyses were performed using the safety population (all patients who received an intracanalicular insert). The last observation carried forward method was used to impute missing data for the primary efficacy endpoints. In addition, patients were considered treatment failures after the visit at which they were prescribed antiinflammatory rescue medication and thus, the last observation carried forward was used for subsequent visits after the rescue visit. The primary endpoint analyses (anterior chamber cell at Day 14 and ocular pain at Day 8) were conducted using the Pearson chi-square statistic with a 2-sided $\alpha = 0.05$. In addition, 95% confidence intervals were constructed around the difference in proportions for each primary outcome using asymptotic normal approximations.

RESULTS

A total of 438 patients from 21 sites throughout the United States were enrolled in the study, 216 of whom were randomized to the dexamethasone insert arm and 222 to the placebo arm. One patient from the dexamethasone insert arm was enrolled but did not receive an intracanalicular insert; thus, 437 patients were in the safety population.

Of the 438 patients enrolled in the intent-to-treat population, 435 completed the study (214 in the dexamethasone insert arm and 221 in the placebo arm). Three patients discontinued because they were lost to follow-up (n = 1), withdrew consent (n = 1), and other nonspecified reason (n = 1) (Figure 2). At all postoperative visits through Day 14, more than 98% of intracanalicular inserts in each arm were visualized by the investigators. At the Day 30 visit, 91.9% of dexamethasone inserts and 93.9% of placebo inserts were visualized by the investigators.

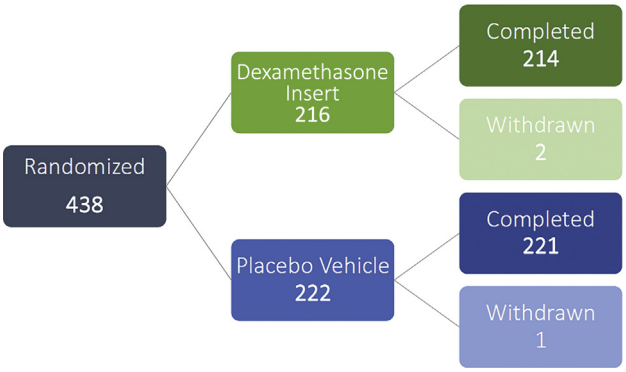

Figure 2. Disposition of patients.

Table 1 shows the demographics and baseline characteristics of the intent-to-treat population, which were comparable between treatment groups. The population was primarily white, of non-Hispanic or Latino ethnicity, with a median age of 68.0 years. Nearly half of the population had brown eyes. There was a greater proportion of female versus male patients.

Efficacy Results

Primary Endpoints As Figure 3 shows, the study met both primary endpoints. At Day 14, significantly more patients had an absence of anterior chamber cells in the dexamethasone insert arm compared with the placebo arm (52.3% versus 31.1%; $P < .0001$). At Day 8, significantly more patients had an absence of ocular pain in the dexamethasone insert arm compared with the placebo arm (79.6% versus 61.3%; $P < .0001$).

Inflammation At each timepoint between Day 4 and Day 45, significantly more patients had an absence of anterior chamber cells in the dexamethasone insert arm compared with the placebo arm ($P < .05$) (Figure 4). The mean anterior chamber cell score in the dexamethasone insert arm was lower than that in the placebo arm at all postoperative study visits. The mean anterior chamber cell score (on a scale of 0 to 4 units) peaked in both treatment arms at one day postoperatively/Day 2 (dexamethasone insert, 1.12 units; placebo, 1.21 units); these scores declined rapidly in the dexamethasone insert arm to a mean score of 0.44 units by Day 14, and declined slowly in the placebo arm, averaging 0.92 units at the Day 14 visit. At all postoperative visits, a lower proportion of eyes in the dexamethasone insert arm versus the placebo arm had a cell score of Grade 3 or higher, the level at which investigators could consider prescribing rescue medication.

At each timepoint between Day 2 and Day 30, significantly more patients had an absence of anterior chamber flare in the dexamethasone insert arm compared with the placebo arm ($P < .05$) (Figure 5). In addition, a significantly greater proportion of patients in the dexamethasone insert arm was observed to have 5 or fewer anterior chamber cells (ie, scores of 0 [absence of cells] or 0.5+ [1 to 5 cells]) at the Day 14 visit, as compared with placebo (81.5% versus 52.3%; $P < .0001$). The mean anterior chamber flare score in the dexamethasone insert arm was maximal at the Day 2 visit, with a score of 0.8 units (on a scale of 0 to 4 units), declining steadily and reaching 0.1 units by the Day 30 visit. In comparison, the mean flare score for the placebo arm was maximal at the Days 2, 4, and 8 visits, with a score of 0.9 units, declining to 0.2 units by Day 45. Few eyes experienced a flare score of Grade 3 or higher, the level at which investigators could consider prescribing rescue medication.

Pain The treatment effect over placebo for resolution of ocular pain occurred as early as 1 day after surgery. At each timepoint between Day 2 and Day 30, significantly more patients had an absence of ocular pain in the dexamethasone insert arm compared with the placebo arm

Table 1. Demographics and baseline characteristics.

Characteristic	Dexamethasone Insert (n = 216)	Placebo (n = 222)	Total (N = 438)
Age (y)			
Mean ± SD	67.3 ± 9.09	68.6 ± 8.37	68.0 ± 8.75
Median	68.0	69.0	68.0
Range	35, 86	46, 91	35, 91
Age, n (%)			
<65 years	78 (36.1)	69 (31.1)	147 (33.6)
65 to 74 years	95 (44.0)	99 (44.6)	194 (44.3)
≥75 years	43 (19.9)	54 (24.3)	97 (22.1)
Sex, n (%)			
Male	96 (44.4)	92 (41.4)	188 (42.9)
Female	120 (55.6)	130 (58.6)	250 (57.1)
Ethnicity, n (%)			
Hispanic or Latino	37 (17.1)	37 (16.7)	74 (16.9)
Not Hispanic or Latino	179 (82.9)	185 (83.3)	364 (83.1)
Race, n (%)			
White	174 (80.6)	189 (85.1)	363 (82.9)
Black or African American	28 (13.0)	25 (11.3)	53 (12.1)
Asian	8 (3.7)	1 (0.5)	9 (2.1)
American Indian or Alaska Native	2 (0.9)	2 (0.9)	4 (0.9)
Native Hawaiian or other Pacific Islander	1 (0.5)	1 (0.5)	2 (0.5)
Other	3 (1.4)	4 (1.8)	7 (1.6)
Iris color, n (%)			
Brown	106 (49.1)	101 (45.5)	207 (47.3)
Blue	61 (28.2)	64 (28.8)	125 (28.5)
Hazel	32 (14.8)	37 (16.7)	69 (15.8)
Green	15 (6.9)	18 (8.1)	33 (7.5)
Gray	2 (0.9)	0 (0.0)	2 (0.5)
Black	0 (0.0)	2 (0.9)	2 (0.5)

($P < .05$; Figure 6). The mean ocular pain score in the study eyes of the dexamethasone insert arm peaked at 0.6 score units (on a scale of 0 to 10) at the Day 2 visit and subsequently declined to a mean value of 0.2 units at the Day 45 visit. In comparison, the mean pain score in the study eyes of the placebo group was 1.2 score units at the Day 2 visit, and declined to 0.5 units by Day 45. At the Day 2 visit, 5.6% of patients receiving the dexamethasone insert compared with 11.3% of patients receiving placebo reported moderate to severe ocular pain (Grade ≥4, which was the level at which investigators could consider prescribing rescue medication). At Day 8, 4.3% of patients receiving the dexamethasone insert reported moderate to severe pain, as compared with 10.4% of patients receiving placebo.

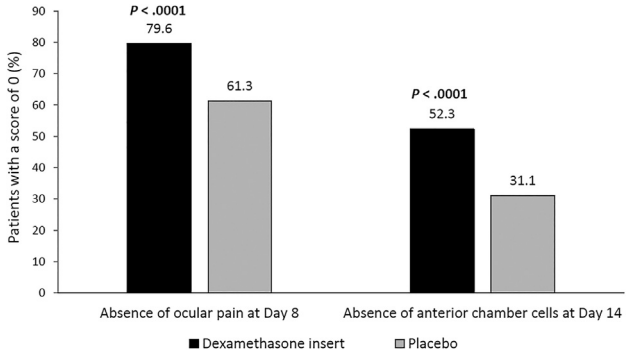

Figure 3. Primary efficacy endpoints (intent-to-treat population, last observation carried forward).

Rescue Medication As Figure 7 shows, less than 5% of patients in both arms used rescue medication through Day 8. At Day 14, 5.6% of patients in the dexamethasone insert arm, compared with 10.9% of patients in the placebo arm used rescue medication.

Ease of Insertion Investigators rated the product as easy or moderate to insert in 98.9% of all eyes. Investigators reported difficulty in placing the intracanalicular inserts on 5 occasions, but insertions were ultimately successful (Table 2).

Safety

Table 3 shows the adverse events in the treatment arm and the placebo arm. Of all reported adverse events, 1 adverse event in the dexamethasone insert arm was judged by the investigator to be related to treatment (increased lacrimation in the study eye). The adverse events were primarily ocular in nature. Of those patients experiencing adverse events, the majority experienced events that were of mild or moderate severity; only 3 patients in each treatment arm experienced an adverse event that was considered severe. Three serious adverse events in the dexamethasone insert arm (cardiac failure acute, retinal detachment, and

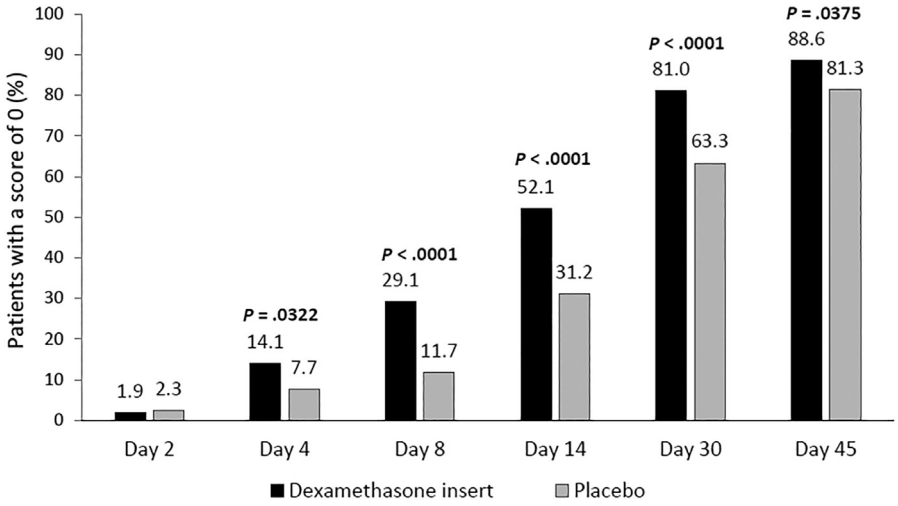

Figure 4. Absence of anterior chamber cells across visits (intent-to-treat population).

lower gastrointestinal hemorrhage) and 2 in the placebo arm (nephrolithiasis and hypoxia) were reported. One serious adverse event in the dexamethasone insert arm was ocular in nature (retinal detachment), but none of the serious adverse events were judged by the investigators to be related to treatment.

The most common ocular adverse events reported in the study eye were eye inflammation, increase in IOP, and anterior chamber inflammation in the dexamethasone insert arm. In the placebo arm, the most common ocular adverse events reported were eye inflammation, increase in IOP, anterior chamber inflammation, worsened CDVA, and CME (Table 4).

The most common nonocular adverse event was headache (3 [1.4%] of 216 patients in the dexamethasone insert arm and 1 [0.5%] of 221 patients in the placebo arm). With the exception of headache, presyncope (1 [0.5%] of 216 patients in the dexamethasone insert arm and 1 [0.5%] of 221 patients in the placebo arm), and sinusitis (1 [0.5%] of 216 patients in the dexamethasone insert arm and 2 [0.9%] of 221 patients in the placebo arm), all other nonocular adverse events occurred in single patients in either treatment arm. No treatment-related nonocular adverse events occurred during the study. No patients were withdrawn from study participation because of adverse events, and no deaths occurred in the study.

Other adverse events considered to be clinically important in this study included a worsening in visual acuity of 2 or more lines from the previous visit in the study eye, and adverse events leading to withdrawal from study participation. Four patients in the dexamethasone insert arm and 6 in the placebo arm exhibited a worsening of visual acuity in the study eye of 2 or more lines from the previous visit. None of these adverse events were suspected of being related to study medication. Additional safety assessments, including slitlamp biomicroscopy parameters, dilated fundus evaluation parameters, CDVA, and punctum examination, did not disclose any additional safety concerns in either treatment arm.

Increased Intraocular Pressure None of the patients with IOP increases in either arm (dexamethasone insert arm, n = 16; placebo arm, n = 6) were judged by the investigators to be related to treatment; these determinations were based on onset and character of elevated IOP. Fourteen of the 16 patients in the dexamethasone insert arm experienced IOP

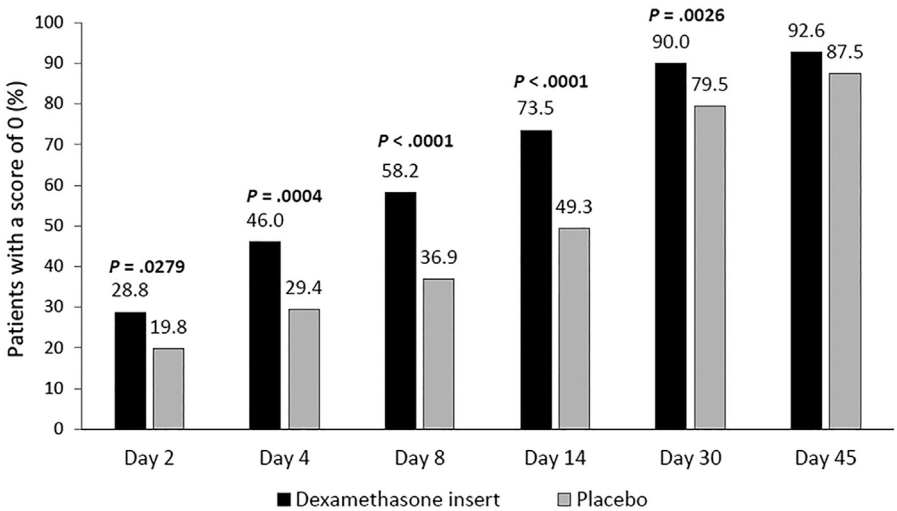

Figure 5. Absence of anterior chamber flare across visits (intent-to-treat population).

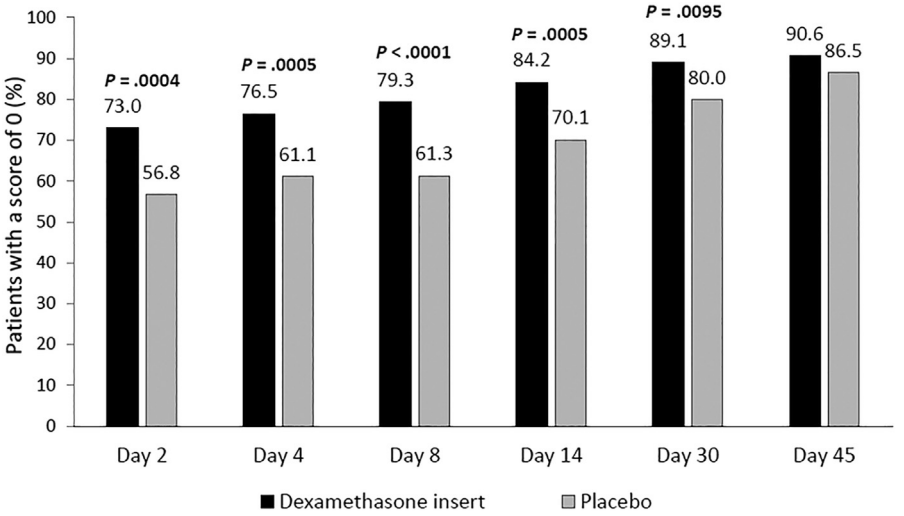

Figure 6. Absence of ocular pain across visits (intent-to-treat population).

increases of 10 mm Hg or higher from baseline at Day 2 only; all these events were suspected to be related to the cataract surgery. Of the 2 remaining patients, one exhibited increased IOP at Days 2 and 4 and the other patient at Days 2, 14, and 30; in both patients, IOP was resolved at the next visit. No action was taken in 6 of these patients; paracentesis or topical medication, or a combination of both was administered to the other patients. Five patients in the placebo arm experienced IOP increases of 10 mm Hg or higher from baseline at Day 2, and similarly, these events were suspected to be attributable to the surgical procedure.

DISCUSSION

According to U.S. Census data, by the year 2020, it is estimated that the number of Americans diagnosed with cataracts will rise to approximately 30 million, representing a 32% increase over current prevalence estimates.[12-13] Ophthalmologists should remain vigilant in the treatment of ocular inflammation and pain, which are expected side effects of this procedure. In 2 recent studies in which patients did not receive topical antiinflammatory medication (no ophthalmic corticosteroid or NSAID) after cataract surgery, approximately 70% to 85% of patients still had anterior chamber cells, 50% to 65% had anterior chamber flare, and 40% to 60% had ocular pain at 2 weeks

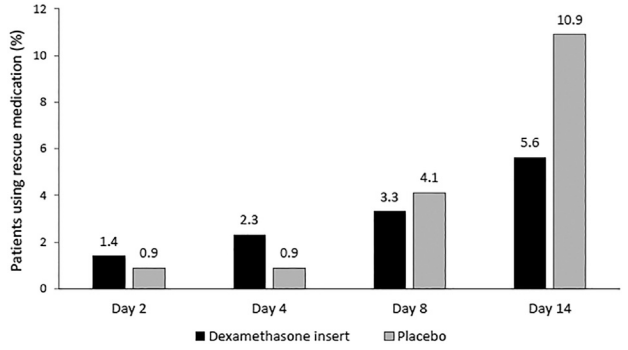

Figure 7. Use of rescue medication before visits (intent-to-treat population).

postoperatively,[10] reinforcing the necessity of these critical postoperative regimens, and suggesting that patient noncompliance might adversely affect outcomes. Optimized delivery of these medications represents an opportunity to meaningfully improve patient outcomes.

Patients receiving the dexamethasone insert experienced a rapid, early onset of pain and inflammation relief, lasting through 45 days. In the current study, the dexamethasone insert produced a significant improvement in anterior chamber flare and ocular pain beginning at Day 2 and a significant improvement in anterior chamber cells beginning at Day 4 ($P < .05$). Both of the primary endpoints, absence of anterior chamber cells (score of 0) at Day 14 and absence of ocular pain (score of 0) at Day 8, were met in this study, showing a significant improvement in patients receiving the dexamethasone insert compared with patients receiving placebo ($P < .0001$). Approximately twice as many patients receiving placebo required rescue medication by Day 14, as compared with patients in the dexamethasone insert cohort. Other clinical markers of inflammation and pain support and strengthen the superiority of the dexamethasone insert over placebo.

Two previous randomized phase 3 vehicle-controlled trials of the sustained-release dexamethasone insert with identical primary endpoints to the current trial have been published.[10] In both of those studies, the dexamethasone insert arm had significantly more patients with an absence of ocular pain at Day 8 ($P < .01$). In one of the 2 studies, the dexamethasone insert arm had significantly more patients with an absence of anterior chamber cells at Day 14 ($P < .01$). The second study did not reach statistical significance for this endpoint (39.4% versus 31.3%; $P = .2182$), but other measures of inflammation control at the Day 14 timepoint were demonstrated. These measures included an improvement in the absence of anterior chamber flare ($P < .01$) and a reduction in mean anterior chamber cells ($P = .0001$).

An integrated assessment of efficacy across all three of these trials show that the dexamethasone insert cohort achieved statistical significance in both primary efficacy endpoints, with 42.7% of patients observed to have no

Table 2. Ease of intracanalicular insert placement.

Ease of Placement, n (%)	Dexamethasone Insert (n = 216)	Placebo (n = 222)	Total (N = 438)
Easy	172 (79.6)	202 (91.0)	374 (85.4)
Moderate	39 (18.1)	20 (9.0)	59 (13.5)
Difficult	5 (2.3)	0 (0.0)	5 (1.1)

anterior chamber cells at Day 14 (placebo: 56.9%; $P < .0001$), and 79.2% of patients observed to have no ocular pain at Day 8 (placebo: 27.5%; $P < .0001$).

The spectrum of adverse events experienced with the dexamethasone insert were generally mild, transient, resolved quickly after onset, and were consistent with the underlying disease pathophysiology. One adverse event in the study was judged by the investigators to be related to treatment. In the dexamethasone insert arm, 14 patients had elevated IOP, and all IOP adverse events were considered by investigators to be related to the cataract surgery rather than to study treatment. There were no intracanalicular complications reported, providing evidence of the safety of intracanalicular inserts as a drug delivery method for dexamethasone. The safety results in the current study are remarkably similar to the other dexamethasone insert studies, with both previous phase 3 trials showing no increase compared with placebo in incidence of all adverse events, ocular adverse events, or serious adverse events.[10]

Table 3. Summary of adverse events.

Parameter	Dexamethasone Insert (n = 216)	Placebo (n = 221)
AEs		
Number	91	109
Patients w/≥1 AE, n (%)	63 (29.2)	86 (38.9)
Treatment-related AEs		
Number	1	0
Patients w/≥1 treatment-related AE, n (%)	1 (0.5)	0 (0.0)
AEs by maximum severity, n (%)		
Patients w/mild AEs	40 (18.5)	56 (25.3)
Patients w/moderate AEs	20 (9.3)	27 (12.2)
Patients w/severe AEs	3 (1.4)	3 (1.4)
Ocular AEs		
Number	75	94
Patients w/≥1 ocular AE, n (%)	57 (26.4)	79 (35.7)
Ocular AEs in study eye		
Number	67	86
Patients w/≥1 ocular AE in study eye, n (%)	55 (25.5)	75 (33.9)
SAEs		
Number	3	2
Patients w/≥1 SAE, n (%)	3 (1.4)	2 (0.9)
Treatment-related SAEs		
Number	0	0
Patients w/≥1 treatment-related AE, n (%)	0 (0.0)	0 (0.0)

AE = adverse event; SAE = serious adverse event

Only 1 IOP increase in the dexamethasone insert arm (0.2%) out of 538 patients across 3 studies was considered by the investigator to be related to treatment.

Compared with topical corticosteroid use, the sustained-release intracanalicular dexamethasone insert has a number of key similarities and differences. Most obviously, corticosteroids delivered to the ocular surface, whether topically or via insert form, work to rapidly quell inflammation and ocular pain. In the event of an adverse reaction, both treatment modalities are reversible; topical drop administration might be stopped while the insert can be removed from the canaliculus. However, key differences in the dexamethasone insert include the self-tapering nature of the insert, the constant low-dose drug load on the ocular surface, the absence of preservatives, improved bioavailability, and most importantly, the elimination of the risk for poor patient compliance. With a self-tapered sustained drug release, the treatment burden of a complex postoperative regimen of topical eyedrops on cataract surgery patients is alleviated and the potential risk for ocular rebound inflammation with improper (ie, too rapid) corticosteroid tapering is mitigated. A constant dispersion of a low-dose corticosteroid on the ocular surface requires less active ingredient to produce the same effect, with a favorable safety profile. In addition, the insert occludes the canaliculus, thereby reducing the rate of tear film clearance from the ocular surface, which might be beneficial to patients who usually have decreased tear production and/or a compromised ocular surface after surgical insult. The intracanalicular insert is formulated preservative-free, eliminating the risk for preservative-induced toxicity and ocular surface damage.[14] Finally, it circumvents concerns associated with poor medication compliance and frees

Table 4. Patients with ocular adverse events of 1% or higher incidence in the study eye.

System Organ Class/Preferred Term	Number (%)	
	Dexamethasone Insert (n = 216)	Placebo (n = 221)
Eye disorders	40 (18.5)	72 (32.6)
Eye inflammation	18 (8.3)	45 (20.4)
Anterior chamber inflammation	6 (2.8)	6 (2.7)
CDVA worsened	4 (1.9)	6 (2.7)
Cystoid macular edema	3 (1.4)	6 (2.7)
Corneal edema	3 (1.4)	1 (0.5)
Posterior capsule opacification	1 (0.5)	3 (1.4)
Vitreous detachment	3 (1.4)	1 (0.5)
Intraocular pressure increased	16 (7.4)	6 (2.7)

CDVA = corrected distance visual acuity

patients and surgeons from the maintenance of complication, postoperative corticosteroid regimens.

As with all studies, the current study does have some limitations. Although the placebo-controlled design of this study was developed to align with regulatory requirements and has been a standard design for pivotal studies of ocular corticosteroids and NSAIDs, future studies might consider the use of an active control, such as topical dexamethasone or prednisolone acetate.

In conclusion, the efficacy and safety data presented in this study demonstrate that the sustained-release dexamethasone intracanalicular insert provides a statistically significant sustained reduction in inflammation after cataract surgery and statistically significant sustained reduction in ocular pain starting in the first few days after cataract surgery and continuing for a month after surgery, while maintaining a favorable safety profile.

WHAT WAS KNOWN

- Two phase 3 clinical trials evaluating the safety and efficacy of a dexamethasone insert were previously conducted.
- A statistically significantly greater proportion of patients receiving the dexamethasone insert in both studies were found to have an absence of pain at Day 8, compared with patients receiving placebo.
- Similarly, a greater proportion of patients receiving the dexamethasone insert had an absence of anterior chamber cells at Day 14 in both studies, but this difference did not achieve statistical significance in the second study

WHAT THIS PAPER ADDS

- Both primary endpoints, absence of anterior chamber cells (score of 0) at Day 14 and absence of ocular pain (score of 0) at Day 8, were met in this study, showing a significant improvement in patients receiving the dexamethasone insert compared with patients receiving placebo.
- Patients receiving the dexamethasone insert experienced a rapid, early onset of pain and inflammation relief, lasting through 45 days. In the current study, the dexamethasone insert produced a significant improvement in anterior chamber flare and ocular pain as early as Day 2 and a significant improvement in anterior chamber cells as early as Day 4 ($P < .05$).
- Pooled analysis from all 3 clinical trials provide a robust assessment of the safety and efficacy of the dexamethasone insert. An integrated assessment of efficacy show that the dexamethasone insert cohort achieved statistical significance in both primary efficacy endpoints, with 42.7% of patients observed to have no anterior chamber inflammation at Day 14, and 79.2% of patients observed to have no ocular pain at Day 8.
- Only 1 (0.2%) IOP increase in the dexamethasone insert arm out of 538 patients across 3 studies was considered to be related to treatment.

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