

Vehicle-Controlled, Phase 2 Clinical Trial of a Sustained-Release Dexamethasone Intracanalicular Insert in a Chronic Allergen Challenge Model

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Abstract

Purpose: To evaluate the efficacy and safety of a sustained-release dexamethasone intracanalicular insert (Dextenza™) in a model of allergic conjunctivitis.

Methods: This was a randomized, double-masked, vehicle-controlled, Phase 2 study. Subjects had to have a positive conjunctival allergen challenge (CAC) reaction to allergen (bilateral +2 itching and redness on 5-point, 0–4 scales) at Visit 1, and for 2 of 3 time points on subsequent visits. Subjects who met entry criteria were randomized to receive Dextenza or PV (vehicle insert). Challenges occurred over 42 days, with efficacy assessed at 14 (primary endpoint visit), 28, and 40 days postinsertion. Outcome measures included the evaluation of ocular itching, redness, tearing, chemosis, eyelid swelling, rhinorrhea, and congestion.

Results: Twenty-eight subjects completed the study in the Dextenza group and 31 in the vehicle group. At 14 days postinsertion, Dextenza was statistically superior to PV, with least square mean differences for ocular itching of –0.76, –0.97, and –0.87 at 3, 5, and 7 min post-CAC, and for conjunctival redness of –0.46, –0.66, and –0.68 at 7, 15, and 20 min post-CAC. Clinical significance, defined as a 1-U decrease from PV, was not met for primary efficacy. Secondary endpoints, including number of subjects reporting itching and conjunctival redness, indicated superior performance of Dextenza compared with vehicle. Eleven Dextenza-treated (35.5%) and 10 vehicle-treated (30.3%) subjects each experienced a single adverse event.

Conclusion: This Phase 2 study demonstrated preliminary efficacy and safety data of Dextenza for treatment of allergic conjunctivitis.

Keywords: allergy, corticosteroid, Dextenza, drug delivery, conjunctivitis, intracanalicular insert

Introduction

ALLERGY IS THE fifth leading group of chronic diseases, affecting 50 million Americans.¹ Ongoing epidemiological efforts have estimated approximately 30% to 40% prevalence worldwide.² Seasonal and perennial allergic conjunctivitis (SAC and PAC, respectively) are the most common of the allergic ocular diseases, accounting for 90% of ocular allergic manifestations.³ Seasonal variation is common when one or multiple pollen sensitizations are involved; however, in a mild climate, SAC might not disap-

pear completely in the colder seasons, and is chronic or perennial when caused by sensitization to ubiquitous allergens such as dust mites and animal dander.

Both SAC and PAC are defined by variability from day to day, from patient to patient, and in the same patient throughout the day and season. These intersubject and intrasubject variations in disease presentation made it historically very difficult to study and treat allergic conjunctivitis, as well as to test for new modalities of therapy. These obstacles were mitigated with the development of the conjunctival allergen challenge (Ora-CAC®) model of allergic conjunctivitis, designed to

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mimic the signs and symptoms of ocular allergy in a precise and consistent manner, reproducing what occurs in allergic conjunctivitis in a controlled clinical setting in which the external and internal factors are minimized.^{4,5}

Dextenza™ (Ocular Therapeutix, Bedford, MA) is a resorbable intracanalicular insert designed to serve as a delivery vehicle for dexamethasone. This is a proprietary, polyethylene glycol-based hydrogel plug that is inserted into the vertical canaliculus. The dried plug swells on contact with tear fluid and continues to expand until firmly secured within the canaliculus, where it remains until it is hydrolyzed and cleared through the nasolacrimal duct. Dextenza contains approximately 394 µg of dexamethasone, released in a sustained and tapered fashion over a period of 30 days. The dose selection was driven partly by the formulation; however, preclinical studies for various doses confirmed that therapeutic levels in tear fluid were obtained with this dose (Ocular Therapeutix Data on File).

In vivo preclinical studies have demonstrated that the drug release rate is approximately 20 µg/day in week 1, and tapers to approximately 10 µg/day in week 4, and can be averaged to a daily delivery of less than 15 µg/day over the 30-day implant period (Ocular Therapeutix Data on File). When compared with the 200 µg of dexamethasone provided daily with the postop 2-week regimen of qid dexamethasone sodium phosphate 0.1% suspension, Dextenza delivers a dose approximately 13 times lower. Another common postop regimen involves a decremental regimen of 4-3-2-1-0 drops/day over 4 weeks. Dextenza was designed to mimic these pharmacokinetics, delivering a bolus of drug at the onset of acute inflammation, followed by attenuated delivery as disease control is achieved.

While the pharmacokinetics of Dextenza were originally designed for treatment of postoperative inflammation, the 4–6 week duration and slow-tapering characteristic of this depot are ideal for other inflammatory indications such as ocular allergy. Many allergy sufferers would benefit from treatment for the duration of a given pollen season. Slow tapering is necessary for all steroid treatments, thus the decreasing delivery over time assures that cessation of treatment occurs safely and slowly. Furthermore, the necessity of monitoring and insertion by the ophthalmologist means that potential side effects will be well monitored, and the risk of abuse due to the benefit associated with steroid use would not be an issue.

The first in human study (Phase 2) completed for Dextenza was conducted in patients undergoing uncomplicated cataract, for the indication of postoperative pain and inflammation. This study demonstrated not only the efficacy of the product for the postoperative indication, but also the overall safety of the product in 29 treated subjects.⁶ The decision to proceed immediately into the Phase 2 trial for the allergic conjunctivitis indication was made under the guidance of the appropriate regulatory agency, and after careful consideration of the demonstrated clinical safety of the product as well as the 5-decade clinical safety record of the approved active pharmaceutical ingredient, dexamethasone.

The objective of this study was to evaluate the clinical efficacy and safety of Dextenza in acute and chronic allergic conjunctivitis using a modified conjunctival allergen challenge (CAC) model comprised of a series of repeated CACs. Models of ocular allergy have been used previously in clinical studies to demonstrate the efficacy of steroids with varying success.^{7,8} A modified, repeat challenge model is more appropriate for the testing of anti-inflammatory/antiallergic

drugs that have more complex targets than histamine receptor antagonism or mast cell stabilization.^{9,10} This model, in fact, is an ideal high-throughput screening tool for determining in a relatively rapid manner important information about the clinical efficacy of anti-inflammatory agents.

Subjects and Methods

This was a prospective, multicenter, randomized, double-masked, vehicle-controlled, Phase 2 study to evaluate the efficacy and safety of Dextenza compared with a vehicle insert (PV) for the treatment of the signs and symptoms of chronic allergic conjunctivitis. The PV was manufactured in an identical process as Dextenza without the drug substance, dexamethasone, and was designed to degrade and be cleared through the nasolacrimal duct in the same manner and with the same kinetics as Dextenza.

This study was conducted in accordance with the ethical principles that originated with the Declaration of Helsinki. One central Institutional Review Board was used for all participating sites (Alpha IRB, San Clemente, CA). Subjects provided a written informed consent and signed the HIPAA form. This trial is registered on clinicaltrials.gov under the number NCT02062905.

The trial was conducted at 2 sites in the United States, and comprised 12 study visits over a period of 50 days. Four screening visits were used to select a subject population who responded reproducibly to 4 challenges administered over a 2-day interval to induce the inflammatory component of chronic allergic conjunctivitis. Randomization (1:1) was stratified by average itching scores (≤ 2.5 and >2.5) at baseline.

Inclusion and exclusion criteria

Eligible subjects were required to be at least 18 years of age; to have a visual acuity of 0.7 logMAR or better in each eye; to not be pregnant or nursing; to be able and willing to avoid all prohibited medications for the appropriate washout period and during the study; and to discontinue wearing contact lenses for at least 72 h before and during the study trial period. Additionally, eligible subjects had to have a positive history of ocular allergies and a positive skin test reaction to a perennial allergen (cat dander, dog dander, dust mites, cockroaches) and a seasonal allergen (trees, grasses, and/or ragweed) within the past 24 months. Testing was provided if the subject had never been tested or if a skin test was not performed within the required time frame. Subjects had to have a positive bilateral CAC reaction (ie, ≥ 2 redness in the conjunctival vessel bed and ≥ 2 itching) to a perennial allergen within 10 min of instillation of the last titration of allergen, and a positive bilateral reaction for at least 2 of the 3 post-CAC time points at 3 subsequent screening challenges prerandomization.⁴

Subjects were not eligible for participation if they had any contraindication to the investigational products; or any systemic (including but not limited to autoimmune disease; severe cardiovascular disease, including arrhythmias; alcohol or drug abuse; poorly controlled hypertension or diabetes; moderate or severe asthma) or ocular condition (including but not limited to narrow angle glaucoma; retinal detachment or active retinal disease; active bacterial, viral, or fungal infection; clinically significant blepharitis; trichiasis; follicular conjunctivitis; iritis; pterygium, or a diagnosis of dry eye) that could have affected the subject's safety or trial parameters.

Subjects could not have had any ocular surgical intervention planned, or within 3 months of screening, or used an investigational drug or device during or within 30 days of the trial period. Subjects could not have had a score of >0 for itching and/or >1 for conjunctival redness before challenge at baseline in either eye.

Two procedural exclusion criteria related to the size of the punctum. A punctum size smaller than 0.4 mm or ≥ 1.0 mm was not allowed, as well as punctum too small to allow transient dilation to 0.7 mm before insertion of the Dextenza or vehicle depot.

Study design

The study design is included in Fig. 1. Part 1 consisted of 5 visits in which screening, titration, and repeat challenges occurred. Visual acuity and baseline ocular and nasal allergic signs and symptoms were assessed. Subjects exhibiting signs and symptoms of allergic conjunctivitis were excluded. The punctum and surrounding area were assessed under the slit lamp. A titration CAC was performed as previously described.⁴ Subjects who failed to test positively were excluded from the study. An intraocular pressure (IOP) measurement and a dilated fundus examination were also performed.

Confirmatory challenges were conducted on 3 subsequent visits. Visual acuity, slit lamp biomicroscopy, and pre-challenge allergic signs and symptoms were assessed. CACs were performed with the final threshold dose instilled at the previous visits to ascertain that the dose was not cumulative. Assessment of itching was made by the subject at $3(\pm 1)$, $5(\pm 1)$, and $7(\pm 1)$ min post-CAC. Assessments of redness and chemosis were graded by the investigator, and assessments of eyelid swelling, tearing, and nasal symptoms were made by the subject at $7(\pm 1)$, $15(\pm 1)$, and $20(\pm 1)$ min postchallenge. If the subject failed to react positively in both eyes in at least 2

out of the 3 time points (not necessarily at the same time point) within a 20-min interval, he/she was excluded from the study. Subjects had to react positively at all 4 baseline challenges to continue in the study.

Eligible subjects were asked to return to the office approximately 2–3 days from the time of their baseline challenge to attempt test article insertion. Subjects who met all of the inclusion criteria and none of the exclusion criteria and qualified to continue in the study were randomly assigned to masked treatment using a 1:1 (Dextenza: PV) assignment ratio.

Part 2 consisted of 4 visits in which subjects were challenged 4 times in a 2-day period, with the primary efficacy visit occurring on Visit 6, 2 weeks postinsertion. After visual acuity, prechallenge signs and symptoms assessment, baseline slit lamp biomicroscopy, and punctum examination, subjects received one drop of the predefined dose of allergen solution bilaterally. Assessments of itching and redness were performed as in Part 1.

During Part 3, a third cycle of visits in which subjects were challenged 4 times in 2 days occurred. These visits were identical to those in Part 2. On Visit 9, the efficacy of Dextenza was assessed 28 days postinsertion. This visit was identical to Visit 6.

Finally, in Part 4, a fourth series of challenges was conducted in which subjects were challenged 4 times in 2 days. These visits were also identical to those described for the previous 3 parts. On Visit 12, the efficacy of Dextenza was assessed at 42 days postinsertion. This was the final study visit and thus the exit procedures were also performed.

Statistical Analyses

Power calculation

A total of 30 subjects per treatment arm provided 99.7% power to demonstrate a statistically significant difference in

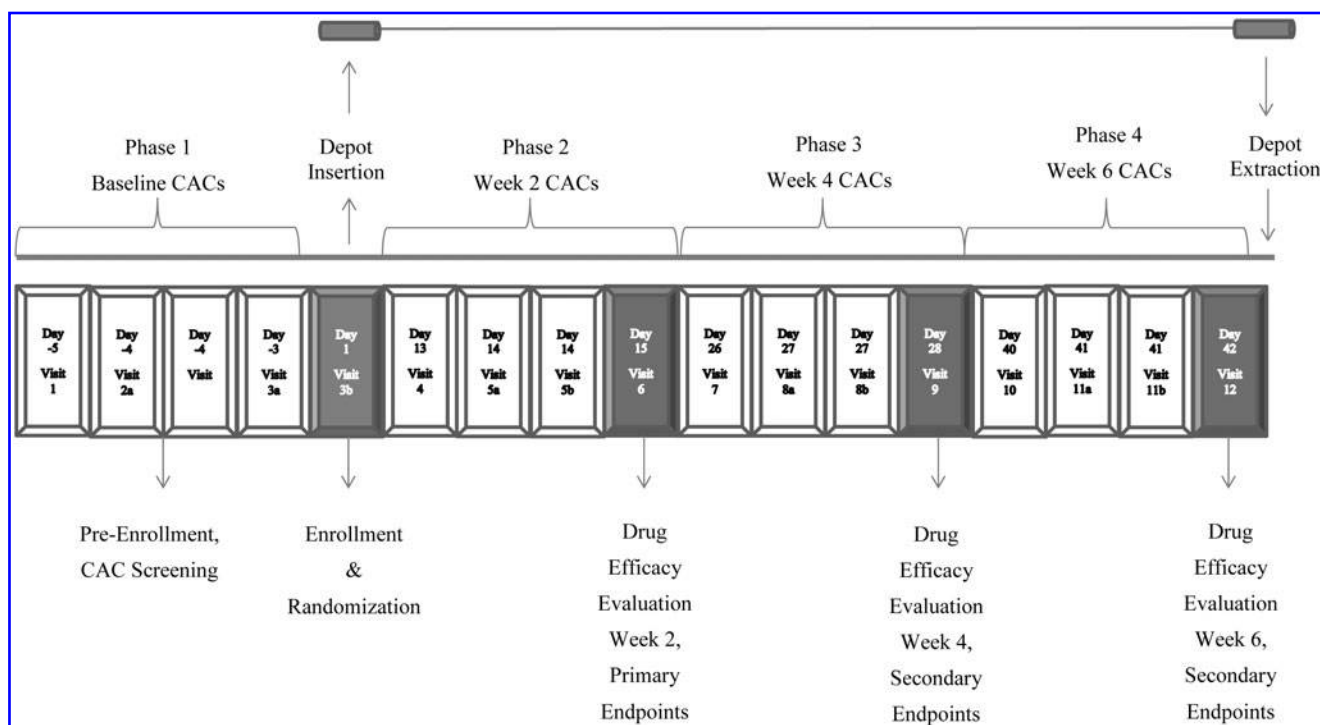


FIG. 1. Phase 2 Modified CAC Study Design. CAC, conjunctival allergen challenge.

ocular itching between groups assuming a difference of 1.25 U, a standard deviation of 1.0 U, and a 2-sided Type I error rate of 0.05 (yielding 99.1% power over all post-CAC time points at Visit 6 for ocular itching between groups conservatively assuming independence). The same assumptions yielded the same power and sample size for conjunctival redness, yielding 98.2% power over all post-CAC time points at Visit 6 for both primary endpoints assuming independence.

Additionally, 30 subjects in each treatment group yielded 92% probability of showing a point estimate difference for itching between OTX-DP and PV-treated subjects of at least 1.0 U for a majority of the post-CAC time points and 0.5 U for all of the post-CAC time points at Visit 6 assuming a common standard deviation of 1.0 U, a difference of 1.25 U, and independence between time points. The same assumptions yielded the same probability for conjunctival redness, yielding 85% probability of showing clinically important differences for both primary endpoints assuming independence.

Randomization

Once a subject met all qualification criteria, they were to be randomly assigned to masked treatment using a 1:1 (OTX-DP: PV) assignment ratio. Subjects were to be randomized on Visit 3b (Day 1) by assignment of the lowest 5-digit randomization number available within the appropriate stratum at each investigative site. Randomization was stratified by average post-CAC itching scores (≤ 2.5 and >2.5) at baseline (Visit 3a) to ensure balance for the primary endpoint of ocular itching between treatments. A computer-generated randomization schedule was produced before study enrollment by an unmasked statistician who was not otherwise involved in the study.

Primary efficacy endpoints

The *a priori* primary efficacy endpoints were the following:

- Ocular itching evaluated by the subject on Visit 6 (Day 15, 14 days postinsertion) at 3 (± 1), 5 (± 1), and 7 (± 1) min post-CAC (0–4 scale, allowing half unit increments)
- Conjunctival redness evaluated by the investigator on Visit 6 (Day 15, 14 days postinsertion) at 7 (± 1), 15 (± 1), and 20 (± 1) min post-CAC (0–4 scale, allowing half unit increments)

Unit of analysis

The subject was considered the unit of analysis for all efficacy variables. For the variables using subject as the unit of analysis, the average of both eyes of each subject was used for statistical summaries and analyses in cases where data were collected for each eye. For safety variables (slit lamp biomicroscopy, dilated fundus examination, VA and IOP results), the eye was the unit of analysis, and summaries were provided for all eyes combined. In addition, the eye was the unit of analysis for categorical punctum examination and punctum size, test article insertion, test article visualization, and test article removal variables.

Criteria for efficacy

To demonstrate clinical efficacy, OTX-DP was required to show clinical superiority over PV by at least 0.5 U of a

5-point scale for all 3 post-CAC time points, 3 (± 1), 5 (± 1), 7 (± 1) min post-CAC for ocular itching and 7 (± 1), 15 (± 1), 20 (± 1) min post-CAC for conjunctival redness, and at least 1 U for the majority (2 out of 3) of the post-CAC time points measured for both ocular itching and conjunctival redness.

Secondary efficacy endpoints

Secondary efficacy measures included all other post-CAC ocular and nasal allergic signs/symptoms: eyelid swelling, tearing, rhinorrhea, nasal pruritis, ear/palate pruritis, episcleral and ciliary redness, chemosis, and a composite present/absent score for nasal symptoms at all visits. Ocular itching and conjunctival redness were also considered secondary efficacy measures at all visits other than the primary efficacy assessment at Visit 6.

Scoring systems

Signs and symptoms were graded on a 0–4 scale, except for nasal symptoms, graded on a 0–3 scale. Itching, redness, and chemosis grading allowed for half-unit increments. Itching alone was measured at 3, 5, and 7 min postchallenge; all others were measured at 7, 15, and 20 min postchallenge. All scales have been used to assess ocular allergic signs and symptoms in Phase 2 and 3 CAC trials in support of the FDA approval of ocular allergy drugs for almost 25 years.⁵

Statistical analyses

The analyses for primary efficacy were conducted on the intent-to-treat population carrying forward the last postchallenge observation within the same visit to handle missing and incomplete efficacy data. The average of both eyes was used as the unit of analysis. A separate ANCOVA model was used for each postchallenge time point at Visit 6, with the time appropriate postchallenge scores at the final baseline challenge as a covariate and treatment group as the sole factor (Dextenza compared with PV). Two-sample *t*-tests were used as unadjusted sensitivity analyses, as well as nonparametric Wilcoxon rank-sum tests (Dextenza compared with PV). Treatment differences were considered statistically significant for each primary endpoint at a 2-sided significance level of $\alpha=0.05$. Analyses were performed on quantitative secondary endpoints in a manner similar to primary endpoints. Qualitative measures were analyzed using a Fisher's exact test or a Chi-Square test, as appropriate. There were no adjustments for multiplicity for having 2 endpoints as statistical significance was required for both ocular itching and conjunctival redness for treatment success.

The safety of the Dextenza and PV was assessed by collection of adverse events, assessment of visual acuity, measurement of IOP, and findings on slit lamp biomicroscopy and dilated fundus examination.

In a *post hoc* analysis, responder subgroups were further explored to assess the number and percentage of subjects with a score=0 and a score ≤ 1 in itching or conjunctival redness in each group. These data were collected both to further explore the efficacy of Dextenza, and to further develop this modified CAC model and relevant endpoints of chronic ocular allergy.

Results

A total of 68 subjects were entered into the study and comprised the ITT population: 35 in the Dextenza group and 33 in the PV group. Seven subjects in the Dextenza arm and 2 in the vehicle arm did not complete the study, for a final complete number of subjects of 28 (80.0%) in the Dextenza group and 31 (93.9%) in the vehicle group. These numbers reflect the Per Protocol Population. Since 4 of the randomized subjects did not receive the intracanalicular insert and were discontinued, the final number of subjects in the Safety Population was 31 in the Dextenza group and 33 in the vehicle group. Table 1 reports the subject disposition. No treatment unmasking was necessary during the conduct of the study.

Aside from allergic conjunctivitis, which was present in 100% of subjects, the ocular medical histories of subjects were primarily single instances of pinguecula, nonclinically significant blepharitis, lid papilloma or nevus, history of cataract, pseudophakia and intraocular lens insertion, conjunctival cyst, myopia, photorefractive surgery, corneal opacity, arcus senilis, vitreous floaters or posterior vitreous detachment, and borderline glaucoma suspect.

For nonocular medical histories, subjects reported allergic rhinitis, pharyngitis or asthma most frequently. Headaches, hypertension, hypercholesterolemia, osteopenia/osteoporosis, dysmenorrhea, menopause, female sterilization procedures,

and musculoskeletal and/or connective tissue disorders were also common.

The mean age of the participants was 43.1 years (range 20–69 years) for the Dextenza group and 45.5 years (range: 21–71 years) for the vehicle group. There were similar proportions of males and females in the Dextenza (17 males, 18 females) and vehicle (16 males, 17 females) groups. The majority of randomized subjects were white (68.6% in Dextenza; 72.7% in PV groups). See Table 1 for a complete description of demographics.

Primary endpoints

At 14 days postinsertion (Visit 6), Dextenza was shown to be statistically significantly superior to PV in ocular itching at all time points (3, 5, and 7 min postchallenge) with treatment group differences of: -0.76 ($P=0.0030$), -0.97 ($P=0.0001$), and -0.87 ($P=0.0007$), respectively, as shown in Table 2. Similarly, at 14 days postinsertion, Dextenza was statistically significantly superior to PV for conjunctival redness at all time points (7, 15, and 20 min) postchallenge with treatment group differences of: -0.46 ($P=0.0097$), -0.66 ($P=0.0003$), and -0.68 ($P=0.0002$) (Table 2). Clinical significance was defined in this study as superiority over PV by at least 0.5 U of a 5-point scale for all 3 post-CAC time points for ocular itching and conjunctival redness, and by at least 1 U for the

TABLE 1. SUBJECT DISPOSITION AND DEMOGRAPHICS IN A MODIFIED CONJUNCTIVAL ALLERGEN CHALLENGE STUDY OF THE SAFETY AND EFFICACY OF 6-WEEK TREATMENT WITH A SUSTAINED-RELEASE DEXAMETHASONE INSERT (DEXTENZA) COMPARED TO A PLACEBO VEHICLE INSERT IN ELIGIBLE SUBJECTS WITH A HISTORY OF BOTH SEASONAL AND PERENNIAL ALLERGIC CONJUNCTIVITIS

Subject disposition	Dextenza	Vehicle
Number of randomized subjects: intent-to-treat (ITT) population ^a	35 (100.0%)	33 (100.0%)
Number of subjects in the per protocol population	28 (80.0%)	31 (93.9%)
Number of subjects in the safety population	31 (88.6%)	33 (100.0%)
ITT subjects who completed the study		
Yes	28 (80.0%)	31 (93.9%)
No	7 (20.0%)	2 (6.1%)
Reasons for discontinuations from study		
Investigator decision	1 (2.9%)	0
Adverse events	1 (2.9%)	1 (3.0%)
Consent withdrawn	1 (2.9%)	0
Other	4 (11.4%)	1 (3.0%)
Demographics		
Age in years: Mean (Standard deviation)	43.1 (13.1)	45.5 (12.9)
Range	20–69	21–71
Gender	Male: 17 (48.6%) Female: 18 (51.4%)	Male: 16 (48.5%) Female: 17 (51.5%)
Ethnicity	Hispanic: 5 (14.3%) Non-Hispanic: 30 (85.7%)	Hispanic: 4 (12.1%) Non-Hispanic: 29 (87.9%)
Race	American Indian: 1 (2.9%) African American: 7 (20.0%) White: 24 (68.6%) Other: 3 (8.6%)	American Indian: 0 African American: 7 (21.2%) White: 24 (72.7%) Other: 2 (6.1%)
Iris color	Black: 0 Blue: 22 (31.4%) Brown: 32 (45.7%) Green: 10 (14.3%) Hazel: 6 (8.6%)	Black: 4 (6.1%) Blue: 16 (24.2%) Brown: 32 (48.5%) Green: 2 (3.0%) Hazel: 12 (18.2%)

Subjects were challenged in 4 series of repeated CACs to simulate chronic AC.

^aThe ITT population included all randomized subjects, although 4 of these did not receive Dextenza and were discontinued from the study. The number of subjects in the Safety population (31) reflects this discrepancy. The Per Protocol population reflects the actual number of subjects in each group who completed the study with no protocol violations.

TABLE 2. OCULAR ITCHING AND CONJUNCTIVAL REDNESS IN A MODIFIED CONJUNCTIVAL ALLERGEN CHALLENGE STUDY OF THE SAFETY AND EFFICACY OF A 6-WEEK TREATMENT WITH A SUSTAINED-RELEASE DEXAMETHASONE INSERT (DEXTENZA) COMPARED WITH A PLACEBO VEHICLE INSERT IN ELIGIBLE SUBJECTS WITH A HISTORY OF BOTH SEASONAL AND PERENNIAL ALLERGIC CONJUNCTIVITIS

Time point statistics	Dextenza (N=35)	Vehicle (N=33)
Pre-CAC		
Mean (SD) Itching	0.13 (0.571)	0.06 (0.281)
Mean (SD) conjunctival redness	0.78 (0.695)	0.90 (0.779)
3 min Post-CAC		
ANCOVA LS means itching	1.81	2.57
Itching treatment difference (95% CI); <i>P</i> value ^a	-0.76 (-1.26, -0.27); <i>P</i> =0.0030	
5 min post-CAC		
ANCOVA LS means itching	1.73	2.70
Itching treatment difference (95% CI); <i>P</i> value ^a	-0.97 (-1.45, -0.50); <i>P</i> =0.0001	
7 min post-CAC		
ANCOVA LS means itching	1.66	2.53
Itching treatment difference (95% CI); <i>P</i> value ^a	-0.87 (-1.36, -0.38); <i>P</i> =0.0007	
ANCOVA LS means conjunctival redness	1.63	2.09
Redness treatment difference (95% CI); <i>P</i> value ^a	-0.46 (-0.81, -0.12); <i>P</i> =0.0097	
15 min post-CAC		
ANCOVA LS means conjunctival redness	1.55	2.21
Redness treatment difference (95% CI); <i>P</i> value ^a	-0.66 (-1.00, -0.32); <i>P</i> =0.0003	
20 min post-CAC		
ANCOVA LS means conjunctival redness	1.54	2.21
Redness treatment difference (95% CI); <i>P</i> value ^a	-0.68 (-1.01, -0.34); <i>P</i> =0.0002	

Subjects were challenged in 4 series of repeated CACs to simulate chronic AC. The primary efficacy endpoints of itching and conjunctival redness were assessed after repetitive challenges at 14 days postinsertion. Bold treatment differences are statistically significant.

SD=standard deviation; CI=Confidence intervals

N in the headers represents the total number of subjects enrolled in each respective treatment group within the Intent-to-Treat population.

Ocular itching was assessed on a 0–4 scale at 3, 5, and 7 min post-CAC; 0.5 increments were allowed. A lower score was indicative of less itching. Conjunctival redness was assessed on a 0–4 scale at 7, 15, and 20 min post-CAC; 0.5 increments were allowed. A lower score was indicative of less conjunctival redness.

^a*P* value calculated using an ANCOVA model with treatment, time point, and baseline (time appropriate Visit 3a post-CAC) scores in the model and comparing Dextenza to Vehicle.

majority (2 out of 3) of the post-CAC time points. While this study met the first 0.5-U difference benchmark of clinical significance at all time points for both the sign and symptom, the second clinical significance benchmark, a majority of 1-U differences from PV, was not met.

Secondary endpoints

Itching and redness were also highly statistically significantly improved over the course of the entire study, with mean differences observed in the Dextenza group compared with the PV group after 2, 4, and 6 weeks of therapy. Figures 2 and 3 illustrate the ocular itching and conjunctival redness results, respectively, at each of the 4 series of CACs for Dextenza and PV.

High responders were defined as subjects who achieved low post-CAC itching and redness scores (less than or equal to 1 at a given assessment) at 2, 4, and 6 weeks of treatment. There was a 5–8 times greater number of high responders in the Dextenza group than in the vehicle group at 8 of 9 assessments postchallenge at weeks 2, 4, and 6 for both itching and redness. At Week 2, a total of 8, 10, and 10 subjects were high responders in the Dextenza group (26%–37%) compared with 1, 2, and 2 subjects (0%–6.5%) in the vehicle group, respectively, at 3, 5, and 7 min post-CAC. At Week 4, this effect was still observed, with a 7–10 times

greater number of high responder subjects with minimal itching post-CAC in the Dextenza group compared with the vehicle group. Redness responders showed a similar but less marked trend. At Week 6, the differences between the 2 groups were less notable since vehicle-treated subjects exhibited less of an allergic response to challenge. Table 3 reports the findings for high itching and redness responders (≤ 1) at each visit and postchallenge time point.

Dextenza improved the associated signs and symptoms of allergic conjunctivitis evaluated at 14, 28, and 42 days posttreatment, as demonstrated by statistically significant differences in ocular itching, conjunctival redness, ciliary redness, episcleral redness, chemosis, tearing, and rhinorrhea, when compared with subjects receiving PV. In other relevant signs and symptoms, such as eyelid swelling, nasal pruritis, ear/palate pruritis, and nasal congestion, statistically significant differences between the Dextenza and vehicle groups were seen, but not achieved at all time points (Table 4).

While the clinical significance benchmark, defined as a ≥ 1 U treatment difference, was not observed for any parameter at any postchallenge time point, the second clinical significance benchmark, defined as a ≥ 0.50 U treatment difference, was observed in favor of Dextenza at 9 of 12 post-CAC time points for ocular itching, and 10 of 12 post-CAC time points for conjunctival redness.

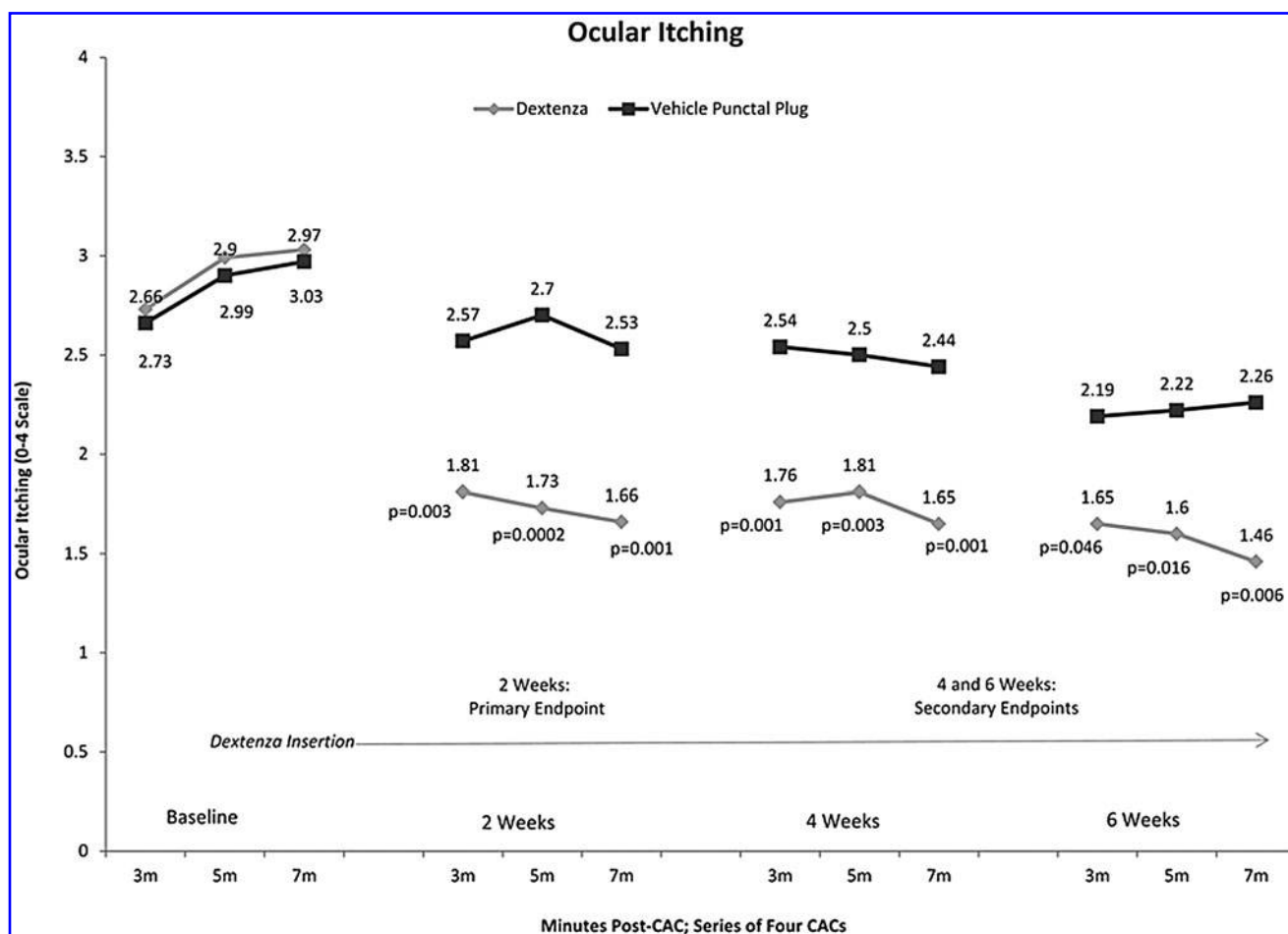


FIG. 2. Ocular Itching. The efficacy of Dextenza™ (resorbable hydrogel intracanalicular insert containing approximately 0.494 µg of dexamethasone) ($N=35$) versus a vehicle insert ($N=33$) over a 6-week treatment period against ocular itching induced by a modified CAC model of chronic allergic conjunctivitis (ANCOVA P -values illustrated).

Safety Results

Eleven subjects (35.5%) in the Dextenza treatment group and 10 (30.3%) in the PV group experienced at least one adverse event. All adverse events were of mild or moderate severity, with the majority being ocular in nature. One serious adverse event in the Dextenza group (depression, resulting in hospitalization) was deemed unrelated to treatment.

Two subjects (one in the active and one in the vehicle group) were withdrawn from the study due to an adverse event (Table 5). A total of 10 treatment-emergent ocular adverse events occurred in each group: in 9 subjects in the Dextenza group and in 8 subjects in the vehicle group. All events but 3 were suspected to be related to treatment. Details of ocular TEAEs are reported in Table 6. No nonocular events were suspected of being related to treatment.

Two subjects were IOP responders in this study (Incidence: 6.5%). One male, 50 years of age, was treated for the entire study (43 days of Dextenza use), and on the last visit, presented with a greater than 10 mm Hg increase in IOP. Baseline IOP was 22 OU, increasing to 25 OU, 26 OU, and 34 OD, 26 OS on visits 1, 6, 9, and 12, respectively. One dose of timolol maleate 0.5% was given and after 20 days, IOP returned to 19 OD and 21 OS. A second male, also 50 years of age, was treated up to Visit 9, with 29 days of Dextenza use. This subject had baseline IOP of 16 OU, increasing to 17 OU at

Visit 6, and 30 OD, 28 OS at Visit 9. The subject was discontinued at this point from drug use and the insert was removed. One drop of timolol maleate 0.5% was provided. At the follow-up visits 2 days later and 1 month later, the subject had an IOP of 16 OD, 17 OS, and 13 OU, respectively.

No changes in lens, anterior chamber, eyelid, conjunctiva, or cornea were noted by slit lamp biomicroscopy conducted at every visit throughout the study.

Discussion

In terms of efficacy, topical corticosteroids are the mainstay of therapy for the management of all anterior segment inflammation. There is precedent and rationale for treating allergic conjunctivitis with topical corticosteroids.^{7-8,11-15} Particularly for treatment of acute flare-ups, pulse therapy with topical steroids is quite common in the proliferative forms of allergy such as vernal keratoconjunctivitis and atopic keratoconjunctivitis.¹⁶ While topical corticosteroid drops may exhibit peaks and troughs in concentration of active drug, Dextenza has been constructed to deliver a course of therapy that is optimal for acute inflammation: a bolus of corticosteroid initially,¹⁷⁻²⁰ followed by gradually decreasing daily doses delivered throughout the life of the insert, and independent of patient compliance. Topical corticosteroids have been evaluated, often in combination with an

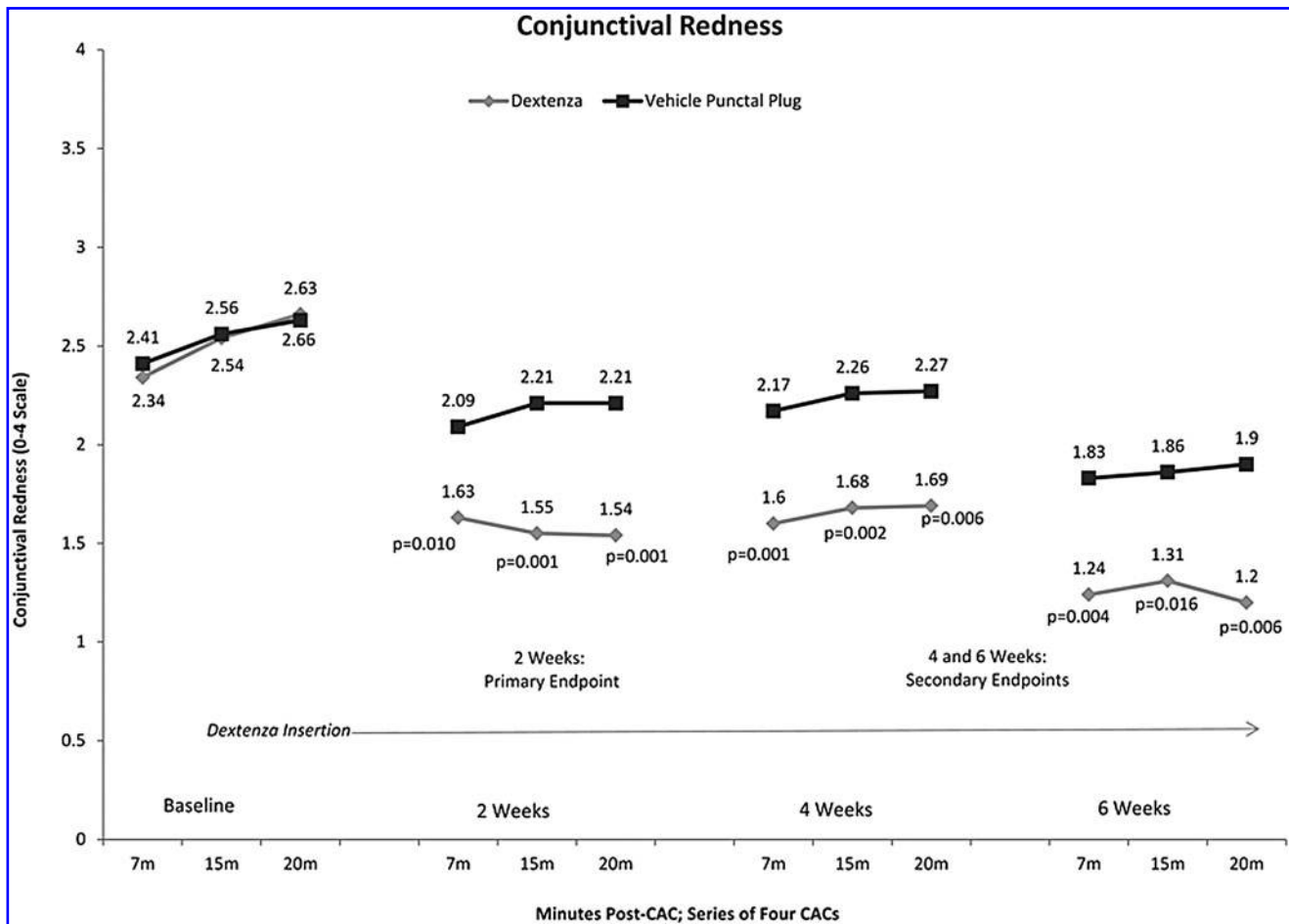


FIG. 3. Conjunctival Redness. The efficacy of Dextenza (resorbable hydrogel intracanalicular insert containing approximately 0.4 mg of dexamethasone) ($N=35$) versus a vehicle insert ($N=33$) over a 6-week treatment period against conjunctival redness induced by a modified CAC model of chronic allergic conjunctivitis (ANCOVA P -values illustrated).

antihistamine, to provide treatment for itching and inflammation,^{13,14} yet research has indicated that patients may be less compliant when prescribed multiple medications for allergic disease.²¹

This study was designed to augment existing data regarding the safety and efficacy of Dextenza with subjects who had both seasonal and perennial allergies, as these subjects were most likely to have chronic and recalcitrant signs and symptoms. This population of chronic allergic conjunctivitis sufferers also may not respond sufficiently or at all to topical antihistamines or dual-acting agents, thus a safe corticosteroid option would be an appropriate avenue for secondary therapy.²²

In susceptible individuals, a 4–6 week course of topical corticosteroid therapy can result in the well-known adverse effect of elevated IOP. These potential side effects are minimized with a decremental drug delivery method such as Dextenza, since the release of a minimally effective dose is guaranteed, and periodic visits to the physician are necessary for reinsertion of the Dextenza insert. Furthermore, by removing topical corticosteroid from the hands of patients, there is no potential for abuse, particularly in the case of patients who often are able to refill their prescriptions, and might continue to administer steroid drops for months on a PRN basis to treat perceived allergic signs. This type of abuse

could lead to the permanent adverse effects of steroids such as cataract formation and glaucoma.

While primary efficacy defined as clinical significance with a 1-U grade difference in itching and redness between active and vehicle groups was not met, the results of this study did demonstrate statistically significant improvements in favor of this novel delivery system of dexamethasone. Highly statistically significant improvements in allergic inflammation were demonstrated at 2, 4, and 6 weeks from drug insertion. This 6-week duration of action is uniquely advantageous for ocular allergy therapy, as such an extended duration fulfills both an unmet need (over topical once-daily therapies), and is able to cover a complete allergy season.

The *post hoc* analysis of responder rates has provided a greater understanding about the heterogeneous nature of steroid activity in a given population. A statistically significantly higher number of subjects responded to Dextenza treatment with little to no itching after allergen challenge: from 26% to 37% of Dextenza-treated subjects had minimal itch after challenge at Weeks 2 and 4, compared with 0%–6.5% in the vehicle group, a 5–8-fold higher frequency. Identifying responder rates with this experimental endpoint has provided additional valuable information about the drug, and will be added to future modified CAC studies of

TABLE 3. OCULAR ITCHING AND CONJUNCTIVAL REDNESS IN A MODIFIED CONJUNCTIVAL ALLERGEN CHALLENGE STUDY OF THE SAFETY AND EFFICACY OF A 6-WEEK TREATMENT WITH A SUSTAINED-RELEASE DEXAMETHASONE INSERT (DEXTENZA) COMPARED WITH A PLACEBO VEHICLE INSERT IN ELIGIBLE SUBJECTS WITH A HISTORY OF BOTH SEASONAL AND PERENNIAL ALLERGIC CONJUNCTIVITIS

<i>Itching minutes post-CAC/ redness minutes post-CAC</i>		<i>Number of subjects itching ≤1</i>	<i>Number of subjects conjunctival redness ≤1</i>
	<i>N</i>	<i>n (%) P-value</i>	<i>n (%) P-value</i>
Week 2, day 14 of treatment			
3 min/7 min			
Dextenza	28	8 (28.6%) <i>P</i> =0.0098*	4 (14.3%) <i>P</i> =0.6978
Vehicle Plug	31	1 (3.2%)	3 (9.7%)
5 min/15 min			
Dextenza	28	10 (35.7%) <i>P</i> =0.0083*	7 (25.0%) <i>P</i> =0.0215*
Vehicle Plug	31	2 (6.5%)	1 (3.2%)
7 min/20 min			
Dextenza	28	10 (35.7%) <i>P</i> =0.0083*	7 (25.0%) <i>P</i> =0.0215*
Vehicle Plug	31	2 (6.5%)	1 (3.2%)
Week 4, day 28 of treatment			
3 min/7 min			
Dextenza	28	7 (25.9%) <i>P</i> =0.0227*	10 (37.0%) <i>P</i> =0.0020*
Vehicle Plug	31	1 (3.4%)	1 (3.4%)
5 min/15 min			
Dextenza	28	8 (29.6%) <i>P</i> =0.0104*	8 (29.6%) <i>P</i> =0.0104*
Vehicle Plug	31	1 (3.4%)	1 (3.4%)
7 min/20 min			
Dextenza	28	10 (37.0%) <i>P</i> =0.0002*	8 (29.6%) <i>P</i> =0.0104*
Vehicle Plug	31	0	1 (3.4%)
Week 6, day 42 of treatment			
3 min/7 min			
Dextenza	28	7 (33.3%) <i>P</i> =0.0805*	12 (57.1%) <i>P</i> =0.0046*
Vehicle Plug	31	3 (11.1%)	4 (14.8%)
5 min/15 min			
Dextenza	28	9 (42.9%) <i>P</i> =0.0056*	11 (52.4%) <i>P</i> =0.0108*
Vehicle Plug	31	2 (7.4%)	4 (14.8%)
7 min/20 min			
Dextenza	28	10 (47.6%) <i>P</i> =0.0080*	12 (57.1%) <i>P</i> =0.0074*
Vehicle Plug	31	3 (11.1%)	5 (18.5%)

Subjects were challenged in 4 series of repeated CACs to simulate chronic AC. The number of high responders (defined as the number of subjects with a score of ≤1 at each post-CAC time point) was significantly greater in the Dextenza group than the vehicle group for all itching assessments and 8/9 redness assessments.

Pairwise comparisons of Dextenza to placebo vehicle: number of subjects with an itching or conjunctival redness score ≤1 calculated by Fisher's Exact test. Asterisk indicates statistical significance.

TABLE 4. OCULAR ALLERGIC SIGNS AND SYMPTOMS IN A MODIFIED CONJUNCTIVAL ALLERGEN CHALLENGE STUDY OF THE SAFETY AND EFFICACY OF A 6-WEEK TREATMENT WITH A SUSTAINED-RELEASE DEXAMETHASONE INSERT (DEXTENZA) COMPARED WITH A PLACEBO VEHICLE INSERT IN ELIGIBLE SUBJECTS WITH A HISTORY OF BOTH SEASONAL AND PERENNIAL ALLERGIC CONJUNCTIVITIS

<i>Endpoint</i>	<i>Visit 6 (14 days of treatment, primary endpoint visit)</i>	<i>Visit 9 (28 days of treatment)</i>	<i>Visit 12 (42 days of treatment)</i>
Ocular itching	-0.86 (0.0006)	-0.88 (<0.0001)	-0.67 (0.0118)
Conjunctival redness	-0.59 (0.0012)	-0.61 (0.0010)	-0.65 (0.0014)
Ciliary redness	-0.68 (0.0004)	-0.68 (0.0007)	-0.77 (<0.0001)
Episcleral redness	-0.63 (0.0003)	-0.71 (0.0013)	-0.69 (0.0004)
Chemosis	-0.24 (0.0135)	-0.21 (0.0461)	-0.39 (0.0082)
eyelid swelling	-0.23 (0.1627)	-0.32 (0.0457)	-0.35 (0.0980)
Tearing/watery eyes	-0.80 (<0.0001)	-0.53 (0.0063)	-0.49 (0.0211)
Rhinorrhea	-0.83 (0.0004)	-0.65 (0.0057)	-0.63 (0.0354)
Nasal pruritis	-0.57 (0.0102)	-0.22 (0.3824)	-0.26 (0.2222)
Ear/palate pruritis	-0.53 (0.0199)	-0.21 (0.3418)	-0.48 (0.1061)
Nasal congestion	-0.68 (0.0024)	-0.46 (0.0450)	-0.32 (0.2273)

Subjects were challenged in 4 series of repeated CACs to simulate chronic AC. Secondary efficacy improvements in postrepeat-CAC signs and symptoms of allergy in favor of Dextenza are presented [Repeated Measures ANCOVA model, including treatment, time point and baseline (time-appropriate Visit 3a post-CAC) score in the model: treatment differences (with corresponding p-values for active to vehicle comparisons)] after 14, 28, and 42 days of Dextenza or vehicle treatment. Bold *P* values are statistically significant.

TABLE 5. ADVERSE EVENT SUMMARY FROM A MODIFIED CONJUNCTIVAL ALLERGEN CHALLENGE STUDY OF THE SAFETY AND EFFICACY OF A 6-WEEK TREATMENT WITH A SUSTAINED-RELEASE DEXAMETHASONE INSERT (DEXTENZA) COMPARED WITH A PLACEBO VEHICLE INSERT IN ELIGIBLE SUBJECTS WITH A HISTORY OF BOTH SEASONAL AND PERENNIAL ALLERGIC CONJUNCTIVITIS

	Dextenza (N=31 ^a)	Vehicle (N=33)
Number of TEAEs	14	12
Number of subjects with at least one TEAE	11 (35.5%)	10 (30.3%)
Number of ocular TEAEs	10	10
Number of subjects with at least one ocular TEAE	9 (29.0%)	8 (24.2%)
Number of nonocular TEAEs	4	2
Number of subjects with at least one nonocular TEAE	2 (6.5%)	2 (6.1%)
Number of SAEs	1	0
Number of subjects with at least one SAE	1 (3.2%)	0
Number of treatment-related TEAEs	8	9
Number of subjects with at least one treatment-related TEAE	7 (22.6%)	7 (21.2%)
Number of subjects with TEAEs by severity		
Mild	6 (19.4%)	8 (24.2%)
Moderate	5 (16.1%)	2 (6.1%)
Number of subjects with TEAEs leading to subject withdrawal	1 (3.2%)	1 (3.0%)

Subjects were challenged in 4 series of repeated CACs to simulate chronic AC. Overall adverse events are presented in subjects treated with either Dextenza or a placebo vehicle insert for 6 weeks.

^aThe ITT population included all randomized subjects (Dextenza 35, Vehicle 33), although 4 of these did not receive Dextenza and were discontinued from the study. The number of subjects in the Safety population (31, above) reflects this discrepancy. The Per Protocol population reflects the actual number of subjects in each group who completed the study with no protocol violations.

TABLE 6. OCULAR ADVERSE EVENTS IN A MODIFIED CONJUNCTIVAL ALLERGEN CHALLENGE STUDY OF THE SAFETY AND EFFICACY OF A 6-WEEK TREATMENT WITH A SUSTAINED-RELEASE DEXAMETHASONE INSERT (DEXTENZA) COMPARED WITH A PLACEBO VEHICLE INSERT IN ELIGIBLE SUBJECTS WITH A HISTORY OF BOTH SEASONAL AND PERENNIAL ALLERGIC CONJUNCTIVITIS

	Dextenza		Vehicle	
	N=31 ^a		N=33	
	N	%	N	%
System organ class (SOC)				
Preferred term (PT)				
Total—Ocular TEAEs	9	29.0%	8	24.2%
Eye disorders	7	22.6%	8	24.2%
Eye discharge	1	3.2%	2	6.1%
Lacrimation increased	1	3.2%	2	6.1%
Erythema of eyelid	0	0	2	6.1%
Punctate keratitis	1	3.2%	1	3.0%
Visual acuity reduced	2	6.5%	0	0
Corneal opacity	0	0	1	3.0%
Dacryostenosis acquired	1	3.2%	0	0
Eye irritation	0	0	1	3.0%
Inflammation of lacrimal passage	0	0	1	3.0%
Lacrimal structural disorder	1	3.2%	0	0
Vision blurred	1	3.2%	0	0
Investigations	2	6.5%	0	0
Intraocular pressure increased	2	6.5%	0	0

Subjects were challenged in 4 series of repeated CACs to simulate chronic AC. Ocular treatment-emergent adverse events (TEAEs) are presented in subjects treated with either Dextenza or a placebo vehicle insert for 6 weeks.

^aThe ITT population included all randomized subjects (Dextenza 35, Vehicle 33), although 4 of these did not receive Dextenza and were discontinued from the study. The number of subjects in the Safety population (31, above) reflects this discrepancy. The Per Protocol population reflects the actual number of subjects in each group who completed the study with no protocol violations.

anti-inflammatory drugs as an *a priori* analysis that defines potential subgroups of greater drug effectiveness.

Heterogeneity in response to steroid occurs with regard to IOP effects,²³ and efficacy outcomes might also diverge into high and low responders. This heterogeneity has been identified in other immunologic diseases such as eosinophilic esophagitis²⁴ and systemic lupus erythematosus.²⁵ The results at Week 6 were still significant but less concise, as both vehicle and active groups had less itching at this visit, possibly due to allergen desensitization after multiple challenges. Interestingly, this dampening of the conjunctival mucosal challenge response (ie, less increase in itching/redness scores with repeat CACs compared with the initial baseline CAC response) occurred to a greater extent in the vehicle group than in the active group (Figs. 2 and 3). How steroid use might have dampened allergic desensitization is unknown, has also been observed in association with sublingual immunotherapy in children,²⁶ and should be further explored.

Dextenza has previously been tested and shown to be safe and effective for the treatment of postoperative pain in 325 cataract surgery patients.²⁷

In the present study, adverse event rates in both groups were similar; however 2 subjects receiving Dextenza exhibited an elevated IOP after insert administration. IOP returned to normal for both subjects between 2 and 20 days later. While this incidence (6.55%) is still lower than others found in the literature with chronic use of topical corticosteroid (9.68%,²⁸ 8%²⁹), clinicians should be mindful of this side effect, and potentially exclude from use subjects with a history of steroid-induced ocular hypertension or advanced glaucoma. IOP elevation with short term topical steroid therapy is thought to occur in as much as 18%–36% of the general population.³⁰ IOP generally rises after 2–4 weeks of therapy and usually returns to pretreatment levels within 1–3 weeks of discontinuation.³¹

One weakness of the present study is the exclusion of seasonal allergens from the challenge protocol. However, we

specifically selected subjects with chronic allergies who had a history of allergies to both seasonal and perennial allergens. Furthermore, while this model was designed to closely approximate the natural chronic allergy paradigm, efficacy in the environment can only be inferred due to the 6-week length of the study.

A sustained-release dexamethasone insert has been shown to improve allergic signs and symptoms for 6 weeks, a duration that would be ideal for perennial allergen sufferers such as mite- and dander-allergic subjects. Improvement across all findings showed a widespread drug-induced attenuation of the chronic allergic/inflammatory reaction. This 6-week duration would be beneficial to seasonal subjects as well. Phase 3 development of this drug is ongoing.

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Author Disclosure Statement

Gail Torkildsen was a principal investigator for this trial, and as such, was paid for her participation in this clinical trial by Ora, Inc., and Ocular Therapeutix. She also contributed to the data interpretation and the writing of the article. There were no other relevant conflicts of interest in the 36 months before publication of this article. No patents, planned, pending, or issued, are relevant to this work. No other relationship/conditions or circumstances present a potential conflict of interest.

Mark Abelson is the Founder and Chief Scientific Officer of Ora, Inc., which was paid by Ocular Therapeutix to manage this clinical trial. Ora, Inc. has received or is receiving financial consideration in connection with certain ocular allergy therapeutics. Dr. Abelson has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the article, apart from those disclosed.

Paul Gomes is an employee of Ora, Inc. He has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the article apart from those disclosed.

Eugene McLaurin was a principal investigator for this trial, contributed to the data interpretation and the writing of the article, and was paid for his participation in this clinical trial by Ora, Inc., and Ocular Therapeutix. Dr. McLaurin has been a principal investigator in clinical trials for the following pharmaceutical companies within the last 36 months: Aciex Pharmaceuticals, Aerie Pharmaceuticals, Alcon Research, Ltd., Allergan, Bausch & Lomb, Foresight Vision5, Eleven Biotherapeutics, Inc., Encore Vision, Inotek Pharmaceuticals, Corp., INsite Vision, Inc., Lexitas Pharmaceuticals, Mati Therapeutics, Mimetogen Pharmaceuticals, USA, Inc., Oculeve, Inc., Sanofi, Seikagaku Corp, Xigen SA. Dr. McLaurin has no other relevant conflicts of interest in the 36 months before publication of this article. No patents, planned, pending, or issued, are relevant to this work. No other relationship/conditions or circumstances present a potential conflict of interest.

Francis Mah was a paid consultant to Ocular Therapeutix to be the Medical Monitor and to offer clinical expertise in

the execution and safety of the clinical trial, as well as data interpretation and the writing of the article. Dr. Mah is also a speaker and consultant for Alcon, Allergan, and Bausch & Lomb. Dr. Mah has no other relevant conflicts of interest in the 36 months before publication of this article. No patents, planned, pending, or issued, are relevant to this work. No other relationship/conditions or circumstances present a potential conflict of interest.

Susan L. Potts is Senior Principal Biostatistician of the Statistics and Data Corporation (SDC), in Tempe Arizona. This firm was paid by Ocular Therapeutix to develop the statistical analysis plan, data management plan, and analysis of the trial results. Ms. Potts has no other relevant conflicts of interest in the 36 months before publication of this article. No patents, planned, pending, or issued, are relevant to this work. No other relationship/conditions or circumstances present a potential conflict of interest.

References

1. Singh, K., Axelrod, S., and Bielory, L. The epidemiology of ocular and nasal allergy in the United States, 1988–1994. *J. Allergy Clin. Immunol.* 126:778–783, 2010.
2. Bjorksten, B., Clayton, T., Ellwood, P., et al. Worldwide time trends for symptoms of rhinitis and conjunctivitis: phase III of the International Study of Asthma and Allergies in Childhood. *Pediatr. Allergy Immunol.* 19:110–124, 2008.
3. Butrus, S., and Portela, R. Ocular allergy: diagnosis and treatment. *Ophthalmol. Clin. North Am.* 18:485–492, 2005.
4. Abelson, M.B., Chambers, W., and Smith, L.M. Conjunctival allergen challenge. *Arch. Ophthalmol.* 108:84–88, 1990.
5. Abelson, M.B., and Loeffler, O. Conjunctival allergen challenge: models in the investigation of ocular allergy. *Curr. Allergy Asthma Rep.* 3:363–368, 2003.
6. Walters, T., Endl, M., Elmer, T.R., Levenson, J., Majumdar, P., and Masket, S. Sustained-release dexamethasone for the treatment of ocular inflammation and pain after cataract surgery. *J. Cataract. Refract. Surg.* 41:2049–2059, 2015.
7. Leonardi, A., Papa, V., Milazzo, G., et al. Efficacy and safety of desonide phosphate for the treatment of allergic conjunctivitis. *Cornea.* 21:476–481, 2002.
8. Abelson, M., Howes, J., and George, M. The conjunctival provocation test model of ocular allergy: utility for assessment of an ocular corticosteroid, loteprednol etabonate. *J. Ocul. Pharmacol. Ther.* 21998;14:533–544.
9. Goldstein, M.H., Tubridy, K.L., Agahigian, J., et al. A Phase 2 exploratory study of a novel interleukin-1 receptor inhibitor (EBI-005) in the treatment of moderate-to-severe allergic conjunctivitis. *Eye Contact Len.* 41:145–155, 2015.
10. Gomes, P., Slocum, C., Smith, L.M., and Abelson, M.B. Challenges faced in clinical trials for chronic allergic conjunctivitis. *Exp. Rev. Ophthalmol.* 2015 [Epub ahead of print]; DOI: 10.1586/17469899.2015.1081563.
11. Dell, S.J., Shulman, D.G., Lowry, G.M., et al. A controlled evaluation of the efficacy and safety of loteprednol etabonate in the prophylactic treatment of seasonal allergic conjunctivitis. Loteprednol Allergic Conjunctivitis Study. *Am. J. Ophthalmol.* 123:791–797, 1997.
12. Shulman, D.G., Lothringer, L.L., Rubin, J.M., et al. A randomized, double-masked, placebo-controlled parallel study of loteprednol etabonate 0.2% in patients with seasonal allergic conjunctivitis. *Ophthalmology.* 106:362–369, 1999.
13. Celik, T., and Turkoglu, E.B. Comparative evaluation of olopatadine 0.1% combined fluorometholone 0.1% treatment versus olopatadine 0.1% combined ketorolac 0.4% treatment

- in patients with acute seasonal allergic conjunctivitis. *Curr. Eye Res.* 39:42–46, 2014.
14. Gong, L., Sun, X., Qu, J., et al. Loteprednol etabonate suspension 0.2% administered QID compared with olopatadine solution 0.1% administered BID in the treatment of seasonal allergic conjunctivitis: a multicenter, randomized, investigator-masked, parallel group study in Chinese patients. *Clin. Ther.* 34:1259–1272, 2012.
 15. Zwiwei, L., Mu, G., Chen, W., et al. Comparative evaluation of topical pranoprofen and fluorometholone in cases with chronic allergic conjunctivitis. *Cornea.* 32:579–582, 2013.
 16. Mantelli, F., Calder, V.L., and Bonini, S. The anti-inflammatory effects of therapies for ocular allergy. *J. Ocul. Pharmacol. Ther.* 29:786–793, 2013.
 17. Awan, M.A., Agarwal, P.K., Watson, D.G., McGhee, C.N., and Dutton, G.N. Penetration of topical and subconjunctival corticosteroids into human aqueous humour and its therapeutic significance. *Br. J. Ophthalmol.* 93: 708–713, 2009.
 18. Watson, D., Noble, M.J., Dutton, G.N., Midgley, J.M., and Healey, T.M. Penetration of topically applied dexamethasone alcohol into human aqueous humor. *Arch. Ophthalmol.* 106: 686–687, 1988.
 19. McGhee, C.N., Watson, D.G., Midgley, J.M., Noble, M.J., Dutton, G.N., and Fern, A.I. Penetration of synthetic corticosteroids into human aqueous humour. *Eye.* 4: 526–530, 1990.
 20. Weijtens, O., Schoemaker, R.C., Romijn, F.P., Cohen, A.F., Lentjes, E.G., and van Meurs, J.C. Intraocular penetration and systemic absorption after topical application of dexamethasone disodium phosphate. *Ophthalmology.* 109: 1887–1891, 2002.
 21. O'Brien, T.P. Allergic conjunctivitis: an update in diagnosis and management. *Curr. Opin. Allergy Clin. Immunol.* 13:543–549, 2013.
 22. Spangler, D.L., Abelson, M.B., Ober, A., et al. Randomized, double-masked comparison of Olopatadine ophthalmic solution, mometasone furoate monohydrate nasal spray, and fexofenadine hydrochloride tablets using the conjunctival and nasal allergen challenge models. *Clin. Ther.* 25:2245–2267, 2003.
 23. Pleyer, U., Ursell, P.G., and Rama, P. Intraocular pressure effects of common topical steroids for post-cataract inflammation: are they all the same? *Ophthalmol. Ther.* 2:55–72, 2013.
 24. Albert, D., Heifert, T.A., Min, S.B., et al. Comparisons of fluticasone to budesonide in the treatment of eosinophilic esophagitis. *Dig. Dis. Sci.* 61:1996–2001, 2016.
 25. Melo, A.K.G., Melo, M.R., Saramago, A.B.A., Demartino, G., Souza, B.D.B., and Longui, C.A. Persistent glucocorticoid resistance in systemic lupus erythematosus patients during clinical remission. *Gen. Mol. Res.* 12:2010–2019, 2013.
 26. Majak, P., Rychlik, B., and Stelmach, I. The effect of oral steroids with and without vitamin D₃ on early efficacy of immunotherapy in asthmatic children. *Clin. Exp. Allergy.* 39: 1830–1841, 2009.
 27. Walters, T., Bafna, S., Vold, S., et al. Efficacy and safety of sustained release dexamethasone for the treatment of ocular pain and inflammation after cataract surgery: results from two Phase 3 studies. *J. Clin. Exp. Ophthalmol.* 7:1000572, 2016.
 28. Makornwattana, M., and Suphachearaphan, W. Incidence of steroid induced-ocular hypertension in postoperative pterygium excision. *J. Med. Assoc. Thai.* 98(Suppl 2):S151–S157, 2016.
 29. Maier, A.K., Wolf, T., Gundlach, E., et al. Intraocular pressure elevation and post-DMEK glaucoma following Descemet membrane endothelial keratoplasty. *Graefes Arch. Clin. Exp. Ophthalmol.* 252:1947–1954, 2014.
 30. Tripathi, R.C., Parapuram, S.K., Tripathi, B.J., et al. Corticosteroids and glaucoma risk. *Drugs Aging.* 15:439–450, 1999.
 31. Bartlett, J.D., Woolley, T.W., and Adams, C.M. Identification of high intraocular pressure responders to topical ophthalmic corticosteroids. *J. Ocul. Pharmacol.* 9:35–45, 1993.

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