CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208742Orig1s000

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 208-742
Class 2 Resubmission

NDA 208-742 SDN-45	Submission Date: 6/28/18 Received Date: 6/28/18 Review Date: 10/3/18
Applicant:	Ocular Therapeutixs, Inc. 15 Crosby Drive Bedford, MA 01730 Contact: Nicole Oliynyk 781-357-4056
Drug:	DEXTENZA (dexamethasone ophthalmic insert) 0.4mg, for intracanalicular use
Pharmacologic Category:	steroid
Dosage Form and Route of Administration:	ophthalmic insert (punctal plug) for intracanalicular use

Submitted:
Submitted is the second resubmission of NDA 208-742, DEXTENZA (dexamethasone ophthalmic insert) 0.4mg, for intracanalicular use.

Ocular Therapeutix considers this resubmission to be a complete response to the deficiencies outlined in the July 10, 2017, CR letter. The applicant believes that the deficiency identified in the CR regarding the good manufacturing practice (GMP) status of the drug substance manufacturer has been rectified. Included in this submission is a resubmission of a proprietary name review, updated labeling, and a safety update.

Reviewer's Comments:
No new information was identified in the safety update provided in the 6/28/18 submission. From a clinical perspective, our conclusion on the safety and efficacy of DEXTENZA for the treatment of ocular pain occurring after ophthalmic surgery is unchanged. See original Clinical review dated 7/7/16 in DARRTS. Attached is the applicant's labeling submitted on 11/20/18.

Conclusion/Recommended Regulatory Action:
NDA 208-742 is recommended for approval from a clinical perspective with the labeling identified in this review, pending resolution of any remaining CMC or facility issues.

Sonal D. Wadhwa, MD
Medical Officer

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SONAL D WADHWA
11/26/2018

WILLIAM M BOYD
11/27/2018

Medical Officer's Review of NDA 208-742
Resubmission

NDA 208-742 **Resubmission**	Submission Date: 1/19/17 Received Date: 1/19/17
SDN-33 through SDN-38	Review Date: June 26, 2017
Applicant:	Ocular Therapeutixs, Inc. 15 Crosby Drive Bedford, MA 01730 Contact: Eric P. Ankerud, JD 781-357-4013
Drug:	DEXTENZA (dexamethasone ophthalmic insert)
Pharmacologic Category:	steroid
Dosage Form and Route of Administration:	punctal plug for intracanalicular insert

Submitted:
Submitted is a resubmission of NDA 208-742 DEXTENZA (dexamethasone ophthalmic insert) 0.4mg, for intracanalicular use. The original NDA was submitted on 9/25/15. A Complete Response (CR) letter dated July 19, 2016 was issued. Four amendments to the resubmission were submitted on the following dates: 2/28/17 (SDN-35), 3/15/17 (SDN-36), 3/22/17 (SDN-37), and 6/21/17 (SDN-38). Applicant now believes that the deficiency identified in the CR regarding the good manufacturing practice (GMP) status of the drug substance manufacturer has been rectified. Included in this submission is a resubmission of a proprietary name review and a safety update.

Reviewer's Comments:
No new information was identified in the safety update provided in the January 19, 2017, submission. From a clinical perspective, our conclusion on the safety and efficacy of DEXTENZA for the treatment of ocular pain occurring after ophthalmic surgery is unchanged. See original Clinical review dated 7/7/16 in DARRTS. Attached is the Agency's recommended draft labeling with its edits to the applicant's labeling submitted on May 17, 2017. Carton/container labeling should be updated with revisions to product name c/w the attached PI.

Conclusion/Recommended Regulatory Action:
NDA 208-742 is recommended for approval from a clinical perspective with the labeling identified in this review, pending resolution of any remaining CMC or facility issues.

Sonal D. Wadhwa, MD
Medical Officer

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SONAL D WADHWA
07/06/2017

WILLIAM M BOYD
07/06/2017

CLINICAL REVIEW of NDA 208-742

Application Type	Original Application
Letter Date	9/24/15
Stamp Date	9/24/15
PDUFA Goal Date	7/24/16
Reviewer Name	Sonal D. Wadhwa, MD
Review Completion Date	4/29/16
Established Name	dexamethasone insert
(Proposed) Trade Name	Dextenza Intracanalicular Depot, 0.4 mg
Therapeutic Class	corticosteroid
Applicant	Ocular Therapeutixs
Priority Designation	S
Formulation	Intracanalicular insert
Dosing Regimen	One unit placed into the canaliculus following the conclusion of cataract surgery
Indication	Treatment of pain associated with (b) (4) surgery
Intended Population	Patients with ocular pain after (b) (4) surgery

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 208-742 is recommended for approval with the revised labeling identified in this review. The clinical studies contained in this submission support the use of Dextenza for treatment of ocular pain associated with ophthalmic surgery. This is a 505(b)(2) application which references NDA 13-422 Maxidex (dexamethasone ophthalmic suspension) 0.1% and NDA 11-984 Decadron (dexamethasone sodium phosphate ophthalmic solution) Sterile Ophthalmic Solution.

1.2 Risk Benefit Assessment

The benefits of using this drug product outweigh the risks for the above indication.

1.3 Recommendations for Post-Marketing Risk Management Activities

There are no proposed risk management actions except the usual post-marketing collection and reporting of adverse experiences associated with the use of drug product.

1.4 Recommendations for other Post-Marketing Study Commitments

There are no recommended Phase 4 clinical study commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Dextenza Intracanalicular Depot (dexamethasone insert) 0.4mg is a single administration, sterile dosage form. The Dextenza drug product consists of (b) (4) dexamethasone and a 4-arm polyethylene glycol (PEG) glutarate-trilysine hydrogel conjugated with fluorescein. Dextenza is (b) (4). The single solid dose form is placed in a foam insert, (b) (4) within a (b) (4) foil pouch (b) (4). Dextenza is (b) (4) sterilized (b) (4). The finished product is stored under refrigerated conditions between 2°-8°C.

Throughout this review, Dextenza Intracanalicular Depot (dexamethasone insert) 0.4mg is also referred to as OTX-DP.

2.2 Table of Currently Available Treatments for Proposed Indication

NDA	Drug	Indication
22-212	Difluprednate ophthalmic emulsion 0.05% (Durezol)	DUREZOL is a topical corticosteroid that is indicated for the treatment of inflammation and pain associated with ocular surgery. DUREZOL is also indicated for the treatment of endogenous anterior uveitis.
202-872	Loteprednol etabonate ophthalmic gel 0.5% (Lotemax)	LOTEMAX is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.
203-168	Bromfenac ophthalmic solution 0.07% (Prolensa)	PROLENSA is a NSAID indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.
21-664	Bromfenac sodium ophthalmic solution 0.09% (Xibrom)	XIBROM is a NSAID indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.
21-664 201-211 202-030 203-395	Bromfenac sodium ophthalmic solution 0.09% (Bromday)	BROMDAY is a NSAID indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.
21-862	Nepafenac ophthalmic suspension 0.1% (Nevanac)	NEVANAC ophthalmic suspension is a NSAID indicated for the treatment of pain and inflammation associated with cataract surgery.
203-491	Nepafenac ophthalmic suspension 0.3% (Ilevro)	ILEVRO (nepafenac ophthalmic suspension), 0.3% is a NSAID indicated for the treatment of pain and inflammation associated with cataract surgery.
22-427	Ketorolac tromethamine ophthalmic solution 0.45% (Acuvail)	ACUVAIL ophthalmic solution is a NSAID indicated for the treatment of pain and inflammation following cataract surgery.
20-037	Diclofenac sodium ophthalmic solution 0.1% (Voltaren Ophthalmic)	VOLTAREN ophthalmic is indicated for the treatment of post-operative inflammation in patients who have undergone cataract extraction and for the temporary relief of pain and photophobia in patients undergoing corneal refractive surgery.
206-911	BromSite (bromfenac ophthalmic solution) 0.075%	Treatment of post-operative inflammation and prevention of ocular pain in patients undergoing cataract surgery

2.3 Availability of Proposed Active Ingredient in the United States

FDA-Approved Ophthalmic Dexamethasone Products

NDA	Drug	Sponsor, Date Approved
NDA 13-422	Maxidex (dexamethasone ophthalmic suspension) 0.1%	Alcon, 1962
NDA 50-023	Maxitrol (dexamethasone 0.1%/neomycin 0.35%/polymyxin B sulfate 10,000 IU ophthalmic suspension)	Alcon Labs, 1963
NDA 50-065	Maxitrol (dexamethasone 0.1%/neomycin 3.5 gm/polymyxin B sulfate 10,000 IU ophthalmic ointment)	Alcon Labs,1963
ANDA 62-341	Dexamethasone 0.1%/neomycin 0.35%/polymyxin Bsulfate 10,000 IU ophthalmic suspension	Alcon, 1984
NDA 50-592 NDA 50-616	Tobradex (dexamethasone/tobramycin ophthalmic suspension) 0.1%/0.3% Tobradex (dexamethasone/tobramycin ophthalmic ointment) 0.1%/0.3%	Alcon, 1988
NDA 50-818	Tobradex ST (dexamethasone/tobramycin ophthalmic suspension) 0.3%/0.05%	Alcon, 2009
NDA 22-315	Ozurdex (dexamethasone intravitreal implant) 0.7mg	Allergan, 2014

2.4 Important Safety Issues with Consideration to Related Drugs

Dexamethasone is a corticosteroid. Ocular AEs generally associated with ophthalmic steroids include elevated IOP (which may be associated with optic nerve damage and visual acuity and field defects), posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Other reactions include acute anterior uveitis, systemic hypercorticoidism, keratitis, conjunctivitis, corneal ulcers, mydriasis, conjunctival hyperemia, loss of accommodation, and ptosis.

2.5 Summary of Pre-Submission Regulatory Activity Related to Submission

5/16/12 PIND 114720 Meeting
9/13/13 EOP2 Meeting
2/11/14 Type C Meeting
8/26/14 pre-NDA CMC Meeting
12/12/14 EOP 2 Meeting (For allergic conjunctivitis indication)
4/14/15 pre-NDA Meeting

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

DSI was consulted for routine inspections. The clinical sites of Drs. Walters, Levenson, and Silverstein were inspected in support of this NDA. None of these sites were issued a Form FDA 483. The final classification of each of these inspections was No Action Indicated (NAI). The studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

Name of CI/ Site #	Protocol #, # of Subjects enrolled	Inspection Dates	Final Classification
Site 01 Thomas Walters Austin, TX 78731	OTX-13-002 38 subjects	1/11-15/2016	NAI
Site 02 Jeffrey Levenson Jacksonville, FL 32204	OTX-13-002 33 subjects	12/14 -16/2015	NAI
Site 04 Bruce Silverstein Redding, CA 96002	OTX-14-003 48 subjects	2/22-25/3026	NAI

3.2 Compliance with Good Clinical Practices

There is no evidence to suggest that the clinical trials were not conducted in compliance with good clinical practices.

3.3 Financial Disclosures

See Financial Disclosure template found in Appendix #1.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Dextenza (sustained release dexamethasone) 0.4 mg Intracanalicular Depot consists of (b) (4) the active ingredient, dexamethasone; and a known polyethylene glycol hydrogel conjugated with fluorescein (b) (4) . Dextenza intracanalicular depot is inserted into the inferior punctum, where it is retained in the vertical canaliculus for tapered release of dexamethasone for up to 30 days. Over this time and through hydrolysis, the hydrogel drug product softens, liquefies, and clears through the nasolacrimal duct.

4.2 Clinical Microbiology

This product is not an anti-infective.

4.3 Preclinical Pharmacology/Toxicology

This is a 505(b)(2) application which references NDA 13-422 Maxidex (dexamethasone ophthalmic suspension) 0.1% and NDA 11-984 Decadron (dexamethasone sodium phosphate ophthalmic solution) Sterile Ophthalmic Solution.

No significant safety issues have been identified in the Pharm/Tox review. See Pharm/Tox review for full details.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Corticosteroids, such as dexamethasone, suppress inflammation by inhibiting edema, fibrin deposition, capillary dilation, and phagocytic migration of the acute inflammatory response.

4.4.2 Pharmacodynamics

No human pharmacodynamic or drug-drug interaction studies were conducted.

4.4.3 Pharmacokinetics

One clinical study (OTX-14-009) was conducted in healthy volunteers to evaluate the systemic exposure to dexamethasone from DEXTENZA. The study was conducted in 16 healthy volunteers with a mean age of 31.7 years (range: 19 to 55 years) who received DEXTENZA for up to 28 days. Plasma samples were collected on Day 1 (1 hour pre-insertion, and 1, 2, 4, 8, and 16 hours post insertion), Day 2 (24 hours post-insertion), and Days 4, 8, 15, 22, and 29.

Plasma concentrations were below the lower limit of quantitation (LLOQ = 0.05 ng/mL) at all time-points in five of the 16 subjects. Additionally, plasma concentrations were below LLOQ at the Day 15, 22 and 29 Visits in the remaining subjects. Plasma dexamethasone concentrations from only 11% of samples (21 of 190) were above the LLOQ, ranging from 0.05 ng/mL to 0.81 ng/mL. Plasma dexamethasone pharmacokinetics did not appear to be related to age, gender, or body weight of subjects.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Study	Design	Study Control and Drugs	Number of Subjects by Arm Completed Study	Diagnosis/Inclusion Criteria	Primary Endpoint
OTX-12-002 (Phase 2)	Prospective, randomized, double-masked, vehicle-controlled, parallel group	OTX-DP (dexamethasone implant) 0.4 mg PVPP (no drug punctum plug)	OTX-DP: 28 PVPP: 29	≥ 21 years who underwent cataract surgery with implantation of an IOL	Absence of anterior chamber cells on Day 8 Absence of ocular pain on Day 8
OTX-13-002 (First Phase 3 Study)	Prospective, randomized, double-masked, vehicle-controlled, parallel group	OTX-DP (dexamethasone implant) 0.4 mg PVPP (no drug punctum plug)	OTX-DP: 163 PVPP: 81	≥ 18 years who underwent cataract surgery with implantation of an IOL	Absence of anterior chamber cells on Day 14 Absence of ocular pain on Day 8
OTX-14-003 (Second Phase 3 Study	Prospective, randomized, double-masked, vehicle-controlled, parallel group	OTX-DP (dexamethasone implant) 0.4 mg PVPP (no drug punctum plug)	OTX-DP: 159 PVPP: 76	≥ 18 years who underwent cataract surgery with implantation of an IOL	Absence of anterior chamber cells on Day 14 Absence of ocular pain on Day 8

5.2 Review Strategy

The sources of clinical data utilized in this review include the studies listed in Section 5.1.

5.3 Discussion of Individual Studies

Study OTX-12-002

OTX-12-002 was a prospective, multicenter, randomized, parallel-arm, double-masked, vehicle controlled phase 2 study evaluating the safety and efficacy of OTX-DP for the treatment of ocular inflammation and pain after cataract surgery. The primary endpoints in OTX-12-002 were the proportion of subjects with an absence of cells (i.e. score of "0") in the anterior chamber of the study eye at Day 8, and the proportion of subjects with an absence of pain (i.e. score of "0") in the study eye at Day 8.

Study OTX-13-002

The objective of the study was to evaluate the safety and efficacy of OTX-DP as a sustained release drug (dexamethasone) depot when placed in the canaliculus of the eyelid for the treatment of ocular inflammation and pain in subjects who had undergone cataract extraction with intraocular lens implantation.

This was a prospective, multicenter, randomized, parallel-arm, double-masked, vehicle-controlled study to evaluate the safety and efficacy of OTX-DP compared to PVPP for the treatment of ocular inflammation and pain in subjects who underwent ophthalmic surgery. A total of 240 subjects who had undergone cataract extraction with intraocular lens implantation were to be enrolled to evaluate the safety and efficacy of OTX-DP for the treatment of ocular inflammation and pain following cataract extraction surgery. Subjects enrolled in the study were to be randomized (2:1) to receive either OTX-DP or PVPP. The test or control article was to be inserted into the inferior vertical canaliculus of the operated eye, within minutes following the completion of cataract surgery.

Subjects were to undergo follow-up visits at post-operative Days 2, 4, 8, 14, 30, and 60. If at any visit prior to the Day 60 Visit the test or control article was no longer present in the canaliculus, the subject was to return one week later for their last follow-up visit, and if the test or control article was confirmed to be no longer present, the subject was to be exited from the study at the conclusion of that visit. If the test or control article was confirmed to be no longer present using visual technique via slit lamp at the Day 60 Visit, subjects were to be exited at the completion of the Day 60 Visit. If intra-operative test or control article placement on Day 1 was not successful, subjects were to be exited with no additional required follow-up visits unless necessitated by an adverse event. If the test or control article was confirmed to be present at the Day 60 Visit, subjects were to return for a visit at Day 120 for the assessment of the presence of the test or control article using a patency check. If patency was confirmed, subjects were to be exited from the study. If any resistance was observed during the patency check at the Day 120 Visit, subjects were to return for the assessment of the presence of the test or control article using a patency check every 30 (± 10) days until patency could be confirmed. At any time during the follow-up period, subjects may have been prescribed anti-inflammatory medication at the Investigator's discretion. Investigators were to consider prescribing anti-inflammatory medications for subjects returning for the Day 2 and later visits who exhibited >=Grade 2+ (>=16) anterior chamber cells, >=Grade 3+ (Marked: iris and lens details hazy) flare, and/or ≥ Grade 4 (moderate to severe) ocular pain.

The primary efficacy endpoints evaluated were:

- Absence of cells (ie. score of '0') in the anterior chamber of the study eye at Day 14

- Absence of pain (ie. score of '0') in the study eye at Day 8

The secondary efficacy endpoints evaluated were:

- Cells in the anterior chamber in the study eye at Days 2, 4, 8, and 30
- Flare in the anterior chamber in the study eye at Days 2, 4, 8, and 30
- Pain in the study eye at Days 2, 4, 14, and 30

The study was conducted at 16 sites in the USA.

The vehicle, PVPP, was the same fluorescent PEG hydrogel as OTX-DP, except that it lacked the active ingredient dexamethasone. The vehicle controlled study aided with treatment masking since the active and vehicle were identical in appearance.

Inclusion Criteria

- Had provided written informed consent, approved by the appropriate IRB; and were able to comply with study requirements and visit schedule
- Were 18 years of age or older
- Had a cataract and were expected to undergo clear corneal cataract surgery with phacoemulsification and implantation of a posterior chamber intraocular lens
- Had a potential post-operative pin-holed corrected Snellen VA of at least 20/200 or better in both eyes

Pre-Procedural Exclusion Criteria

- Any intraocular inflammation in the study eye present during the screening slit lamp examination
- Score greater than "0" on the Ocular Pain Assessment in the study eye at Screening
- Compromised immune system or an autoimmune disease that in the opinion of the Investigator could affect the quality of the ocular surface
- Active or chronic/recurrent ocular or systemic disease that was uncontrolled and would likely affect wound healing
- Currently had suspected or known malignancy or was currently receiving antineoplastic therapy
- Pregnant or breast-feeding women, women who wished to become pregnant during the length of study participation, or women of child-bearing potential (ie. those where were not post-menopausal or surgically sterile) who were not using adequate birth control
- Required use of non-diagnostic topical ophthalmic solution (other than prophylactic antibiotics or artificial tears for the management of dry eye) in the study eye for the duration of the study
- Used the following anti-inflammatory or immunomodulating agents (ie. cyclosporine) systemically, or in the study eye, for the duration of the study (excluding inhalants)
- Washout periods for medications prior to surgery were as follows:
    - Systemic corticosteroids – 2 weeks
    - Periocular injection of any corticosteroid solution – 4 weeks
    - Corticosteroid depot in the study eye – 2 months
    - Topical ocular corticosteroid – 7 days
    - Topical ocular NSAID – 7 days
    - Glaucoma or was on medications to treat glaucoma;

- Had ocular hypertension (IOP of ≥ 21 mmHg), was on medications to treat hypertension or had a history of IOP spikes in either eye including steroid-related IOP increases
- Congenital or ocular anomaly including ectropion, entropion, trichiasis, supernumerary puncta and anomalies of the punctum in the study eye
- Presence of nasolacrimal duct obstruction in the study eye based on assessment by the Investigator
- Active epiphora in the study eye
- Active or history of chronic or recurrent inflammatory eye disease (ie. iritis, scleritis, uveitis, iridocyclitis, rubeosis iritis) in the study eye
- Evidence of acute external ocular infections (bacterial, viral and/or fungal such as vaccinia, varicella, and other viral diseases of the cornea and conjunctiva); tuberculosis of the eye; corneal dystrophies; active corneal ulcers; intraocular infections, dysthyroid ophthalmopathy, active chalazion, or uncontrolled blepharitis in the study eye
- Current or history of herpes simplex keratitis;
- Clinically significant dry eye syndrome in the study eye
- Proliferative diabetic retinopathy (PDR), compromised macular function, significant macular disease, clinically significant macular edema (CSME), or history of cystoid macular edema in the study eye
- Corneal or retinal surgery or procedure (laser or incisional) within the past 6 months, or was planning to have laser or incisional surgery (except for study cataract surgery) or procedure during the study period in the study eye
- Planned to have corneal or retinal surgery of procedure (laser or incisional) in the fellow eye two weeks prior to the study procedure through the Day 14 Visit
- Previous ocular trauma with visible scarring or any deformities due to the trauma in the study eye
- Required the use of a contact lens or a collagen shield within 72 hours of treatment or during the study period in the study eye
- Known allergy or sensitivity to the investigational product or its components
- Previous enrollment in the clinical study, previous enrolment in an OTX-DP study, or would be participating in another clinical trial within 30 days prior to entry in this study or during the follow-up period that could confound the treatment or outcomes of this investigation
- The Investigator determined that the subject should not be included for reasons not already specified (ie. systemic or other ocular disease/abnormality) if the health of the subject or the validity of the study outcomes might be compromised by the subject's enrollment

Procedural Exclusion Criteria

- Required multiple procedures (ie. limbal relaxing incisions) during cataract surgery
- Had another intraoperative condition that in the opinion of the Investigator precluded further participation in the study (ie. subjects with intraoperative complications such as posterior capsule rupture, anterior vitrectomy, torn or ruptured zonules, phacoemulsification burns, or torn incisions)
- Punctum size was smaller than 0.4 mm or greater than or equal to 1.0 mm
- Unsuccessful dilation of the study eye (if needed) or the punctum was too small to allow transient dilation to 0.7 mm prior to insertion of the OTX-DP or PVPP

Test Article OTX-DP was provided to the Investigator as a (b) (4) sterilized dried intracanalicular depot, packaged in a (b) (4) foil pouch to maintain stability and sterility over time. OTX-DP was to be placed into the canaliculus by the Investigator following the conclusion of the cataract surgery.

Control Article PVPP, was the same fluorescent PEG hydrogel as OTX-DP, except that it did not contain the active ingredient. PVPP was to be placed into the canaliculus by the Investigator following the conclusion of the cataract surgery.

Table 9-2: Schedule of Assessments

	Screening	Surgery and Insertion of Test or Control Article	Follow-Up Assessments						
Study Parameter	**≤ 30 days prior to Surgery**	**Day 1**	**Day 2**	**Day 4** *(+1 day)*	**Day 8** *(± 1 days)*	**Day 14** *(± 2 days)*	**Day 30** *(± 2 days)*	**Day 60[1]** *(± 5 days)*	**Day 120** *(± 7 days)*
Obtain Informed Consent	X								
Medical/Ophthalmic History	X								
Concomitant Medications	X	X	X	X	X	X	X	X	X
Demographic Information	X								
Urine Pregnancy Test[2]	X								
Ocular Pain Assessment	X		X	X	X	X	X	X	
Visual Acuity Examination	X		X	X	X	X	X	X	
Slit Lamp Biomicroscopy[3]	X		X	X	X	X	X	X	
Punctum Examination	X		X	X	X	X	X	X	X
IOP Measurement	X		X	X	X	X	X	X	
Dilated Fundus Exam	X							X	
Test or Control Article Presence by Patency Check[4]			X	X	X	X	X	X	
Punctum Size Assessment		X							X
Randomization		X							
Test or Control Article Insertion		X							
Record Adverse Events		X	X	X	X	X	X	X	X

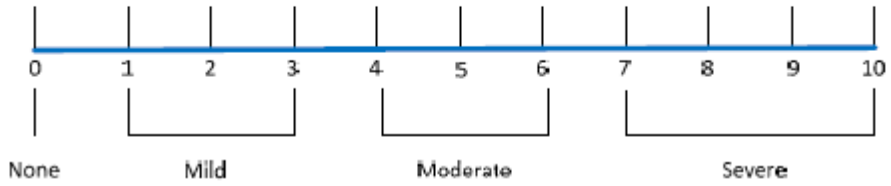
[1] These assessments were to occur on Day 60, or 7 days (± 2 days) after last visit in which the test or control article was not visualized at visits prior to Day 60.
[2] A negative urine pregnancy test was required for women with childbearing potential.
[3] Slit Lamp Biomicroscopy was to include anterior chamber cell count and flare.
[4] If any resistance was observed during the patency check at the Day 120 visit, the subject was to return for the assessment of the presence of the test or control article using a patency check every 30 (± 10) days until patency can be confirmed.

Ocular Pain Assessment
Ocular pain was to be assessed by the subject at the Screening Visit and at each follow-up visit, utilizing a numerical rating scale graded from 0 to 10. Subjects were to assess the level of pain they were experiencing in the operated (study) eye at the time of the assessment. At the Screening Visit, the subject was to be asked about the eye *scheduled* for surgery. The examiner was to provide the below chart to the subject. The examiner then verbally asked the following question to the subject, and asked the subject to mark their response on the chart:

What number would you give your pain right now?

The numeric rating scale could have been further explained or conceptualized in the following manner:

0 = No Pain
1-3 = Mild Pain (nagging, annoying, interfering little with Activities of Daily Living (ADLs))
4–6 = Moderate Pain (interferes significantly with ADLs)
7-10 = Severe Pain (disabling; unable to perform ADLs)



Anterior Chamber Cells and Flare

Anterior Chamber Cells

Grade	Number of Cells in Field
0	0
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50

Anterior Chamber Flare

Grade	Number of Cells in Field
0	None
1+	Faint
2+	Moderate: iris and lens details clear
3+	Marked: iris and lens details hazy
4+	Intense: fibrin or plastic aqueous

Primary Efficacy Analysis

The primary analysis was to first test the difference in the proportion of subjects with absence of anterior chamber cells in the study eye between treatments at Day 14 using the Pearson chi-squared statistic. If the test of the difference in the proportion of study eyes with absence of anterior chamber cells was statistically significant at the two-sided alpha = 0.05 level in favor of OTX-DP, then the study was to be considered a success; OTX-DP was to be declared to be superior to PVPP in the proportion of study eyes with absence of anterior chamber cells at Day 14; and the difference in the proportion of subjects with absence of ocular pain between treatments at Day 8 was to be tested using the Pearson chi-squared statistic at the two-sided alpha = 0.05 level. If in addition to a statistically significant test of the difference in the proportion of study eyes with absence of anterior chamber cells at Day 14 in favor of OTX-DP, the test of the difference in the proportion of

study eyes with absence of ocular pain at Day 8 was statistically significant in favor of OTX-DP, then OTX-DP was to be declared to be superior to PVPP in both the proportion of study eyes with absence of anterior chamber cells at Day 14 and the proportion of study eyes with absence of ocular pain at Day 8.

The primary analysis was to utilize the ITT population. For subjects with missing data at the primary analysis visit (Day 14 for anterior chamber cells and Day 8 for ocular pain), the last observation following test or control article insertion was to be carried forward to impute the missing data. Subjects who were prescribed rescue medication prior to the primary analysis visit were to be imputed as failures. To evaluate the robustness of the primary analysis results, the primary efficacy analyses were to be repeated for the following populations and imputation methods:

- Using the ITT population, observed data only, with subjects who were prescribed rescue medication prior to the primary analysis visit imputed as failures;
- Using the PP population, observed data only, with subjects who were prescribed rescue medication prior to the primary analysis visit imputed as failures.

Figures of anterior chamber cells and ocular pain were to be presented, showing mean scores for each treatment by visit, imputing data for subjects requiring rescue medication as failures, using both observed data and using LOCF to impute missing data. Anterior chamber cells and flare, including cell counts, and ocular pain scores were to be presented by visit in subject listings.

Secondary Efficacy Analyses
All secondary efficacy analyses were to be performed based on the ITT population.
The primary efficacy variables: study eyes with absence of anterior chamber cells and study eyes with absence of pain, were to be summarized and analyzed by visit (Days 2, 4, 8, and 30 for anterior chamber cells and Days 2, 4, 14, and 30 for ocular pain) similar to the primary efficacy summaries and analyses.

Missing data were not to be imputed. Subjects requiring rescue mediation at any time prior to each respective visit were to be imputed as failures. Similar summaries and analyses were to be provided for the absence of anterior chamber flare by visit. Additionally, for the secondary endpoints of anterior chamber cells, anterior chamber flare, and ocular pain, results at each visit and changes from baseline were to be summarized using continuous and discrete summary statistics. Statistical significance was not to be assessed for these secondary endpoints. For ocular pain, scores were to be categorized discretely every two points on the 10 point scale: 0, 1 to 2, 3 to 4, 5 to 6, 7 to 8, and 9 to 10. Missing data were not to be imputed. Subjects requiring rescue mediation at any time prior to each respective visit were to be imputed using LOCF (the last observation prior to rescue medication use and after the test or control article insertion). All secondary endpoints were to be presented by visit in subject listings.

Table 6-1: List of Principal Investigators

Site Number	Investigator	Address	Number of Subjects Randomized
01	Thomas Walters	5715 Balcones Dr., Austin, TX 78731	38
02	Jeffrey Levenson	751 Oak St., Ste. 200, Jacksonville, FL 32204	33
03	Subha Gollamudi	825 Ridge Lake Blvd., Memphis, TN 38120	18
04	Stephen Smith	4225 Evans Ave., Ft. Myers, FL 33901	7
05	Shamik Bafna	1180 E. Broad St., Elyria, OH 44035	22
06	Steven Silverstein	4240 Blue Ridge Blvd., Ste 1000 Kansas City, MO 64133	17
07	Paul Harton	550 Redmond Rd., Rome, GA 30165	6
08	Stephen Vold	2783 N. Shiloh Dr., Fayetteville, AR 72704	14
09	Stephen Scoper	241 Corporate Blvd., Norfolk, VA 23502	11
10	Eugene Protzko	2023 Pulaski Hwy., Havre de Grace, MD 21078	14
11	Michael Graham	1911 N. Mills Ave., Orlando, FL 32803	6
12	John Linn	6060 Primacy Pkwy., Ste. 200 Memphis, TN 38119	7
14	John Hovanesian	24401 Calle De La Louisa, Ste 300, Laguna Hills, CA 92653	13
15	Michael Depenbusch	604 W. Warner Rd., Suite B6, Chandler, AZ 85225	20
16	Gary Wortz	120 N. Eagle Creek Dr., Ste 431, Lexington KY 40509	12
17	Timothy Peters	267 Rte. 108, Somersworth, NH 03878	9

Study OTX-14-003

The two Phase 3 trials (OTX-13-002 and OTX-14-003) were designed to be similar well-controlled studies. The major difference between OTX-13-002 and OTX-14-003 pertained to the Study Schedule. OTX-13-002 had the Day 120 visit as the next visit post-Day 60 and OTX- 14-003 had the Day 90 visit as the next visit post-Day 60. There are no other major differences in study design, inclusion/exclusion criteria, etc. between the two Phase 3 trials as reflected in the table below.

TABLE 1: OTX-13-002 STUDY SCHEDULE

	Screening	Surgery and Insertion of Test Article	Follow-Up Assessments						
Study Parameter	**≤ 30 days prior to Surgery**	**Day 1**	**Day 2**	**Day 4** *(+1 day)*	**Day 8** *(±1 day)*	**Day 14** *(± 2 days)*	**Day 30** *(± 2 days)*	**Day 60[1]** *(± 5 days)*	**Day 120** *(± 7 days)*
Obtain Informed Consent	X								
Medical/Ophthalmic History	X								
Concomitant Medications	X	X	X	X	X	X	X	X	X
Demographic Information	X								
Urine Pregnancy Test[2]	X								
Ocular Pain Assessment	X		X	X	X	X	X	X	
Visual Acuity Examination	X		X	X	X	X	X	X	
Slit Lamp Biomicroscopy[3]	X		X	X	X	X	X	X	
Punctum Examination	X		X	X	X	X	X	X	X
IOP Measurement	X		X	X	X	X	X	X	
Dilated Fundus Examination	X							X	
Test Article Presence by Visual Technique			X	X	X	X	X	X	
Test Article Presence by Patency Check[4]									X
Punctum Size Assessment		X							
Randomization		X							
Test Article Insertion		X							
Record Adverse Events		X	X	X	X	X	X	X	X

1 These assessments will occur on Day 60, or 7 days (± 2 days) after last visit in which the test article was not visualized at visits prior to Day 60.
2 A negative UPT is required for women with childbearing potential.
3 Slit Lamp Biomicroscopy will include anterior chamber cell count and flare.
4 If any resistance is observed during the patency check at the Day 120 visit, the subject will return for the assessment of the presence of the test article using a patency check every 30 (± 10) days until patency can be confirmed.

Table 6-1: List of Principal Investigators

Site Number	Investigator	Address	Number of Subjects Randomized
01	Joseph Gira	12990 Manchester Rd, Ste. 201, Des Peres, MO 63131	32
03	Donald Bennett	1935 Bluegrass Ave., Ste. 200, Louisville, KY 40215	19
04	Bruce Silverstein	3190 Churn Creek Rd, Redding, CA 96002	48
05	Reginald Sampson	229 E. Beverly Blvd., Montebello, CA 90640	29
06	Thomas Elmer	2825 Niagara Falls Blvd., Amherst, NY 14228	8
07	Kenneth Olander	622 Smithview Rd, Maryville, TN 37803	11
08	David Vroman	137 Gateway Dr., Ladson, SC 29456	12
09	Aaron Waite	930 Madison Ave., Ste. 470, Memphis, TN 38163	8
10	Francis Mah	10666 North Torrey Pines Rd, MS214, La Jolla, CA 92037	1
11	Jeffrey Whitman	2801 Lemmon Ave., Ste 200, Dallas, TX 75204	14
12	Kevin Waltz	8103 Clearvista Pkwy, Indianapolis, IN 46256	8
13	Richard Damiano	8381 SouthPark Lane, Littleton, CO 80120	4
14	John Berdhal	3101 W. 57th St., Sioux Falls, SD 57108	9
15	Navin Tekwani	9911 Kennerly Rd, Ste A, St. Louis, MO 63128	6
16	Janet Kim	1739 West Ave. J, Lancaster, CA 93534	17
17	Kevin Jong	1415 North Loop, Ste 400, Houston, TX, 77008	15

6 Review of Efficacy

6.1 Indication

6.1.1 Methods

The support for efficacy is from 3 adequate and well-controlled clinical studies (Studies OTX-12-002, OTX-13-002 and OTX-14-003).

6.1.2 Demographics

Study OTX-13-002: Demographics

	OTX-DP N=164	**PVPP N=83**
Age		
Mean	67.4	69.9
Min, max	47, 87	46, 93
Age		
<65	56	16
>=65 to <75	76	44
>=75	32	23
Gender		
Male	61	39
Female	103	44

	OTX-DP N=164	**PVPP N=83**
Ethnicity		
Hispanic or Latino	8	2
Not Hispanic or Latino	156	81
Race		
American Indian	1	0
Asian	3	3
African American	22	18
Native Hawaiian	2	0
White	136	62
Iris Color		
Blue	58	26
Brown	75	40
Hazel	16	7
Green	15	8
Gray	0	2

Study OTX-14-003: Demographics

	OTX-DP N=161	**PVPP N=80**
Age		
Mean	69.0	68.3
Min, max	43, 86	49, 84
Age		
<65	49	22
>=65 to <75	66	39
>=75	46	19
Gender		
Male	63	41
Female	98	39
Ethnicity		
Hispanic or Latino	29	9
Not Hispanic or Latino	132	71
Race		
American Indian	2	0

	OTX-DP N=161	**PVPP N=80**
Asian	1	1
African American	20	8
Native Hawaiian	0	0
White	138	71

	OTX-DP N=161	**PVPP N=80**
Iris Color		
Blue	45	18
Brown	78	40
Hazel	25	17
Green	11	4
Gray	2	1

Reviewer's Comment:
There are no remarkable differences between treatment groups in demographics.

6.1.3 Patient Disposition

Study OTX-13-002: Subject Disposition

	OTX-DP	**PVPP**
Number of randomized subjects	164	83
Treated	163	83
ITT population	164	83
PP population	149	74
Safety population	162	84
Study completed	163	81
Study withdrawal	1	2
Reason for subject withdrawal		
AE	0	1
Protocol violation	0	0
Lost to f/u	0	0
Consent withdrawn	0	0
Other	1	0

Study OTX-14-003: Subject Disposition

	OTX-DP	PVPP
Number of randomized subjects	161	80
Treated	160	80
ITT population	161	80
PP population	148	78
Safety population	160	80
Study completed	159	76
Study withdrawal	2	4
Reason for subject withdrawal		
AE	0	0
Protocol violation	0	0
Lost to f/u	0	2
Consent withdrawn	0	0
Investigator decision	1	1
Other	1	1

Reviewer's Comment:
There are no remarkable differences between treatment groups in subject disposition.

6.1.4 Analysis of Primary Endpoint(s)

Study OTX-12-002: Absence of Anterior Chamber Cells at Day 8 and Ocular Pain at Day 8, Intent-to-Treat Population with LOCF (Last Observation Carried Forward)

	OTX-DP N=164	PVPP N=83	Difference-DP-PVPP Estimate	Difference-DP-PVPP P-value
Absence of Anterior Chamber Cells at Day 8				
Yes	6 (20.7%)	3 (10%)	10.7%	0.1495
No	23 (79.3%)	27 (90.0%)		
Absence of Pain at Day 8				
Yes	23 (79.3%)	9 (30.0%)	49.3%	<0.0001
No	6 (20.7%)	21 (70.0%)		

Study OTX-12-002: Absence of Anterior Chamber Cells and Ocular Pain by Visit (ITT Population)

	OTX-DP N=161	PVPP N=80	Difference-DP-PVPP Estimate	Difference-DP-PVPP P-value
Day 1				
Absence of AC Cells	0	0		-
Absence of Pain	18 (62.1%)	5 (17.2%)	44.8%	0.0002

	OTX-DP N=161	**PVPP N=80**	**Difference-DP-PVPP Estimate**	**Difference-DP-PVPP P-value**
Day 4				
Absence of AC Cells	2 (6.9%)	0	6.9%	0.1186
Absence of Pain	24 (82.8%)	7 (23.3%)	59.4%	<0.0001
Day 8				
Absence of AC Cells	6 (20.7%)	3 (10.3%)	10.3%	0.2351
Absence of Pain	23 (79.3%)	9 (31.0%)	48.3%	0.0001
Day 11				
Absence of AC Cells	6 (20.7%)	2 (6.9%)	13.8%	0.1265
Absence of Pain	23 (79.3%)	7 (24.1%)	55.2%	<0.0001
Day 14				
Absence of AC Cells	10 (34.5%)	1 (3.4%)	31.0%	0.0027
Absence of Pain	23 (79.3%)	7 (24.1%)	55.2%	<0.0001
Day 30				
Absence of AC Cells	18 (62.1%)	4 (13.8%)	48.3%	0.0002
Absence of Pain	23 (79.3%)	21 (72.4%)	51.7%	<0.0001

Reviewer's Comment:

Study OTX-12-002 did not demonstrate the superiority of Dextenza over vehicle for the proportion of subjects with absence of anterior chamber cells at Day 8. However, a significantly higher proportion of subjects in the Dextenza arm reported no pain at all study days compared with the vehicle arm.

Study OTX-13-002: Absence of Anterior Chamber Cells at Day 14 and Ocular Pain at Day 8, ITT Population with LOCF (Last Observations Carried Forward)

	OTX-DP N=164	**PVPP N=83**	**Difference-DP-PVPP Estimate**	**Difference-DP-PVPP P-value**
Absence of Anterior Chamber Cells at Day 14				
Yes	54 (33.1%)	12 (14.5%)	18.7%	0.0018
No	109 (66.9%)	71 (85.5%)		
Absence of Pain at Day 8				
Yes	131 (80.4%)	36 (43.4%)	37.0%	<0.0001
No	32 (19.6%)	47 (56.6%)		

Study OTX-13-002: Absence of Anterior Chamber Cells at Day 14 and Ocular Pain at Day 8, PP Population with Observed Data

	OTX-DP N=164	**PVPP N=83**	**Difference-DP-PVPP Estimate**	**Difference-DP-PVPP P-value**
Absence of Anterior Chamber Cells at Day 14				
Yes	49 (32.9%)	12 (16.2%)	16.7%	0.0086
No	100 (67.1%)	62 (83.8%)		
Absence of Pain at Day 8				
Yes	119 (79.9%)	31 (42.5%)	37.4%	<0.0001
No	30 (20.1%)	42 (57.5%)		

Study OTX-14-003: Absence of Anterior Chamber Cells at Day 14 and Ocular Pain at Day 8, ITT Population with LOCF (Last Observations Carried Forward)

	OTX-DP N=161	**PVPP N=80**	**Difference-DP-PVPP Estimate**	**Difference-DP-PVPP P-value**
Absence of Anterior Chamber Cells at Day 14				
Yes	63 (39.4%)	25 (31.3%)	8.1%	0.2182
No	97 (60.6%)	55 (68.8%)		
Absence of Pain at Day 8				
Yes	124 (77.5%)	47 (58.8%)	18.8%	0.0025
No	36 (22.5%)	33 (41.3%)		

Study OTX-14-003: Absence of Anterior Chamber Cells at Day 14 and Ocular Pain at Day 8, PP Population with Observed Data

	OTX-DP N=148	**PVPP N=78**	**Difference-DP-PVPP Estimate**	**Difference-DP-PVPP P-value**
Absence of Anterior Chamber Cells at Day 14				
Yes	59 (39.9%)	25 (32.1%)	7.8%	0.2479
No	89 (60.1%)	53 (67.9%)		
Absence of Pain at Day 8				
Yes	114 (77.0%)	47 (60.3%)	16.8%	0.0081
No	34 (23.0%)	31 (39.7%)		

Reviewer's Comment:

Study OTX-14-003 failed to achieve the primary endpoint of absence of anterior chamber cells at Day 14. Both studies (OTX-13-002 and OTX-14-003) achieved the endpoint of absence of pain at Day 8.

6.1.5 Analysis of Secondary Endpoints(s)

Study OTX-13-002: Absence of Anterior Chamber Cells and Ocular Pain by Visit (ITT Population)

	OTX-DP N=164	**PVPP N=83**	**Difference-DP-PVPP Estimate**	**Difference-DP-PVPP P-value**
Day 2				
Absence of AC Cells	4 (2.5%)	2 (2.4%)	0	0.9830
Absence of Pain	116 (71.22%)	38 (45.8%)	25.4%	0.0001
Day 4				
Absence of AC Cells	15 (9.2%)	6 (7.3%)	1.9%	0.6189
Absence of Pain	127 (77.9%)	43 (52.4%)	25.5%	0.0001
Day 8				
Absence of AC Cells	22 (13.5%)	9 (11.0)	2.5%	0.5754
Absence of Pain	131 (80.4%)	35 (42.7%)	37.7%	<0.0001
Day 14				
Absence of AC Cells	54 (33.3%)	12 (14.5%)	18.9%	0.0016
Absence of Pain	129 (79.6%)	33 (39.8%)	39.9%	<0.0001
Day 30				
Absence of AC Cells	101 (62.0%)	22 (28.4%)	33.6%	<0.0001
Absence of Pain	135 (83.3%)	38 (46.9%)	36.4%	<0.0001
Day 60				
Absence of AC Cells	103 (71.0%)	31 (39.2%)	31.8%	<0.0001
Absence of Pain	116 (80.0%)	41 (51.9%)	31.9%	<0.0001

Study OTX-14-003: Absence of Anterior Chamber Cells and Ocular Pain by Visit (ITT Population)

	OTX-DP N=161	**PVPP N=80**	**Difference-DP-PVPP Estimate**	**Difference-DP-PVPP P-value**
Day 2				
Absence of AC Cells	9 (5.6%	4 (5.1%)	0.6%	0.8571
Absence of Pain	105 (65.6%)	32 (40.0%)	25.6%	0.0002
Day 4				
Absence of AC Cells	22 (13.8%)	9 (11.4%)	2.4%	0.5978
Absence of Pain	117 (73.6%)	39 (48.8%)	24.8%	0.0001
Day 8				
Absence of AC	36 (22.5%)	11 (13.8%)	8.8%	0.1073

Cells				
Absence of Pain	123 (77.4%)	47 (58.8%)	18.6%	0.0027
Day 14				
Absence of AC Cells	63 (39.4%)	25 (31.3%)	8.1%	0.2182
Absence of Pain	123 (76.9%)	46 (57.5%)	19.4%	0.0019
Day 30				
Absence of AC Cells	97 (61.4%)	37 (48.1%)	13.3%	0.0525
Absence of Pain	61 (38.6%)	40 (51.9%)	13.3%	0.0015
Day 60				
Absence of AC Cells	103 (73.0%)	36 (50.7%)	22.3%	0.0012
Absence of Pain	111 (78.7%)	41 (57.7%)	21.0%	0.0014

Reviewer's Comment: *The results are consistent with the primary endpoint(s).*

6.1.6 Other Endpoints

Study OTX-13-002: Mean ACC Grade By Visit (ITT Population)

	OTX-DP N=164	**PVPP N=83**
Day 2 (sd)	1.3 (0.8)	1.3 (0.7)
Day 4 (sd)	1.0 (0.7)	1.3 (0.9)
Day 8 (sd)	0.9 (0.8)	1.3 (1.0)
Day 14 (sd)	0.7 (0.8)	1.2 (1.0)
Day 30 (sd)	0.5 (0.8)	1.1 (1.1)
Day 60 (sd)	0.4 (0.8)	1.0 (1.1)

Study OTX-14-003: Mean ACC Grade By Visit (ITT Population)

	OTX-DP N=164	**PVPP N=83**
Day 2 (sd)	1.2 (0.8)	1.4 (0.9)
Day 4 (sd)	0.9 (0.7)	1.2 (0.9)
Day 8 (sd)	0.7 (0.7)	1.2 (0.9)
Day 14 (sd)	0.6 (0.7)	1.1 (1.1)
Day 30 (sd)	0.4 (0.7)	0.8 (1.0)
Day 60 (sd)	0.3 (0.7)	0.8 (1.1)

Study OTX-13-002: Product Visualization (ITT Population)

	OTX-DP	**PVPP**	**Difference-DP-PVPP Estimate**	**Difference-DP-PVPP P-value**
Day 2	N=163	N=83		
Product Was Visualized	163 (100%)	80 (96.4%)	3.6%	0.0146
Day 4	N=163	N=79		
Product Was Visualized	163 (100%)	78 (98.7%)	1.3%	0.1500
Day 8	N=163	N=79		
Product Was Visualized	163 (100%)	78 (98.7%)	1.3%	0.1500
Day 14	N=162	N=78		
Product Was Visualized	162 (100%)	77 (98.7%)	1.3%	0.1487
Day 30	N=162	N=77		
Product Was Visualized	144 (88.9%)	71 (92.2%)	-3.3%	0.4250
Day 60	N=143	N=71		
Product Was Visualized	100 (69.9%)	47 (66.2%)	3.7%	0.5793

Study OTX-14-003: Product Visualization (ITT Population)

	OTX-DP	**PVPP**	**Difference-DP-PVPP Estimate**	**Difference-DP-PVPP P-value**
Day 2	N=160	N=80		
Product Was Visualized	160 (100%)	80 (100%)		
Day 4	N=159	N=80		
Product Was Visualized	159 (100%)	80 (100%)		
Day 8	N=160	N=80		
Product Was Visualized	160 (100%)	80 (100%)		
Day 14	N=160	N=80		
Product Was Visualized	159 (99.4%)	80 (100%)	-0.6%	0.4786
Day 30	N=158	N=77		
Product Was Visualized	1472 (89.9%)	70 (90.9%)	-1.0%	0.8020
Day 60	N=140	N=67		
Product Was Visualized	71 (50.7%)	31 (46.3%)	4.4%	0.5495

Study OTX-13-002: Investigator Rating of Ease of Product Use At Insertion (ITT Population)

	OTX-DP N=164	**PVPP N=83**
Ease of insertion		
Easy	120 (73.6%)	73 (88.0%)
Moderate	31 (19.0%)	10 (12.0%)
Difficult	12 (7.4%)	0

Study OTX-14-003: Investigator Rating of Ease of Product Use At Insertion (ITT Population)

	OTX-DP N=160	**PVPP N=80**
Ease of insertion		
Easy	123 (76.4%)	76 (95.0%)
Moderate	33 (20.5%)	4 (5.0%)
Difficult	5 (3.1%)	0

6.1.7 Subpopulations

Demographic subgroup results were generally consistent with the overall results. Subgroups analyzed were age (>65, >=65-<75, and >=75), gender, race, ethnicity (Hispanic/Latino and Not Hispanic/Latino), and iris color (blue vs. non-blue). In each subgroup having at least one subject in both treatment groups, OTX-DP was numerically superior to PVPP in absence of pain at Day 8. Statistical significance was only achieved for age, gender, and iris color.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations
Only one dosing regimen was studied in both Studies C-13-002 and C-14-003**.**

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects
Long-term effectiveness was not evaluated for the clinical studies.

6.1.10 Additional Efficacy Issues/Analyses - None.

7 Review of Safety

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety
Two adequate and well-controlled clinical studies OTX-13-002 and OTX-14-003 were used to evaluate safety.

7.1.2 Adequacy of Data
Between the 2 studies there were 324 patients in the safety database who received OTX-DP.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence
Two studies are used to support the safety of Dextenza. See Section 7.4.1 of this review.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations –Only one dose was studied.

7.2.2 Explorations for Dose Response- Only one dosing regimen was studied.

7.2.3 Special Animal and/or In Vitro Testing -No special animal or in vitro testing was performed.

7.2.4 Routine Clinical Testing -Not applicable.

7.2.5 Metabolic, Clearance, and Interaction Workup
Studies to evaluate metabolism, clearance, and interaction were not performed.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class
See section 2.4.

7.3 Major Safety Results

7.3.1 Deaths -OTX-13-002: There were no deaths in the study.
-OTX-14-003: One death from cardiac failure congestive occurred in the study.

74-year-old white female with senile cataract underwent cataract surgery OD on (b) (6) and was randomized to PVPP. The subject had a medical history of menopause, heart disease, diabetes, hypertension and bronchitis. Systemic medications included albuterol, furosemide, metformin, metolazone, metoprolol, Novolin 70/30, and warfarin. The subject suffered from symptoms of fatigue, dyspnea and lower leg extremity edema and on day 24 of the study was diagnosed with CHF which was severe and not suspected of being related to treatment. The subject was hospitalized and underwent cardiac catheterization, echocardiogram, electrocardiography, X-rays, and laboratory testing and received IV Lasix diuresis, Tylenol, Norco, morphine sulfate, dopamine drip, heparin drip, insulin, Lopressor, Zofran, Protonix, K-Dur, Revatio, blood transfusions, and hemodialysis, and was placed on an intra-aortic balloon pump. No other AEs were reported. The subject was hospitalized until study day 68 at which time she died of CHF.

7.3.2 Nonfatal Serious Adverse Events

Eight SAEs were reported for five subjects in the study.

Study OTX-13-002: Serious Adverse Events

Subject	Group	SAE	Description
S (b) (6)	**PVPP**	Hypopyon	71 yo white female with cataracts, underwent cataract surgery OD on (b) (6) and was randomized to PVPP. At the Day 4 Visit, the subject was observed to have excessive inflammation with hypopyon in the study eye. The event, was considered severe and sight-threatening,. Treatment masking was broken and the subject was prescribed Prolensa (bromfenac) administered 1 gtt QD from day 4 through 30, and Durezol (difluprednate) administered Q2H on days 4 and 5, QH on day 6, Q2H on days 7 to 9, QID on days 10 to 16, and BID on days 17 to 30. The event resolved on study day 9. The subject was subsequently treated OD with prednisolone acetate 1% administered QID from study days 41 to 52, and BID from days 53 to 73. The subject experienced no other AEs and completed the study on day 118.
S (b) (6)	**OTX-DP**	**Retroperitoneal Bleed**	63 yo white female with cataract, underwent cataract surgery OS on (b) (6) and was randomized to OTX-DP. The subject had an ocular history of prior cataract surgery with IOL implantation OD, and posterior vitreous detachment OD. The non-ocular history was positive for hypertension, hypercholesterolemia, GERD, hysterectomy, tubal ligation and peripheral vascular disease. At study entry, non-ocular medications included Amlodipine, Cymbalta, Endocet, Percocet, lisinopril, and simvastatin. On study

			day 44 the subject experienced a retroperitoneal hemorrhage which was severe, life-threatening and required hospitalization with surgical intervention (bilateral repair of the femoral arteries). The subject was also treated with Plavix 75, IV fluids, and Lortab. The suspected cause of the hemorrhage was severe peripheral vascular disease which was observed via arteriogram and angiogram. On study day 10, the subject had experienced worsening of peripheral vascular disorder and underwent an unsuccessful stent placement. The retroperitoneal hemorrhage was resolved on study day 52; however, the peripheral vascular disease remained ongoing at study completion. The subject experienced one additional AE (constipation) which had an onset at day 45, was treated with Sennoside laxative, and resolved by day 52. The subject completed the study on study day 122.
S (b) (6)	**OTX-DP**	**Dehydration and Gout**	74 yo white male with senile cataract, underwent cataract surgery OD on (b) (6) and was randomized to OTX-DP. The subject's ocular medical history was positive for prior cataract surgery with IOL implantation OS, vitreous floaters OU, optic disc drusen OU, and retinal degeneration OU. Non-ocular medical history was positive for bladder cancer, irregular heart rate, arthritis, HTN and blood potassium decreased. Concomitant medications included carvedilol, furosemide, gabapentin, metolazone, potassium chloride, tramadol 5, and warfarin. On study day 24, the subject experienced dehydration which was severe, and required hospitalization for 7 days. The subject underwent CT scan, chest X-rays, and blood work and was treated with IV fluids. The suspected cause was the subject's concomitant medications; metolazone was stopped on study Day 29 and warfarin was increased to 7.5 mg QD for 10 days and then reduced back to 5 mg QD, and the event resolved on study day 31. Subsequently on study day 38, the subject experienced an initial episode of gout which was manifested as pain and swelling in the left foot with tenderness to touch, inability to walk, and teacolored urine. The event was of mild severity and required hospitalization for two days. The subject was treated acutely with 1 tablet of Vicodin and one dose of ketorolac, and subsequently prescribed acetaminophen/hydrocodone, prednisone, and allopurinol. The event resolved on study day 40 and the subject completed the study on day 41.
S (b) (6)	**PVPP**	**Lumbar Stenosis and Hydronephrosis**	81yo white female with senile cataract, underwent cataract surgery OS on (b) (6) and was randomized to PVPP. The subject's ocular history was positive for pterygium, dry eye, superficial punctate keratitis and borderline glaucoma OU. Additionally, ocular history for the right eye included vitreous detachment, prior cataract surgery with intraocular lens implantation, and posterior capsule opacification, while that for the left eye was positive for cataract and

			corneal opacity. The subject's non-ocular history was positive for appendectomy, blood cholesterol increased, cervical cancer with removal of the cervix, hysterectomy, back pain, pain in extremity (left leg pain, occasional right leg pain), cholecystectomy, osteoarthritis, arthralgia (bilateral hip pain), osteoporosis, and GERD. Prior medications included aspirin and lovastatin. On study day 22, the subject was diagnosed by MRI with diffuse lumbar spinal stenosis. The event which was severe, required hospitalization, was treated with surgical intervention (L4 and L5 laminectomy) and unspecified narcotic medications, and resolved by study day 26. On study day 42, the subject experienced hydronephrosis diagnosed by CT scan following symptoms of nausea, vomiting and abdominal pain. The event was moderate in severity and required hospitalization. The subject was treated with Zofran, Tylenol, and Prilosec. The event resolved by day 46. Other AEs experienced by the subject included worsening of left knee pain on day 11 which was moderate in severity, treated by fluid drainage and an injection of cortisone, and resolved at day 38. Ocular AEs which occurred in the subject's study eye included IOP ≥ 10 mmHg over baseline from days 2 to 4, and corneal edema from study days 17 to 38. The corneal edema was treated with Ilevro (nepafenac) and PredForte . The subject completed the study on study day 121.
S (b) (6)	**PVPP**	**Developmental Hip Dysplasia and Medical Device Complication**	93 yo white female with a history of senile cataract, underwent cataract surgery OS on (b) (6) and was randomized to PVPP. The subject's ocular history was positive for macular degeneration (drusen) OU, prior cataract surgery with IOL implantation OD, peripheral retinal degeneration OD, YAG laser therapy OD, as well as retinal cobblestone degeneration and cataract OS. The subject's non-ocular medical history was positive for dyspepsia, arthritis, blood cholesterol increased, peripheral vascular disease, cardiac disorder, menopause, as well as prior right hip fracture and surgery. Prior medications included clopidogrel, meloxicam, omeprazole, and simvastatin. On study day 104 the subject experienced eversion of the superior and posterior acetabulum (hip dysplasia) which required hospitalization and surgical intervention. On study day 121, the subject experienced a medical device complication (migration of the acetabular component) requiring hospitalization and surgical intervention. Both events were of moderate severity. The subject, who did not complete the study, was lost to follow up after study day 177.

Study OTX-14-003: Serious Adverse Events (Safety Population)

Subject	Group	SAE	Description
S (b) (6)	**OTX-DP**	**Colon Cancer**	65 yo white female with senile cataract underwent cataract surgery OD on (b) (6) and was randomized to OTX-DP. The subject's medical history was positive for hypothyroidism and hypertension. Concomitant medications included amlodipine, aspirin, estradiol, levothyoxine, losartan, and metoprolol. The subject underwent a colonoscopy during which polyps were observed in the colon. On study day 20 (b) (6)), the subject was diagnosed with colon cancer, which was severe and not suspected of being related to study treatment. The subject was hospitalized from (b) (6) to (b) (6) and underwent colon resection. The event was considered resolved on (b) (6) (study day 56) and the subject successfully completed the study on (b) (6) (study day 70). The subject experienced no other AEs.
S (b) (6)	**PVPP**	**CHF**	**See section 7.3.1**
S (b) (6)	**PVPP**	**Mental Disorder (Nervous Breakdown)**	67 yo white female with senile cataract underwent cataract surgery OS on (b) (6) and was randomized to PVPP. The subject had a medical history of hysterectomy, hypertension, diabetes, anxiety, hypercholesterolaemia, and urinary incontinence. Systemic medications included gabapentin, glipizide, lisinopril, metformin, oxybutynin, paroxetine, and simvastatin. The subject completed study visits through the Day 14 Visit. On study day 24 the subject experienced nervousness, hallucinations and panic attacks diagnosed as a nervous breakdown. The event was severe, not suspected of being related to study treatment, and required hospitalization. No other AEs were reported for the subject who was lost to further follow-up.
S (b) (6)	**PVPP**	**Angina Pectoris**	57 yo white male with senile cataract, underwent cataract surgery OS on (b) (6) and was randomized to PVPP. The subject's medical history was positive for blood cholesterol increased, headache, myocardial infarction, coronary arterial stent insertion, cardiovascular disorder, peripheral neuropathy, GERD, Barrett's esophagus, colonoscopy, and prostatomegaly. Systemic medications included aspirin, Effient, Flomax, Neurontin, Prevacid, and Zocor. The subject experienced angina pectoris of moderate severity which was not suspected of being related to study treatment, and resulted in hospitalization from (b) (6) to (b) (6). A diagnostic procedure was performed on (b) (6) for which the subject received IV administration of thallium 3.5 mL. The event was of moderate severity and was not suspected of being related to study drug. The subject experienced no other AEs. The subject completed the study at the Day 90 Visit on (b) (6).
S (b) (6)	**OTX-DP**	**Peripheral Arterial**	66 yo white male with senile cataract, underwent cataract surgery OD on (b) (6). The subject's history included prior myocardial

		Occlusive Disease	infarction, coronary arterial stent insertion, bone lesion excision, Barrett's esophagus, vascular stent insertion, peripheral artery bypass, hip arthroplasty, coronary artery bypass, cholelithiasis, gallbladder operation, and nasal septal operation. Ongoing conditions included spinal osteoarthritis, cardiac failure congestive, cardiac disorder, hypertension, blood cholesterol increased, sinus disorder, sleep apnea syndrome, hypoaesthesia (right foot), gastrooesophageal reflux disease, insomnia and erectile dysfunction. Systemic medications included Ambien, amiodarone, atorvastatin, carvedilol, furosemide, gabapentin, irbesartan, panteprazole, Plavix, Ultram, and Viagra. The subject was hospitalized on study days 83 to 84 for bypass surgery on his right leg, following pain in his right leg which was diagnosed via an ultrasound and angiogram as peripheral arterial occlusive disease. Medications administered during hospitalization included a IV administration of Fentanyl, hydralazine, lidocaine, a single administration of Midazolam and three 1 mg administrations of Midazolam. The event was considered to be severe and was not suspected of being related to study treatment. Other AEs experienced by the subject included a broken left leg on study day 2. The subject completed the study on study day 90.

7.3.3 Dropouts and/or Discontinuations

OTX-13-003:

One subject experienced an AE leading to study withdrawal. Subject S(b) (6), a 78 yo white male was randomized to PVPP and underwent cataract surgery OD. The subject had a positive history for HTN, cardiac disease, myocardial infarction, hypothyroidism, vertigo, prostate cancer, and prostatectomy. On study day 34, the subject was diagnosed with prostate cancer of moderate severity. On study day 72 the subject was withdrawn from study, at which time the event remained ongoing.

OTX-14-003:

One subject randomized to OTX-DP experienced an AE leading to study withdrawal (categorized as "investigator decision"). Subject S(b) (6) experienced anterior chamber inflammation (2+ cells at the Day 2 and 4 Study Visits, 0.5+ cells at the Day 8 Visit, followed by 2+ at the Day 14 Visit) and a pain score of 2 at the Day 14 Visit in the study eye (OS). The AC inflammation was of mild severity and not suspected of being related to study treatment. The subject was prescribed Lotemax and Prolensa, and was withdrawn from study.

7.3.4 Significant Adverse Events

See Section 7.3.2.

7.3.5 Submission Specific Primary Safety Concerns -None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study OTX-13-002: Ocular AE in the Study Eye (Safety Population)

	OTX-DP N=162	**PVPP N=84**
Any ocular AE	62	43
Eye disorders	47	38
IOP increased	13	3
AC inflammation	10	7
Corneal edema	2	5
Ocular discomfort	3	4
Visual acuity reduced	3	3
Eye inflammation	0	5
Iritis	1	4
Conjunctival hyperemia	3	1
Cystoid macular edema	4	0
Conjunctivitis	2	1
Lacrimation increased	2	1
Posterior capsular opacification	2	1
Corneal disorder	1	1
Eye pain	2	0
Eye pruritus	2	0
Conjunctival edema	0	1
Diabetic retinal edema	1	0
Eye discharge	1	0
Eye irritation	1	0
Eyelid irritation	1	0
Hypotony	1	0
Iridocyclitis	0	1
Macular edema	1	0
Ocular ischemic neuropathy	1	0
Photophobia	1	0
Punctate keratitis	0	1
Pupillary disorder	1	0
Refraction disorder	0	1
Trichiasis	1	0
Vitreous Floaters	0	1
Injury		
Corneal abrasion	0	1

Incision site edema	1	0
Infections		
Hypopyon	0	1
Neoplasms		
Benign neoplasm of eyelid	1	0

Study OTX-14-003: Ocular AE in the Study Eye (Safety Population)

	OTX-DP N=160	**PVPP N=80**
Any ocular AE	46	31
Eye disorders		
Iritis	12	11
IOP increased	7	4
Corneal edema	3	4
Eye pain	2	2
Conjunctival hyperemia	1	2
Cystoid macular edema	1	2
Ciliary hyperemia	1	1
Eye irritation	1	1
Keratitis	2	0
Visual acuity reduced	2	0
AC cell	0	1
Conjunctivitis allergic	1	0
Conjunctivochalasis	1	0
Corneal disorder	1	0
Diplopia	1	0
Dry eye	1	0
Eye hemorrhage	0	1
FBS	1	0
Hypotony	1	0
Lacrimation increased	1	0
Photophobia	1	0
Pinguecula	1	0
Vitreous disorder	1	0
Injury		
Corneal abrasion	1	3
Infections		
Dacrocanaliculitis	0	1
Hordeolum	1	0

Reviewer's Comment:

The most common ocular adverse events in any treatment group or study were anterior chamber inflammation (described as anterior chamber inflammation, iritis, iridocyclitis, anterior chamber cell), corneal edema, ocular discomfort, visual acuity reduced, eye inflammation, IOP increased, and corneal abrasion.

Study OTX-13-002: Non-Ocular AE (Safety Population)

	OTX-DP N=162	**PVPP N=84**
Any Non-Ocular AE	24	12
Infections		
Body tinea	1	0
External ear cellulitis	1	0
Viral gastroenteritis	1	0
Nasopharyngitis	1	0
Sinusitis	1	0
Skin bacterial infection	0	1
Tooth infection	1	0
Upper respiratory tract infection	0	1
GI disorders		
Constipation	1	0
Oral pain	1	0
Retroperitoneal hemorrhage	1	0
Vomiting	1	0
Injury, Poisoning, and Procedural Complications		
Arthropod bite	1	0
Thermal burn	0	1
Tooth fracture	1	0
Neoplasms		
Basal cell carcinoma	1	0
Malignant melanoma	0	1
Prostate cancer	0	1
Nervous system disorder		
Headache	1	1
Sinus headache	1	0
General disorders		
Medical device complication	0	1
Peripheral edema	1	0
Musculoskeletal disorders		
Arthralgia	0	1
Lumbar spinal stenosis	0	1

Muscle spasms	0	1
Respiratory disorders		
Nasal congestion	1	0
Upper airway cough syndrome	1	0
Vascular disorders		
HTN	1	0
Peripheral vascular disorder	1	0
Congenital, Familial, and Genetic Disorders		
Developmental hip dysplasia	0	1
Ear Disorders		
Vertigo	1	0
Metabolism Disorders		
Hydronephrosis	0	1
Skin disorders		
Rash	1	0

Study OTX-14-003: Non-Ocular AE (Safety Population)

	OTX-DP N=160	**PVPP N=80**
Any Non-Ocular AE	**10**	**6**
Infections		
Atypical pneumonia	0	1
Cystitis	0	1
Sinusitis	1	0
Urinary tract infection	1	0
Nervous system disorders		
Headache	2	0
Dizziness	0	1
Cardiac disorders		
Angina	0	1
CHF	0	1
GI disorders		

Nausea	2	0
Injury, Poisoning, and Procedural Complications		
Contusion	1	0
Lower limb fracture	1	0
Investigations		
Blood pressure increased	1	0
ECG abnormal	1	0
Neoplasms		
Colon CA	1	0
Psychiatric disorders		
Mental disorder	0	1
Skin disorders		
Diabetic ulcer	1	0
Vascular disorders		
Peripheral arterial occlusive disease	1	0

Reviewer's Comment:
The most common non-ocular adverse events were headache, nausea, pneumonia and sinusitis.

7.4.2 Laboratory Findings
Not applicable. There were no clinical laboratory evaluations conducted in either study.

7.4.3 Vital Signs
Not applicable. Vital signs were not collected in either study.

7.4.4 Electrocardiograms (ECGs)
Not applicable. ECGs were not performed in either study.

7.4.5 Special Safety Studies

IOP Increase of >=10 mmHg in the Study Eye

OTX-13-002
AEs were reported for 11 OTX-DP (6.8%) and three PVPP (3.6%) subjects who exhibited an IOP increase of ≥ 10 mmHg in the study eye. In the majority of these subjects the IOP increase was observed at the Day 2 Visit and resolved within days.

OTX-14-003
AEs were reported for seven (4.4%) OTX-DP and four (5.0%) PVPP subjects who exhibited an IOP increase of ≥ 10 mmHg in the study eye. In the majority of these subjects, the IOP increase was observed on the Day 2 Visit and resolved within days.

Endothelial Cell Counts
At the pre-NDA meeting on 4/14/15 the Agency recommended if ECC are not performed in the trial the Applicant should provide a justification for not doing so. The following is the justification provided by the applicant.

"Endothelial cell density was not assessed in any of the clinical trials with Dextenza. This is justified since the entire quantity of dexamethasone (0.4 mg) in Dextenza is less than that administered in one day of intense dosing with Maxidex Ophthalmic Suspension, 0.1% assuming hourly dosing of one 50 µL eye drop (Maxidex Product Information). Moreover, intracameral (0.4 mg in 0.1 mL) injection of dexamethasone has been shown to be safe to the corneal endothelium resulting in a mean endothelial cells loss of 7.63% at 3 months following cataract surgery (Jamil et al. 2014). This rate of loss is consistent with that reported in the scientific literature following phacoemulsification (Rosado-Adames & Afshari, 2012). Additionally, the hydrogel material comprising Dextenza is (b) (4) The drug product also contains fluorescein as a visualization aid. Fluorescein has been used safely in numerous topical ophthalmic applications."

Reviewer's Comment:
The justification provided is acceptable.

Punctum Examination
Study OTX-13-002
Lid apposition, punctal appearance, and tear meniscus of the study eye were evaluated at screening, and all subsequent visits. Each parameter was to be assessed as normal, abnormal (not clinically significant) or abnormal (clinically significant). No study eye in either treatment group had a clinically significant abnormal finding for lid apposition, punctal appearance or tear meniscus at any study visit.

Study OTX-14-003
Lid apposition, punctal appearance, and tear meniscus of the study eye were evaluated at screening, and all subsequent visits. Each parameter was to be assessed as normal, abnormal (not clinically significant) or abnormal (clinically significant). Lid apposition was graded as normal in 100% of study eyes in both treatment groups at all study visits. Punctal appearance was graded as normal in 100% of study eyes in both treatment groups at all study visits with the exception of one eye at the Day 30 Visit. One subject in the PVPP group had a clinically significant abnormality of the punctum at the Day 30 Visit. This subject (S (b) (6)) had experienced an AE of dacryocanaliculitis. Tear meniscus was graded as normal or not clinically significant abnormal in 100% of study eyes at all study visits with the exception of one study eye at the Day 14 Visit and one at the Day 30 Visit. At the Day 14 Visit, one subject in the PVPP group had a clinically significant abnormal tear meniscus; the subject (S (b) (6)) was described as having a "very large tear lake". At the Day 30 Visit, one subject in the PVPP group had a tear meniscus described as "contains pus consistent with canaliculitis Dx". This subject (S (b) (6)) had experienced an AE of dacryocanaliculitis.

7.4.6 Immunogenicity -Not applicable.

7.5 Other Safety Exploration

7.5.1 Dose Dependency for Adverse Events - Not performed.
7.5.2 Time Dependency for Adverse Events - Not performed.
7.5.3 Drug-Demographic Interactions -See section 6.1.17.
7.5.4 Drug-Disease Interactions - Dextenza was not studied with any drug-disease interaction analysis.

7.5.5 Drug-Drug Interactions - No studies were conducted to evaluate a drug-drug interaction between Dextenza and any of the concomitant medications allowed in those studies.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity - No carcinogenicity studies were conducted by Ocular Therapeutixs. Dosing is less than 6 months, it has an ocular route of administration, and has been shown to have no systemic exposure.

7.6.2 Human Reproduction and Pregnancy Data - This drug has not been tested in pregnant women.

7.6.3 Pediatrics and Effect on Growth - Safety and effectiveness of Dextenza in pediatric patients below the age of 18 years has not been established. Height and weight data were not collected as part of this protocol.

This application was presented at PeRC on May 11, 2016. Per the agreed Pediatric Study Plan, deferrals (for each or all age groups) were deemed acceptable since the adult studies are completed and ready for approval.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound - Dextenza is a non-narcotic and does not have abuse potential.

7.7 Additional Submissions

In a submission on 10/16/15 (SDN #2) the Applicant submitted the following:
Ocular Therapeutixs, Inc. submitted an initial Pediatric Study Plan (PSP) to the IND #114720 on November 13, 2013, which was agreed to on May 20, 2014. In the PSP, the Agency agreed with Ocular Therapeutixs' proposal to defer the initiation of the pediatric trial until Phase 3 trial data had been obtained to confirm the safety and efficacy of DEXTENZA in adults. The timeline specified that the protocol for the pediatric study would be submitted no later than March 2016, and the clinical trial would be initiated no later than June 2016. However, since the primary endpoint in the pediatric trial is mean grade of anterior chamber inflammation in subjects 0 to 3 years of age, and the efficacy of DEXTENZA for treatment of anterior chamber inflammation has not yet been confirmed in adult subjects, Ocular Therapeutixs plans to submit an amended PSP to reflect the revised timeline. Therefore, at this time a request for deferral is being submitted.

Reviewer's Comment:
The alteration in the pediatric study plan timeline will require a revised PSP be submitted to the IND.

8 Postmarketing Experience - None. This product is not approved in any country.

9 Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting

10 Appendices

10.1 Literature Review/References

A pub med search did not reveal any new information on Dextenza.

10.2 Labeling Recommendations

See Appendix # 2.

.

APPENDIX #1

Clinical Investigator Financial Disclosure
Review Template

Application Number: 208-742
Submission Date(s): 9/24/15
Applicant: Ocular Therapeutixs
Product: Dextenza
Sustained release dexamethasone 0.4mg intracanillicular depot

Reviewer: Sonal D. Wadhwa, MD
Date of Review: 4/11/16
Covered Clinical Study (Name and/or Number): OTX-13-002 and OTX-14-003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 32		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: 2		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (Request details from applicant) *see below
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (Request information from applicant) *see below
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether

these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Reviewer's Comment:

(b) (6) *patients in the trial* (b) (6) *only enrolled* (b) (6) *patients in the trial which would not be enough to alter the results.*

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[1] See [web address].

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILEY A CHAMBERS
07/07/2016
For Sonal D. Wadhwa, MD