

Efficacy and Safety of Sustained Release Dexamethasone for the Treatment of Ocular Pain and Inflammation after Cataract Surgery: Results from Two Phase 3 Studies

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Abstract

Background: These studies evaluated the safety and efficacy of a single-dose sustained release dexamethasone depot (DEXTENZA™, Intracanalicular Depot) for the treatment of pain and inflammation following cataract surgery.

Methods: Patients were randomized (2:1) on Day 1 to receive a sustained release dexamethasone depot, (0.4 mg; Study 1, n=164; Study 2, n=161) or placebo vehicle depot (Study 1, n=83; Study 2, n=80) in the inferior canaliculus.

Results: A significantly greater proportion of patients in the dexamethasone groups (Study 1, 80.4% [131/164] vs. 43.4% [36/83], P<0.0001; Study 2, 77.5% [124/161] vs. 58.8% [47/80], P=0.0025) had an absence of ocular pain at Day 8. At Day 14 more patients in the dexamethasone groups had an absence of anterior chamber cells (Study 1, 33.1% [54/164] vs. 14.5% [12/83], P=0.0018; Study 2, 39.4% [63/161] vs. 31.3% [25/80], P=0.2182). Statistically significant differences favoring dexamethasone were observed in both studies for proportions of patients with: an absence of ocular pain at days 2, 4, 8, and 14; an absence of anterior chamber flare at days 8 and 14; mean anterior cell scores at days 8 and 14. Significantly fewer patients in the dexamethasone groups required rescue medications on days 8 and 14. No serious adverse events related to treatment occurred in either group. Transient IOP increases of ≥ 10 mmHg in the study eye were observed in similar proportions of patients in the sustained release dexamethasone groups, (6.8% in Study 1 and 4.4% in Study 2) and the placebo groups (3.6% and 5.0%, respectively). However, only 1 incidence of IOP elevation was thought to be product related (0.3%).

Conclusions: These two studies demonstrate that a single dose, sustained release dexamethasone intracanalicular depot is safe and effective for the treatment of ocular pain and inflammation following cataract surgery.

Keywords: Cataract; Cataract surgery; Dexamethasone; Inflammation; Phacoemulsification

Abbreviations

AE: Adverse Event; ASCRS: American Society of Cataract and Refractive Surgery; CME: Cystoid Macular Edema; CSME: Clinically Significant Macular Edema; GCP: Good Clinical Practices; ICH: International Conference on Harmonization; IOP: Intraocular

Pressure; ITT: Intent to Treat; LOCF: Last Observation Carried Forward Method; NSAIDs: Nonsteroidal Inflammatory Drugs; PEG: Polyethylene Glycol; VA: Visual Acuity

Introduction

Cataract is a leading cause of blindness worldwide and the leading cause of vision loss in the US [1]. Cataract surgery is also on the rise due, in part, to the overall aging of the world's population [2]. The Centers for Disease Control and Prevention estimates the number of people with cataracts in the US will be about 30.1 million by 2020 [1]. In 2006, the Centers for Disease control reported over 3 million cataract surgeries were performed in the United States [3]. In 2015, this number was estimated at approximately 3.6 million procedures [4].

Although recent innovations in surgical techniques and intraocular lenses have improved results, inflammation is still a common side effect following cataract surgery [5]. Postoperative inflammation can cause eye pain, photophobia, intraocular pressure (IOP) spikes, as well as increase the likelihood of cystoid macular edema (CME), synechia formation, posterior capsule opacification, and secondary glaucoma. All of these associated conditions can prolong visual recovery time, enlarge the treatment burden through additional office visits and elevate the risk of poor visual outcomes [6].

Topical corticosteroids are widely used to address inflammation and improve patient outcomes following cataract surgery. Steroids and nonsteroidal inflammatory drugs (NSAIDs) are used in the prophylaxis and treatment of pain and inflammation associated with cataract surgery, either alone or as combination therapy [7-11]. In a 2014 ASCRS clinical survey [12], 41.2% of the 1,500 ophthalmic surgeons strongly agreed that low-to-moderate levels of intraocular inflammation can significantly impact postoperative visual acuity and visual quality. Roughly 35% of the survey respondents thought a score of 1+ cell/flare to be a normal level of inflammation 3-7 days after cataract surgery. More than 80% of respondents in a 2013 ASCRS clinical survey thought it was important to use both NSAIDs and corticosteroids to block inflammation after cataract surgery [12]. Due to the wide array of patient factors involved in any given case that may cause or exacerbate inflammation (e.g., general medical history and ocular comorbidities), the therapeutic regimen to manage postoperative pain and inflammation should be carefully considered for each individual patient [13].

Steroid medications used to treat postoperative pain and inflammations are available as topical drop formulations. However, patient compliance with prescribed eye drop regimens is often poor [14-16]. A study of 54 cataract patients without previous eye drop experience found 92.6% used improper instillation techniques [16], including: failure to wash hands before drop instillation, contaminating the medication bottle tip, missing the eye entirely, or instilling an incorrect number of drops. A number of factors interfere with optimal patient adherence to their topical therapeutic regimens, such as: the complexity of the regimen, side effects (e.g., burning and stinging), forgetfulness (e.g. remembering to take the medication or shake the bottle for suspensions), and lack of manual strength/dexterity [14]. Complicated tapered dosing schedules, normally associated with topical steroids, may also present a challenge for the patient in terms of applying their medications as prescribed.

Injected intravitreal steroids via a transzonular approach have recently become alternatives to topical steroids [17]. However, this approach causes blurred vision that accompanies injecting an opaque

substance into the ocular media and introduces risks inherent in compounding drugs and disrupting zonular support.

Sustained release intracanalicular drug depots have been developed for delivery of ophthalmic medications to the ocular surface. These depots have been used successfully in both preclinical animal models (moxifloxacin, travoprost, NSAIDs, dexamethasone) and human clinical trials (moxifloxacin, travoprost, and dexamethasone) [18,19]. Such devices allow for one-time administration of post-operative medication or glaucoma medication to consistently deliver the active drug over a period of approximately one week to three months and are tailored for either tapered or consistent release of drug depending on the indication for use. For chronic conditions requiring a steady dose of medication, such as glaucoma or ocular hypertension, depots are designed to release the same daily dose of medication over duration of three months. For postoperative pain and inflammation, topical steroid drop medications are usually administered in declining amounts over a period of several weeks, so the intracanalicular depot for these indications has been designed accordingly. The results of two multicenter Phase 3 human clinical trials evaluating the safety and efficacy of sustained release dexamethasone (DEXTENZA[®], Ocular Therapeutix, Inc., Bedford, MA) for the treatment of post-surgical pain and inflammation in patients who had undergone cataract surgery are presented here.

Methods

Study design

Two prospective, Phase 3, multicenter, randomized, parallel-arm, double-masked, vehicle-controlled studies (referred to as Study 1 and Study 2) were conducted across 32 private practice sites in the United States. A total of 488 patients (247 in Study 1 and 241 in Study 2) were randomized 2:1 on Day 1 to receive either the sustained release dexamethasone depot or placebo vehicle, respectively. Study visits were conducted at post-operative Days 2, 4, 8, 14, 30, and 60. If the test article was present at the Day 60 visit, patients also returned for a visit at Day 120 (Study 1) or Day 90 (Study 2).

Both studies were approved by the Salus Independent Review Board (Austin, TX) and registered on ClinicalTrials.gov (NCT02034019 and NCT02089113). These studies complied with the International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines, and were consistent with the 1996 version of the Declaration of Helsinki.

The objectives of both studies were to evaluate the safety and efficacy of a sustained release drug (dexamethasone) depot when placed in the canaliculus of the eyelid for the treatment of post-surgical pain and inflammation in patients who had undergone cataract surgery. Outcome measures included the patient-rated absence of pain (e.g., score of '0') in the study eye at Days 2, 4, 8, 14, and 30; the investigator-rated absence of cells (e.g., score of '0') in the anterior chamber of the study eye at Days 2, 4, 8, 14, and 30; and the investigator-rated absence of flare in the anterior chamber in the study eye at Days 2, 4, 8, 14, and 30. Anterior chamber cell scores were assessed at each of the time points above. The ease of product insertion by the surgeon (easy, moderate, or difficult) was also assessed.

The absence of pain at Day 8 and the absence of anterior chamber cells at Day 14 served as the primary endpoints, with the others serving as secondary endpoints. Numeric Rating Scales were used to assess pain, cell and flare. Pain was assessed on a scale from 0 (no

pain), 1-3 (mild pain), 4-6 (moderate pain), and 7-10 (severe pain). Anterior chamber cell and flare scores were assessed on scales of 0-4. The anterior chamber cell count and flare were graded using the grading criteria established by the Standardization of Uveitis Nomenclature Working Group [20]. Safety assessments included dilated fundus exams, slit lamp, visual acuity (VA), intraocular pressure (IOP), and adverse event (AE) recordings.

Inclusion/Exclusion criteria

To be eligible for participation, patients had to be ≥ 18 years of age, with a visually significant cataract and scheduled to undergo clear corneal cataract surgery with phacoemulsification and implantation of a posterior chamber intraocular lens. The participants were required to have a potential post-operative pinhole corrected Snellen visual acuity (VA) of 20/200 or better in both eyes.

Key exclusion criteria at the screening exam were: intraocular inflammation present; score greater than "0" on the Ocular Pain Assessment; active or history of chronic or recurrent inflammatory eye disease; acute external ocular infections; significant macular disease, clinically significant macular edema (CSME), or history of cystoid macular edema; corneal or retinal surgery or procedure (laser or incisional) within the past 6 months or planned (except for the study cataract surgery) during the study period.

Patients were not allowed to participate if they had a history of glaucoma, ocular hypertension or were taking medications to treat either of those conditions; a history of IOP spikes in either eye including steroid-related IOP increases or plans to have corneal or retinal surgery (laser or incisional) in the fellow eye. Punctum sizes smaller than 0.4 mm or greater than or equal to 1.0 mm also disqualified patients from participation in the study.

Exclusion criteria during the study included: the use of non-diagnostic topical ophthalmic solutions (other than artificial tears [up to four times daily] or prophylactic antibiotics); and the use of certain topical or systemic anti-inflammatory or immuno-modulating agents (e.g., cyclosporine). While topical non-steroidal anti-inflammatory (NSAID) use was specifically prohibited, systemic NSAID usage was allowed.

Treatments

Sustained release of dexamethasone is achieved through the use of a polyethylene glycol (PEG)-based hydrogel depot containing the active ingredient, dexamethasone (0.4 mg, dexamethasone USP). The rod-shaped depot is inserted through the inferior punctum, and expands on contact with fluid so that it is secured in the canaliculus, allowing sustained and tapered release of preservative-free dexamethasone to the ocular surface for up to 30 days [21]. Through gradual hydrolysis of the PEG hydrogel, the device slowly softens over time and is eventually cleared through the nasolacrimal duct without the need for removal. The PEG hydrogel in the depot is conjugated with fluorescein dye so that the depot illuminates when excited with a blue light source and yellow filter (such as the one that is part of a slit lamp) to provide a means to confirm presence of the product in the canaliculus. The placebo device consisted of the same fluorescing PEG hydrogel as the sustained release dexamethasone depot, but without the active ingredient.

Cataract surgery was performed using topical anesthesia or a regional block in accordance with the standard operating procedures

of each participating ophthalmic surgeon investigator. Anti-inflammatory rescue medications were allowed at each investigator's discretion any time during the follow-up period, if clinically indicated. Specifically, investigators were allowed to consider prescribing anti-inflammatory medications for patients returning for the Day 2 and later visits who exhibited \geq Grade 2+ (≥ 16) anterior chamber cells, \geq Grade 3+ (Marked: iris and lens details hazy) flare, and/or \geq Grade 4 (moderate to severe) ocular pain. Both the patients and investigators were masked to the treatment assignment throughout the study.

Statistical analysis

The intent to treat (ITT) population included all randomized patients. The primary efficacy analysis was performed for all efficacy endpoints using the ITT population. The per protocol (PP) population served as secondary efficacy analysis and included all ITT patients who remained in the study through Day 14 and who did not deviate from the protocol in any way likely to affect the primary outcome. The safety population included all patients who received an intracanalicular depot. The last observation carried forward method (LOCF) was used to impute missing data for the primary efficacy endpoints; patients were considered treatment failures after the visit at which they were prescribed rescue medication (e.g., anti-inflammatory medication) and as such LOCF was used for visits after the rescue visit.

The primary endpoint analyses (Day 14 for anterior chamber cells and Day 8 for ocular pain) were conducted using the Pearson chi-squared statistic with the two-sided alpha=0.05 level. In addition, 95% confidence intervals were constructed around the difference in proportions for each primary outcome. Fisher's exact tests were used in cases of expected counts less than five.

For each study, calculations using 148 study eyes in the active arm and 74 study eyes in the placebo arm yields $>99\%$ power to conclude superiority of sustained release dexamethasone over placebo in the proportion of study eyes with absence of pain (score of 0) at Day 8 assuming the proportion of study eyes with absence of pain is 0.80 and 0.30 for sustained release dexamethasone and placebo respectively and a two-sided alpha=0.05. Furthermore, 222 patients and study eyes (148 in the active arm and 74 in the placebo arm) yields 90% power to achieve statistical superiority of sustained release dexamethasone over placebo in the proportion of study eyes with absence of anterior chamber cells (score of 0) at Day 14 assuming the proportion of study eyes with absence of anterior chamber cells is 0.35 and 0.15 for sustained release dexamethasone and placebo respectively and a two-sided alpha=0.05. Therefore, 247 and 241 patients were enrolled in each study, respectively, to account for patient discontinuations.

Results

Patient disposition and demographics

The intent-to-treat (ITT) population comprised a total of 247 patients randomized into Study 1 (sustained release dexamethasone, N=164; placebo, N=83) and 241 into Study 2 and (sustained release dexamethasone, N=161; placebo, N=80). A complete summary of Patient Disposition and Demographics are presented in Table 1 and Table 2, respectively.

	Study 1		Study 2	
	Dexamethasone	Placebo	Dexamethasone	Placebo
Number of Randomized Patients	164	83	161	80
Randomized but Not Treated	1 (0.6%)	0	0	0
Treated	163	83	160	80
Treated as Randomized	162 (98.8%)	83 (100.0%)	160 (99.4%)	80 (100.0%)
Treated Not as Randomized	1 (0.6%)	0	0	0
Analysis Population ¹				
Intent-to-Treat (ITT)	164 (100.0%)	83 (100.0%)	161 (100.0%)	80 (100.0%)
Per-Protocol (PP)	149 (90.9%)	74 (89.2%)	148 (91.9%)	78 (97.5%)
Safety	162 (98.8%)	84 (101.2%)	160 (99.4%)	80 (100.0%)
Study Completion				
Completed	163 (99.4%)	81 (97.6%)	159 (98.8%)	76 (95.0%)
Withdrawn	1 (0.6%)	2 (2.4%)	2 (1.2%)	4 (5.0%)
Reason for Patient Withdrawal ²				
Adverse Event(s)	0	1 (50.0%)	0	0
Protocol Violation(s)	0	0	0	0
Lost to Follow-Up	0	1 (50.0%)	0	2 (50.0%)
Consent Withdrawn	0	0	0	0
Sponsor Termination of Study	0	0	0	0
Investigator Decision	0	0	1 (50.0%)	1 (25.0%)
Other	1 (100.0%)	0	1 (50.0%)	1 (25.0%)

¹The ITT population includes patients as randomized, whereas the Safety population includes patients as treated. The PP population includes Patients as treated and as randomized, since patients in this population must have received their randomized treatment.
² Percentages are based on the total number of withdrawn patients.

Table 1: Patient disposition.

	Study 1		Study 2	
	Sustained Release Dexamethasone	Placebo	Sustained Release Dexamethasone	Placebo
	(N = 164)	(N = 83)	(N = 161)	(N = 80)
Age, mean (years), n (%)	67.4	69.9	69	68.3
< 65	56 (34.1)	16 (19.3)	49 (30.4)	22 (27.5)
≥65 to < 75	76 (46.3)	44 (53.0)	66 (41.0)	39 (48.8)
≥75	32 (19.5)	23 (27.7)	46 (28.6)	19 (23.8)

Gender, n (%)	61 (37.2)	39 (47.0)		
Male	103 (62.8)	44 (53.0)	63 (39.1)	41 (51.3)
Female			98 (60.9)	39 (48.8)
Ethnicity, n (%)				
Hispanic or Latino	8 (4.9)	2 (2.4)	29 (18.0)	9 (11.3)
Not Hispanic or Latino	156 (95.1)	81 (97.6)	132 (82.0)	71 (88.8)
Race, n (%)				
American Indian or Alaskan Native				
Asian	1 (0.6)	0	2 (1.2)	0
Black or African American	3 (1.8)	3 (3.6)	1 (0.6)	1 (1.3)
Native Hawaiian or Other Pacific Islander				
White	22 (13.4)	18 (21.7)	20 (12.4)	8 (10.0)
Other				
	2 (1.2)	0	0	0
	136 (82.9)	62 (74.7)	138 (85.7)	71 (88.8)
	0	0	0	0
Iris Color, n (%)				
Black	0	0	0	0
Blue	58 (35.4)	26 (31.3)	45 (28.0)	18 (22.5)
Brown	75 (45.7)	40 (48.2)	78 (48.4)	40 (50.0)
Hazel	16 (9.8)	7 (8.4)	25 (15.5)	17 (21.3)
Green	15 (9.1)	8 (9.6)	11 (6.8)	4 (5.0)
Gray	0	2 (2.4)	2 (1.2)	1 (1.3)
Other	0	0	0	0

Table 2: Patient demographics and baseline disease characteristics.

Efficacy

In both studies, patients receiving sustained release dexamethasone experienced consistent reductions in pain (as measured on a scale from 0 (no pain) to 10 (severe pain) and inflammation (as measured by the absence of anterior chamber cells, absence of anterior chamber flare, mean anterior chamber cell scores, and the use of rescue medications) (Figures 1-5).

Significant differences were observed for proportions of patients with: an absence of ocular pain at days 2, 4, 8, and 14; an absence of anterior chamber cells at day 14; an absence of flare at days 8 and 14; and mean anterior cell scores at days 8 and 14.

A summary of rescue medication use during the first two weeks following surgery is shown in Figure 5. Significantly fewer patients on sustained release dexamethasone required rescue medications on Days 8 and 14 in both studies ($P \leq 0.0321$). This is particularly noteworthy since up to 40% of patients in Study 2 were taking high dose prescription systemic NSAIDs concomitantly.

In most instances, the sustained release dexamethasone depot was rated as easy or moderately easy to insert (Table 3). The investigators rated the sustained release dexamethasone depot as easy or moderately easy to insert in 92.1% (151/164) of study eyes in Study 1 and 96.9% (156/161) of study eyes in Study 2.

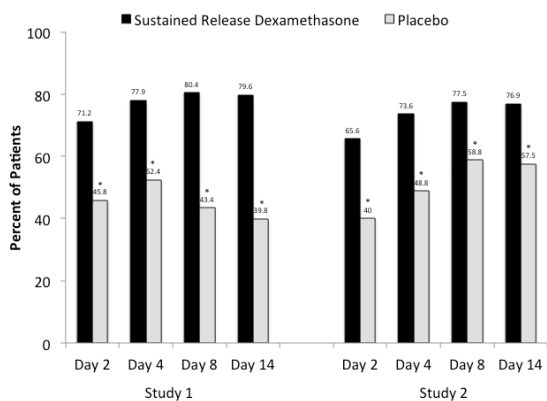


Figure 1. Absence of Ocular Pain at Days 2, 4, and 8. In Study 1, a significantly greater proportion of study eyes in the sustained release dexamethasone group, compared with those in the placebo group, had an absence of ocular pain at Day 2, (71.2% versus 45.8%; $P=0.0001$), Day 4 (77.9% versus 52.4%; $P=0.0001$), Day 8 (80.4% versus 43.4%; $P<0.0001$; primary endpoint), and Day 14 (79.6% versus 39.8%; $P<0.0001$). In Study 2, a significantly greater proportion of study eyes in the sustained release dexamethasone group, compared with those in the placebo group, had an absence of ocular pain at Day 2 (65.6% versus 40.0%; $P=0.0002$), Day 4 (73.6% versus 48.8%; $P=0.0001$), Day 8 (77.5% versus 58.8%; $P = 0.0025$; primary endpoint), and Day 14 (76.9% versus 57.5%; $P=0.0019$).

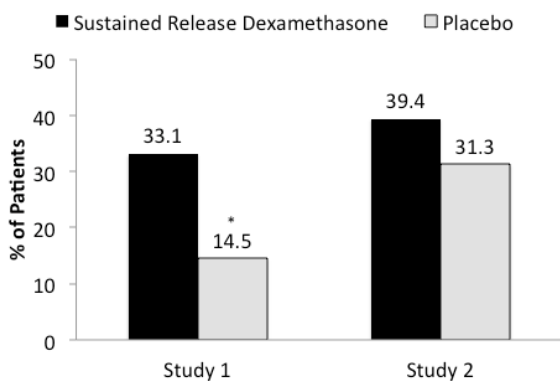


Figure 2: Absence of Anterior Chamber Cells at Day 14. In Study 1, a significantly greater proportion of study eyes in the sustained release dexamethasone treatment group, compared with those in the placebo group, had an absence of anterior chamber cells at Day 14 (33.1% [54/164] vs. 14.5% [12/83]; $P=0.0018$). In Study 2 a numerically greater proportion of study eyes in the sustained release dexamethasone treatment group, compared with those in the placebo group, had an absence of anterior chamber cells at Day 14 (39.4% [63/161] versus 31.3% [25/80]; $P=0.2182$).

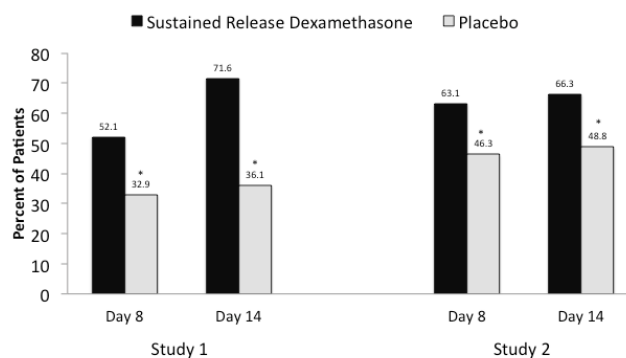


Figure 3: Absence of Anterior Chamber Flare. There were significantly more patients with an absence of anterior chamber flare in the sustained release dexamethasone group, compared with those in the placebo group in Study 1 at Day 8 (52.1% versus 32.9%; $P=0.0044$) and Day 14 (71.6% versus 36.1%; $P < 0.0001$) and in Study 2 at Day 8 (63.1% versus 46.3%; $P=0.0127$) and Day 14 (66.3% versus 48.8%; $P<0.0090$).

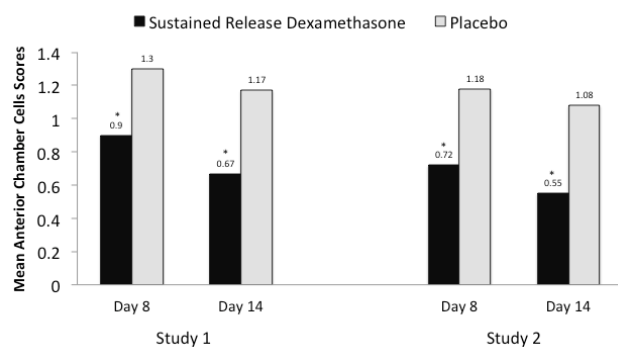


Figure 4: Mean Anterior Chamber Cell Scores. Patients in the sustained release dexamethasone group had significantly lowered mean anterior chamber cell scores compared with those in the placebo group in Study 1 at Day 8 (0.90 versus 1.30; $P=0.0008$) and Day 14 (0.67 versus 1.17%; $P=0.00002$) and in Study 2 at Day 8 (0.72 versus 1.18; $P=0.00002$) and Day 14 (0.55 versus 1.08; $P=0.0001$).

Safety

There were no unexpected AEs in either study. None of the patients in either group or either study experienced any serious adverse event (SAE) related to treatment. All AEs were transient in nature and resolved over the course of the study. An overall summary of AEs is provided in Table 4 and for Ocular AEs in Table 5. Several patients in both treated and placebo groups of both studies had clinically significant abnormalities of the cornea, conjunctiva, or anterior chamber in the study eye from Day 2 through 14, which were reported as AEs and deemed related to the cataract surgery (Tables 4 and 5). Ocular AEs in the study eye were experienced by 29.6% and 40.5% of

patients on sustained release dexamethasone and placebo, in Study 1 and 28.8% and 38.8% of patients in Study 2, respectively (Table 4).

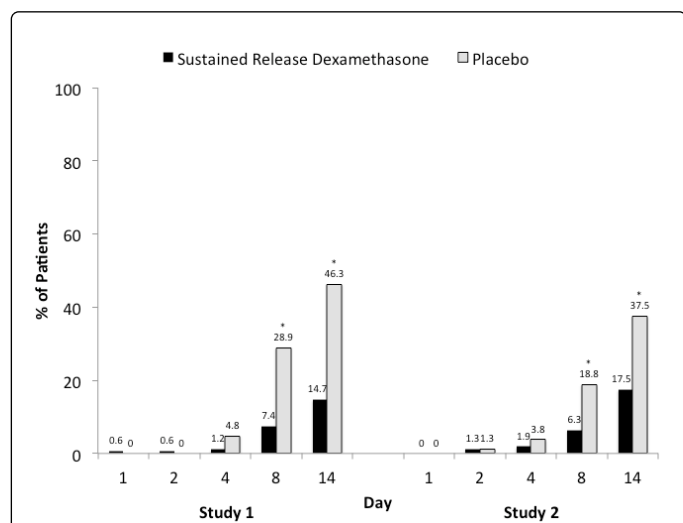


Figure 5: Rescue Medication Use by Visit. P-values for the difference in rescue medication use between patients in the sustained release dexamethasone groups and those in the placebo groups: Study 1, Day 1 P=0.4759, Day 2 P=0.4746, Day 4 P=0.0842, Day 8 P=0.0321, and Day 14 P<0.0001; Study 2, Day 1 no patients rescued, Day 2 P>0.9999, Day 4 P=0.3805, Day 8 P=0.0028, and Day 14 P=0.0006.

Ease of Insertion	Study 1		Study 2	
	Sustained Release Dexamethasone	Placebo	Sustained Release Dexamethasone	Placebo
	N=164	N=83	N=161	N=80
	n (%)	n (%)	n (%)	n (%)
Easy	120 (73.6)	73 (88)	123 (76.4)	76 (95.0)
Moderate	31 (19.0)	10 (12.0)	33 (20.5)	4 (5.0)
Difficult	12 (7.4)	0	5 (3.1)	0

Table 3: Ease of device insertion.

A subset of 1.2% and 0.6% of these AEs were classified as being related to treatment for sustained release dexamethasone compared with 1.2% and 1.3% for placebo in Study 1 and Study 2, respectively. Three ocular AEs, determined to be product related, were reported in Study 1; 2 (eyelid irritation and lacrimation increased) in the sustained release dexamethasone group and 1 (conjunctivitis) in the placebo group. Two ocular AEs, determined to be product-related, were reported in Study 2; 1 (0.6%) in the sustained release dexamethasone group (intraocular pressure increased) and 1(1.3%) in the placebo group (dacryocanaliculitis). Most of the AEs in both studies were mild in severity. None of the patients in either group or either study experienced any serious adverse event related to treatment.

	Study 1		Study 2	
	Sustained Release Dexamethasone	Placebo	Sustained Release Dexamethasone	Placebo
	N=162	N=84	N=160	N=80
	n (%)	n (%)	n (%)	n (%)
Number of AEs	98	59	74	47
Number of Patients with at least one AE	67 (41.4%)	39 (46.4%)	57 (35.6%)	38 (47.5%)
Number of Ocular AEs	74	47	61	41
Number of Patients with at least one Ocular AE	55 (34.0%)	36 (42.9%)	50 (31.3%)	33 (41.3%)
Number of Ocular AEs in the Study Eye	62	43	54	38
Number of Patients with at least one Ocular AE in the Study Eye	48 (29.6%)	34 (40.5%)	46 (28.8%)	31 (38.8%)
Number of Serious Non-ocular AEs	3	4	2	3
Number of Serious Ocular AEs	0	1	0	0
Number of Patients with at least one Serious AE	2 (1.2%)	3 (3.6%)	2 (1.3%)	3 (3.8%)
Number of Treatment-Related AEs	2	1	1	1
Number of Patients with at least one Treatment-Related AE	2 (1.2%)	1 (1.2%)	1 (0.6%)	1 (1.3%)
Number of Treatment-Related Serious AEs	0	0	0	0

Number of Patients with at least one Treatment-Related Serious AE	0	0	0	0
Number of Patients with AEs by Maximum Severity				
Mild	42 (25.9%)	23 (27.4%)	45 (28.1%)	19 (23.8%)
Moderate	22 (13.6%)	13 (15.5%)	9 (5.6%)	16 (20.0%)
Severe	3 (1.9%)	3 (3.6%)	3 (1.9%)	3 (3.8%)
Unknown/Missing	0	0	0	0
Number of Patients with AEs Resulting in Withdrawal	0	1 (1.2%)	1 (0.6%)	1 (1.3%)
Safety population. AE: Adverse Event				

Table 4: Overall Summary of Adverse Events (AEs).

The most common adverse reactions reported by $\geq 2\%$ of patients treated with either sustained release dexamethasone or placebo were anterior chamber inflammation and iritis (Table 5).

Event	Study 1		Study 2	
	Sustained Release Dexamethasone N=162 n (%)	Placebo N=84 n (%)	Sustained Release Dexamethasone N=160 n (%)	Placebo N=80 n (%)
Eye disorders				
Anterior chamber inflammation	10 (6.2)	7 (8.3)	9 (5.6)	5 (6.3)
Cystoid macular edema	4 (2.5)	0	1 (0.6)	2 (2.5)
Ocular discomfort	3 (1.9)	4 (4.8)	0	0
Reduced visual acuity	3 (1.9)	3 (3.6)	2 (1.3)	0
Conjunctival hyperemia	3 (1.9)	1 (1.2)	1 (0.6)	2 (2.5)
Corneal edema	2 (1.2)	5 (6.0)	3 (1.9)	4 (5.0)
Eye pain	2 (1.2)	0	2 (1.3)	2 (2.5)
Iritis	1 (0.6)	4 (4.8)	12 (7.5)	11 (13.8)
Eye inflammation	0	5 (6.0)	0	0
Investigations				
IOP increased*	11 (6.8)*	3 (3.6)*	7 (4.4)	4 (5.0)
Injury				
Corneal abrasion	0	1 (1.2)	1 (0.6)	3 (3.8)
Safety population *As described in text, IOP elevation was felt to be product related in 1/322 (0.3%) eyes in the Sustained Release Dexamethasone Group				

Table 5: Adverse Events in the Study Eye with an Incidence $\geq 2\%$.

IOP elevation was deemed to be possibly product related in only 1 eye, an incidence of 0.3%. Transient IOP increases of ≥ 10 mmHg in the study eye were seen in a similar proportion of patients in the sustained release dexamethasone groups, (6.8% in Study 1 and 4.4% in Study 2) compared with the placebo group (3.6% and 5.0%, respectively).

Discussion

Postoperative pain and inflammation play significant roles in patient satisfaction, outcomes, and overall surgical success [22]. Trauma to the ocular tissues that occurs during cataract surgery triggers inflammation, pain, and cystoid macular edema in some cases [8]. The added out-of-pocket expense associated with premium IOLs can serve to raise patient expectations in terms of postoperative visual acuity and comfort. Modern therapies, such as sustained release medications, and high patient expectations can help drive cataract surgeons toward the minimization, and possibly eventual elimination, of post-cataract surgical inflammation [22].

The results of the two large studies presented here demonstrate that a greater proportion of patients receiving sustained release dexamethasone experienced reduced pain and inflammation when compared to patients receiving placebo treatment, which by most metrics was statistically significant. Dexamethasone is a powerful corticosteroid, and these data confirm the utility of the sustained release intracanalicular depot for delivery to the ocular surface following ocular surgery. At the same time, these data demonstrate the lack of IOP elevation from the single-dose sustained release dexamethasone compared to IOP spikes linked to steroid drops. The improved IOP safety may be due to the reduced Cmax of sustained release compared to topical drops.

In study 2, the performance of sustained release dexamethasone was generally similar to its performance in the first study. However a higher level of success was noted in the placebo group for absence of cells. Other markers of inflammation, including average cell scores and elimination of flare, did show statistical improvement in both studies, thus confirming the anti-inflammatory efficacy of sustained release dexamethasone.

Individual results from Study 1 demonstrated achievement of primary endpoints for sustained release dexamethasone versus placebo

for pain and inflammation (as defined by an absence of ocular pain at Day 8 and the absence of anterior chamber cells at Day 14). While the primary endpoint for ocular pain was met in Study 2, the corresponding inflammation endpoint was not. A numerically higher proportion of patients in the sustained release dexamethasone group (39.4%) than in the placebo group (31.3%) of Study 2 had an absence of anterior chamber cells in the study eye at the Day 14 visit, but the difference was not statistically significant. This finding was not due to a reduction of effect in the sustained release dexamethasone cohort, which actually increased slightly in Study 2 (33.1% for Study 1 versus 39.4% for Study 2, a 6.3% difference), but rather to a more dramatic increase in the proportion of eyes in the placebo group from Study 2 without anterior chamber cell (14.5% for Study 1 versus 31.3% for Study 2, a 17.3% difference). Multiple factors could have contributed to this result. First, up to 40% of patients in Study 2 were taking systemic NSAIDs concomitantly, which may have masked the effect of the steroid inhibition of the inflammatory cascade. For example, 2 patients in the placebo group used naproxen at a total daily dose of 1,000 mg or higher, while no patients in the dexamethasone treatment group used that high a dose. Second, the high rate of rescue medication use prior to the 14-day inflammation endpoint reduced the statistical power to detect differences between cohorts in the ITT population. Up to four times more patients in the placebo group required rescue treatment compared with those in the sustained release dexamethasone group. Since randomization of sustained release dexamethasone to placebo was 2:1, any patient dropout in the placebo group was potentially more impactful in this regard. Lastly, it is possible that investigator thresholds for grading absence of cells were lower in Study 2, which when combined with a high rescue rate in the placebo group could have led to the observed result. This tendency could be the result of a “regression to the mean” effect [23], since investigators became accustomed to seeing a higher proportion of patients with minimal inflammation and might have been more inclined to record an observation of “absence of cells”.

While the primary endpoint result for inflammation was not achieved in Study 2, other indicators of inflammation were reduced, strongly suggesting that inflammation was well controlled by sustained release dexamethasone relative to placebo in both studies. Additional efficacy endpoints included the absence of ocular pain at days 2, 4, and 14, mean anterior chamber cell scores at days 8 and 14, and absence of anterior chamber flare at days 8 and 14 in the study eye. All of these metrics demonstrated statistical superiority of sustained release dexamethasone relative to placebo in both Study 1 and Study 2.

Pain relief was rapid in the sustained release dexamethasone groups, with significantly more patients having an absence of ocular pain as early as the first postoperative visit on Day 2 compared to placebo. The first postoperative day is a clinically important endpoint for pain, since the most significant discomfort typically occurs during the first 24 hours after cataract surgery. Taken together, the results from these two studies indicate that both pain and inflammation were controlled during the full postoperative course with sustained release dexamethasone treatment relative to placebo.

The favorable absence of pain results at days 2, 4, 8, and 14 from Study 1 and Study 2 confirm those from a previous Phase 2 study with sustained release dexamethasone [19], as do the significant reductions in the other parameters observed in the Phase 3 clinical trial program discussed above. The previous Phase 2 study of sustained release dexamethasone treatment demonstrated a numerical, but not statistically significant advantage over placebo in the proportion of

study eyes with no anterior chamber cells at Day 8 ($P=0.1495$) [19]. It should be noted that this trial consisted of only 60 patients, and as a result was not powered for statistical significance. The Phase 3 study protocol was revised based on data from the Phase 2 and other studies showing significant differences with 14- or 15-day endpoints using either steroids [24] or non-steroidal anti-inflammatory drugs [25,26].

Other clinical studies have demonstrated the efficacy of dexamethasone in the reduction of pain and inflammation due to cataract surgery [6,27-29]. Two different formulations of three times daily topical dexamethasone demonstrated efficacy at reducing cells and flare after cataract surgery in a small study of 20 patients [29]. In the group receiving 0.1% dexamethasone sodium phosphate, the median aqueous cells were 1+ on the 1st and 3rd postoperative days and in the group receiving 0.7% dexamethasone cyclodextrin the median aqueous cells were 2+ on the 1st postoperative day and 0.5 on the 3rd postoperative day. No aqueous cells were seen on the 7th and 21st postoperative days in either group. The cell scores for dexamethasone phosphate drops were comparable to the current results achieved with sustained release dexamethasone in this study, where the median anterior chamber scores were 1 at Day 2 and Day 4 and 0.5 at Day 14 (data not shown). In a randomized prospective clinical trial, Zaczek et al. [9], reported 22.1% of patients receiving topical dexamethasone (0.1%) three times a day for 3 weeks were pain-free 1 day after cataract surgery.

In the two sustained release dexamethasone Phase 3 studies reported herein, 71.2% and 65.6% of patients were pain-free at 1 day after insertion of the depot in Study 1 and Study 2 respectively, indicating sustained release dexamethasone compared favorably in terms of pain and inflammation control to topical drop formulations of dexamethasone.

The results of both Phase 3 studies showed a greater proportion of patients in the placebo groups versus the sustained release dexamethasone groups experienced at least one ocular AE in the study eye. The majority of these events were of mild or moderate severity. Most adverse events were likely related to the cataract surgical procedure itself. Very few of the adverse events were related to treatment (1.2% [2/162] for Study 1 and 0.6% [1/160] for Study 2), supporting a favorable safety profile for sustained release dexamethasone.

Intraocular pressure increases related to steroid treatment have been attributed to mucopolysaccharide accumulation within the trabecular meshwork, which is thought to increase aqueous outflow resistance [30]. The incidence of steroid-induced glaucoma appears to be related to dose and duration of application of the medication [31].

Steroid-eluting intracanalicular depots are designed to provide sustained and tapered dosing of the active ingredient for up to 30 days with the goal of inhibiting post-operative inflammation without causing IOP spikes by administering a small fraction of the drop-equivalent dose over this time period. This importance of total drug dosage exposure is supported by the fact that the incidence of product-related increased ocular pressure was low (1 of 325 patients in the two studies combined, or 0.3% overall) in these two clinical trials. All but one of the incidents of transient elevation $IOP \geq 10$ mmHg were observed at the first postoperative study visit and thus thought to be related to cataract surgery. One patient experienced a 10 mmHg rise in IOP at Day 8. The same patient had cataract surgery in the non-study eye on study day 15 and experienced a similar increase in IOP in that eye for which she was prescribed an IOP-lowering medication from

days 28 through 56. Overall, increases in IOP either resolved without treatment or were addressed by medication or paracentesis.

Other steroids have been also studied for their effect on IOP after ophthalmic surgery. Results reported in the NDA for difluprednate 0.05% ophthalmic emulsion for post-surgical studies, showed 3.6% (12/329) of patients had increased IOP ≥ 10 mmHg higher than baseline [32]. Donnenfeld and colleagues [33] conducted a study with cataract surgery patients in which the first eye received either difluprednate 0.05% or prednisolone acetate 1%, while the fellow eye received the alternative drug. Prior to surgery, 7 doses of corticosteroid were administered over 2 hours; 3 additional doses were given after surgery. For the remainder of the day of surgery, corticosteroids were administered every 2 hours, then 4 times daily during week 1 and twice daily during week 2. A similar postoperative rise in IOP at day 1 was observed in both treatment groups, averaging 3.52 mmHg in the difluprednate-treated group and 2.92 mmHg in the prednisolone-treated group ($P=0.467$). The NDA for loteprednol etabonate ophthalmic gel 0.5% showed 0.2% (1/409) of patients experienced a ≥ 10 mmHg increase in IOP and 3.4% (14/409) had a ≥ 5 mmHg increase in IOP above baseline [34]. Lane and Holland [35] compared the efficacy of loteprednol etabonate 0.5% versus prednisolone acetate 1.0% for the control of postoperative inflammation for patients undergoing routine cataract surgery. The mean changes in IOP from baseline were 4.5 mmHg for loteprednol and 5.7 mmHg for prednisolone on Day 1. In the current two studies, the incidences of transient IOP increases were low and only one patient experienced increases in IOP that were related to dexamethasone treatment.

Historically, compliance with dosing of topical ocular medications in eye drop form has been poor [14,15,36]. Patients, particularly the elderly, can find the complicated dosing regimens required with some topical ophthalmic medications to be challenging [14]. An electronic monitoring study in cataract surgery patients who were asked to dose steroid and antibiotic drops five times daily for 2 weeks, found only about half were compliant with their medication dosing [36]. This noncompliance, combined with inaccurate drop administration problems discussed above, can put patients at risk for post-surgical complications. The one-time administration of sustained release dexamethasone by the physician should help to overcome issues of patient compliance with a topical corticosteroid eye drop regimen that varies in frequency over several weeks after eye surgery. The intracanalicular depot provides prolonged tapered drug delivery, which may translate to better control of postoperative pain and inflammation compared to topical drops.

A large body of evidence from both experimental and clinical studies suggests that some preservatives used to inhibit microbial growth in multiple use bottles can have deleterious effects on the ocular surface [37]. Benzalkonium chloride, a powerful cationic surfactant, is the most frequently used ophthalmic preservative and has been shown to produce ocular irritation, tear film instability, a loss of goblet cells, conjunctival squamous metaplasia, and apoptosis. The mechanisms for these effects are yet to be fully elucidated; however the compound is known to interact with cell membranes (the understood mechanism of its bactericidal/microbicidal action) and lipid components of the tear film [23]. Although such deleterious effects are often thought of as resulting from long-term exposure to preservatives, *in vitro* studies have found reductions in corneal epithelial cell viability from as little as 20 minutes of exposure to 0.001% benzalkonium chloride [38]. These toxic effects are particularly problematic for cataract surgery patients with comorbidities that have already

compromised the ocular surface, such as glaucoma or dry eye disease. These patients often take multiple topical medications in order to manage these other conditions, exposing the ocular surface to chronic dosing of ophthalmic preservatives. The sustained release dexamethasone intracanalicular depot provides preservative-free medication for up to 1 month after surgery, helping to minimize the overall preservative load applied to the ocular surface during therapy, which may lead to less patient discomfort and faster visual recovery.

The allowance of systemic NSAID use in the protocol could be considered a limitation of these studies. However, some of these elderly patients scheduled for cataract surgery had other comorbidities that required the use of systemic NSAIDs. This patient cohort may be more representative of the patients that would be encountered in routine clinical practice than a group of patients for whom systemic NSAID use would have been prohibited.

Conclusions

Results from these two Phase 3 clinical studies demonstrated that a sustained-release dexamethasone intracanalicular depot was safe and efficacious for the reduction of ocular pain and inflammation following cataract surgery in two well controlled, prospective, double masked clinical trials. Significant differences favoring sustained release dexamethasone relative to placebo were demonstrated for several clinical endpoints related to pain and inflammation, despite the fact that more patients on placebo received rescue therapy. The lack of IOP elevation from the single-dose sustained release dexamethasone can be compared favorably to IOP spikes linked to steroid drops. The improved IOP safety may be due to the reduced C_{max} of sustained release compared to topical drops. Additionally, the sustained release depot provided long-term medication delivery without the compliance issues or preservative-related ocular surface toxicity of topical drops.

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