

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208742Orig1s000

PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: 208742
Supporting document: SD 33 (Class 2 resubmission)
Applicant's letter date: January 19, 2017
CDER stamp date: January 19, 2017
Product: Dextenza™ (dexamethasone insert) for
intracanalicular use
Indication: Treatment of ocular pain following ophthalmic
surgery
Applicant: Ocular Therapeutix, Inc.
Review Division: Division of Transplant and Ophthalmology
Products (DTOP), Office of Antimicrobial
Products (OAP), CDER, HFD-590
Reviewer: Andrew J. McDougal, PhD, DABT, DTOP
Supervisor/Team Leader: Lori E. Kotch, PhD, DABT, DTOP
Division Director: Renata Albrecht, MD, DTOP
Project Manager: Judit Milstein, DTOP

1 Executive Summary

1.1 Introduction

- On September 24, 2015, Ocular Therapeutix submitted NDA 208742 as a new drug application (NDA) under the 505(b)(2) pathway for DEXTENZA™.
- A Complete Response (CR) letter was sent to the Applicant on July 21, 2016. The Applicant's Class 2 resubmission was received January 19, 2017.
- The NDA was submitted electronically (available internally via <\\CDSESUB1\EVSPROD\NDA208742\208742.enx>)
- The purpose of this review is to document the lack of regulatory concern for the specifications of four specific impurities in the drug substance.

1.2 Brief Discussion of Nonclinical Findings

- Reference is made to the nonclinical Pharmacology/Toxicology (P/T) review (McDougal, 7/11/2016, NDA 208742) of the original NDA submission.
- In June 2017, the Quality team alerted P/T (Tiwari and Zhang/McDougal, personal communication) to the presence of four specific impurities in the drug substance, (b) (4), with specifications set to not more than (NMT) (b) (4) %.
 - Based on the structures, Quality considered them to be (b) (4) and of potential concern.
 - P/T acknowledges that the 4 structurally-related impurities are expected to be mutagenic. P/T confirms that exposures to these impurities are not a regulatory concern for Dextenza™.
- The Applicant has a letter of authorization for drug master file (DMF) # (b) (4). The NDA directly provided information from the DMF. This reviewer verified structures using the published literature. Only published information without trade names, NDA #s, or DMF #s were considered for review. This approach is consistent with best review practices for 505(b)(2) NDAs.

1.3 Recommendations

1.3.1 Approvability

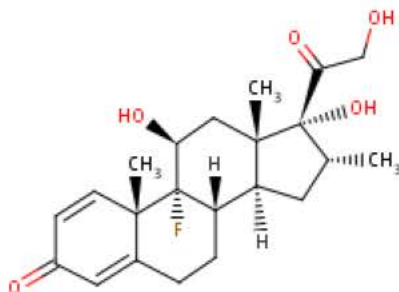
From a nonclinical perspective, DTOP recommends approval of this NDA.

1.3.2 Additional Non Clinical Recommendations

None.

2 Drug Information

2.1 Drug

CAS Registry Number	50-02-2
Generic Name	Dexamethasone
Code Names	• OTX-DP • Dexamethasone punctum plug
Chemical Name	9-fluoro-11 β ,17,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione
Molecular Formula	C ₂₂ H ₂₉ FO ₅
Molecular Weight	392.47 g/mol
Structure	 Figure 1: Chemical structure of dexamethasone
Pharmacologic Class	anti-inflammatory 9-fluoro-glucocorticoid

2.5 Comments on Impurities/Degradants of Interest

- Module 3.2.S.4.5 Justification of Specification (Dexamethasone, (b) (4) explains that the Applicant has a letter of authorization to DMF # (b) (4) a wholly owned subsidiary of (b) (4) is the manufacturer of the (b) (4) dexamethasone, USP drug substance incorporated into DEXTENZA.” The letter was provided in NDA module 1.4.1 (dated April 11, 2012).
 - The Applicant reports that the drug substance is in compliance with USP and ICH guidelines. Under module 3.2.S.4.1, the Applicant provided USP Monograph for Dexamethasone
- For the NDA, module 3.2.S.4 Control of Drug Substance [Dexamethasone, (b) (4) ([\\cdsesub1\evsprod\nda208742\0000\m3\32-body-data\32s-drug-sub\dexamethasone-\(b\) \(4\)\32s4-contr-drug-sub\32s41-spec\specification.pdf](\\cdsesub1\evsprod\nda208742\0000\m3\32-body-data\32s-drug-sub\dexamethasone-(b) (4)\32s4-contr-drug-sub\32s41-spec\specification.pdf)]

), the Applicant provided the same specification information provided in the DMF. This information is summarized in the table below.

Table 1: Impurity specifications for the dexamethasone drug substance

Name	Specification (chromatographic purity by HPLC)	Total exposure per 2 inserts ^a	Information from DMF (b) (4) or the published literature
Total impurities	≤ (b) (4) %	≤ (b) (4) μg	
Unspecified impurities	≤ (b) (4) %	≤ (b) (4) μg	
Any individual impurity	≤ (b) (4) %	≤ (b) (4) μg	
(b) (4)	≤ (b) (4) %	≤ (b) (4) μg	Synonyms: (b) (4)
(b) (4)	≤ (b) (4) %	≤ (b) (4) μg	Synonyms: (b) (4)

¹ Structures and CAS registry numbers (CASRN) obtained from Toxnet: US National Institutes of Health (NIH). U.S. National Library of Medicine. Toxnet Toxicology Data Network. Accessed via <https://chem.nlm.nih.gov/chemidplus>

	(b) (4)
(b) (4)	
(b) (4)	

^aEach Dextenza insert contains a 0.4 mg dose of dexamethasone. A protective approach is to assume placement of inserts in both eyes.

Notes regarding general qualification of the impurities

- Per ICH Q3A², the identification threshold is (b) (4) %, and the qualification threshold is (b) (4) %.
- For the 35-day toxicity study of the dexamethasone punctum plug in dogs (report # TR0161) tested drug product lots 02151201 and 02151203, manufactured by the Applicant using drug substance with the same specification (i.e. referenced to (b) (4) DMF (b) (4)). Therefore, this reviewer considers the impurities qualified.
 - Note that this determination is made without prejudice to other toxicology studies that may have been conducted using (b) (4) dexamethasone drug substance.

Notes regarding potential mutagenic potency

- Neither the Applicant nor the referenced DMF identified toxicity information for these impurities. Likewise, a literature search by this reviewer identified no experimental information relevant to genotoxicity or carcinogenicity.
- As the Quality team noted, the presence of (b) (4) raise concern for (b) (4) activity, and therefore genotoxicity. In the absence of additional information, this reviewer presumes each of these four impurities are mutagenic.
- Dextenza is an ophthalmic intracanalicular insert that is inserted in the lower lacrimal punctum and into the canaliculus following ophthalmic surgery. A single Dextenza releases a 0.4 mg dose of dexamethasone for up to 30 days following insertion.
 - A protective approach is to assume Dextenza treatment of both eyes.
- Per ICH M7³, intake of an individual mutagenic impurity at 120 µg/day for ≤ 1 month is acceptable. Intake of an individual impurity at 1.5 µg/day for a lifetime is acceptable. Therefore, DTOP has no regulatory concerns for the safety of the exposures listed in Table 1 of this review.

² CDER/CBER 2008 Guidance for Industry. ICH Q3A Impurities in New Drug Substances. Accessed via:
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073385.pdf>

³ CDER/CBER 2015 Guidance for Industry. ICH M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk. Accessed via
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf>

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/s/

ANDREW J MCDOUGAL
06/21/2017

LORI E KOTCH
06/21/2017

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: 208742

Supporting documents SD1 (new NDA)

(SD): SD20 (Nonclinical response to information request, received 5/05/2016)

SD30 (Nonclinical response to information request, received 6/23/2016)

Applicant's letter date: September 24, 2015

CDER stamp date: September 24, 2015

Product: Dextenza™ (dexamethasone insert) for ophthalmic intracanalicular use

Indication: Treatment of ocular pain associated with ophthalmic surgery

Applicant: Ocular Therapeutix, Inc.

Review Division: Division of Transplant and Ophthalmology Products (DTOP), Office of Antimicrobial Products (OAP), CDER, HFD-590

Reviewer: Andrew J. McDougal, PhD, DABT, DTOP

Supervisor/Team Leader: Lori E. Kotch, PhD, DABT, DTOP

Division Director: Renata Albrecht, MD, DTOP

Project Manager: Judit Milstein, DTOP

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1 Executive Summary

1.1 Introduction

- On September 24, 2015, Ocular Therapeutix submitted NDA 208742 as a new drug application (NDA) under the 505(b)(2) pathway, requesting a standard review designation for DEXTENZA™.
- DEXTENZA™ (dexamethasone insert) for ophthalmic intracanalicular use is a 3 millimeter cylindrical shaped rod, comprised of 0.4 mg of USP dexamethasone with a fluorescent PEG-based hydrogel (b) (4).
 - The proposed indication is single-use, for treatment of ocular pain occurring after ophthalmic surgery.
 - The physician will dilate the lacrimal punctum if necessary, then place the drug product into the inferior vertical canaliculus of the eye, so that the (b) (4) is placed just below the punctal opening. The physician may hydrate the product with saline (to cause it to expand and fill the space).
 - The product has a small amount of fluorescein conjugated (b) (4) % of the product by weight), so that it can be visualized (when illuminated with a blue slit lamp, and viewed with a yellow filter).
 - The product is intended to deliver a tapered dose of dexamethasone to the surface of the eye for approximately 30 days.
 - The hydrogel vehicle hydrolyses (softening and liquefying), to allow for sustained release of dexamethasone. As the product dissolves, the residual is cleared into the nasolacrimal duct.
- This clinical development was performed under the Applicant's IND 114720
- The NDA was submitted electronically (available internally via <\\CDSESUB1\EVSPROD\NDA208742\208742.enx>)
- The nonclinical data package is comprised of data submitted to the NDA, and data for two listed drugs upon which the Applicant relies in seeking approval of its NDA. The data package is, from a Nonclinical Pharmacology and Toxicology (P/T) perspective, adequate to support approval. P/T has no objection to approval of the NDA.

1.2 Brief Discussion of Nonclinical Findings

- Dexamethasone is an anti-inflammatory corticosteroid. Corticosteroids act via the glucocorticoid receptor. Multiple NDAs are approved for dexamethasone, and specifically for ocular dosing of dexamethasone.
- The Dextenza™ drug product is a punctum plug.
 - FDA's Center for Devices and Radiologic Health (CDRH) has approved punctum plugs (e.g. silicone plugs) as medical devices. An example indication¹ is "for use in patients experiencing dry eye symptoms such as redness, burning, reflex tearing, itching or foreign body sensations which

¹ 510(k) summary for K040231 accessed via http://www.accessdata.fda.gov/cdrh_docs/pdf4/k040231.pdf

- can be relieved by occluding the lacrimal drainage system in order to increase tear volume.”
- The Dextenza™ drug product is different than medical devices, in that it is intended to deliver a tapered dose of dexamethasone, and is intended to hydrolyze and dissolve.
 - The nonclinical studies to support this drug product were completed prior to the initial testing of the sustained release dexamethasone intracanalicular (b) (4) in patients.
 - This nonclinical P/T review:
 - Identified no new safety issues related to the dexamethasone drug substance
 - Predicted irritation related to the placement of the (b) (4) in the puncta, and also predicted the loss of the implant (presumably dislodged by rubbing the eye; possibly dissolving enough to enter further into the nasolacrimal duct, away from the surface of the eye).
 - Qualified the new formulation of the (b) (4) drug product.
 - For study # TR0161, dogs received the dexamethasone (b) (4) placed into the inferior punctum of the right eye, for up to 35 days. The implants caused ocular discharge, and an increased incidence and severity of reduced pupillary light reflex (PLR).
 - The Applicant provided additional nonclinical studies, which support the safety of the vehicle/excipients used in the final drug product.
 - The drug product uses USP dexamethasone, which supports bridging of nonclinical pharmacology and toxicology data.
 - The Applicant submitted NDA 208742 under the 505(b)(2) pathway, relying on the Agency’s findings of safety for two listed drugs approved for topical ocular use: Maxidex (NDA 13-422)² and Decadron (NDA 11-984).
 - At the DTOP Filing Meeting for this NDA, Clinical Pharmacology confirmed that the patient systemic exposure to dexamethasone from Dextenza™ is lower than the patient systemic exposure from Maxidex® 0.1% dexamethasone ophthalmic suspension (Abhay/McDougal, 11/04/2015).
 - Because the systemic exposure of Dextenza® is less than Maxidex®, the Agency’s finding of safety for Maxidex® supports the systemic safety of Dextenza™. [The ocular safety of Dextenza™ is supported by the Applicant’s study # TR0161].
 - For Maxidex®, Section 8.1 of the label summarized two papers (Kasirsky and Lombardi 1970, and Ballard et al. 1977).
 - The Applicant submitted three published papers important from a nonclinical perspective to support safety. These papers have previously been reviewed by P/T:

² For NDA 13-422, the most recent labeling available at Drugs@FDA was approved April 17, 2003, and is accessible via: http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/13422slr035_maxidex_lbl.pdf

- Kasirsky and Lombardi 1970³, which tested a commercial dexamethasone product, Decadron. The Applicant's reliance on this paper is acceptable, because the Applicant listed the same commercial drug product.
 - Ballard et al. 1977⁴, which tested dexamethasone acetate and dexamethasone alcohol (no commercial drug product names mentioned). The Applicant's reliance on this paper is acceptable.
 - Singh et al. 1994⁵, a genotoxicity evaluation of dexamethasone (no commercial drug product name mentioned). The Applicant's reliance on this paper is acceptable.
- P/T concludes that the combination of submitted primary data, the listed drugs, and the published papers are adequate to support safety of the NDA.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical perspective, DTOP recommends approval of this NDA.

1.3.2 Additional Non Clinical Recommendations

None.

³ Kasirsky G, Lombardi L. 1970. Comparative teratogenic study of various corticoid ophthalmics. Toxicology and Applied Pharmacology 16:773-778. <http://www.ncbi.nlm.nih.gov/pubmed/5422219>

⁴ Ballard PD, Hearney EF, Smith MB. 1977. Comparative teratogenicity of selected glucocorticoids applied ocularly in mice. Teratology 16:175-180. <http://www.ncbi.nlm.nih.gov/pubmed/929433>

⁵ Singh H, Singh JR, Dhillon VS, Bali D, Paul H. 1994. *In vitro* and *in vivo* genotoxicity evaluation of hormonal drugs. II. Dexamethasone. Mutat Res. 308(1):89-97. <http://www.ncbi.nlm.nih.gov/pubmed/7516489>

1.3.3 Labeling

The Applicant submitted annotated draft labeling in the original NDA (9/24/2015⁶), and then on revised annotated draft labeling on 10/30/2015, 11/04/2015, 3/30/2016, and 5/05/2016⁷. To the extent feasible, P/T recommendations use the Applicant's language (e.g. from a previous draft of the labeling, if the previous language is acceptable but the current language isn't). P/T comments on selected portions of the proposed draft package insert:

Applicant's version (5/05/2016 version)	P/T version
8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy <i>Risk Summary</i> There are no adequate or well-controlled studies with DEXTENZA in pregnant women. Animal reproduction studies (b) (4) topical ocular (b) (4) [REDACTED]	There are no adequate or well-controlled studies with DEXTENZA in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, administration of topical ocular dexamethasone to pregnant mice and rabbits during organogenesis produced embryofetal lethality, cleft palate and multiple visceral malformations [see Data].
<i>Animal Data</i> [REDACTED] (b) (4)	Animal Data Topical ocular administration of 0.15% dexamethasone (0.75 mg/kg/day) on gestational days 10 to 13 produced embryofetal lethality and a high incidence of cleft palate in a mouse study. A daily dose of 0.75 mg/kg/day in the mouse is approximately 5 times the entire dose of dexamethasone in the DEXTENZA product, on a mg/m² basis. In a rabbit study, topical ocular administration of 0.1% dexamethasone throughout organogenesis (0.36 mg/day, on gestational day 6 followed by 0.24 mg/day on gestational days 7-18) produced intestinal anomalies,

⁶ Accessible internally via: <\\cdsesub1\evsprod\nda208742\0000\m1\us\draft-annotated-labeling.pdf>

⁷ Accessible internally via: <\\cdsesub1\evsprod\nda208742\0017\m1\us\draft-annotated-labeling.pdf>

	intestinal aplasia, gastroschisis and hypoplastic kidneys. A daily dose of 0.24 mg/day is approximately 6.5 times the entire dose of dexamethasone in the DEXTENZA product, on a mg/m² basis.
8.2 Lactation Systemically administered corticosteroids appear in human milk and could suppress growth and interfere with endogenous corticosteroid production. (b) (4) [REDACTED]	8.2 Lactation Systemically administered corticosteroids appear in human milk and could suppress growth and interfere with endogenous corticosteroid production; however the systemic concentration of dexamethasone following administration of DEXTENZA is low [see Clinical Pharmacology 12.3]. There is no information regarding the presence of DEXTENZA in human milk, the effects of the drug on the breastfed infant or the effects of the drug on milk production to inform risk of DEXTENZA to an infant during lactation. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DEXTENZA and any potential adverse effects on the breastfed child from DEXTENZA (b) (4) [REDACTED]
12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action (b) (4) [REDACTED]	12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action Dexamethasone, a corticosteroid, has been shown to suppress inflammation by inhibiting multiple inflammatory cytokines resulting in decreased edema, fibrin deposition, capillary leakage, and migration of inflammatory cells.

(b) (4)	
13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
(b) (4)	No adequate studies in animals have been conducted to determine whether DEXTENZA (b) (4) has the potential for carcinogenesis.
(b) (4)	(b) (4) Dexamethasone was not mutagenic in the Ames/Salmonella assay, both with and without metabolic activation. Dexamethasone was genotoxic in two <i>in vitro</i> assays using human lymphocytes (chromosomal aberration assay and sister chromatid exchange assay) and was genotoxic in two mouse <i>in vivo</i> assays (micronucleus assay and sister chromatid exchange assay).

(b) (4)

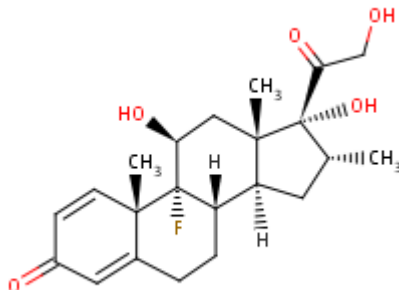
Fertility studies have not been conducted in animals using DEXTENZA.

Fertility studies have not been conducted in animals using DEXTENZA.

(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number	50-02-2
Generic Name	Dexamethasone
Code Names	• OTX-DP • Dexamethasone punctum plug
Chemical Name	9-fluoro-11 β ,17,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione
Molecular Formula	C ₂₂ H ₂₉ FO ₅
Molecular Weight	392.47 g/mol
Structure	 Figure 1: Chemical structure of dexamethasone
Pharmacologic Class	anti-inflammatory 9-fluoro-glucocorticoid

2.2 Relevant INDs, NDAs, and DMFs

- The Applicant developed Dextenza™ under IND 114720.
- IN The Applicant provided a letter of authorization from (b) (4) for DMF # (b) (4) Dexamethasone USP (b) (4) ([\\cdsesub1\evsprod\nda208742\0000\m1\us\loa-\(b\) \(4\) dmf-\(b\) \(4\) pdf](#))
- The Applicant listed Decadron®, NDA 011-984 solution/drops; ophthalmic, 0.1% phosphate.
 - Note: Decadron® is the tradename for multiple Merck NDAs for dexamethasone, all discontinued (NDAs 011664, 011977, 011983, 011984, 012071, 012376).
- The Applicant listed Maxidex® (NDA 13-422)
- In Section 2.4 of the NDA, the Applicant provided a list of other FDA-approved ophthalmic dexamethasone products:

Table 1: Applicant's listing of other FDA-approved ophthalmic dexamethasone products

NDA	Product
011977	Decadron® dexamethasone sodium phosphate 0.05% ointment

011984	Decadron® dexamethasone sodium phosphate 0.1% solution/drops
013422	Maxidex® 0.1% dexamethasone ophthalmic suspension
050023	Maxitrol® dexamethasone 0.1%/neomycin 0.35%/polymyxin B sulfate 10,000 IU ophthalmic suspension
050065	dexamethasone 0.1%/neomycin 3.5 gm/polymyxin B sulfate 10,000 IU ophthalmic ointment
062341	dexamethasone 0.1%/neomycin 0.35%/polymyxin B sulfate 10,000 IU ophthalmic suspension
050592	Tobradex® dexamethasone 0.1%/tobramycin 0.3% ophthalmic suspension
050616	Tobradex® dexamethasone 0.1%/tobramycin 0.3% ophthalmic ointment)
050818	Tobradex® ST dexamethasone 0.05%/tobramycin 0.3% ophthalmic suspension
022315	Ozurdex® dexamethasone 0.7 mg implant; intravitreal

2.3 Drug Formulation

- The Applicant's proposed dosage form language is "Fluorescent yellow 3 mm cylindrical shaped (b) (4) containing dexamethasone 0.4 mg (b) (4)
- The Applicant's proposed description is "DEXTENZA (b) (4) dexamethasone) is a fluorescent yellow 3 mm cylindrical shaped (b) (4). DEXTENZA contains 0.4 mg dexamethasone in a polyethylene glycol (PEG) based hydrogel conjugated with fluorescein."
- The dimensions of the drug product are (NDA module 3.2.P.5 Control of Drug Product):
 - Dry diameter (b) (4) 0.55 mm
 - Dry length (b) (4) 3 (b) (4) mm
- The drug formulation is presented in the NDA's module 2.3.P.1 Description and Composition of the Drug Product:

Table 2: Formulation of the DEXTENZA Drug Product

Ingredient	Amount (%)	Amount (µg)	Function
Dexamethasone, (b) (4) USP	(b) (4)	400	Active pharmacologic ingredient (API)
4-arm 20K PEG-SG		(b) (4) (4)	
Trilysine acetate			
NHS-fluorescein			
Sodium phosphate dibasic, USP			
Sodium phosphate			

monobasic, (b) (4) USP			
---------------------------	--	--	--

Note: the pivotal nonclinical study (report # TR0161) studies tested two formulations, one of which (formulation B) is similar to (but not the same as) the clinical formulation (see Table 8 and Table 10 of this review, below). Notable differences that the nonclinical (b) (4)

2.4 Comments on Novel Excipients

- Exposure to fluorescein, trilycine, (b) (4) are adequately qualified by the 35-day dog toxicity study (TR-0161), and are not safety concerns for this NDA.
- The “4-arm 20K PEG” is 4-arm PEG N-Hydroxysuccinimide Glutarate (20K), described as (b) (4) (NDA file: ps-10-2001-001-4-arm-20k-peg-sg.pdf). The Supplier is (b) (4) (part # 10-2001-001). The supplier’s website⁸ provided a CAS # (b) (4) and structure:

(b) (4)

(b) (4)

(b) (4)

2.5 Comments on Impurities/Degradants of Concern

P/T confirmed for CMC (personal communication 3/11/2016) that that the 4-arm 20K PEG succinmidyl glutarate, trilysine acetate, NHS-fluorescein, sodium phosphate dibasic, and sodium phosphate monobasic are adequately qualified for this drug product, and are not safety concerns.

2.6 Proposed Clinical Population and Dosing Regimen

- The Applicant's proposed indication for DEXTENZA ((b) (4) dexamethasone) is "treatment of ocular pain (b) (4) ophthalmic surgery"
- The Applicant proposes that the 0.4 mg (b) (4) be placed into the canaliculus following ophthalmic surgery (i.e. single dose only) for one or both eyes.

2.7 Regulatory Background

- For Ocular Therapeutix Inc.'s IND 114720:
 - A type B preIND meeting was held on May 16, 2012
 - The Sponsor submitted the IND to DTOP on August 20, 2012
 - At the end-of-phase 2 (EOP2) meeting on September 13, 2013 for IND 114720, P/T concurred that no additional nonclinical studies would be needed to support an NDA for the proposed indication (i.e. the indication sought under this NDA).
- For Ocular Therapeutix Inc.'s NDA 208742, the new NDA was submitted on September 24, 2015.

3 Studies Submitted

3.1 Studies Reviewed

Table 3: Toxicology testing for the drug product

Report #	Report title
TR0161	35 day toxicity study of the dexamethasone punctum plug with a 2 week recovery period
TR 0183	Dexamethasone punctum plug pharmacokinetic study in the canine eye model

Table 4: Toxicology testing for test articles other than the drug product

Report #	Report title
TR 0235	Cytotoxicity testing of foil pouch and & [sic] (b) (4)
(b) (4)	
TD0263	Cytotoxicity study using the ISO agarose overlay method - solid
TD 0167	Dexamethasone punctum plug prolonged exposure biocompatibility testing
(b) (4)	

Note: despite the titles, these six studies did not test plug material containing dexamethasone.

3.2 Studies Not Reviewed

Report #	Report title
RPT-OCUTX-DEXA-02022012	Method validation for dexamethasone <i>in vivo</i> quantitation for beagle plasma and tear using liquid chromatography with tandem mass spectrometric detection (LC_MS_MS assay)



3.3 Previous Reviews Referenced

This P/T review references:

- The P/T reviews for the predecessor IND 114720 (Rivera, 5/03/2012; McDougal, 8/31/2012; McDougal, 9/19/2012; McDougal, 9/12/2013)
- The P/T review for Maxidex® (NDA 13-422)
- The P/T review for Decadron 0.1% (NDA 11-984)

4 Pharmacology

No nonclinical pharmacology studies were submitted to support this NDA.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Study title: Dexamethasone punctum plug pharmacokinetic study in the canine eye model

Study no.:	TR0183
Report date:	July 2012
Study report location:	NDA Module 4.2.3 (Nonclinical study reports – Toxicology) - Study report (\\cdsesub1\evsprod\nda208742\0000\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\tr0183\tr0183-rev-b-canine-pharmacokinetic-study.pdf) - Study protocol (\\cdsesub1\evsprod\nda208742\0000\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\tp0183\tp0183-rev-b-canine-pharmacokinetic-study.pdf)
Conducting laboratory and location:	(b) (4) - Tear fluid analysis at (b) (4)
GLP compliance:	No
Drug, lot #, and % purity:	Dexamethasone punctum plug manufactured at Ocular Therapeutix, lot #s NB082-114A, B and C. Composition: (b) (4) 4a20K SG hydrogel containing approximately 380 µg of dexamethasone

Key Study Findings

- Note: this study did not test the clinical drug product. A different formulation was tested (i.e. relatively (b) (4)) than both the clinical product, and the test articles for the pivotal dog study (report # TR0161).
- For dogs bearing 380 µg dexamethasone punctum plugs, the authors report tapered drug delivery of 28 days.
 - 70% (267 µg) by D7
 - 77% (293 µg) by D15
- No signs of ocular toxicity were detected.

Method notes

- 20 female beagle dogs (non-naïve), weighing 5 to 10 kg, were fasted, sedated, and then both eyes received punctal implants:
 - 1 or 2 drops of 0.5% proparacaine hydrochloride were instilled to each eye
 - Punctum gently dilated with a stainless steel dilator, as needed (data not recorded)
 - Dexamethasone punctum plug inserted into the inferior canaliculus if present/normal, or the superior canaliculus (if the inferior canaliculus was defective/absent) just under the punctal opening using forceps (data not recorded)

- After insertion, the plug area was hydrated with either balanced salt solution or 0.9% sodium chloride for injection USP
- Gross ocular exam for irritation was performed pre-insertion and every 7 days (D0, D7, D14, D21, D28) for all animals
- Plug retention was assessed every 7 days (D7, D14, D21, D28)
 - Using a cobalt blue flashlight and NightSea yellow glasses to visualize
 - The location of the plug relative to the punctal open was recorded (at surface, middle, or deep)
 - If plug not found, flushing was used to determine if the canal was plugged
- Intraocular pressure (IOP) was reportedly measured on D0 (pre-implantation), D14 and D28 for all remaining animals
- Tear fluid was collected from 6 eyes on D7, 14, 21 and 28
 - “A Schirmer tear strip cut at the 10 mm line will be placed just inside the eyelid of the eye. Tear fluid will be allowed to reach the 10 mm line, if possible, and will be transferred to a vial” for analysis
- Aqueous humor was collected from 6 eyes on D 7, 14, 21, and 28
 - Collected after presence of the plug was verified
 - After collection of the aqueous humor, the plug was removed for content analysis
- *Reviewer comment:* This reviewer was unable to discern when overlap occurred between the eyes/dogs subjected to tear fluid collection and aqueous humor collection

Results notes

- Gross ocular examination found all eyes normal
- No remarkable changes in IOP apparent
- Note: The results section mentions a different study (report # TR0159, not provided to this IND) that tested 462 µg plugs

Table 5: Tear and aqueous humor PK, plug presence/absence for the dog PK study (report # TR0183)

Endpoint	Day 7	Day 15	Day 21	Day 28
Aqueous humor concentration (ng/ml)	4.1 ± 2.6	7.0 ± 3.9	0.7 ± 1.0	0.1 ± 0.2
Tear fluid concentration (ng/ml)	2796 ± 1184	1535 ± 750	1146 ± 320	190 ± 294
Drug content of the explanted plugs (µg)	267 ± 18	87 ± 39	57 ± 34	24 ± 45
Plug present	36	28	17	8
Plug absent	1	3	6	3
Retention rate	97%	90%	74%	73%

PK values presented as mean ± standard deviation

Table 6: Dexamethasone did not affect IOP in the dog PK study (report # 0183)

Endpoint	Day 0	Day 15	Day 28
N =	19 dogs (38 eyes)	17 dogs (28 eyes)	6 dogs (8 eyes)
IOP (mm Hg)	20.7 $\pm$ 2.8	24.4 $\pm$ 3.5	20.5 $\pm$ 3.0

6 General Toxicology

6.2 Repeat-Dose Toxicity

- The Applicant provided one 35-day dog study (report TR0161), testing a formulation similar to the clinical OTX-DP formulation (formulation B), as well as a different formulation (formulation A). OTX-DP was well tolerated.
- The Applicant submitted a 4 week toxicology study in rats following subcutaneous implantation of a vehicle implant (report # TR0174).

Study title⁹: 35 day dexamethasone punctum plug toxicity study with a 2 week recovery period

Study no.:	- TR0161 - Study laboratory report # 12-0419-G1
Study report location:	NDA Module 4.2.3 (Nonclinical study reports – Toxicology) - Study report \\cdsesub1\evsprod\nda208742\0000\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\tr0161\tr0161-rev-b-35-day-toxicity-study.pdf - Study protocol \\cdsesub1\evsprod\nda208742\0000\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\tp0161\tp0161-rev-b-35-day-toxicity-study.pdf
Conducting laboratory and location:	(b) (4)
Report dates:	- Amended final report: March 1, 2013 - Original final report: July 20, 2012
Date of study initiation:	February 23, 2012
GLP compliance:	- Yes, signed - Exception: the TK sample analysis reports are not GLP.
QA statement:	Yes, signed

⁹ This title is used by the Applicant, on their sections of the study report. The study laboratory used a slightly different title, “35 day dexamethasone punctum plug toxicity study with a 14 day recovery period”

- Drug, lot #, and % purity:
- 4 different test articles were compared (two dexamethasone plugs, and their respective placebo plugs).
 - Test article B corresponds to the clinical drug product.
 - Total impurities in each test article were $\leq$ (b) (4) %

Table 7: Test articles and placebos for the 35-day dog study (report # TR0161)

	Dexamethasone (μ g)	Lot #
Test article A	(b) (4)	02151201
Placebo A	0	02151202
Test article B	(b) (4)	02151203
Placebo B	0	02151204

Key Study Findings

- The design and results of this study were adequate to support the safety of investigational clinical trials with the dexamethasone punctum plug, and to qualify two formulations for administration into the lacrimal punctum (puncta lacrimalia).
 - P/T considers this study adequate to qualify the formulation's excipients for use in both the inferior and superior punctum. Due to design limitations (e.g. loss of placement of the drug product), P/T recommends caution in generalizing these results to other route of administration.
 - The B formulation (made with (b) (4)) corresponds to the clinical drug product.
- No true negative control was used (i.e. no treatment, or sham-insertion). Both eyes of each dog on study received a punctum plug. This study did not identify a no observed adverse effect level (NOAEL) for either of the test article plugs or placebo plugs. Compared to the placebo implants, the dexamethasone implants were associated with:
 - decreases in pupillary light reflex (PRL) and increased eye discharge (clear, brown, green, white, yellow) in female dogs
 - Ocular histopathology suggestive of infection (minimal to moderate bacterium in the punctum; mononuclear cell infiltrate in most eyelids, occasional mixed cell infiltrate)
- Plug retention: a key purpose of this study was to assess the adequacy of the route-of-exposure (e.g. the placement procedure, local irritation, plug retention)
 - The plugs are intended to absorb fluid after placement and swell. The authors provided *in vitro* hydration data that demonstrate swelling.
 - Plug B (test article and placebo) was retained better than plug A (test article and placebo).
- TK:
 - No dexamethasone was detected in plasma samples

- Dexamethasone was detected in tear fluid to up 35 days after placement of the punctum plug. The tear TK results are consistent with tapered release of dexamethasone from the punctum plug.

Methods

Table 8: Design of the 35-day dog study (report # TR0161)

Group	# of dogs per sex	OD plug placement	OS plug placement	Day 36 main necropsy	Day 49 recovery necropsy
1 (placebo)	8M / 8F	Placebo A	Placebo B	5M / 5F	3M / 3 F
1 (treated)	8M / 8F	Test article A	Test article B	5M / 6F*	3M / 3 F

*One extra female (the laboratory had intended to remove the female from the study, but the female was not removed early – see below).

Table 9: Formulations used in the 35-day dog study (report # TR0161)

Ingredient (µg/plug)	Test article A	Placebo A	Test article B	Placebo B
Dexamethasone	(b) (4)	0	(b) (4)	0
(b) (4)		(b) (4)		(b) (4)
4-arm 20K PEG SG				
Sodium phosphate dibasic				
Sodium phosphate monobasic				
Trilysine acetate				
NHS-fluorescein				

Note: the excipient amounts (µg/plug) presented in this table were calculated by this reviewer, using the reported data for the (b) (4) (pdf page 313) and the reported amount of dexamethasone per cut plug (pdf page 316).

Table 10: Plug dimensions for the 35-day dog study (report # TR0161)

Dimensions (mm/plug)	Test article A	Placebo A	Test article B	Placebo B
Dry width				(b) (4)
Dry diameter				(b) (4)

Doses:	• Nominally one dose. Most eyes only received 1 plug. • For some eyes, the plugs were observed to be not present; replacement plugs were placed
Route of administration:	Insertion into the inferior or superior canaliculus (i.e. lacrimal punctum) • The inferior punctum was used for most eyes. The inferior punctum was used for all but one dog on D1 (31/32), and was used 12 times when the plug was found to be not present, and was replaced. • Procedure: under sedation, the (inferior or superior) punctum was gently dilated using a stainless steel dilator. The plug was inserted into the canaliculus of the eye using forceps. The plug was then hydrated with balanced salt solution following placement. A surgical scope was used as needed.
Species/Strain:	Beagle dogs
Number/Sex/Group:	8/sex/group
Age:	“at least 6 months of age” (not further specified)
Weight:	5.60 to 8.90 kg

Observations and Results

Mortality

- No animals died prematurely.
- Three dogs were replaced; this is acceptable and not concerning.
 - One dog's OS punctum was too small for placement (i.e. not dosed).
 - The protocol specified that if the plug was not successfully retained during the first week, that the dog would be replaced with another naïve animal. Two dogs were replaced for this reason (#1005 in the placebo group lost both plugs; # 2101 in the treated group lost test article A from the OD punctum).
- One treated female (#1105) was found not to have an OD plug during the first week, and a replacement female was added. Due to an oversight, female # 1105 was not removed. This dog received a second OD plug on D11 (which she retained until the end of study).

Plug Assessment

- D1 (the day of plug placement) was staggered, from 2/28/2012 to 3/13/2012.
- Punctum plugs were assessed twice weekly until Friday, 3/16/2012. The protocol was amended, and punctum plugs were assessed daily Monday through Friday thereafter. The plugs were visualized by:
 - direct visualization (using yellow glasses and a blue-filtered flashlight to excite the fluorescein in the plug),
 - transillumination of the lid, and

- back pressure (i.e. irrigating the canaliculus with saline, to determine whether the plug is blocking the punctum).
- Assessments of the location of the punctum plug relative to the punctal opening were recorded (0 = not present, 1 = surface, 2 = middle, or 3 = deep). If punctum plugs were not present in one or both eyes after the first week, the animal was anesthetized and the plug(s) re-inserted as per the original insertion procedure.

Table 11: Plug reinsertion incidence for the 35-day dog study (report # TR0161)

Dose group	# of replacements	
	Males (8/group)	Females (8/group)
Test article A (OD)	2	10
Test article B (OS)	2	4
Placebo A (OD)	4	14
Placebo B (OS)	2	3

- The authors noted that the A formulation (test article and placebo) was found not present more often than the B formulation (the clinical formulation). This reviewer notes that the difference appears limited to female dogs. The basis for this apparent sex-difference is unclear. Possibly, the dimensions and the expansion upon hydration of placebo A affected its retention.

Clinical Signs

- Clinical signs were assessed daily. Treatment-related observations were limited to ocular discharge, and (for one dog) local edema.
- Female # 2107 was found to be missing the OD plug on D22. The D1 plug had been placed into the inferior punctum; the replacement plug (on D22) was placed into the superior punctum.
 - Slight OD edema was observed on D24 and D25 (resolved by D26)
 - The area around the plug was noted to be red in color from D24 to D28. [pdf page 143].
- The authors considered the eye discharge to be related to the presence of the plug.
 - Increased eye discharge is consistent with the blockage of the puncta by the (placebo and test article) plugs.
 - In the absence of a negative control group without plugged puncta, the true incidence/severity cannot be assessed.
- Discharge was noted in males and females in all groups:
 - Higher incidence in placebo males and test article females
 - Usually clear; colored discharge (clear > brown > green > yellow > white) was infrequently observed
 - The authors conclude that there is no relationship of discharge to dexamethasone (i.e. placebo versus test article), and no difference between the two formulations. This reviewer concurs.

Table 12: Eye discharge results for the 35-day dog study (report # TR0161)

Eye discharge		Placebo plugs				Dexamethasone plugs			
None during study	# dogs	Male		Female		Male		Female	
		A	B	A	B	A	B	A	B
Clear	# dogs	4/8	5/8	5/8	4/8	3/8	3/8	8/9	6/9
	# occurrences	60	31	25	19	28	32	64	45
Brown	# dogs	4/8	4/8	3/8	2/8	2/8	1/8	4/9	2/9
	# occurrences	11	9	12	5	3	3	12	2
Green	# dogs	4/8	4/8	1/8	1/8	2/8	1/8	4/8	2/9
	# occurrences	4	6	2	1	2	3	7	5
Yellow	# dogs	2/8	3/8	1/8	0/8	0/8	1/8	1/9	2/9
	# occurrences	3	3	2	0	0	2	1	3
White	# dogs	3/8	3/8	0/8	0/8	1/8	1/8	3/9	3/9
	# occurrences	3	3	0	0	1	1	3	3

Note: table compiled by this reviewer from the report's individual animal data (pdf pages 127-142), combining main-group and recovery group results.

Body Weights

- No remarkable observations
- Recorded weekly. Animals were fasted prior to necropsy.
- For dexamethasone treated dogs, the mean body weights were:
 - Males on D1: 8.169 kg. Males on D35: 8.515 kg
 - Females on D1: 6.444 kg. Females on D35: 6.566 kg

Feed Consumption

- No remarkable observations
- Assessed quantitatively during a 24-hour period, once per week. Food and water were available *ad libitum*.

Ophthalmoscopy

- Dexamethasone treatment was associated with an increase in "sluggish to absent" pupillary light reflex (PLR) in females on D14 and D35, compared to the placebo plugs.
 - This finding is presumably related to the increased ocular discharge for dexamethasone-treated females compared to placebo-treated females.
- No other treatment-related findings were apparent.
- Fundoscopy was performed prior to dosing (D1) and D35
- Other ophthalmic examinations were performed pre-dose on D1, D14 and D35: slit lamp biomicroscopy (to examine the cornea, conjunctiva, iris, anterior chamber, and lens), assessment of the corneal surface using fluorescein stain, and tonometry. Eyes were scored using a 'combined Draize and McDonald-Shadduck scoring system'

- Ophthalmology examinations were not performed at the end of recovery, based on the author's conclusion that no treatment-related findings had been observed previously.
 - The failure to measure PLR at the end of recovery is a minor study limitation.

Table 13: Decreased pupillary light reflex in dexamethasone-treated female dogs in the 35-day study (report # TR0161)

PLR grade	Day	Placebo plugs				Dexamethasone plugs			
		Male		Female		Male		Female	
		A	B	A	B	A	B	A	B
Grade 1 PLR	1	0	0	0	0	0	0	0	0
	14	1	0	1	1	0	0	0	0
	35	0	0	0	1	0	0	0	0
Grade 2 PLR	1	0	0	0	0	0	0	0	0
	14	0	0	0	0	0	0	1	2
	35	0	0	0	0	0	0	2	2

Note: For PLR, grade 0 was “normal”, grade 1 was “sluggish” and grade 2 was “no pupillary light reflex”.

Hematology

- No remarkable findings
- Blood collected pre-dose (D0) and on D36 and D49 for hematology, clinical chemistry and coagulation endpoints

Clinical Chemistry

No apparent differences identified by the authors or this reviewer.

Urinalysis

- No remarkable findings
- Urine was collected on D36, via cystocentesis [bladder puncture] for main-group animals, and via pan collection for recovery animals

Gross Pathology

- No remarkable findings
- Standard full gross pathology was performed.

Organ Weights

- No remarkable findings
- A standard battery of organs were weighed (adrenals, brain, epididymis, heart, kidneys, liver, lung, ovaries, pituitary, prostate, mandibular salivary gland, spleen, testes, thymus, thyroid, and uterus). For the eye, the specific tissues to be examined were specified: “eyelids, conjunctiva, cornea, lens, iris/ciliary body,

retina/choroid, and optic nerve of each specimen and the punctal area (implant site)”

Histopathology

Adequate Battery: Histopathology was limited to the eyes, eye lid, punctal region (implant site), nasal turbinate, adrenal gland, and gross lesions.

Peer Review: No

Histological Findings:

- **NOTE: The histopathology evaluation is only minimally adequate, because too many critical tissue samples were not evaluated / not present: 30% of the upper left punctal area (10/33 missing), 18% of the upper right punctal area (6/33), 9% of the lower punctal areas (missing 3/33 left and 3/33 right samples)**
- Notably histology findings were limited to the punctal areas:
 - The authors noted that treatment appeared to have “exacerbated” the presence of bacteria within the lumen of the punctum
 - “Foreign material” was detected in the punctal area, and presumed by the authors to be residual test material.

Table 14: Selected histology results for the 35-day dog study (report # TR0161): dexamethasone-related increase in punctal region bacteria

Histopathology observation	Severity score	Placebo plug group		Dexamethasone plug group	
		Male	Female	Male	Female
Upper right punctal area					
Not examined / not present		1/8	2/8	2/8	1/9
Mononuclear cell infiltration, dermal, multifocal	Present	4	2	3	1
Foreign material, luminal, multifocal	Present	0	0	1	0
Foreign material, luminal, focal	Present	1	0	0	0
Lower right punctal area					
Not examined / not present		2/8	0/8	1/8	0/9
Bacterium, luminal, multifocal	Present	1	1	0	3
Bacterium, luminal, focal	Present	0	1	0	0
Hemorrhage, luminal, focal	Present	0	1	0	0

Mononuclear cell infiltration, multifocal	Present	3	3	4	2
Mononuclear cell infiltration, focal	Present	0	0	1	0
Foreign material, luminal, multifocal	Present	0	3	0	2
Foreign material, luminal, focal	Present	0	0	0	1
Foreign material, luminal, diffuse	Present	0	0	1	0
Upper left punctal area					
Not examined / not present		4/8	2/8	1/8	3/9
Bacterium, luminal, multifocal	Present	0	0	0	1
Mononuclear cell infiltration, dermal, multifocal	Present	1	2	0	0
Mononuclear cell infiltration, dermal, focal	Present	0	0	1	0
Foreign material, luminal, focal	Present	0	0	1	0
Lower left punctal area					
Not examined / not present		1	2	0	0
Bacterium, luminal, multifocal	Present	0	0	0	3
Bacterium, luminal, focal	Present	0	0	0	1
Mononuclear cell infiltration, multifocal	Present	1	1	1	1
Mononuclear cell infiltration, focal	Present	0	0	0	1
Foreign material, luminal, multifocal	Present	3	1	1	3
Foreign material, luminal, focal	Present	1	0	0	0

Plasma Toxicokinetics

- Blood samples were collected for TK pre-dose, following implantation on D1 (at 30 minutes and 6 hours), D14 and D35
- Samples were sent to

(b) (4)

(b) (4)

- Dexamethasone concentrations were below the limit of quantitation (LOQ) for all samples. However, the LOQ was not reported. The failure to report the LOQ is a study limitation.

Tear Toxicokinetics

- Tear film samples were collected with Schirmer tear test strips, at D1 (6 hours after implant), D7, D14, D21, D28, and D35.
- Samples were also sent to (b) (4)
- T_{max} was formulation dependent: D10 for test plug A, D5 for test plug B

Table 15: Tear TK results for the 35-day dog study (report # TR0161)

	Formulation B (OS) Mean $\pm$ SD	Formulation B Range	Formulation A (OD) Mean	Formulation A Range
C_{max} (ng/ml)	5795 $\pm$ 1870	2640-8450	6355 $\pm$ 2403	3250-13,700
T_{max} (day)	5 $\pm$ 8	0.25 to 28	10 $\pm$ 11	0.25 to 28
AUC ₀₋₃₅ (ng*day/ml)	100,200 $\pm$ 30900	57,000 to 174,000	119,000 $\pm$ 62100	55,800 to 300,000

Table 16: Formulation B (OS, the clinical formulation) tear fluid TK for the 35-day dog study (report # TR0161)

Time (days)	Median (ng/ml)	Average (ng/ml)	Standard deviation (mg/ml)	N
0.25	4600	4534	2520	14
7	2990	3418	1660	14
14	2558	2538	540	14
21	1980	2114	940	14
28	1840	1814	640	12
35	1153	1182	950	10

Dosing Formulation Analysis

- Dry (i.e. pre-implanted) punctum implants were analyzed by HPLC for dexamethasone concentration and impurities. The analyses were adequate.
- On D35, remaining punctum plugs were harvested at necropsy, and sent to the Sponsor for analysis. The study report has no results for these residual samples.

Study titles:

- Author's title: **4 week systemic toxicity study in rats following subcutaneous implantation**
- Applicant's title¹⁰: **Subchronic toxicity testing of the travoprost 60 day fluorescent punctum plug**

- Study no.:
- TR0174 (Applicant's study number)
 - TO118_904 (Study laboratory's study number)

- Study report location:
- NDA Module 4.2.3 (Nonclinical study reports – Toxicology)
- Study report
(\\cdsesub1\evsprod\nda208742\0000\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\tr0174\tr0174-rev-a-subchronic-toxicity-testing.pdf)
 - Study protocol
(\\cdsesub1\evsprod\nda208742\0000\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\tp0174\tp0174-rev-a-subchronic-toxicity-testing.pdf)

Conducting laboratory and location:

(b) (4)

Report date: August 20, 2012

Date of study initiation: May 14, 2012

Test article implanted: June 4, 2012

End of in-life: July 2, 2012

GLP compliance: Yes, signed

QA statement: Yes, signed

- Test and control articles:
- Note: the test article is a placebo plug. It did not contain travoprost (or dexamethasone).
 - Test article: "PEG hydrogel containing fluorescein and (b) (4) identification # 03291201, "composition: (b) (4) 4a20KSG (b) (4) (b) (4) and (b) (4) fluorescein"
 - No purity information
 - Control article: high density polyethylene (HDE)
 - Cut to 1 mm x 1 mm x 13 mm sections
 - Steam sterilized

Key Study Findings

- The placebo plug was found to be non-irritating in this screening study.
- Limited toxicity endpoints were assessed (clinical observations, body weight, hematology and clinical chemistry, histopathology for selected tissues).

¹⁰ Note: this was a 4-week study. The '60 day' in the title refers to the intended release rate. The word 'travoprost' in the title refers to this placebo test article being developed as to support development of a travoprost-containing plug.

- Note: the test article was not the clinical formulation (i.e. tested a (b) (4), rather than using only the 4-arm 20K PEG). The authors noted that this product is relevant to the dexamethasone punctum plug “as they share common components”. This test article is similar to the placebo B tested in the pivotal nonclinical study (report # TR0161).

Methods

Doses:	Single dose study (one implant per rat) of either the placebo plug, or a plastic (control) plug
Route of administration:	Subcutaneous implant: “one incision large enough to accommodate the article was made on the left side of the back through the skin and parallel to the spinal column. A pocket was formed by blunt dissection in the subcutaneous tissue ... One test article section (along with a location marker) was implanted ... the skin was closed with stainless steel wound clips”
Species/Strain:	Sprague Dawley rat
Number/Sex/Group:	6/sex/dose
Age:	Approximately 7 weeks old at acclimation
Weight:	Males 224 to 247 grams at start of acclimation Females 160 to 182 grams at start of acclimation

Observations and Results

Test article characterization

- The report notes that the test articles were larger than the punctum plugs, “to provide a larger volume of material required for the test”.
 - The report references ISO 10993-1 “Biological evaluation of medical devices – Part 1: evaluation and testing within a risk management process” and ISO 10993-11 “Biological evaluation of medical devices – Part II: tests for systemic toxicity”
- The plugs were 13 mm (compared to 3 mm for the Dextenza). Two placebo plugs (lot # 03291201) were weighed, and were 25.1 and 34.45 mg, respectively (i.e. substantially larger than the Dextenza clinical product).

Mortality

- No premature deaths

Clinical Signs

- No remarkable findings
- Cage checks were performed daily. Detailed clinical observations were assessed weekly.

Body Weights

- No remarkable findings
- Body weight was measured weekly
- Food consumption was not measured. Animals were fasted overnight prior to necropsy on D28.

Hematology and Clinical Chemistry

- No remarkable findings
- Blood was collected at necropsy (D28) only. The standard battery of hematology and clinical chemistry endpoints were evaluated.
- Notably, no coagulation endpoints were assessed.

Gross Pathology

- No remarkable findings
- The implant sites were all reportedly normal.

Organ Weights

- No remarkable findings.
- The list of weighed tissues was: adrenals, brain, heart, kidneys, liver, ovaries, spleen, testes, and thymus.

Histopathology

Adequate Battery: No. Tissues evaluated were: liver, spleen, kidneys, submandibular lymph node, adrenal, heart, thymus, mesenteric lymph node, lung, testes, and ovaries.

Peer Review: No

Histological Findings: Histopathology of the sc implant site is not concerning. Several observations are remarkable, but the relationship to treatment is unclear in the absence of an untreated group. The implant sites all exhibited minimal infiltration of macrophages and lymphocytes, with minimal-to-mild fibrosis.

- Traumatic necrosis at the implant site was noted for 3 control rats (implanted with the HDPE plastic), but not for the test article-treated rats.

Table 17: Histopathology results from the sc rat study with the placebo formulation (report # TR0174)

Organ/tissue lesion	Severity	Control article (HPDE)		Test article (PEG hydrogel containing fluorescein)	
		Male	Female	Male	Female
Liver - hepatocellular c topasmic vacuolation, periportal, multifocal	Minimal	0/6	3/6	0/6	1/6
	Mild		1/6		1/6

Heart – cardiomyopathy, multifocal	Minimal	0/6	0/6	2/6	0/6
Kidneys					
Progressive nephropathy, bilateral or unilateral	Minimal	3/6	4/6	5/6	6/6
	Mild	1/6	0/6	0/6	0/6
Dilated renal pelvis	Minimal	0/6	1/6	1/6	2/6
	Mild	0/6	1/6	0/6	0/6
Mineralization, unilateral or bilateral	Minimal	0/6	5/6	2/6	3/6
	Mild	1/6	1/6	0/6	2/6
Lungs					
Alveolar hemorrhage	Minimal	3/6	0/6	1/6	1/6
	Mild	0/6	1/6	0/6	0/5
Alveolar histiocytosis	Minimal	2/6	1/6	1/6	0/6

7 Genetic Toxicology

- The Applicant provided adequate information to assess the genotoxic potential of Dextenza®.
 - The Applicant did not conduct any genotoxicity studies with Dextenza™ (or other dexamethasone-containing formulations).
 - The Applicant listed Decadron®. The Decadron® label is outdated, noting “No adequate studies have been conducted in animals to determine whether corticosteroids have a potential for carcinogenesis or mutagenesis.”
 - The Applicant also listed Maxidex®. The Maxidex® labeling does not address the potential for genotoxicity.
 - The Applicant submitted a published paper, Singh et al. 1994¹¹.
- Singh et al. 1994 has previously been reviewed by P/T. Briefly, dexamethasone was negative in the Ames test, and positive in three other tests (human lymphocytes, sister-chromatid exchange, and mouse micronucleus test).

Summary of Singh et al. 1994	
Dexamethasone test article	- The authors tested dexamethasone in dimethylsulfoxide (DMSO) vehicle. - The source of the dexamethasone a drug manufacturer, (b) (4) - No trade names were mentioned.
Ames test - negative	Only 4 strains were tested: <i>Salmonella</i> TA97a,

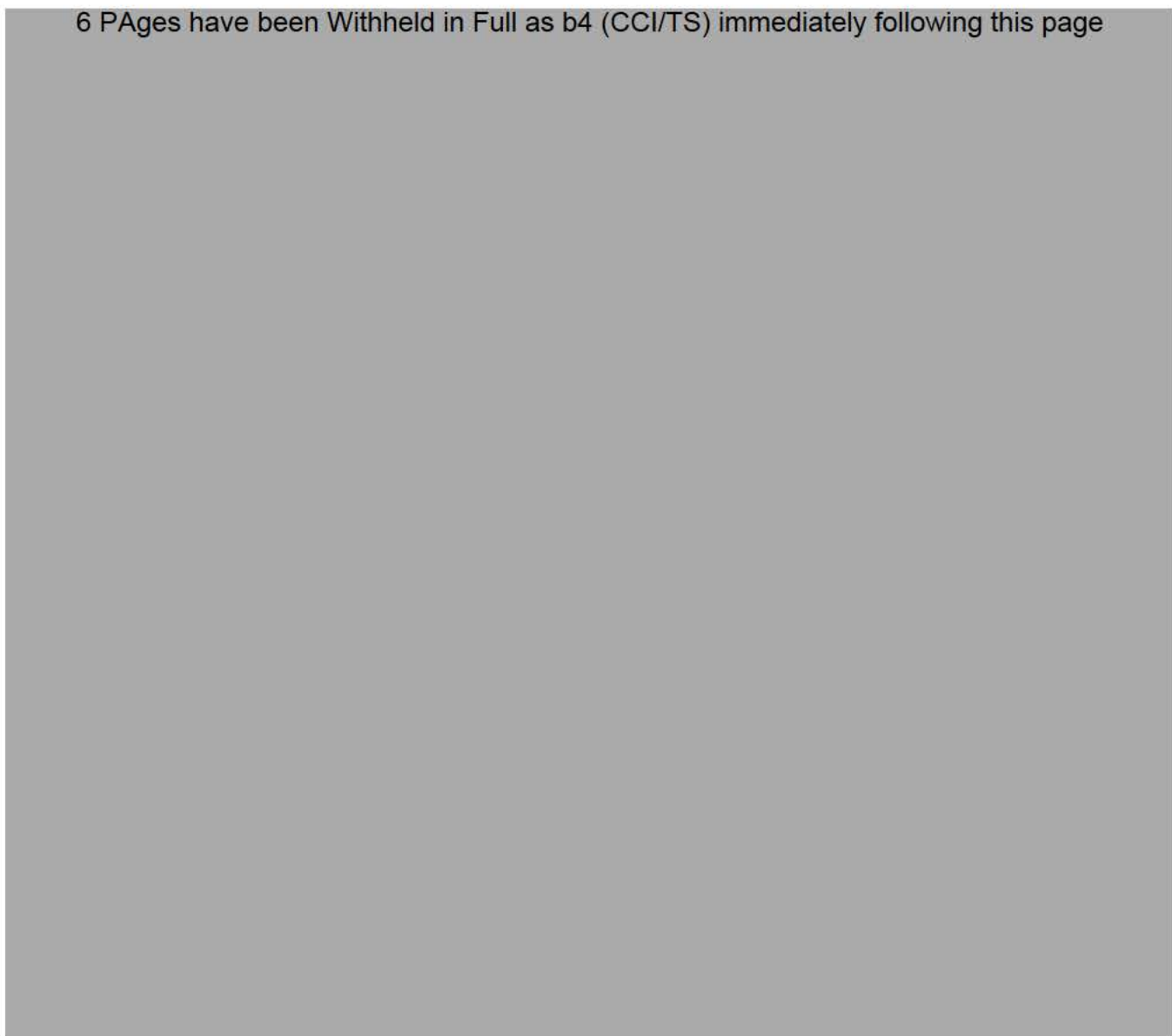
¹¹ Singh H, Singh JR, Dhillon VS, Bali D, Paul H. 1994. *In vitro* and *in vivo* genotoxicity evaluation of hormonal drugs. II. Dexamethasone. *Mutat Res.* 308(1):89-97.
<http://www.ncbi.nlm.nih.gov/pubmed/7516489>

	TA91, TA100, and TA1535 $\pm$ S9. The omission of strain TA98 and one of TA102 or <i>E. coli. uvrA</i> are study limitations. • The range of concentrations was 1 to 10,000 $\mu\text{g}/\text{plate}$ (i.e. beyond the limit test of 5 mg/plate) • 2-aminofluorene (2AF) was the only positive control + S9. The omission of a positive control requiring metabolic activation is a study limitation. • Dexamethasone was reportedly negative at all concentrations. • The positive and negative controls produced the expected responses
<i>In vitro</i> chromosomal aberration test in human lymphocytes - positive	• Clearly positive at 72 hours only, at 10 and 100 $\mu\text{g}/\text{ml}$ ◦ Clear dose response (1, 10, 100 $\mu\text{g}/\text{ml}$) • The type of chromosomal aberration induced was chromatid aberrations (not chromosomal aberrations or gaps) • Positive control was methyl methanesulphonate (MMS, an acceptable choice, since the cells did not need S9) • For the dexamethasone groups, 50 cells were scored (x2 replicates). For the positive and negative controls, 100 cells were scored (x2 replicates). OECD473 recommends scoring at least 300 cells per concentration (e.g. 150x2). This is a trivial omission, since the results are clearly positive. • The positive and negative controls produced the expected responses
<i>In vitro</i> sister chromatid exchange (SCE) assay in human lymphocytes - positive	• Clearly positive at all three concentrations (1, 10, 100 $\mu\text{g}/\text{ml}$) at both 24 and 48 hours • Positive control was MMS • The positive and negative controls produced the expected responses • Note: the OECD 479 guideline¹² for the SCE assay was deleted in 2014; the reliability of this test method to predict genotoxicity is unclear.
<i>In vivo</i> mouse micronucleus assay – positive	• Clearly positive at 1, 5, and 10 mg/kg ip • 5 Swiss albino male mice per group were used • 1000 polychromatic erythrocytes (PCEs) were

¹² OECD 479. Genetic toxicology: in vitro sister chromatid exchange assay in mammalian cells. Adopted 23 Oct 1986. Effective date of deletion 2 April 2014. Accessed online via: http://www.oecd.org/env/ehs/testing/E479_Genetic_Toxicology.pdf

	scored per animal. • The positive control was N'-nitro-N-nitrosoguanidine (MNNG) • The positive and negative controls produced the expected responses
<i>In vivo</i> SCE assay	• Clearly positive at 10, 50 and 100 µg/kg ip • 5 Swiss albino male mice per group were used • 25 second division metaphase cells were scanned per animal • The positive controls were bromodeoxyuridine (BrdU) and MNNG • The positive and negative controls produced the expected responses

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8 Carcinogenicity

- The Applicant did not conduct nonclinical carcinogenicity studies.
- The Applicant relies upon the Agency's finding of safety for the listed drugs, Maxidex (NDA013-422) and Decadron 0.1% drops (NDA 011-984). The labeling for these two drugs has no carcinogenicity data.
- A literature review by this reviewer found no carcinogenicity data for dexamethasone adequate for labeling:
 - NIH's Carcinogenic Potency Database (CPDB)²³ reports that a 52-week rat study was negative for tumors, citing a personal communication ("Shibata; carc,14,1265-1269;1993 /pers.comm.").
 - NIH's Chemical Carcinogenesis Research Information System (CCRIS)²⁴ database lists several reports of dexamethasone being used in the treatment of patients with cancer.

9 Reproductive and Developmental Toxicology

- The Applicant did not conduct any fertility or developmental and reproductive toxicity studies. The Applicant relies upon the Agency's finding of safety for the listed drugs, Maxidex® (NDA013-422) and Decadron 0.1% drops (NDA 011-984).
- P/T identified two published papers relevant to ophthalmic dosing with dexamethasone: Kasirsky & Lombardi 1970²⁵, and Ballard et al. 1977²⁶. Both of these papers were submitted by the Applicant.
- The 2003 Maxidex® labeling summarizes the results from these two papers (Kasirsky & Lombardi 1970; Ballard et al. 1997) as
"Pregnancy Category C. Dexamethasone has been shown to be teratogenic in mice and rabbits following topical ophthalmic application in multiples of the therapeutic dose.

In the mouse, corticosteroids produce fetal resorptions and a specific abnormality, cleft palate. In the rabbit, corticosteroids have produced fetal resorptions and multiple abnormalities involving the head, ears, limbs, palate, etc.

There are no adequate or well-controlled studies in pregnant women. Maxidex® (dexamethasone ophthalmic suspension) should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the embryo or fetus. Infants born of mothers who have received substantial doses of

²³ <https://toxnet.nlm.nih.gov/cpdb/chempages/DEXAMETHAZONE.html>

²⁴ <https://toxnet.nlm.nih.gov/newtoxnet/ccris.htm>

²⁵ Kasirsky G, Lombardi L. 1970. Comparative teratogenic study of various corticoid ophthalmics. Toxicology and Applied Pharmacology 16:773-778. <http://www.ncbi.nlm.nih.gov/pubmed/5422219>

²⁶ Ballard PD, Hearney EF, Smith MB. 1977. Comparative teratogenicity of selected glucocorticoids applied ocularly in mice. Teratology 16:175-180. <http://www.ncbi.nlm.nih.gov/pubmed/929433>

corticosteroids during pregnancy should be observed carefully for signs of hypoadrenalism.”

- As noted above, at the DTOP Filing Meeting for this NDA, Clinical Pharmacology confirmed that the patient systemic exposure to dexamethasone from Dextenza™ is lower than the patient systemic exposure from Maxidex® 0.1% dexamethasone ophthalmic suspension (Abhay/McDougal, 11/04/2015).
 - Therefore, this reviewer concludes that the Applicant’s reliance on the Agency’s previous finding of safety for Maxidex® for developmental toxicity is adequate to support a 505(b)(2) application.
 - Because the Maxidex® label does not present human equivalent dose (HED) values for the nonclinical studies, and does not report clinical PK values, this reviewer did not identify a basis for estimating HED values for Dextenza™ based on clinical exposure data.
 - Deferring the Clinical Pharmacology regarding review of the clinical PK data, this reviewer notes that clinical trial OTX-14-009²⁷ reported that healthy volunteers receiving a unilateral implant had plasma concentrations above LOQ in 11% of samples; the quantifiable sample “plasma dexamethasone concentrations ranged from 0.05 ng/mL to 0.81 ng/mL.”
 - Because the Applicant has patient serum TK data, the Applicant has the option to search the literature for nonclinical embryofetal studies that measured serum TK for dexamethasone (e.g. Hanson et al. 1999²⁸), to support HED estimates. However, the Applicant did not submit such papers to the NDA.
- This reviewer concludes that both papers should be summarized in labeling in more detail than were presented in the 2003 (pre-PLLR) Maxidex® label. The Pregnancy and Lactation Labeling Rule (PLLR)²⁹: “Requires that when animal data are available, the labeling must summarize the findings in animals and based on these findings, describe, for the drug, the potential risk of any adverse developmental outcome(s) in humans. The final rule requires that the risk statement include: The number and type(s) of species affected, the timing of exposure, animal doses expressed in terms of human exposure or dose equivalents, and outcomes for pregnant animals and offspring.”

²⁷ The report for trial OTX-14-009 was submitted to the NDA in module 5.3.3.1, accessible via: <\\cdsesub1\evsprod\nda208742\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\otx-14-009\otx-14-009-report-body.pdf>

²⁸ Hansen DK, LaBorde JB, Wall KS, Holson RR, Young JF. 1999. Pharmacokinetic considerations of dexamethasone-induced developmental toxicity in rats. Toxicological Sciences 48:230-239. Accessed online via: <http://www.ncbi.nlm.nih.gov/pubmed/10353314>

²⁹ Federal Register. Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling. Published Thursday, December 4, 2014. Accessed via: <https://www.federalregister.gov/articles/2014/12/04/2014-28241/content-and-format-of-labeling-for-human-prescription-drug-and-biological-products-requirements-for>

These two papers have previously been reviewed by CDER, and were re-reviewed for this P/T review. Briefly:

Ballard et al. 1977	- Pregnant CD-1 mice were dosed from GD10-13 with 0, 0.15%, 0.75%, or 1.5% dexamethasone by topical ocular administration (applied directly to the cornea). The mice were C-sectioned on GD18. - The group sizes were not reported (but can be inferred from the numbers of fetuses/group) - Note: GD10-13 is shorter exposure duration than is recommended by ICH S5. - Dosing was 5 drops per day OU, 1 µl drop volume. - Fetal examination included number live and dead, weight, external examination under low magnification, and then fixation in Bouin's solution for internal examination (i.e. no skeletal evaluation). Results: dexamethasone exposure produced embryofetal lethality and a high incidence of cleft palate in mice.
Kasirsky and Lombardi 1970	Methods: - Groups of 5 pregnant New Zealand white rabbits were dosed via application in to the conjunctival sac on days 6 through 18 of gestation: 1 drop every 6 hours on GD6, and then 1 drop every 4 hours on GD7-18 - Two groups of 5 rabbits received 0.1% dexamethasone (Decadron®). - C-section was performed on one group at GD29. - The other group was allowed to come to term. - The authors calculate the dexamethasone dose as 0.36 mg on GD6, and 0.24 mg on GD7-18 - The fetuses were observed (under a binocular microscope) for gross anomalies, weighed, and sexed. - Every third fetus was processed for evaluation of skeletal evaluations. The remainder were fixed and sectioned freehand.
	Results: - For both dexamethasone groups, the average weight of the pregnant rabbits was 13 pounds. - Note: The paper does not specify when the pregnant rabbits were weighed, or which days of gestation were averaged to calculate the average weight result. - Presuming that the developmental toxicities observed occurred relatively earlier rather than later in gestation, the appropriate body weight to use in the estimation of dose would be from early gestation, rather than from the end of gestation. - In the absence of adequately detailed experimental body weight data, this reviewer's understanding of P/T policy is to use the default reference body weight from the

	guidance³⁰ (i.e. 1.8 kg for rabbits) and the corresponding default reference allometric scaling factor (i.e. 12 kg/m² for rabbits). • The findings for the two dexamethasone groups included: hypoplastic kidneys, intestinal disorders, intestines absent, herniated abdominal viscera. • No skeletal findings were reported for any fetus. • TK was not evaluated.
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Table 18: Total dose of Dextenza™ (µg/m² basis)

Description	Number	Units
Total dose of the Dextenza™ implant	0.4	mg
Assumed adult human body weight	60	kg
Total dose of Dextenza™ implant	0.00667	mg/kg
Dose conversion factor (from mg/kg to mg/m ²) for adult humans	37	kg/m ²
Total dose of Dextenza™ implant (mg/m ²)	0.246667	mg/m ²
Conversion from mg to µg	1000	µg/mg
Total dose of Dextenza™ implant (µg/m ²)	246.6667	µg/m ²

Table 19: Human equivalent dose (HED) calculation notes for the mouse EFD paper (Ballard et al. 1977)

Description	Number	Units
# of drops/eye/day	5	Drops/eye/day
Both eyes dosed (OU)	2	Eyes dosed per dose
# of drops/mouse/day	10	Drops/mouse/day
Dexamethasone concentration (%)	0.15	%
Conversion: % to µg/µl	10	µg/(% * µl)
Dexamethasone concentration (µg/µl)	1.5	µg/µl

³⁰ CDER 2005 Guidance for Industry. Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. Table 3. Accessed online via: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm078932.pdf>

Dexamethasone dose per mouse per day	15	µg/mouse/day
Default mouse body weight	0.02	kg
Dexamethasone dose (µg/kg/day)	750	µg/kg/day
Dose conversion factor (from µg/kg to µg/m ²) for mice	3	kg/m ²
Mouse dose of dexamethasone (µg/m ²)	1125	µg/m ²
Exposure margin (mouse dose divided by the adult patient dose of 246.6667 µg/m ²)	4.560811 x	[unitless]

Table 20: HED calculation notes for the rabbit EFD paper (Kasirsky and Lombardi 1970)

Description	Number	Units
Dose per rabbit on gestation day (GD6) (value reported by authors)	0.36	mg/rabbit/day
Daily dose per rabbit on GD7 to GD18 (value reported by authors)	0.24	mg/rabbit/day
Default reference body weight for rabbits	1.8	kg
Dose (mg/kg) on GD6	0.20	mg/kg
Dose conversion factor (from µg/kg to µg/m ²) for rabbits	12	kg/m ²
Rabbit dose of dexamethasone (mg/m ²) on GD6	2.4	mg/m ²
Rabbit dose of dexamethasone (µg/m ²) on GD6	2400	µg/m ²
Exposure margin for GD6 (rabbit dose divided by the adult patient dose of 246.6667 µg/m ²)	9.7297 x	[unitless]
Dose (mg/kg) on GD7-18	0.1333	mg/kg
Dose conversion factor	12	kg/m ²

(from $\mu\text{g/kg}$ to $\mu\text{g/m}^2$) for rabbits		
Rabbit dose of dexamethasone (mg/m^2) on GD6	1.6	mg/m^2
Rabbit dose of dexamethasone ($\mu\text{g/m}^2$) on GD7-18	1600	$\mu\text{g/m}^2$
Exposure margin for GD7-18 (rabbit dose divided by the adult patient dose of $246.6667 \mu\text{g/m}^2$)	6.4865 x	[unitless]
Exposure margin for GD7-18 rounded to two significant figures	6.5 x	[unitless]

10 Special Toxicology Studies

The sponsor submitted a report entitled “Dexamethasone punctum plug prolonged exposure biocompatibility testing”, report #0167. This report is comprised of a short preface, followed by four sub-reports, each for a different experiment.

Study title: Dexamethasone punctum plug prolonged exposure biocompatibility testing

Study no: 0167
Study report location: volume 4, tab 8-2 and also as a pdf file (“021_Appendix 8-2_TR0167.pdf”), 137 pages
Conducting laboratory and location:  (b) (4)
GLP compliance: Yes, signed
QA statement: Yes, signed
Test article:

- The test article was extracted from a ‘4arm20K SG with fluorescein’ dried hydrogel product, which is similar to the clinical drug product vehicle formulation.
- The exact formulation of the hydrogel was not reported (i.e. not clear if it corresponds to the placebo for Dextenza)

Key Study Findings

- These four tests are of limited value for the safety assessment of OTX-DP: uncharacterized extracts were tested, and no reporting regarding the composition, strength, purity or stability of the articles tested was reported. Relatedly, no information regarding the stability of the hydrogel under the extract conditions was provided.
- Reportedly, an extract of the hydrogel caused mice to appear greasy / ungroomed at 4 hours post-dose. This may have been an artifact of handling.
- Under the conditions tested, no signs cytotoxicity, eye irritation, or skin irritation were observed following exposure to extracts of the hydrogel.

Cytotoxicity assay

- Title: "Cytotoxicity study using the ISO elution method"
- Lab #: 12T_23571_03
- Report # V0014_130
- Method notes:
 - The test article was an uncharacterized extract from (b) (4) % 4arm20K SG with (b) (4) % fluorescein", identification # 03011201. 0.2 g of this was extracted in 17 ml of single strength Minimum Essential Medium (MEM) at 37°C for 24 hours with continuous agitation
 - Extracts from the controls were similarly prepared:
 - Negative control: HDPE plugs, CAS # 9002-88-4, purity "meets USP <61> polyethylene containers"
 - Reagent control: 1x MEM
 - Positive control: power-free latex gloves. Composition: "natural rubber latex, zinc carbamate accelerators, zinc oxide, and titanium oxide" (no ID #s)
 - L-929 mouse fibroblast cells were plated into wells, and then wells were exposed in triplicate for 48 hours, and then "reactivity" was rated on a 0 to 4 scale (none, slight, mild, moderate, severe)
- The authors report "no cytotoxicity or cell lysis" was noted for any of the wells exposed to the test article, negative control or reagent control. The positive control caused a "severe" response, with 100% cell rounding, 100% cells with intracytoplasmic granules, and 100% cell lysed

Rabbit eye irritation study

- Title: "ISO modified ocular irritation study in rabbits"
- Lab #: 12T_23571_06 and 12T_23571_07
- Report # T1252_800
- Method notes:
 - The test article was an uncharacterized extract from (b) (4) % 4arm20K SG with (b) (4) % fluorescein", identification # 03011201. 0.2 g of this was extracted in either 17 ml of USP sodium chloride for injection, or sesame oil, NF, at 37°C for 72 hours with continuous agitation.
 - Dosing on April 12, 2012
 - Six young adult male New Zealand White rabbits were used:

- 0.1 ml of extract was instilled into the lower right conjunctival sac and then held gently closed for 1 second (3 rabbits/extract). Vehicle control was instilled into the left eye of each rabbit.
- Eyes were examined at 1, 24, 48 and 72 hours post-instillation.
- Pre-dose and 24 hours post-dose, eyes were treated with fluorescein stain, flushed, and viewed under a UV lamp to inspect for corneal injury.
- Results notes
 - No eye toxicity (cornea, iris, or conjunctivae) were observed for any of the animals on study

Mouse acute toxicity test

- Title: "ISO systemic toxicity study in mice"
- Lab #: 12T_23571_04 and 12T23571_05
- Report # T0625_500
- Method notes:
 - The test article was extracted the same as for the rabbit eye irritation study above (sodium chloride or sesame oil)
 - Dosing on April 12, 2012
 - Groups of 5 male Hla®: (ICR) CVR® mice were dosed intravenously with vehicle (sodium chloride) or the sodium chloride extract. Groups of 5 mice were dosed intraperitoneally with either vehicle (sesame oil) or the sesame oil extract
 - Clinical signs were monitored immediately post-dose, 4, 24, 48 and 72 hours post-dose. Body weight was measured at D0, D1, D2 and D3 (no necropsy)
- Results notes:
 - A treatment-related effect was noted for the test extract in sesame oil: at 4 hours post-dose, all 5 mice appeared "ungroomed". All mice appeared normal at all other time points.
 - The authors attributed this effect "to the unctuous nature of the extract", and did not consider these results evidence of systemic toxicity.
 - Not clear to this reviewer whether the authors mean that sesame oil was smeared on the mice (e.g. by the technicians), causing them to appear greasy. No information regarding how extensive, or what areas of the body were affected.
 - No mortalities
 - No apparent effect on body weight

Guinea pig sensitization test

- Title: "ISO guinea pig maximization sensitization test"
- Lab # 12T_23571_08 and 12T23571_09
- Report # T1261_300
- Method notes:

- The test article was extracted the same as for the rabbit eye irritation study and the mouse acute toxicity study (above)
- Dosing began April 23, 2012
- Freund's Complete Adjuvant (FCA) was mixed 50:50 with test extract or vehicle extract for the first induction.
- It is not clear to this reviewer whether or not the 10% sodium lauryl sulfate (SLS) suspension in petrolatum was mixed with the test extract or vehicle extract for the second induction.
- 30 female young adult Hartley albino guinea pigs, Hla®: (HA) CVF® were used. 10/test article and 5/vehicle control.
- First induction: on D1, the dorsoscapular hair was clipped, and animals were injected intradermally 6 times (three rows of 2 injections/row) within a 2 cm x 4 cm rectangle.
- Second induction: 6+1 days after the first induction, the skin was re-clipped, then covered with 10% sodium lauryl sulfate (SLS) suspension in petrolatum, which was massaged into the skin without covering. The purpose of the SLS was to induce "mild acute inflammation." 24 ± 2 hours after the SLS, the skin was wiped clean. A 2 cm x 4 cm section of filter paper was saturated with 0.3 ml of extract, then placed over the injection site, secured with a non-reactive tape, and wrapped with an elastic bandage for 48 hours.
- Challenge: 14 +1 days after the second induction, the fur was clipped. Nonwoven cotton disks were saturated with 0.3 ml of extract, an applied to the right or left flank of each animal. The trunk was wrapped with an elastic bandage for 24 hours.
- Dermal reaction at 24 and 48 hours was recorded (0 to 3 scale).
- Results notes:
 - No clinical signs were noted for any animal
 - No dermal reactions were noted for any animal
 - The authors report that a positive control, 1-chloro-2,4-dinitrobenzene (DNCB) scored 2-3 at 24 hours (moderate and confluent to intense and swelling erythema) and 1-2 at 48 hours (discrete or patchy erythema to moderate and confluent erythema), when tested in 10 guinea pigs. It is not clear whether DNCB was tested concurrently with the extracts.

11 Integrated Summary and Safety Evaluation

- The Applicant did not submit nonclinical pharmacology (or safety pharmacology) studies. The pharmacology of dexamethasone is well-understood.
- The Applicant submitted one GLP ocular toxicology study, in dogs (report # TR0161).
 - Treated dogs received one implant per eye, of different formulations (i.e. one implant per dog of the clinical drug product).
 - For the implant matching the clinical drug product (Formulation B), the actual dexamethasone dose was 718.5 µg/eye (nominally 750 µg/eye).

- For dexamethasone treated dogs, the mean body weights increased from D1 to D35.
 - Males on D1: 8.169 kg. Males on D35: 8.515 kg
 - Females on D1: 6.444 kg. Females on D35: 6.566 kg
- Because female dogs appeared more sensitive (for ocular discharge and PLR), this reviewer uses the weight for female treated dogs, averaging the D1 and D35 values: 6.505 kg. Using this body weight, the dose of dexamethasone was 110.4535 µg/kg from Formulation B only (i.e. considering only one eye).
- Based on the serum PK results and the histopathology of the punctal area, this reviewer concludes that the OTX-DP product had essentially cleared by D35 in the dogs. These results support the proposed single-use administration of Dextenza™ in patients.
- The Dextenza™ drug product is 400 µg/eye. Exposure margins can be estimated:

Table 21: Exposure margin estimates for the GLP dog study (report TR0161)

Dose basis	Female dog dose	Human dose	Exposure margin*
µg/eye	718.5	400	1.80 x
µg/kg	110.4535 [using a body weight of 6.505 kg]	6.667 [assuming a human body weight of 60 kg]	16.6 x
µg/m ²	2209.07 [using a conversion factor of 20 for the dog]	246.667 [using a conversion factor of 37 for adult humans]	8.96 x

**Note: this table calculates the exposure margin for dosing one patient eye, compared to dosing one dog eye. The dexamethasone-treated dogs were actually dosed in both eyes*

Notes regarding the dexamethasone USP drug substance

The application relies on the standard for dexamethasone set by the U.S. Pharmacopeial Convention (USP). The Applicant reported (NDA module 2.3.S Drug Substance) that the dexamethasone drug substance is manufactured by (b) (4) a wholly owned subsidiary of (b) (4). The Applicant submitted a letter of authorization for drug master file (DMF) # (b) (4) Dexamethasone USP (b) (4) from the DMF holder (b) (4). The Applicant claims that the drug substance meets the specifications of both the USP and the independent confirmatory tests performed by the Applicant in the manufacturer of the drug product, and is in compliance with ICH guidelines (NDA module 2.3.S.4 Control of the Drug Substance).

The pivotal nonclinical toxicology study (report # TR0161) included the results of analytical characterization of the dexamethasone by HPLC (pdf page 316), which support the identity and potency of the dexamethasone test article.

Notes regarding the Applicant's proposed labeling section 12.1 Mechanism of Action

- In NDA module 2.2 Introduction, section 1.3 Mode of Action, the Applicant uses the same wording as is proposed for labeling (citing Zoorob & Cender, 1998):

(b) (4)

- Notably, the Applicant did not cite this review article (Zoorob & Cender, 1998³¹) in the annotated labeling, or in the P/T sections of the NDA. This review article does not mention any commercial drug product. A table from the article is notable:

Table 22: Reported comparative systemic potencies of glucocorticoids (from Zoorob and Cender, 1998)

TABLE 1
Relative Potencies of Systemic Glucocorticoids

<i>Corticosteroid</i>	<i>Activity</i>	<i>Relative potency</i>	<i>Equivalent dose (mg)</i>
Dexamethasone	Long-acting	25	0.75
Prednisone	Intermediate-acting	4	5.0
Methylprednisolone	Intermediate-acting	5	4.0
Hydrocortisone	Short-acting	1.0	20.0

Information from Drug facts and comparisons. St. Louis: Facts and Comparisons, 1997:122–23.

- It is not clear to this reviewer that a claim of systemic potency is directly relevant to ocular pain management. This reviewer did not find the relevant cited references in the NDA.

³¹ Zoorob RJ, Cender D. 1998. A different look at corticosteroids. American Family Physician. 1(58):443-450. This paper was submitted to the NDA (section 4.3 Literature References). The abstract and paper were also accessible via: <http://www.ncbi.nlm.nih.gov/pubmed/9713398>

- The Applicant's annotated draft labeling (NDA module 1.14.1.2, <\\cdsesub1\evsprod\nda208742\0021\m1\us\draft-annotated-labeling.pdf>) links to the NDA's section 2.6.2, Section 2.7.2, and four published papers: (b) (4)
- Section 2.6.2 is the Pharmacology Written Summary (7 pages); it includes a one page summary of the primary pharmacology of dexamethasone. It also references the four papers listed above, as well as Rowen 1999; Leopold 1985; Kaiya 1990; Kulkarni 1981; Williams 1987
- Section 2.6.3 is the Pharmacology Tabulated Summary (i.e. no additional information relevant to this section of this review)
- (b) (4) does not support the Applicant's proposed wording for the mechanism of action of dexamethasone. (b) (4)
- (b) (4)
- (b) (4) This reviewer concludes that this paper does not support the Applicant's proposed wording for section 12.1.
- (b) (4) This reviewer concludes that this paper does not support the Applicant's proposed wording for section 12.1.
- (b) (4)
- (b) (4) Although this paper is a useful summary of dexamethasone's mechanism of action, the paper does not provide unique insight into dexamethasone, and does not support the Applicant's proposed wording for section 12.1.

(b) (4)

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/s/

ANDREW J MCDOUGAL
07/11/2016

LORI E KOTCH
07/11/2016

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number: 114720

Supporting document/s: SD 12 (briefing package, sent 8/15/2013)

CDER internal meeting: September 9, 2013

EOP2 teleconference: September 13, 2013

Product: OTX-DP – dexamethasone punctum plug

Indication: Treatment of post-surgical inflammation
associated with ophthalmic surgery

Sponsor: Ocular Therapeutix Inc.
Bedford, Massachusetts 01730

Review Division: Division of Transplant and Ophthalmology
Products (DTOP), Office of Antimicrobial
Products (OAP), CDER, HFD-590

Reviewer: Andrew J. McDougal, Ph.D., D.A.B.T., DTOP

Team Leader: Lori E. Kotch, Ph.D., D.A.B.T., DTOP

Division Director: Renata Albrecht, M.D., DTOP

Project Manager: June Germain

1 Executive Summary

1.1 Introduction

- The investigational product is OTX-PD, a punctum plug containing 394 µg (b) (4) of dexamethasone. The placebo vehicle punctum plug is designated placebo vehicle punctum plug (PVPP). The vehicle is “a polyethylene glycol (PEG) based hydrogel conjugated with fluorescein”. The fluorescein allows the physician to visualize the punctum plug location (i.e. blue light source, yellow filter)
- The Sponsor has requested a Type B End of Phase 2 (EOP2) meeting for IND 114720.
 - o The briefing package was received 8/15/2013; it is one paper volume (also electronic in non-ETD format , pdf documents: [\\cdsesub4\NONECTD\IND114720\5352745](#))
 - o No P/T information was submitted in the briefing package.
- The original IND was 4 volumes (paper), submitted 8/20/2012.
 - o This reviewer references the original P/T review (McDougal, 9/12/2012, IND 114720).
 - o Non-hold P/T comments were sent (Willard, 11/05/2012).
 - o The Sponsor submitted on 4/24/2013 (non-eCTD, pdf documents at [\\cdsesub4\NONECTD\IND114720\5282358](#)), a revised report for the dog study that attempts to address the non-hold issues identified. The amended report is adequate, although its usefulness is limited. [The Sponsor did not address the deficiencies noted for the rat study or genotoxicity testing, but those studies are not needed to support the safety of the NDA.]
- For the original IND, the Sponsor had proposed a Phase 2 trial in a total of 60 patients receiving punctum plugs after cataract surgery (two arms, 30/arm)
- The EOP2 briefing package has a draft Phase 3 protocol # OTX-13-002.

1.2 Sponsor's P/T Question for the EOP2 Meeting

The Sponsor is asking one P/T question:

Question 7 – Pharmacology and Toxicology

The hydrogel carrier in the OTX-DP product has been used extensively in investigational and commercially approved medical devices including ReSure Sealant (PMA P130004) and DuraSeal Dural Sealant (PMA PO40034) and

has a well understood safety profile. As cited in the pharmacology package of the OTX-DP Phase 2 IND (#114720), the safety, efficacy, and distribution of dexamethasone to the ocular surface is well understood. The toxicology study to support Phase 2 evaluated 35 days with a 2-week recovery period.

Supporting pharmacokinetic preclinical studies and samples explanted in this toxicology evaluation demonstrate complete drug release by 30 days. The Phase 2 trial results indicate the hydrogel carrier may last longer than this period of time. Because safety of the hydrogel carrier is well understood, complete dexamethasone release was demonstrated in the toxicology evaluation, and no additional safety issues were observed in the Phase 2 clinical evaluation, Ocular Therapeutix proposes using the current Phase 2 IND toxicology study to support Phase 3 IND and NDA submissions. Ocular Therapeutix does not intend to perform additional preclinical safety studies, including carcinogenicity or reproductive toxicology, to support the NDA submission. The OTX-DP product is intended for one time use; therefore, Ocular Therapeutix does not intend to evaluate chronic toxicity. Does the Agency agree that no further preclinical safety testing is required to support an NDA submission?

FDA Response:

FDA concurs that no additional nonclinical studies are needed to support an NDA for the proposed indication. Please be aware that if changes to the formulation or product sterilization result in new impurities, the safety of those impurities should be addressed.

2 Drug Information (copied from a previous review)

2.1 Drug

OTX-DP consists of two components:

- Dexamethasone
- (b) (4) which is PEG hydrogel “conjugated” with fluorescein

Dexamethasone

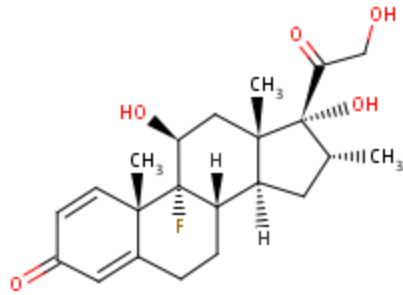
CAS Registry Number: 50-02-2

Drug name: 9-fluoro-11 β ,17,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione

Molecular Formula/Molecular Weight: C₂₂-H₂₉-F-O₅

392.47 g/mol

Structure



Pharmacologic class: anti-inflammatory 9-fluoro-glucocorticoid

Hydrogel

Figure 1: Hydrogel: (b) (4) **and structure**



Figure 2: Hydrogel Structure:

The sponsor provided a batch formula composition table (module 7.3.2 Composition):

Table 1: OTX-DP drug product formula composition

Ingredient	As formulated (% dry basis)	Theoretical composition (mg, dry basis)
Dexamethasone		(b) (4)
4-arm 20K PEG		
Sodium phosphate dibasic		
Trilysine acetate		
NHS-fluorescein		
Water		
Target Weight		

2.1 Prior Clinical Experience – the Phase 2 trial

The protocol (pages 15-16) provides a short summary of the Phase 2 trial results:

- 60 patients (60 eyes) who had undergone cataract extraction surgery were randomized to either OTX-DP or PVPP; evaluated at post-operative days 1, 4, 8, 11, 14 and 30.

- o Three SAEs were noted in the OTX-DP arm: cellulitis of the right arm, syncope episode, and intracranial hemorrhage. The Sponsor did not consider these treatment-related.
- o The Sponsor reports two types of AEs “suspected to be related to the study drug”: punctal stenosis and cellulitis of the lower lid
- o The Sponsor reports statistically significant results for efficacy (fewer patients reporting pain at all visits, fewer patients with anterior chamber cells)

2.2 Proposed Clinical Population and Dosing Regimen

Attachment 2 of the briefing package is the draft protocol.

Protocol title	A prospective, multicenter, randomized, parallel-arm, double-masked, vehicle controlled Phase III study evaluating the safety and efficacy of OTX-DP for the treatment of ocular surgery and pain after cataract surgery
Protocol #	OTX-13-002
Treatment	- o OTX-DP is a resorbable punctum plug containing 0.4 mg dexamethasone and a PEG-based hydrogen conjugated with fluorescein - o PVPP contains the same PEG hydrogel conjugated with fluorescein
Patient population	Plugs will be inserted into the inferior vertical canaliculus of the operated eye intra-operatively (i.e. within minutes after the completion of the cataract surgery) - o Total of 240 patients (240 eyes, randomized 2:1 to OTX-DP or PVPP) - o Age $\geq$ 21 years - o Has a cataract and is planning to undergo clear corneal cataract surgery with phacoemulsification and implantation of a posterior chamber intraocular lens - o Has a potential post-operative visual acuity (VA) of at least 20/200 in both eye
Primary endpoints	- o Absence of cell in anterior chamber of the study eye at D14 - o Absence of pain in the study eye at D14
Secondary endpoints:	- o Evaluation of cells in the anterior chamber in the study eye at D1, 8, 30 - o Evaluation of flare in the anterior chamber of the study eye at D1, 8, 14, 30 - o Evaluation of pain the study eye at D1, 8, 30 - o Presence of punctum plug at all visits - o Ease of product use as assessed by the Investigator - o Ease of product visualization as assessed by the Investigator
Safety endpoints	Slit lamp examination, dilated fundus examination, visual acuity, intraocular pressure (IOP), adverse events (AEs)

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/s/

ANDREW J MCDOUGAL
09/12/2013

LORI E KOTCH
09/12/2013

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number: 114720

Supporting document/s: SD 3 (original new IND)
Paper submission (4 volumes); partially electronic (non-eCTD; documents accessed via the DTOP e-room)

Sponsor's letter date: August 20, 2012

CDER stamp date: August 21, 2012

30-day review goal: September 20, 2012

Product: OTX-DP – dexamethasone punctum plug

Indication: Treatment of post-surgical inflammation associated with ophthalmic surgery

Sponsor: Ocular Therapeutix Inc.
Bedford, Massachusetts 01730

Review Division: Division of Transplant and Ophthalmology Products (DTOP), Office of Antimicrobial Products (OAP), CDER, HFD-590

Reviewer: Andrew J. McDougal, Ph.D., D.A.B.T., DTOP

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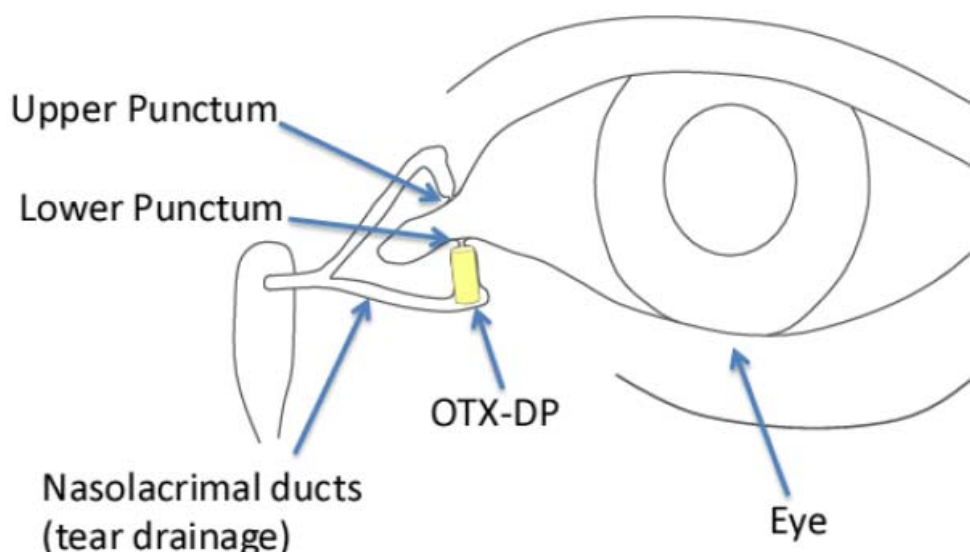
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1 Executive Summary

1.1 Introduction

- The sponsor is proposing a Phase 2 trial in patients after cataract surgery: patients (two arms, 30/arm) will receive a punctum plug either the placebo vehicle punctum plug (PVPP) or OTX-PD, which is a plug containing $394 \mu\text{g} \pm$ (b) (4) of dexamethasone
- The vehicle is “a polyethylene glycol (PEG) based hydrogel conjugated with fluorescein”. This IND appears to be the first-in-human (FIH) exposure to this PEG-based hydrogel.
- The fluorescein will allow the physician to visualize the punctum plug location (i.e. blue light source, yellow filter)
- Plug will be inserted at the end of the cataract surgery into the inferior punctum (preferred location; superior punctum is the second choice location) to be retained in the vertical canaliculus.
 - Patients with punctum size ≤ 0.4 mm at initial measurement are excluded (protocol page 17).
 - Patients whose punctum cannot be dilated to 0.7 mm are also excluded

Figure 1: Placement of OTX-DP into the vertical canaliculus



- The sponsor expects tapered dexamethasone delivery, “through hydrolysis, the punctum plug softens, liquefies and is cleared through the nasolacral duct”
 - Presentation is dry, in a (b) (4) sealed sterilized package
 - The gel is intended to absorb moisture and expand until it blocks the canaliculus
- The sponsor’s listing of potential benefits includes:
 - Reduction of inflammation and pain following cataract surgery
 - Resolving non-compliance issues with daily drops

- Continuous delivery of therapeutic levels of dexamethasone
- The sponsor highlights the risks (protocol pages 24-25):
 - Dexamethasone:
 - Ocular hypertension and or glaucoma
 - Perforation of the cornea
 - Perforation of the globe
 - Masking infection, enhance existing infection
 - Of the punctum plug:
 - Perforation of, trauma to, the punctum and surrounding tissues
 - Punctoplasty
 - Epiphora (overflow of tears)
 - Inflammatory reaction, swelling, allergic reaction
 - Infection
 - Dacrocystitis (inflammation of the nasolacrimal sac)
 - Eye pain and discomfort
 - Decreased/impaired visual acuity
 - Tearing with mucopurulent discharge
 - Stenosis of the punctum
 - Intraocular infection
- **Note:** the dexamethasone plug will expand less than the placebo plug, because the placebo plug is all hydrogel, while the dexamethasone plug is (b) (4) % dexamethasone). This reviewer recommends considering whether any reduction in implantation site irritation is an artifact of the difference in plug swelling.
 - Comparing dry plugs to swollen plugs (after 24 hours in saline), vehicle plugs lost 18% of length and increase in diameter 4.3-fold. The dexamethasone plugs lost 11% of length and increased in diameter only 2.5-fold. [see Table 8 of this review - data from the 35-day dog study, report # 12-0419-G1]

1.2 Brief Discussion of Nonclinical Findings

- The IND was received 8/21/2012 (goal date 9/20); an Information Request was prepared (McDougal, 8/31/2012) and conveyed to the sponsor 9/07/2012 (in DARRTS, Germain). The response appears adequate to resolve the potential clinical hold issues identified.
- Although the nonclinical data submitted have remarkable deficiencies and omissions, in this particular case the data package appears adequate to support a Phase 2 clinical trial. The IND is considered reasonably safe to proceed from a nonclinical perspective because:
 - The dexamethasone exposure is not a safety concern. The plugs will deliver a tapered dose, and the worst-case dose (i.e. all (b) (4) µg of dexamethasone at once) is below what has been previously tested clinically.
 - Exposure to impurities from the hydrogel drug product is not a safety concern.
 - This assessment is largely based on the certificate of analysis (COA) sent 9/11/2012 for the (b) (4) starting material, which

- reported no oligomers or impurities. CMC (Fuqiang/McDougal, personal communications 9/13/2012) noted that the manufacturing facility for the starting material is in compliance with commercial good manufacturing practices (cGMP), and therefore, their COA report is acceptable. It is reasonable to expect that a cGMP facility can manufacture (b) (4) without oligomers or impurities of regulatory concern.
- Based on the expectation that no oligomers or impurities in the (b) (4) starting material, the sponsor's assertion that no oligomers or impurities would be carried over to the (b) (4) is reasonable. Based on the manufacturing process of the other (b) (4), other exposures are not a regulatory concern (please see section 11 of this review for more details).
 - The primary potential concerns are degradation products from the hydrogel carrier, and the potential interaction of these degradation products with the dexamethasone.
 - The hydrogel is intended to degrade (hydrolyse) in the vertical canaliculus. The sponsor provided no analytical information regarding the composition of the degradation products (despite the 9/07/2012 IR). Instead, the sponsor relies upon:
 - Theoretical predictions of the degradation products.
 - Qualification of the degradation products, and any potential interactions with dexamethasone, by the 35-day dog study (report # 12-0419-G1).
 - The sponsor submitted a GLP dog punctum plug toxicity study (report # 12-0419-G1). Dogs received punctum implants, either placebo or containing dexamethasone. Some dogs (unclear) received replacement plugs. On D35, the plugs were removed. 5/sex/dose were necropsied on D36, and 3/sex/dose were necropsied on D49. NOTABLE ISSUES:
 - Formulation of the vehicle/placebo:
 - The clinical hydrogel is (b) (4) with (b) (4) % conjugated fluorescein.
 - The nonclinical lots were prepared without fluorescein; based on the total mass of fluorescein in the plugs, this difference is not a regulatory concern (see section 11 of this review).
 - Dogs received two plugs, an "A" formulation in the right eye - placebo or dexamethasone; prepared with (b) (4) and (b) (4) being the same as the clinical lot), and a "B" formulation in the left eye (placebo or dexamethasone, prepared with (b) (4)).
 - The sponsor reported (in the original IND and the 9/12/2012 response) that the B formulation is made by the same manufacturing process as the clinical lots will be made.

- **Pupillary light reflex was abnormal:** (see Table 10 of this review)
 - “no pupillary light reflex” was observed in one dog on D14, and two dogs on D35
 - Sluggish pupillary light reflex was observed on 4 occasions. **The relationship to treatment is unclear; presumed treatment-related in the absence of a control group not exposed to the hydrogel plug.**
- Eye discharge (clear, brown, green, white, yellow) was noted in most dogs (see Table 9 of this review). The relationship to treatment is unclear; presumed treatment-related in the absence of a control group not exposed to the hydrogel plug.
- Histology of the punctum and eyelid areas detected minimal bacterial presence, and minimal-to-moderate immune response (mononuclear cell infiltrate), indicating infection.
 - This reviewer is inclined to attribute the infection to the frequent manipulation/checks of the dogs’ eyes, but a relationship to treatment is possible.
 - No clear increase in the dexamethasone-treated dogs compared to the placebo-plug dogs (a theoretical concern based on the mechanism of action of dexamethasone)
- Dexamethasone PK:
 - Not detected in serum
 - Detected in tear fluid, tapered concentration observed
- The sponsor submitted a non-GLP dog punctum plug PK study (study # TR0183)
 - Plugs made with (b) (4) 4-arm 20K SG hydrogel (but with no fluorescein)
 - Ophthalmology assessment detected no toxicity
 - Tear TK observed tapered exposure to dexamethasone
- The sponsor submitted supporting data for other hydrogels, that are of very limited usefulness in supporting the safety of this drug product:
 - 4-week sc study in rats with “PEG hydrogel containing fluorescein and (b) (4) 4-arm 20K SG PEG and with (b) (4)
 - No control group not exposed to the hydrogel
 - Rat histology detected toxicity in the liver (minimal to mild hepatocellular cytoplasmic vacuolation), heart (minimal cardiomyopathy), kidneys (mild progressive nephropathy, dilated renal pelvis, mineralization) and lungs (alveolar hemorrhage and histiocytosis). **The relationship to treatment is unclear. If these effects are presumed treatment-related, then this study would raise serious safety concerns for this formulation of hydrogel.**
 - (b) (4)

- Genotoxicity (Ames, MLA, micronucleus) with an uncharacterized extract (report #s 0179 and 0168)
- “Biocompatibility” (cytotoxicity, rabbit eye irritation, mouse IV acute toxicity, guinea pig sensitization) with an uncharacterized extract (report # 0167)

1.3 Recommendations

1.3.1 Clinical Study (ies) Safe to Proceed:

Yes, from a Nonclinical Pharmacology/Toxicology perspective.

1.3.3 Additional Recommendation(s) (Non-hold comments/advice to sponsor) if any.

1. The Instructions for Use (provided in the IND module 7.5.1, page 75) has inaccurate wording. [REDACTED] (b) (4) is inaccurate because [REDACTED] (b) (4).
Revise this document appropriately prior to distributing it to investigators.
2. Regarding the sample informed consent document (ICD, appendix D of the protocol), the statement (page 47 of 60) “OTX-DP is also made of a material called polyethylene glycol (PEG). PEG is one of the most widely used materials in the pharmaceutical industry, and is used in topical drugs such as over the counter eye drops” appears to be inaccurate. Although [REDACTED] (b) (4) for which this trial will be the first-in-human exposure. Please revise the ICD to accurately describe the products.
3. The 35-day dog study (report # 12-0419-G1) observed changes in the pupillary light reflex (sluggish reflex, no reflex); the relationship of these changes to the hydrogel exposure is unclear. Please consider revising the ICD, under “Potential Risks Associated with the use of the OTX-PD or the blank punctum plug” to include this risk.
4. In the 35-day dog study (report # 12-0419-G1), the dogs exhibited eye discharge, the presence of bacteria in the punctal areas, and mononuclear cell infiltrates in the eyelids and punctal areas (suggesting an immune response). In the absence of a control group without exposure to the hydrogel, the relationship of these effects to the product cannot be dismissed.
 - a. Please revise the Investigator Brochure’s “summary of non-clinical data for dexamethasone” to remove statements such as [REDACTED] (b) (4).
 - b. The Biocompatibility section (page 15 of 22) is potentially misleading, [REDACTED] (b) (4).
Please either clarify this section, or delete it from the IB.

- c. In the “summary of pre-clinical studies”, the statement [REDACTED] (b) (4) [REDACTED] appears inaccurate, because the data are for a similar vehicle, but not the OTX-DP vehicle. Either clarify this sentence, or delete it from the IB.
5. The nonclinical dog toxicity study report (# 12-0419-G1) claims that the study was conducted in compliance with **21CFR** Part 58 Good Laboratory Practice for Non-Clinical Laboratory Studies, and also that raw data and final report underwent Quality Assurance. Several omissions, inconsistencies, and apparent protocol violations were noted - the current version of the report is not adequate to support a Phase 3 trial for OTX-DP. As soon as feasible, but at least prior to the initiation of Phase 3 trials for this product, submit an amended report that adequately addresses the following issues. Please be aware that, if the deficiencies of report # 12-0419-G1 cannot be corrected, submission of an adequate report from an adequately conducted nonclinical study would be expected to support initiation of a Phase 3 trial for OTX-PD.
- a. IND module 7.3.6.5.2 “Characterization data demonstrating no interaction between the API and hydrogel components of the dexamethasone punctum plug” reports on “OTX-DP explanted weekly over the duration of a 28-day study”. Report # 12-0419-G1 makes no mention of explant. Indicate whether the data in section 7.3.6.5.2 are from study # 12-0419-G1 or from a different study. If the data are from a different study, provide to the IND all information from that study relevant to safety. If the data in IND module 7.3.6.5.2 are from study # 12-0419-G1, then the study report submitted in the original IND would be dramatically inadequate and misleading.
 - b. 21CFR58.113 Mixtures of articles with carriers provides that testing “shall be conducted: (1) to determine the uniformity of the mixture and to determine, periodically, the concentration of the test or control article in the mixture. (2) to determine the stability of the test and control articles in the mixture as required by the conditions of the study...” Provide this information in the amended report.
 - c. 21CFR 58.185 Reporting of nonclinical laboratory study results, subpart (1) requires reporting of “the test and control articles identified by name ... strength, purity, and composition or other appropriate characteristics” and “stability of the test and control articles under the conditions of administration.” No information regarding the purity of the control, or the stability of the implanted plugs, were identified. The reporting of % impurities for the dexamethasone does not make clear whether the results are only for the dry plug, or whether the results are relevant to the wet plug (i.e. conditions of use). Either provide these data in the amended report, or provide adequate justification for each omission.
 - d. The evaluation of local site toxicity is confounded by the omission of histopathology: tissue samples were missing for 30% (10/33) of upper left punctal area, 18% (6/33) of the upper right punctal area, and 9% (3/33 right and 3/33 left) of the lower punctal areas. Provide an explanation for why histopathology was not performed for these areas. Please address

whether the sectioning of samples was “adequate to insure the quality and integrity of the data generated”, per §58.81 Standard operating procedures. If additional nonclinical testing of punctum plugs is conducted, for OTX-DP or other products, please ensure that punctal areas are examined grossly and histologically.

- e. The graph and table provided in Appendix 9 of Attachment C (pdf page 333) is not interpretable. If the information presented is relevant to the study, provide an explanation of what testing was done, what the abbreviations and headers mean, and what conclusions were reached based on these results.
- f. The methods section specifies 8 dogs/sex/group, but the results indicate nine females were used in the dexamethasone plug group. The animal numbering system suggests that female dog #1105 intended to be a placebo group animal, but was implanted with a dexamethasone plug and was counted in the ‘drug’ group instead of the ‘placebo’ group. Is this interpretation accurate? If so, was the error detected prior to review of the PK data? Provide explanation for this apparent deviation from protocol, why this occurrence was not documented in Attachment E Study Protocol and Amendments/Deviations, and specifically address whether any GLP violations arose in the recording or reporting of results from this apparent error.
- g. Provide the calendar dates of initial plug insertion for each dog (including the three replacement dogs, #1009, 1010 and 2109). The methods note that plug assessments were twice per week “until March 16, 2012, after which evaluations were performed daily Monday through Friday”. Review of the Individual Plug Assessments data found that the Saturday/Sunday non-observation window was not consistent, suggesting that the groups were not dosed concurrently. Explain how the decision was made as to when dogs would be implanted, whether the method was random, and whether any confounding effects are apparent.
- h. Provide additional data for the three replaced dogs (#1002, 1005, 2101), namely: what day(s) were the plugs not retained, which eye(s) did not retain the plug, D1 ophthalmology results, and clinical observations made. FDA does note that Individual Punctum Dilation Data for these three dogs were provided (report pages 155-156).
- i. Provide a clear accounting of which animals received replacement plugs (dog #, day, eye). The report notes, “if the punctum plug was not successfully retained during the first week following the initial insertion, the dog was replaced with a naïve animal” and also “If punctum plugs were not present in one or both eyes, the animal was anesthetized and the plug(s) re-inserted as per the original insertion procedure described in Section 7.3.2 – 7.3.5. The animals remained on study until the planned necropsy date”. The individual animal data appear to indicate that no plug was detected for five dogs during week 1 (i.e. # 1007, 2001, 1107, 1108 and 2108) but these dogs were not replaced. The individual animal data also indicate 62 instances of a plug not being detected. Cross referencing

the Individual Plug Assessments data with the Individual Punctum Plug Dilation Data (the latter presumably being measurements at the time of plug replacement) finds that the data match for 14 dogs (#s 1001, 1002, 1003, 1004, 2004, 2005, 2006, 2007, 2008, 1103, 1105, 1106, 2105, 2109) but do not match for 19 other dogs (#s 1006, 1007, 1008, 1010, 2001, 2002, 2003, 1101, 1102, 1104, 1107, 1108, 1109, 2102, 2103, 2104, 2106, 2107, 2108). Notably, the PK report (pdf page 355) provides summary data “for animals not requiring replacement plugs”, without clearly identifying which animals did not require replacement plugs. Provide line data for each plug replacement.

- j. The methods section notes that the plugs were implanted into the inferior or superior punctum. No justification for choosing one over the other was identified, and no results were identified regarding which punctum was used. If data are available, report for each plug insertion (initial and replacement), whether the inferior or superior punctum site was used. Address whether any correlation is apparent between the histological observations (e.g. mononuclear cell infiltration, mixed cell infiltration of the eyelids and punctal region) to plug location.
- k. The daily clinical observations record ocular effects (e.g. eye discharge, edema), but are not eye specific. Because two different formulations were used for each dog, understanding whether the discharge was present in the right eye, left eye, or both eyes is especially important. If the data are available, provide them in the amended report.
- l. Apparent oversights in the Quality Assurance were noted. Address each in the amended report:
 - The “Individual Necropsy Observations” (report pages 151-154; pdf pages 261-265) do not match the “Macroscopic (Gross) Findings” presented in the Pathology Report (pages 3-4; pdf pages 270-271). When the report is amended, include a complete and accurate summary table of all gross observations.
 - Study day information are omitted for the Punctum Dilation Data for dog #1108 (report page 155; pdf page 265)
 - A Quality Assurance oversight was noted: the “Individual Clinical Observations” data indicate female # 1102 (placebo group) was not terminally sacrificed or necropsied (report page 6 and 7; pdf pages 116-117). However, the Pathology Report provides necropsy data for this animal.
 - The data tables in Appendices 1 and 2 of Attachment C (pages 5 and 6; pdf pages 299 and 300) claim to report “dried dimensions and weight”, but no weight information was provided in these tables or in the subsequent pages of attachment C.
- m. In the amended report, please separate the presentation of main-group animal and recovery-group animal data. In the individual histopathology observations, please provide some visual notation or separation of the main-group animal from the recovery-group animal data

- n. For the amended report, please sequentially paginate the entire report and please provide a useful table of contents (e.g. listing the major sections, attachments, appendices, tables and figures by page number).
6. Regarding the nonclinical study titled “4 week systemic toxicity study in rats following subcutaneous implantation” (report #s 03291201 and TR0174) for the test article “PEG hydrogel containing fluorescein and (b) (4) if Ocular Therapeutix believes that the data are relevant to patient safety for this IND (or other INDs to which this report might be submitted), please address the following:
- No additional information regarding the identity, composition, purity, or strength of the “(b) (4)” was identified. Either provide this information, or provide adequate scientific justification for the omission.
 - No impurity information was provided for the test article, vehicle, or control plugs; these omissions appear to be inconsistent with 21CFR58. Either provide this information, or provide adequate scientific justification for the omission.
 - An apparently important discrepancy was noted regarding the test articles. The methods sections states that both the test article and controls were cut into approximate 13 mm x 1 mm x 1 mm sections. However, the (b) (4) reports sections 2.67 to 3.310 mm thick, and the “Test Process Specification Document” (pdf page 63) describes a “Hydrogel plug, approx. 0.4 x 4 mm”. The variability in thickness suggests an inability to consistently product drug product for testing. Either provide plug dimensions for each test article plug and control plug implanted, or provide adequate scientific justification for the omission.
7. (b) (4)
- please be aware that these studies are wholly inadequate to support safety. The experiments tested extracts of plugs, but no characterization of the extract was provided. It is not clear from the reports if, or to what extent, the plugs might have hydrolyzed. No basis for the dose selection was provided (e.g. solubility, toxicity, test limit).

2 Drug Information

2.1 Drug

OTX-DP consists of two components:

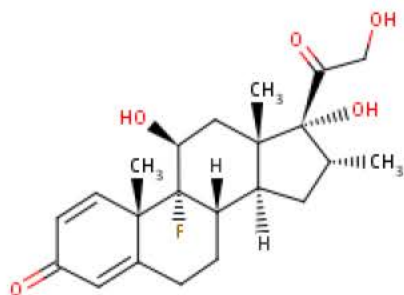
- Dexamethasone
- (b) (4), which is PEG hydrogel “conjugated” with fluorescein

Dexamethasone

CAS Registry Number: 50-02-2

Drug name: 9-fluoro-11 β ,17,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dioneMolecular Formula/Molecular Weight: C₂₂H₂₉F-O₅ 392.47 g/mol

Structure



Pharmacologic class: anti-inflammatory 9-fluoro-glucocorticoid

Hydrogel

(b) (4)

The hydrogel is a polymer. The sponsor uses the term (IND module 7.1) "4-arm PEG N-hydroxysuccinimide glutarate (20K) trilysine hydrogel" (b) (4).

- (b) (4)
-
-

The reply received 9/12/2012 provided a certificate of analysis (COA) indicating that (b) (4) is the supplier for the (b) (4). From their catalog¹:

(b) (4)

Figure 2: Structure of the (b) (4) **starting material**

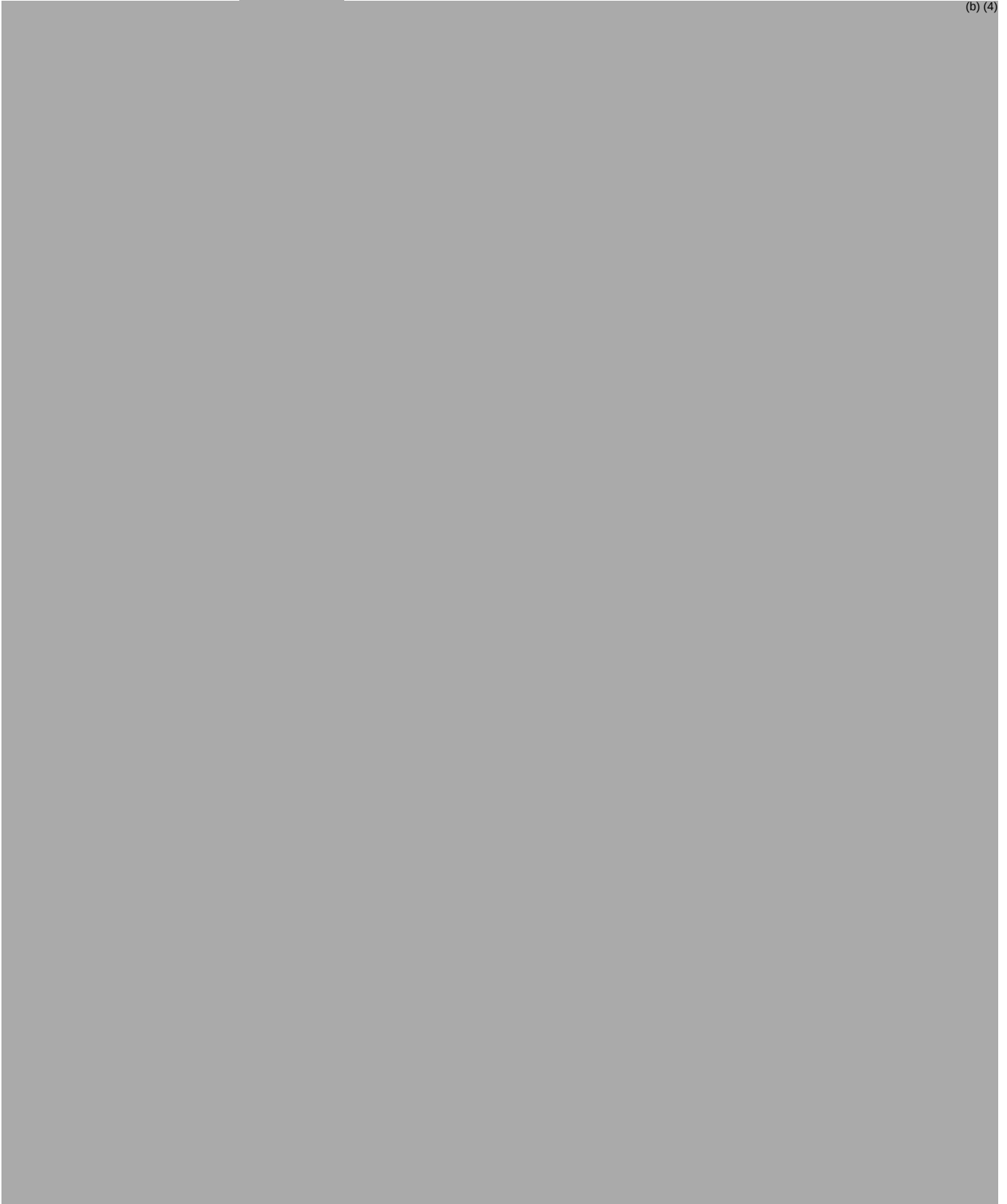


Figure 3: Structure of the (b) (4) **starting material**



- Figure 4 (from IND module 7 CMC Information, figure 7-6 on page 42 of volume 1) shows the (b) (4) and the final structure.

Figure 4: Hydrogel: (b) (4) **and structure**



The same information in Figure 4 is depicted differently in Figure 5 (from the IND module 7.1.1 Principle of Operation)



The sponsor provided a batch formula composition table (module 7.3.2 Composition):

Table 1: OTX-DP drug product formula composition

Ingredient	As formulated (% dry basis)	Theoretical composition (mg, dry basis)
Dexamethasone		
4-arm 20K PEG		
Sodium phosphate dibasic		
Trilysine acetate		
NHS-fluorescein		
Water		
Target Weight		

The sponsor provides dimensions for the OTX-DP (IND module 7.3.4 In Process Controls of Manufacturing)



This reviewer identified batch analysis for 3 lots (IND module 7.3.6.4 batch analysis):

- Lot # 05301202
- Lot # 05301203
- Lot # 05301204

Some information was also provided for lot # 05101201.

2.2 Relevant INDs, NDAs, and DMFs

- The sponsor references active MF (b) (4) held by (b) (4) for dexamethasone USP (b) (4) as manufactured in the (b) (4) facility.
 - Listed on their form 1571
 - Letter of authorization from (b) (4) provided (signed, on company letter head)
- The sponsor also references NDA 013422 (Alcon Inc.'s Maxidex®)
 - Not on the form 1571, no letter of authorization
 - Referenced in module 3 Introductory Statement (page 7)
 - Referenced in the protocol (page 6)

Alcon submitted NDA 13422 for ophthalmic suspension/drops of 0.1% dexamethasone and original approval was granted June 20, 1962. The most recent label is dated 2003.²



² Maxidex® label accessed via:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/13422slr035_maxidex_lbl.pdf

(b) (4)

2.3 Drug Formulation

2.4 Comments on Impurities/Degradants of Concern

(b) (4), and the sponsor has identified three (b) (4). From the IND (module 7 CMC Information, figure 7-5 on page 40 of volume 1):

(b) (4)

(b) (4)



(b) (4)

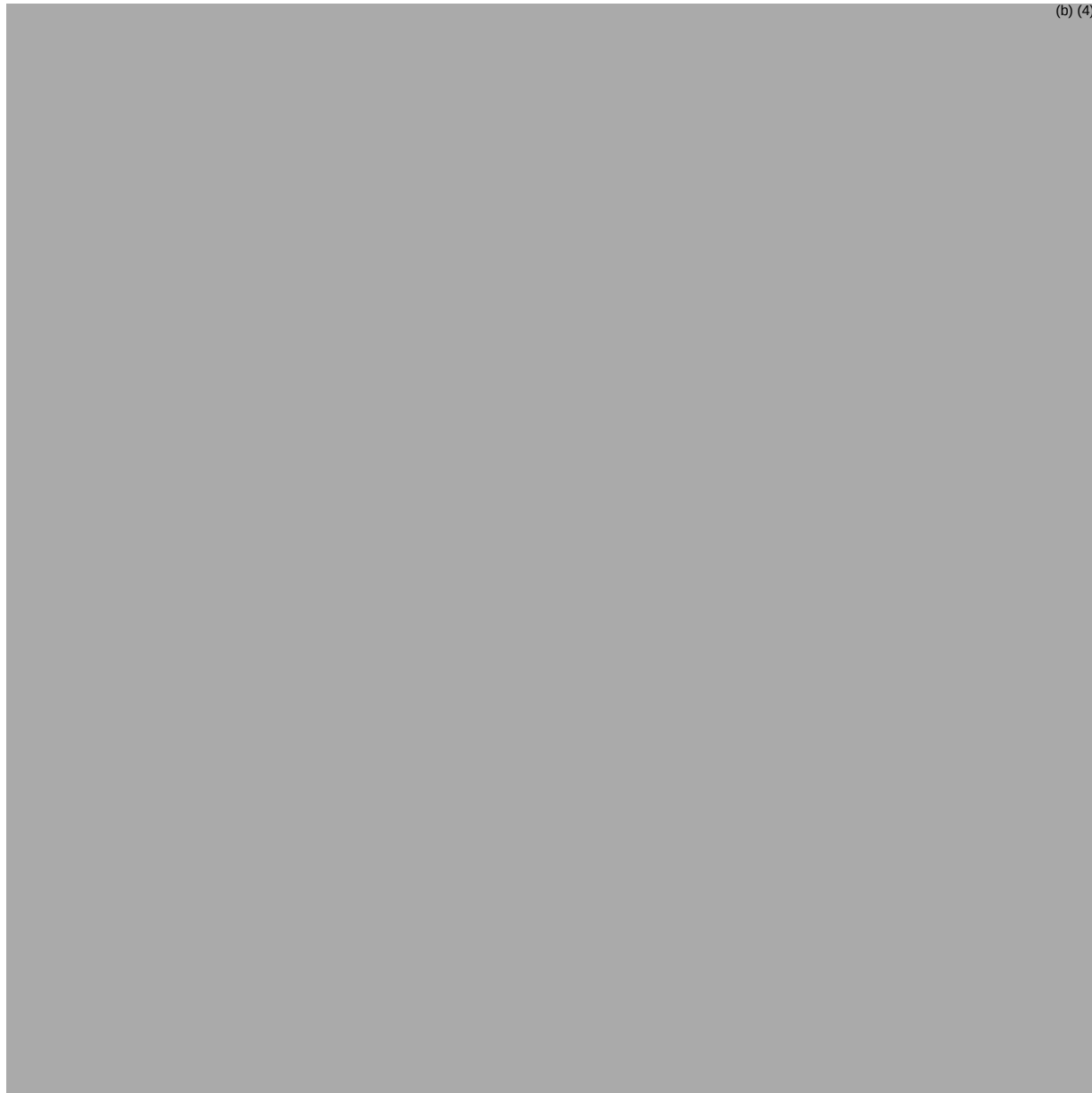


Table 3 was copied from Report # 0184 ("Characterization of the Dexamethasone Punctum Plug (b) (4)", page 3), and is also summarized in IND module 7.3.6.4 Batch Analysis.

Table 3: Characterization of the Dexamethasone Punctum Plug

(b) (4)



In response to the 9/07/2012 IR, the sponsor's 9/11/2012 response included additional impurity information. From the response:

Table 4: Amended (9/11/2012) comparison of impurities: OTX-DP in the design verification lots and the 35-day dog toxicology study lots

Test	Item	Design Verification Lot 05301202	Design Verification Lot 05301203	Design Verification Lot 05301204	Toxicology Lot 02151201	Toxicology Lot 02151203
Assay	Dexamethasone per plug	(b) (4)				
Impurities	Not more than (b) (4) % of total impurities	(b) (4) % of total impurities	(b) (4) % of total impurities	(b) (4) % of total impurities	(b) (4) % of total impurities	(b) (4) % of total impurities

Test	Item	Design Verification Lot 05301202	Design Verification Lot 05301203	Design Verification Lot 05301204	Toxicology Lot 02151201	Toxicology Lot 02151203
	Not more than (b) (4) % of any individual impurity	None > (b) (4) %	None > (b) (4) %	None > (b) (4) %	None > (b) (4) %	None > (b) (4) %
	Reporting of impurities ≥ (b) (4) % or (b) (4) µg, whichever is lower	Impurities RRT (min) (b) (4) %	Impurities RRT (min) (b) (4) %	Impurities RRT (min) (b) (4) %	Impurities RRT (min) (b) (4) %	Impurities RRT (min) (b) (4) %

2.5 Proposed Clinical Population and Dosing Regimen

- Patient population
 - Age ≥ 21 years
 - “Has a cataract and is expected to undergo clear corneal cataract surgery with phacoemulsification and implantation of a posterior chamber intraocular lens”
- Dosing regimen:
 - After surgery, “the punctum plug will be inserted into the inferior vertical canaliculus of the operated eye intraoperatively, within minutes of the completion of cataract surgery”
 - 60 patients total, randomized 1:1 (30/arm) to either OTX-PD (plug containing 394 µg (b) (4) of dexamethasone), or to PVPP (placebo plug)

2.6 Proposed Clinical Protocol

Title	A prospective, multicenter, randomized, parallel-arm, double-masked, vehicle controlled Phase II study evaluating the safety and efficacy of OTX-DP
#	OTX-12-002
Test articles:	1:1 randomization (30/arm, randomized post-surgery) to: • OTX-DP (394 µg of dexamethasone punctum plug) • PVPP (placebo vehicle punctum plug)
Objective	Safety and efficacy
Primary endpoints	• “Absence of cells (i.e. score of ‘0’) in anterior chamber of the study eye at Day 8” • “Absence of pain (i.e. score of ‘0’) in the study eye at Day 8”

Secondary objectives	• Evaluation of cell in the anterior chamber in the study eye on D1, 4, 11, 14 and 30³ • Evaluation of flare in the anterior chamber in the study eye at D1, 4, 8, 11, 14 and 30 • Evaluation of pain in the study eye at D1, 4, 11, 14, 30 • Presence of the punctum plug at all study visits • Ease of product use as assessed by the Investigator • Ease of product visualization as assessed by the Investigator
Exploratory endpoints	• Presence of the punctum plug beyond D30 (follow up visits every 15 days until the plug is no longer present or is removed by the Investigator) • Photophobia • Slit lamp exam on D1, 4, 8, 11, 14 and 30 for: ○ Bulbar conjunctival injection ○ Chemosis ○ Ciliary injection ○ Corneal edema ○ Keratic precipitates
Safety evaluations	• Slit lamp exam • Dilated fundus exam • Visual acuity • Intraocular pressure • Adverse events (AE)
One hour follow-up	> 60 minutes after the insertion procedure, assessment of the study eye only for: • Punctum plug visualization; reposition if necessary • Record adverse events
Subsequent follow-up	• D1, D4_{±1}, D8_{±1}, D11_{±1}, D14_{±2}, D30_{±2} • If plug still present at D30, every 15 days _{±2}
Concomitant eye medication	Prescription “antibiotic drops on a regimen that does not exceed four drops per day” (protocol page 22)

2.7 Previous Clinical Experience

- Dexamethasone is the subject of multiple approved NDA and ANDAs. The sponsor lists 31 applications for the treatment of ocular inflammation.
 - As the sponsor notes (IND module 8.3.1 Dosage Comparison), Maxidex® is 0.1% dexamethasone solution, and the label dosage⁴ of “one or two

³ Cells and pain on D8 are not listed as secondary endpoints because they are primary endpoints; however, these endpoints are being measured at each time point

⁴

http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/13422slr035_maxidex_lbl.pdf

drops topically in the conjunctival sacs(s)", hourly in severe cases and 4 to 6 times daily for mild disease. Assuming one drop = 50 µl, then one drop = 50 µg of dexamethasone. The label would appear to allow > 600 µg/day/eye of dexamethasone topically.

- The sponsor also cites examples of approved oral and injection doses of dexamethasone ≥ 1 mg
- OTX-DP (dexamethasone in hydrogel) has not been previously tested in humans
 - [REDACTED] (b) (4)

2.8 Regulatory Background

A pre-IND meeting was held between Ocular Therapeutix, Inc. and DTOP on May 16, 2012.

3 Studies Submitted

3.1 Studies Reviewed

Report #	Title	Location	GLP?
Submitted in the original IND (8/20/2012)			
0183	Dexamethasone punctum plug pharmacokinetic study in the canine eye model	Volume 2, tab "appendix 7-2) Note: Submitted in the CMC section	no
12-0419-G1 (0161)	35 day dexamethasone punctum plug toxicity study with a 14 day recovery period	Volume 3 (entire volume)	Yes
T0118-904 (TR0174)	"Subchronic toxicity testing of the Travoprost 60 day fluorescent punctum plug", also titled, "4 week systemic toxicity study in rats following subcutaneous implantation" ⁵	Volume 4, tab appendix 8-5	Yes
0167	Dexamethasone punctum plug prolonged exposure biocompatibility testing	Volume 4, tab appendix 8-2	Yes

(b) (4)

⁵ Note: The sponsor (in the table of contents and the 3 page preface) labels this study

(b) (4)

3.2 Studies Not Reviewed

All P/T study reports submitted in the original IND (8/20/2012) and the amendment (9/12/2012) were reviewed.

3.3 Previous Reviews Referenced

Reference is made to the P/T review of the pre-IND briefing package (Rivera, 5/03/2012) and the minutes of the May 16, 2012 meeting (Germain, 6/08/2012)

4 Pharmacology

4.1 Primary Pharmacology

No relevant studies submitted to the original IND.

4.2 Secondary Pharmacology

No relevant studies submitted to the original IND.

4.3 Safety Pharmacology

No relevant studies submitted to the original IND.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Study title: Dexamethasone punctum plug pharmacokinetic study in the canine eye model	
Study no.:	• 0183 • TR0183 (test report 0183)
Report date:	July 2012
Study report location:	Volume 2, tab "appendix 7-3" (not sequentially paginated)
Conducting laboratory and location:	• (b) (4) • Tear fluid analysis at (b) (4)
GLP compliance:	No
Drug, lot #, and % purity:	Dexamethasone punctum plug manufactured at Ocular Therapeutix, lot #s NB082-114A, B and C. Composition: (b) (4) % 4a20K SG hydrogel containing approximately 380 µg of dexamethasone

Key Study Findings

- For dogs bearing 380 µg dexamethasone punctum plugs, the authors report tapered drug delivery of 28 days
 - 70% (267 µg) by D7
 - 77% (293 µg) by D15
- No signs of ocular toxicity were detected

Method notes

- 20 female beagle dogs (non-naïve), weighing 5 to 10 kg, were fasted, sedated, and then both eyes received punctal implants:
 - 1 or 2 drops of 0.5% proparacaine hydrochloride were instilled to each eye
 - Punctum gently dilated with a stainless steel dilator, as needed (data not recorded)
 - Dexamethasone punctum plug inserted into the inferior canaliculus if present/normal, or the superior canaliculus (if the inferior canaliculus was defective/absent) just under the punctal opening using forceps (data not recorded)
 - After insertion, the plug area was hydrated with either balanced salt solution or 0.9% sodium chloride for injection USP
- Gross ocular exam for irritation was performed pre-insertion and every 7 days (D0, D7, D14, D21, D28) for all animals
- Plug retention was assessed every 7 days (D7, D14, D21, D28)
 - Using a cobalt blue flashlight and NightSea yellow glasses to visualize

- The location of the plug relative to the punctal open was recorded (at surface, middle, or deep)
- If plug not found, flushing was used to determine if the canal was plugged
- Intraocular pressure (IOP) was reportedly measured on D0 (pre-implantation), D14 and D28 for all remaining animals
- Tear fluid was collected from 6 eyes on D7, 14, 21 and 28
 - "A Schirmer tear strip cut at the 10 mm line will be placed just inside the eyelid of the eye. Tear fluid will be allowed to reach the 10 mm line, if possible, and will be transferred to a vial" for analysis
- Aqueous humor was collected from 6 eyes on D 7, 14, 21, and 28
 - Collected after presence of the plug was verified
 - After collection of the aqueous humor, the plug was removed for content analysis
- *Reviewer comment:* This reviewer was unable to discern when overlap occurred between the eyes/dogs subjected to tear fluid collection and aqueous humor collection

Results notes

- Gross ocular examination found all eyes normal
- No remarkable changes in IOP apparent
- Note: The results section mentions a different study (report # TR0159, not provided to this IND) that tested 462 µg plugs

Table 5: Tear and aqueous humor PK, plug presence/absence for the dog PK study (report # 0183)

Endpoint	Day 7	Day 15	Day 21	Day 28
Aqueous humor concentration (ng/ml)	4.1 ± 2.6	7.0 ± 3.9	0.7 ± 1.0	0.1 ± 0.2
Tear fluid concentration (ng/ml)	2796 ± 1184	1535 ± 750	1146 ± 320	190 ± 294
Drug content of the explanted plugs (µg)	267 ± 18	87 ± 39	57 ± 34	24 ± 45
Plug present	36	28	17	8
Plug absent	1	3	6	3
Retention rate	97%	90%	74%	73%

PK values presented as mean ± standard deviation

Table 6: Dexamethasone did not affect IOP in the dog PK study (report # 0183)

Endpoint	Day 0	Day 15	Day 28
N =	19 dogs (38 eyes)	17 dogs (28 eyes)	6 dogs (8 eyes)
IOP (mm Hg)	20.7 ± 2.8	24.4 ± 3.5	20.5 ± 3.0

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: 35 day dexamethasone punctum plug toxicity study with a 14 day recovery period

Study no.:	12-0419-G1 - TR 0161
Report date:	July 20, 2012
Study report location:	- Volume 3 (of the original IND, submitted 8/20/2012), not sequentially paginated - Also received electronically ("020 Appendix 8-1_TPTR 0161.pdf")
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes, signed, with the exception (pdf page 12) that the "characterization and stability of the test article", "its mixture with carriers" and urinalysis were not done by (b) (4)
QA statement:	Yes, signed
Drug, lot #, and % purity:	"Dexamethasone punctum plug" "Active A (b) (4)% 4a20K PEG hydrogel [prepared with (b) (4) lot # 02151201 "Active B (b) (4)% 4a20K PEG hydrogel [prepared with (b) (4)% 4a20KSG]", lot # 02151203 "Blank punctum plug (vehicle only)" "Placebo A (b) (4)% 4a20K PEG [prepared with (b) (4) (b) (4)", lot # 02151202 "Placebo B (b) (4)% 4a20K PEG [prepared with (b) (4) 4a20KSG]", lot # 02151204

Key Study Findings

- No true negative control was used (i.e. no treatment, or sham-insertion). Both eyes of each dog on study received a punctum plug.
- 8/sex received either the placebo plug or the dexamethasone plug into both eyes. Two different formulations of the hydrogel were made; each dog received the A formulation in the right eye and the B formulation in the left eye.

- Treatment-related eye discharge (clear, brown, green, white, yellow) and increased infections were noted by clinical observations.
 - Histopathology confirmed the increase in infection (minimal to moderate bacterium in the punctum; mononuclear cell infiltrate in most eyelids, occasional mixed cell infiltrate)
- HISTOPATHOLOGY:
 - Histopathology focused on the eye tissues and a few other organs
 - No effects reported in the cornea, conjunctiva, lens, retina, choroid, iris, optic nerve
 - no effects noted in the adrenal, thymus, aorta, nasal turbinates
 - Local histopathology was only minimally adequate, because too many critical tissue samples were not evaluated / not present:
 - 30% of the upper left punctal area (10/33 missing),
 - 18% of the upper right punctal area (6/33)
 - 9% of the lower punctal areas (missing 3/33 left and 3/33 right samples)
- PK:
 - No dexamethasone detected in plasma
 - Review of the tear PK is complicated by the lack of detail regarding when/which dexamethasone plugs were replaced. The authors report tapered release (highest at 8 hours post-dose, but still detectable by D35) for dogs not receiving replacement plugs (see Table 15 below).

NOTE: This study was ongoing at the time of the pre-IND meeting, and the sponsor asked, “Does the Agency agree that the toxicology plan described in the Pre-IND briefing package is sufficient to support a Phase 2 clinical trial for the Dexamethasone Punctum Plug?”

Methods

Doses:	One punctum plug in each eye, 0 or 750 µg of dexamethasone
Route of administration:	Insertion into the inferior or superior canaliculus
	NOTE: no data recorded for which
Dose volume:	1 plug per eye
Species/Strain:	Treatment naïve beagle dogs
Age:	“at least 6 months of age”
Weight:	5.6 to 8.9 kg

Table 7: Animal assignment for the 35 day dog toxicity study (report # 12-0419-G1)

Group	#	Dosing	Nominal dose frequency	Main group necropsy (D36)	Recovery group necropsy (D49)
1 (blank plug)	8M/8F	Right eye: placebo A Left eye: placebo B	1 insertion of the plug on D1	5M/5F	3M/3F
2 (dexamethasone plug)	8M/9F	Right eye: 750 µg/plug Active A Left eye: 750 µg/plug Active B		5M/6F	3M/3F

- The authors counted D1 as the day of plug insertion
- The Toxikon report has 4 pages of preface material by Ocular Therapeutix, which provides additional information about the characterization.
- Note: Review of the report is complicated by poor organization. The full report is not sequentially paginated; it has 5 appendices and 5 attachments. Several of the appendices and attachments have their own appendices or attachments. Although individual animal data are provided, most of the data lack summary tables (e.g. clinical signs). The tables are not numbered. A non-hold comment has been drafted (#5 m&n in section 1.3.3 of this review).
- Plug insertion procedure:
 - Initial sedation with dexmedetomidine (Dexdomitor®); if the eyes were not stable, isoflurane via inhalation was used.
 - Both eyes received 1-2 drops of proparacaine hydrochloride
 - The diameter of the punctal opening was recorded prior to and after dilation
 - Dilation of the “inferior or superior” canaliculus was “gently” performed using a steel dilator, and the plugs were inserted using forceps
 - The plugs were hydrated with balanced salt solution (BSS) (amount not reported) after insertion
 - “If the punctum plug was not successfully retained during the first week following initial insertion... the dog was replaced with a naïve animal” (pdf page 17 – reviewer not certain if this actually happened)
 - However, “if punctum plugs were not present in one or both eyes, the animals was anesthetized and the plug(s) re-inserted” (pdf page 18). This reviewer is unsure what this is intended to mean, or if this was followed. A non-hold comment has been drafted (#5g,h,i,j in section 1.3.3 of this review)

- Plug removal procedure:
 - On D35, any recovery dog still retaining a punctum plug had the plug removed
 - Dog was anesthetized, given 1-2 drops/eye of proparacaine. The punctum was gently dilated and the plug manually removed if feasible, or irrigated with BSS if necessary to flush out the plug

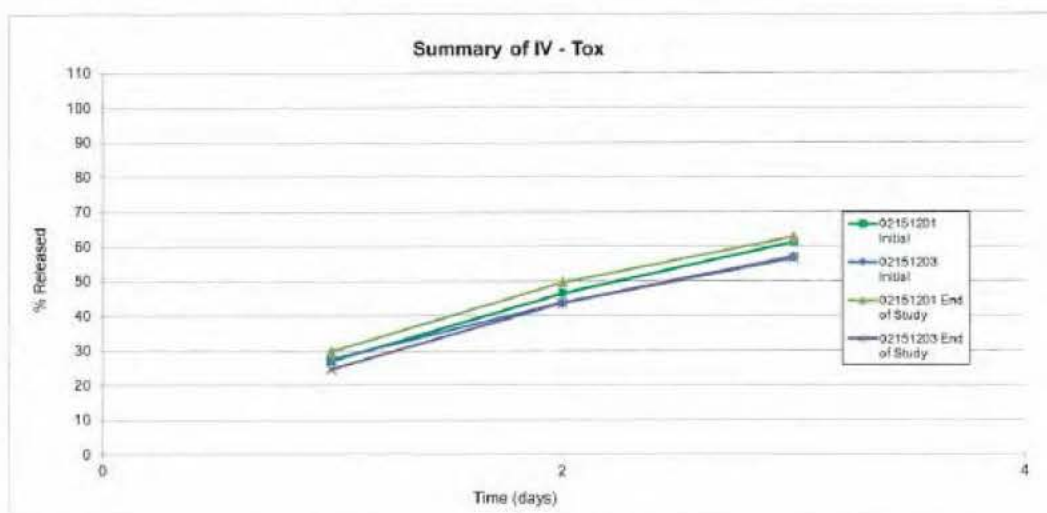
Observations and Results

Dosing Formulation Analysis

- The 4-page preface by Ocular Therapeutix reports:
 - the dexamethasone punctum plug is product code 70-2004-003
 - the blank (placebo) punctum plug is product code 70-2004-003
 - “One version of the hydrogel component of the plugs was made from (b) (4) % 4a20K SG material (Placebo B – lot # 02151204 and Test Article B – Lot # 02151203) and the second version was made from a (b) (4) material (Placebo A – lot # 02151202 and Test Article A – Lot # 02151201).”
 - Each plug was made at Ocular Therapeutix, Bedford MA, sterilized off-site and then sent to (b) (4) for toxicity testing.
 - “The (b) (4) % 4a20K SG employed in the preparation of Placebo B and Test Article B was selected as the hydrogel component to be used in the clinical trial manufacturing of OTX-DP.”
- The authors note (report page 7) that “the sponsor was responsible for all test article characterization data”
- Attachment C of the study report (pdf pages 294-346) is the Characterization Report, technical document # 0239
 - Signed and QA'd
 - Reportedly (pdf page 296) tested for: appearance, dry and hydrated dimensions, identity, assay, *in vitro* release rate, and impurities
 - The *in vitro* release data appear to be pdf page 333. This reviewer could not interpret the page (e.g. no description of the methods were provided, the pass/fail criteria were not provided, the superscript marks were not explained, the meaning of “IV” is unclear) :

Figure 9: *In vitro* dexamethasone release rate data (?) provided in the dog 35-day study (report # 12-0419-G1)

LOT	Description	ID	ASSAY		PURITY	WATER	IV		
		Pass/Fail	% Loading	Dex per plug (µg)	Total Rel Cmpds	% Water	D1	D2	D3
02151201	Tox Initial	Pass	(b) (4)						
02151203	Tox Initial	Pass							
02151201	Tox End of Study	Pass							
02151203	Tox End of Study	Pass							



Characterization determined the product tested at the end of the study is the same as the material at start of study.

NB Ref :	Initial		End Of Study	
	ID	DC-84-019	DM-85-188	DM-85-188
	Assay	DC-84-019	DM-85-188	DM-85-188
	Purity	DM-85-027	DM-85-189	DM-85-189
	IV	DM-85-119	DM-85-183	DM-85-183
	Water	DM-85-068	NA	NA

- The expansion of the plugs after hydration was measured (diameter and width): PBS at 37°C for 10 minutes and 24 hours (summary tables – pdf pages 299 and 300). The dexamethasone-containing plugs were initially larger (0.59 mm diameter vs. 0.36 mm diameter for the placebo plugs), and the placebo-plugs expanded larger than the dexamethasone plugs.

Table 8: Plug expansion (in PBS at 10 minutes or 24 hours) for the 35-day dog study

Plugs → Time point↓	Dexamethasone-plug (lots # 02151201 and 02151203)		Vehicle plug (lots # 02151202 and 02151204)	
	Width (mm)	Diameter (mm)	Width (mm)	Diameter (mm)
Dry	0.56	3.9	0.36	3.5
After 10 minutes hydration with PBS at 37°C	1.28	3.2	1.43	2.7
After 10 minutes hydration with PBS at 37°C	1.46	3.1	1.58	2.9

Mortality

- No premature deaths occurred

Animal Removals

- Three dogs were removed from the study and replaced (pdf page 22):
 - #1002 (male placebo main-group) was removed “due to inability to properly insert the plug” and was replaced by # 1009
 - #1005 (male placebo main-group) was removed “due to poor plug retention” and replaced by # 1010
 - #2101 (female drug main-group) was removed “due to poor plug retention” and replaced by #2109
- The methods section states (pdf page 17) that “if the punctum plug was not successfully retained during the first week following the initial insertion, the dog was replaced with a naïve animal”
- **NOTE:** Not clear if the issue was with one formulation of plug (i.e. the right eyes only, the left eyes only, one or both eyes per dog). The lack of these data is a notable reporting deficiency.
- Aside from the initial Individual Punctum Dilation Data (pdf pages 265-2660, no other data were identified for #1002, 1005 and 2102. Theoretically, the pre-dose data should be available (e.g. ophthalmology), and additional data (i.e. clinical signs, punctum plug assessment data) should be available for #1005 and #2101. The omission of these data from the report is a notable deficiency.

Punctum Plug Assessment

- The report notes that the punctum plug assessments were only evaluated twice per week “until [Friday] March 16, 2012, after which evaluations were performed daily Monday through Friday” (pdf page 18)
 - Evaluation included assessment of the punctal area, visualization of the punctum plug, and an assessment of the location of the plug relative to the punctal opening (0 = not present, 1 = surface, 2 = middle, 3 = deep)

- The methods section states (pdf page 18) that “If punctum plugs were not present in one or both eyes, the animal was anesthetized and the plug(s) re-inserted as per the original insertion procedure described in Section 7.3.2 – 7.3.5. The animals remained on study until the planned necropsy date.”
- The authors concluded that the B plugs (placebo and dexamethasone) had “a higher overall incidence of presence” than the A plugs (pdf page 23).
- Individual Plug Assessments data are reported (pdf pages 161-181). These data explicitly note “plug not present” for only one dog (male # 2001 on D7). The data note plug present ... no” multiple times:
 - Placebo males: 9 instances (range D3 to D33)
 - Drug males: 5 instances (range D7 to D28)
 - Placebo females: 20 instances (range D3 to D34)
 - Drug females: 28 instances (range D1 to D34)
- This reviewer’s reading of the methods would indicate that the plug was replaced each time it was noted as not present. However, animals with no plug detected in the first week were to have been replaced, and several dogs with “plug present... no” during the first week were not replaced (#1007, 2001, 1107, 1108, 2108).
- The depth was usually reported as surface (1). Review of the data did not identify any pattern between reported depths of the plugs and plug absence.
- Individual Punctum Dilation Data are reported (pdf pages 265-266). This reviewer infers that these data tables show when the plugs were replaced. However, the data do not fully align with the Individual Plug Assessment data. For example:
 - Data match for #1001, 1002, 1003, 1004, 2004, 2005, 2006, 2007, 2008, 1103, 1105, 1106, 2105, 2109
 - Data did not match for #1006, 1007, 1008, 1010, 2001, 2002, 2003, 1101, 1102, 1104, 1107, 1108, 1109, 2102, 2103, 2104, 2106, 2107, 2108,
 - **Note:** for dog # 1108, the table (pdf page 265) is missing the third study day; could be D20, D29 or D34.

For convenient reference, the Dilation Data are copied from the report in Figure 10 and Figure 11:

Figure 10: Individual punctum dilation data for the 35-day dog study (report # 12-0419-G1) - Part 1

Animal	Study Day	Punctum Diameter (mm)			
		Initial		After Dilation	
		OD	OS	OD	OS
1001	1	0.9	1.0	1.0	ND
	21	0.8	N/A	ND	N/A
1002*	1	1.0	N/A	ND	N/A
1003	1	0.8	0.7	ND	0.8
1004	1	0.8	0.8	ND	ND
	26	N/A	0.9	N/A	ND
1005	1	1.0	1.0	ND	ND
1006	1	0.5	0.5	0.7	0.7
1007	1	1.0	1.0	ND	ND
	6	1.0	N/A	ND	N/A
	31	1.1	N/A	ND	N/A
1008	1	0.8	0.9	ND	ND
	32	0.8	N/A	1.0	N/A
1009	1	0.8	0.7	ND	0.8
	34	N/A	0.9	N/A	1.0
1010	1	0.8	1.0	ND	ND
	22	0.9	N/A	ND	N/A

* Animal was replaced.

Animal	Study Day	Punctum Diameter (mm)			
		Initial		After Dilation	
		OD	OS	OD	OS
1101	1	1.0	1.0	ND	ND
	14	1.4	N/A	ND	N/A
	28	1.2	N/A	ND	N/A
1102	1	1.0	0.9	ND	1.0
	12	1.0	N/A	ND	N/A
	20	1.0	N/A	ND	N/A
1103	1	0.8	0.7	ND	ND
	14	0.8	N/A	ND	N/A
	28	0.8	N/A	ND	N/A
1104	1	1.0	1.0	ND	ND
	8	1.0	1.0	ND	ND
	19	1.0	N/A	ND	N/A
	32	1.2	N/A	ND	N/A
	34	1.4	N/A	ND	N/A
1105	1	N/A	N/A	N/A	N/A
	13	1.0	0.8	ND	0.9
	23	1.2	N/A	ND	N/A
	27	1.4	N/A	ND	N/A
1106	1	0.6	0.7	0.7	ND
1107	1	0.8	0.9	ND	ND
	21	0.9	N/A	ND	N/A
	31	N/A	1.1	N/A	ND
1108	1	1.2	0.8	ND	ND
	5	0.9	N/A	ND	N/A
	19	1.0	N/A	ND	N/A
		N/A	0.9	N/A	1.0
1109	1	1.0	1.0	ND	ND

ND = No dilation necessary

N/A = Not Applicable

Figure 11: Individual punctum dilation data for the 35-day dog study (report # 12-0419-G1) - Part 2

Animal	Day	Punctum Diameter (mm)			
		Initial		After Dilation	
		OD	OS	OD	OS
2001	1	1.0	0.8	ND	0.9
	13	1.0	N/A	ND	N/A
2002	1	0.9	1.0	ND	ND
	27	N/A	1.1	N/A	ND
2003	1	0.8	1.0	0.9	ND
	21	0.9	N/A	ND	N/A
2004	1	1.0	0.8	ND	0.9
2005	1	0.8	0.8	0.9	0.9
2006	1	0.7	1.0	0.9	ND
2007	1	0.7	0.7	0.9	0.9
2008	1	0.9	0.9	ND	ND

Animal	Day	Punctum Diameter (mm)			
		Initial		After Dilation	
		OD	OS	OD	OS
2101	1	1.0	0.9	ND	1.0
2102	1	0.9	0.9	ND	ND
	12	N/A	1.0	N/A	ND
	16	0.9	N/A	ND	N/A
	27	0.9	N/A	ND	N/A
	30	0.9	N/A	ND	N/A
2103	1	0.8	1.0	0.9	ND
	14	0.9	N/A	ND	N/A
	24	1.0	N/A	ND	N/A
2104	1	1.0	1.0	ND	ND
	22	N/A	1.0	N/A	ND
2105	1	1.0	1.2	ND	ND
2106	1	0.8	0.6	0.9	0.9
	13	1.0	N/A	ND	N/A
2107	1	1.0	1.0	ND	ND
	21	0.9	N/A	ND	N/A
2108	1	1.0	1.1	ND	ND
	5	N/A	1.0	N/A	ND
	8	1.2	N/A	ND	N/A
	15	N/A	1.2	N/A	ND
	19	1.2	N/A	ND	N/A
2109	1	1.0	1.0	ND	ND
	12	N/A	1	N/A	ND

ND = No dilation necessary

N/A = Not Applicable

Clinical Signs

- Daily observation for signs of toxicity. The report provided individual animal data (report Attachment 1 pages 2-10; pdf pages 111-120).
- Note: the clinical signs list “eye discharge” but do not specify left eye or right eye. Because this study tested different formulations in the right eye, this lack of specificity is a study limitation.
- Dog # 2107 (female drug group) exhibited edema for two days (D24 and D25), with “area around the plug red in color) from D24 to D28 (5 days). This dog had eye discharge (clear, green, brown) on 21/36 days (occurring from D3 until D34)
 - The authors noted this edema finding but did not speculate on relationship to treatment; pdf p 22)

- Eye discharge was notable, ranging from clear to brown, green, white and yellow. The authors noted, and this reviewer concurs, that “There was a higher incidence of discharge in the placebo male and test female groups”.
 - The authors state (pdf p 22) “the discharge was considered to be related to the presence of the punctum plug and not specifically the test article”.
 - This reviewer disagrees – although the discharge does not appear to be related to dexamethasone exposure, the discharge DOES appear related to the punctum plugs.
 - The incidence of discharge was variable, among placebo plug males, two dogs exhibited discharge on ≤ 2 days, four exhibited discharge for more than a third of the days observed post-dose. Of these four males, two exhibited discharge on ≥ 28 days ($\geq 78\%$ of the days observed post-dose). Among drug plug females, three dogs exhibited discharge on ≤ 3 days, and five dogs exhibited discharge for more than a third of the days observed post-dose.
 - **NOTE:** Review limited by the lack of data for the occurrence of eye discharge specific for the left eye and right eye, historical control incidence for clear, brown, green, white and yellow eye discharge

Table 9: Eye discharge (clear, brown, green) was notable in the 35 day dog study (report # 12-0419-G1)

Eye discharge		Placebo plug group		Dexamethasone plug group	
		Male	Female	Male	Female
None during study	# dogs	0/8	2/8	2/8	0/9
Brown (2)	# dogs	6/8	5/8	1/8	5/9
	# occurrences	15	16	3	10
Clear (3)	# dogs	6/8	5/8	5/8	9/9
	# occurrences	78	37	38	83
Green (4)	# dogs	5/8	1/8	1/8	5/9
	# occurrences	8	2	3	11
White (6)	# dogs	2/8	1/8	2/8	4/9
	# occurrences	2	2	2	4
Yellow (7)	# dogs	3/8	0/8	1/8	2/9
	# occurrences	5	-	2	4

Data tabulated by this reviewer from the individual animal data. The number in parenthesis after the color (first column) is the authors' code for clinical observations. These data include the main-group dogs (necropsy D36) and the recovery-group dogs (necropsy D49)

- **Note:** Dog # 1102 (female placebo group) reported as not terminally sacrificed (individual clinical observations, pdf pages 116-117), but this appears to be a typographic error (necropsy data were provided).

Body Weights

- No remarkable observations
- Recorded weekly. Animals were fasted prior to necropsy.

Feed Consumption

- No remarkable observations
- Assessed quantitatively during a 24-hour period, once per week. Food and water were available *ad libitum*

Ophthalmoscopy

- Pre-dose pre-randomization examination including: slit lamp biomicroscopy (cornea, conjunctiva, iris, anterior chamber, lens), fluorescein staining of the corneal surface, fundoscopy and tonometry. Only animals with no eye injuries were used.
- Ophthalmology performed on D1, D14 and D35 (but not at the end of recovery)
 - Fundus evaluations were only performed on D1 and D35
 - Not clear to this reviewer whether the D1 ophthalmology evaluation was pre-insertion or post-insertion
- **Note:** no fluorescein staining was reported for the ophthalmology examinations. This reviewer is uncertain if the test article contained conjugated fluorescein, and theoretically confounding might have occurred, but this does not appear to be an issue for this study.
- “Conjunctival congestion, discharge, and sluggish to absent pupillary light reflex (PLR).” “Mild conjunctival congestion (score of 1) and mild discharge (score of 1) noted in some animals across all groups.” The authors did not consider these effects adverse.
- No adverse findings in the posterior segments of the eyes for any of the dogs were detected.
- No clear effect on IOP. The authors note a slight increase in females on D35 for the test article plug B compared to the control plug B. The authors conclude, and this reviewer agrees, that the difference appears to be normal variation

Table 10: Notable pupillary light reflex responses in the 35-day dog study (report # 12-0419-G1)

Ophthalmic examination	Day	Placebo plug group		Dexamethasone plug group	
		Male	Female	Male	Female
OD PLR – grade 1	1	0	0	0	0
	14	1	1	0	0
	35	0	0	0	0
OD PLR – grade 2	1	0	0	0	0
	14	0	0	0	1
	35	0	0	0	2
OS PLR – grade 1	1	0	0	0	0
	14	0	1	0	0
	35	0	1	0	0
OS PLR – grade 2	1	0	0	0	0
	14	0	0	0	2
	35	0	0	0	2

- Grade 2 PLR was noted for dexamethasone plug group females: # 2103 on D14 (left eye), # 2105 on D35 (right eye), and # 2109 (day 14 and D35, both eye on each day).
- The potential relationship of PLR to treatment is unclear.
- The authors provided the grading system for ocular lesions (pdf pages 96-105). For pupillary light reflect, 0 = “normal pupillary light reflex”, 1 = “sluggish pupillary light reflex” and 2 = “no pupillary light reflex)

ECG

- No ECG conducted

Hematology

- Blood collected pre-dose (D0) and on D36 and D49 for hematology, clinical chemistry and coagulation endpoints
- No apparent differences identified by the authors or this reviewer

Clinical Chemistry

- No apparent differences identified by the authors or this reviewer

Urinalysis

- Urine was collected on D36, via cystocentesis [bladder puncture] for main-group animals, via pan collection for recovery animals
- No apparent differences identified by the authors or this reviewer

Gross Pathology

- No treatment-related effects apparent
- The report has a glaring QA violation: “Individual Necropsy Observations” (report pages 151-154; pdf pages 261-264) have listings for only two animals (thymus not collected for female # 1104; male # 2001, main-group necropsy on D36) exhibited an aorta hernia and pitted thymus). However, the Pathology Report (page 3-4 of the Pathology Report, pdf pages 270-271) report two other incidental findings (#1102 had a “very small uterus”; # 1106 had bilaterally enlarged ovaries).

Organ Weights

- Weighed organs: fasting body weight; brain, heart, kidneys (both together), liver, Lung (with main stem), pituitary, adrenal (both together), salivary mandibular gland, spleen, thymus
- Individual absolute organ weights were reported (i.e. no organ:body or organ:brain weight data). This reviewer did not review the relative organ weights (i.e. did not calculate them for review)
- No apparent differences identified by the authors or this reviewer

Histopathology

Battery:

- Ocular tissues (eyelids, conjunctiva, cornea, lens, iris/ciliary body, retina/choroid, optic nerve) and punctal area (implant site)
- Nasal turbinates
- Adrenal glands
- Gross lesions

NOTE: The histopathology evaluation is only minimally adequate, because too many critical tissue samples were not evaluated / not present: 30% of the upper left punctal area (10/33 missing), 18% of the upper right punctal area (6/33), 9% of the lower punctal areas (missing 3/33 left and 3/33 right samples)

Peer Review: No

Histological Findings

- Authors noted “one treatment exacerbated finding of bacteria in the punctal regions” (pdf page 24) and “A few findings within the punctal regions and eyelids, but all were interpreted as normal incidental background or procedurally related findings”
- The Histology Report (attachment B of the main report, pdf pages 267-293) states (pdf page 271):
 - “the presence of bacteria with the lumen of the punctum (right lower and left upper and lower) ... was interpreted to be test article (dexamethasone) exacerbated”

- “the luminal hemorrhage detected histopathologically in one animal (animal # 2003) has been interpreted to be procedurally related or a post mortem artifact”
- “the foreign material encountered histopathologically within the lumens of several punctal regions has been interpreted to be part of the plug left”
- **Note:** Review of the Pathology Report was made more difficult by poor organization:
 - The authors lumped main-group and recovery-group animals together for their summary table (pdf page 273-279), only reporting incidence (not severity)
 - and their individual animal reporting does not identify whether each individual was main- versus recovery-group (pdf page 279-293)
- Selected histopathology results are presented in two tables (Table 11 and Table 12 below) rather than one, for formatting.
 - Most common observations were mononuclear cell infiltration (usually minimal, occasionally mild)
 - Sporadically, mixed cell infiltration (minimal to moderate; not selected for tabulation by this reviewer)) and granuloma (minimal to moderate) were observed
 - This reviewer evaluated the individual animal data (i.e. main-groups versus recovery-groups and each severity rating) but did not tabulate the results at this level of detail here

Table 11: Selected RIGHT EYE histopathology for the 35-day dog study (report # 12-0419-G1)

Histopathology observation	Severity score	Placebo plug group		Dexamethasone plug group	
		Male	Female	Male	Female
Upper right eyelid					
Not examined / not present		0/8	0/8	1/8	0/9
Mononuclear cell infiltration, dermal, multifocal	present	4	3	1	7
Mononuclear cell infiltration, dermal, focal	Present	0	0	1	0
Granuloma, dermal (focal or multifocal)	Present	1	1	1	0
Lower right eyelid					
Mononuclear cell infiltration, dermal, multifocal	Present	8	5	2	6
Mononuclear cell infiltration, dermal.	Present	0	0	1	0

focal					
Granuloma, dermal, multifocal	Present	0	0	1	0
Upper right punctal area					
Not examined / not present		1/8	2/8	2/8	1/9
Mononuclear cell infiltration, dermal, multifocal	Present	4	2	3	1
Foreign material, luminal, multifocal	Present	0	0	1	0
Foreign material, luminal, focal	Present	1	0	0	0
Lower right punctal area					
Not examined / not present		2/8	0/8	1/8	0/9
Bacterium, luminal, multifocal	Present	1	1	0	3
Bacterium, luminal, focal	Present	0	1	0	0
Hemorrhage, luminal, focal	Present	0	1	0	0
Mononuclear cell infiltration, multifocal	Present	3	3	4	2
Mononuclear cell infiltration, focal	Present	0	0	1	0
Foreign material, luminal, multifocal	Present	0	3	0	2
Foreign material, luminal, focal	Present	0	0	0	1
Foreign material, luminal, diffuse	Present	0	0	1	0

Table 12: Selected LEFT EYE histopathology for the 35-day dog study (report # 12-0419-G1)

Histopathology observation	Severity score	Placebo plug group		Dexamethasone plug group	
		Male	Female	Male	Female
Upper left eyelid					
Mononuclear cell infiltration, dermal, multifocal	present	6	5	2	6

Mononuclear cell infiltration, dermal, focal	Present	0	0	2	0
Granuloma, dermal (focal or multifocal)	Present	0	1	2	0
Lower left eyelid					
Mononuclear cell infiltration, dermal, multifocal	Present	4	5	3	4
Mononuclear cell infiltration, dermal, focal	Present	1	0	0	0
Granuloma, dermal, focal	Present	0	0	1	0
Upper left punctal area					
Not examined / not present		4/8	2/8	1/8	3/9
Bacterium, luminal, multifocal	Present	0	0	0	1
Mononuclear cell infiltration, dermal, multifocal	Present	1	2	0	0
Mononuclear cell infiltration, dermal, focal	Present	0	0	1	0
Foreign material, luminal, focal	Present	0	0	1	0
Lower left punctal area					
Not examined / not present		1	2	0	0
Bacterium, luminal, multifocal	Present	0	0	0	3
Bacterium, luminal, focal	Present	0	0	0	1
Mononuclear cell infiltration, multifocal	Present	1	1	1	1
Mononuclear cell infiltration, focal	Present	0	0	0	1
Foreign material, luminal, multifocal	Present	3	1	1	3
Foreign material, luminal, focal	Present	1	0	0	0

Toxicokinetics

- Blood was collected from a peripheral vein pre-dose, on D1 at 30 minutes and 6 hours post-dose, D14 and 35 for TK
- Tear collection:
 - On D1 at 6 hours post-dose, D7, D14, D21, D28 and D35
 - "A Schirmer Tear Test Strip" was cut at the 10 mm line, weighed, then placed "centrally in the lower conjunctival cul de sac of the eye and allowed to absorb tear film up to the 10 mm line" then re-weighed and frozen for analysis
- TK analysis done by (b) (4)
- Report Attachment D is the PK report (pdf pages 347-407)
- Dexamethasone was not detected in the plasma at any time point
- Dexamethasone was detected in the tear fluid
 - T_{max} was formulation dependent: D10 for test plug A, D5 for test plug B
- The data in Table 13 and Table 14 are partially confounded by plug replacement (this reviewer did not determine which/when plugs were replaced). Table 15 (data from pdf page 355) might be more accurate; the authors claim the data are only for dogs that did not receive replacement plugs (but this reviewer is not clear whether only the left eye plug was not replaced)

Table 13: Dexamethasone PK in tear fluid for the 35-day dog study (report # 12-0419-G1)

	Left eye Mean $\pm$ SD	Left eye Range	Right eye Mean	Right eye Range
C_{max} (ng/ml)	5795 $\pm$ 1870	2640-8450	6355 $\pm$ 2403	3250-13,700
T_{max} (day)	5 $\pm$ 8	0.25 to 28	10 $\pm$ 11	0.25 to 28
AUC_{0-35} (ng*day/ml)	100,200 $\pm$ 30900	57,000 to 174,000	119,000 $\pm$ 62100	55,800 to 300,000

Table 14: Dexamethasone Concentrations over time in tear fluid for the 35-day dog study (report # 12-0419-G1)

Eye	Gender	Time	Average (ng/ml)	Standard deviation (ng/ml)
L	F	6 hr	3780	2620
		7 day	4740	2030
		14 day	3400	1160
		21 day	2830	1020
		28 day	2470	1190
		35 day	2160	1620
R	F	6 hr	3490	2330
		7 day	4810	2090
		14 day	5170	2400
		21 day	3910	1960

L	M	28 day	4720	3620
		35 day	2190	2840
		6 hr	4950	2630
		7 day	2900	1100
		14 day	2320	550
		21 day	1740	540
		28 day	2320	2200
		35 day	1250	790
R	M	6 hr	4390	2030
		7 day	2940	1470
		14 day	2920	2070
		21 day	2180	1880
		28 day	1930	1360
		35 day	630	420

Average and standard deviation values rounded by this reviewer for readability

Table 15: Left eye ('active B' formulation) dexamethasone tear fluid PK profile for dogs not requiring replacement plugs (report # 12-0419-G1)

Time (days)	Median (ng/ml)	Average (ng/ml)	Standard deviation (mg/ml)	N
0.25	4600	4530	2520	14
7	2990	3420	1660	14
14	2560	2540	540	14
21	1980	2110	940	14
28	1840	1810	640	12
35	1150	1180	950	10

This reviewer presumes the standard deviation for this table is standard deviation from the average. Values rounded by this reviewer for readability.

NOTE: Although not mentioned in the study report, the IND (Module 7 CMC Information, section 7.3.6.5.2 “Characterization of data demonstrating no interaction between the API and hydrogel components of the dexamethasone punctum plug” has Figure 12. The information provided is markedly different from the 35-day dog study (report # 12-0419-G1); it is not clear to this reviewer whether these data are actually from report # 12-0419-G1, or another dog punctum plug study (not provided to the IND). A non-hold comment has been drafted (#5a) in section 1.3.3 of this review. As an aside, it is not clear why the sponsor believes this data suggests a lack of interaction between the dexamethasone and the hydrogel.

Figure 12: Sponsor’s cryptic information about OTX-DP explanted weekly in a 28-day dog study

7.3.6.5.2 Characterization Data Demonstrating No Interaction between the API and Hydrogel Components of the Dexamethasone Punctum Plug

In Vivo: A preclinical study employing OTX-DP containing an average dexamethasone drug content of 385 µg per plug was performed in beagles. A subset of OTX-DP was removed from the canaliculus at approximate weekly intervals over a 28 day period via manipulation through the punctum opening.

(b) (4)

(u) (9)

Figure 7-8: Images of OTX-DP Explanted Weekly over the Duration of a 28-Day Study

(b) (4)

Study title: 4 week systemic toxicity study in rats following subcutaneous implantation

Study no.: • TO118_904
 • TR0174

Report date: August 20, 2012

Study report location: Volume 4 of the original IND (submitted August 20, 2012), tab "appendix 8-5" (also submitted electronically as "024_Appendix 8-5_TPTR0174.pdf", 76 pages)

Conducting laboratory and location: (b) (4)

Date of study initiation: May 14, 2012

Test article implanted: June 4, 2012

End of in-life: July 2, 2012

GLP compliance: Yes, signed

QA statement: Yes, signed

Drug, lot #, and % purity: • Test article: "PEG hydrogel containing fluorescein and (b) (4) identification # 03291201, (b) (4) "composition: (b) (4) fluorescein"

• Control article: high density polyethylene (HDE)

Key Study Findings

- This was a screening study, with limited endpoints (no ECG, coagulation profile, urinalysis, food or water consumption data, limited necropsy)
- Rats were implanted subcutaneously with either plugs of PEG hydrogel containing (b) (4) (term not defined) or with plastic plugs (as a control)
- Authors identified no treatment-related effects
 - Endpoints were daily clinical signs, weekly detailed observations, body weight, hematology and clinical chemistry at necropsy, gross pathology and organ weights at necropsy
 - Rats on study exhibited histopathology in the **lung** (alveolar hemorrhage, alveolar histiocytosis), **kidney** (progressive nephropathy and mineralization), **liver** (hepatocellular cytoplasmic vacuolation), and **heart** (cardiomyopathy). The relationship of these effects to treatment is unclear.
- The lack of adequate characterization of the test article drug product (e.g. composition of the hydrogel, impurities) is not consistent with GLP.

Methods

- Doses:
- Test article: “PEG hydrogel containing fluorescein and (b) (4)
 - identification # 03291201,
 - no purity or strength information provided
 - composition: (b) (4) fluorescein”
 - yellow rods
 - Control article: high density polyethylene (HDPE)
 - Cut to 1 mm x 1 mm x 13 mm sections
 - (b) (4) sterilized
 - “A 10 mm length of 4-0 prolene suture was aseptically cut to serve as the location marker”

Frequency of dosing, route of administration: Single dose – subcutaneous implantation: under anesthesia, “one incision large enough to accommodate the article was made on the left side of the back through the skin and parallel to the spinal column. A pocket was formed by blunt dissection in the subcutaneous tissue ... One test article section (along with a location marker) was implanted ... the skin was closed with stainless steel wound clips”

Species/Strain: Rat, Hla®(SD)CVF® from (b) (4)

Number/Sex/Group: 6/sex/dose

Age: Approximately 7 weeks at pre-treatment

Weight: Males 224 to 247 grams pre-treatment
Females 160 to 182 grams pre-treatment

Note: The abbreviation “PLA” was not defined in the IND, and their composition was not defined. A literature search found that abbreviation refers to (b) (4)

(b) (4)

11 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

10 Special Toxicology Studies

The sponsor submitted a report entitled “Dexamethasone punctum plug prolonged exposure biocompatibility testing”, report #0167. This report is actually a short preface, followed by four full study reports.

Study title: Dexamethasone punctum plug prolonged exposure biocompatibility testing

Study no: 0167

Study report location: volume 4, tab 8-2 and also as a pdf file (“021_Appendix 8-2_TR0167.pdf”), 137 pages

Conducting laboratory and location:

(b) (4)

GLP compliance: Yes, signed

QA statement: Yes, signed

⁹ Reference is made to Redbook 2000: IV.C.1.d Mammalian erythrocyte micronucleus test. Accessed online via: <http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/Redbook/ucm078338.htm>

Key Study Findings

- These four tests are of limiting value for the safety assessment of OTX-DP: uncharacterized extracts were tested, and no reporting regarding the composition, strength, purity or stability of the articles tested was reported. Relatedly, no information regarding the stability of the hydrogel under the extract conditions was provided.
- Reportedly, an extract of the hydrogel caused mice to appear greasy / ungroomed at 4 hours post-dose. This may have been an artifact of handling.
- Under the conditions tested, no signs cytotoxicity, eye irritation, or skin irritation were observed following exposure to extracts of the hydrogel.

Cytotoxicity assay

- Title: "Cytotoxicity study using the ISO elution method"
- Lab #: 12T_23571_03
- Report # V0014_130
- Method notes:
 - The test article was an uncharacterized extract from (b) (4) % 4arm20K SG with (b) (4) % fluorescein", identification # (b) (4) 0.2 g of this was extracted in 17 ml of single strength Minimum Essential Medium (MEM) at 37°C for 24 hours with continuous agitation
 - Extracts from the controls were similarly prepared:
 - Negative control: HDPE plugs, CAS # 9002-88-4, purity "meets USP <61> polyethylene containers"
 - Reagent control: 1x MEM
 - Positive control: power-free latex gloves. Composition: "natural rubber latex, zinc carbamate accelerators, zinc oxide, and titanium oxide" (no ID #s)
 - L-929 mouse fibroblast cells were plated into wells, and then wells were exposed in triplicate for 48 hours, and then "reactivity" was rated on a 0 to 4 scale (none, slight, mild, moderate, severe)
- The authors report "no cytotoxicity or cell lysis" was noted for any of the wells exposed to the test article, negative control or reagent control. The positive control caused a "severe" response, with 100% cell rounding, 100% cells with intracytoplasmic granules, and 100% cell lysed

Rabbit eye irritation study

- Title: "ISO modified ocular irritation study in rabbits"
- Lab #: 12T_23571_06 and 12T_23571_07
- Report # T1252_800
- Method notes:
 - The test article was an uncharacterized extract from (b) (4) % 4arm20K SG with (b) (4) % fluorescein", identification # (b) (4) 0.2 g of this was extracted in either 17 ml of USP sodium chloride for injection, or sesame oil, NF, at 37°C for 72 hours with continuous agitation.
 - Dosing on April 12, 2012
 - Six young adult male New Zealand White rabbits were used:

- 0.1 ml of extract was instilled into the lower right conjunctival sac and then held gently closed for 1 second (3 rabbits/extract). Vehicle control was instilled into the left eye of each rabbit.
- Eyes were examined at 1, 24, 48 and 72 hours post-instillation.
- Pre-dose and 24 hours post-dose, eyes were treated with fluorescein stain, flushed, and viewed under a UV lamp to inspect for corneal injury.
- Results notes
 - No eye toxicity (cornea, iris, or conjunctivae) were observed for any of the animals on study

Mouse acute toxicity test

- Title: "ISO systemic toxicity study in mice"
- Lab #: 12T_23571_04 and 12T23571_05
- Report # T0625_500
- Method notes:
 - The test article was extracted the same as for the rabbit eye irritation study above (sodium chloride or sesame oil)
 - Dosing on April 12, 2012
 - Groups of 5 male Hla®: (ICR) CVR® mice were dosed intravenously with vehicle (sodium chloride) or the sodium chloride extract. Groups of 5 mice were dosed intraperitoneally with either vehicle (sesame oil) or the sesame oil extract
 - Clinical signs were monitored immediately post-dose, 4, 24, 48 and 72 hours post-dose. Body weight was measured at D0, D1, D2 and D3 (no necropsy)
- Results notes:
 - A treatment-related effect was noted for the test extract in sesame oil: at 4 hours post-dose, all 5 mice appeared "ungroomed". All mice appeared normal at all other time points.
 - The authors attributed this effect "to the unctuous nature of the extract", and did not consider these results evidence of systemic toxicity.
 - Not clear to this reviewer whether the authors mean that sesame oil was smeared on the mice (e.g. by the technicians), causing them to appear greasy. No information regarding how extensive, or what areas of the body were affected.
 - No mortalities
 - No apparent effect on body weight

Guinea pig sensitization test

- Title: "ISO guinea pig maximization sensitization test"
- Lab # 12T_23571_08 and 12T23571_09
- Report # T1261_300
- Method notes:

- The test article was extracted the same as for the rabbit eye irritation study and the mouse acute toxicity study (above)
- Dosing began April 23, 2012
- Freund's Complete Adjuvant (FCA) was mixed 50:50 with test extract or vehicle extract for the first induction.
- It is not clear to this reviewer whether or not the 10% sodium lauryl sulfate (SLS) suspension in petrolatum was mixed with the test extract or vehicle extract for the second induction.
- 30 female young adult Hartley albino guinea pigs, Hla®: (HA) CVF® were used. 10/test article and 5/vehicle control.
- First induction: on D1, the dorsoscapular hair was clipped, and animals were injected intradermally 6 times (three rows of 2 injections/row) within a 2 cm x 4 cm rectangle.
- Second induction: 6±1 days after the first induction, the skin was re-clipped, then covered with 10% sodium lauryl sulfate (SLS) suspension in petrolatum, which was massaged into the skin without covering. The purpose of the SLS was to induce "mild acute inflammation." 24 ± 2 hours after the SLS, the skin was wiped clean. A 2 cm x 4 cm section of filter paper was saturated with 0.3 ml of extract, then placed over the injection site, secured with a non-reactive tape, and wrapped with an elastic bandage for 48 hours.
- Challenge: 14 +1 days after the second induction, the fur was clipped. Nonwoven cotton disks were saturated with 0.3 ml of extract, an applied to the right or left flank of each animal. The trunk was wrapped with an elastic bandage for 24 hours.
- Dermal reaction at 24 and 48 hours was recorded (0 to 3 scale).
- Results notes:
 - No clinical signs were noted for any animal
 - No dermal reactions were noted for any animal
 - The authors report that a positive control, 1-chloro-2,4-dinitrobenzene (DNCB) scored 2-3 at 24 hours (moderate and confluent to intense and swelling erythema) and 1-2 at 48 hours (discrete or patchy erythema to moderate and confluent erythema), when tested in 10 guinea pigs. It is not clear whether DNCB was tested concurrently with the extracts.

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(b) (4)

11 Integrated Summary and Safety Evaluation

The sponsor is proposing a Phase 2 trial, where cataract patients will receive a single plug, implanted into the punctum at the end of surgery.

Dexamethasone safety evaluation

The Nonclinical Pharmacology/Toxicology Discipline has no safety concerns regarding the proposed clinical exposure to dexamethasone in this trial.

- The plugs will either be placebo (vehicle) or contain 394 µg of dexamethasone. Based on the allowed variability of the plug dimensions (i.e. (b) (4)) the actual dose of dexamethasone will (b) (4) µg of dexamethasone.
- Nominally, this dose will be delivered over several days, a tapered delivery as the PEG-based hydrogel dissolves in the punctum.
- Because clinical data regarding the safety of topical ocular doses substantially greater than 400 µg/eye/day of dexamethasone are available, the worst case for this trial (i.e. dumping the entire dose of dexamethasone into the eye) is reasonably safe.

Safety evaluation of the PEG-based hydrogel

This reviewer searched the CDER Inactive Ingredients Search for Approved Drug Products Database¹⁰ found no listings for multi-arm PEG, and multiple listings for 20K PEG:

Table 16: The CDER Inactive Ingredients database has multiple entries for 20K PEG

Inactive ingredient	Route, dose	CAS #	UNII (the unique ingredient identified)	Maximum potency (the maximum amount)
Polyethylene glycol 20000	Oral capsule	25322683	5WKN5KL208	18 mg
	Oral capsule, hard gelatin			13.5 mg
	Oral tablet			0.3 mg
	Oral tablet, delayed action, enteric coated			0.008 mg
	Oral-28, tablet			0.3 mg

¹⁰ Accessed online via: <http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm>

- Multiple listings for lower molecular weight PEGs, including for respiration, nasal spray, IV and IM injection, intralesional injection, intrasynovial injection, soft tissue injection, suppository, topical, and ophthalmic exposures:

Table 17: The CDER Inactive Ingredients database has multiple entries for ophthalmic uses of lower molecular weight PEG

Inactive ingredient	Route, dose	CAS #	UNII (the unique ingredient identified)	Maximum potency (the maximum amount)
PEG 300	Ophthalmic ointment	2615158	5655G9YAQ	Not reported (2 entries)
PEG 400	Ophthalmic ointment	25322683	B697894SGQ	4.997%
PEG 8000	Ophthalmic solution	25322683	Q662QK8M3B	2%

- One listing for fluorescein as an inactive ingredient (68 ng, oral capsule).
- No matches for “trilysine”

The amendment received 9/11/2012 by email (not yet formally submitted to the IND) included a COA (attachment 1) that reports no impurities:

Figure 15: From the (b) (4) COA for the (b) (4) starting material



Safety review of the hydrolysis/degradation products (b) (4)

- The sponsor asserts, and this reviewer concurs, that the 35-day dog punctum plug toxicity study qualifies the degradation products, despite the lack of analytical characterization.
- (b) (4)
 - The worst-case amounts of ANY degradation product related to the (b) (4) starting material and (b) (4) starting material are calculated in Table 18 below
 - ICH Q3A(R2) Impurities in New Drug Substances sets
 - an identification threshold of “0.10% or 1.0 mg per day (whichever is lower)”
 - a qualification threshold of “0.15% of 1.0 mg per day whichever is lower”
 - ICH Q3B(R2) Impurities in New Drug Products sets
 - an identification threshold of “1.0% or 5 µg TDI [total daily intake], (whichever is lower)”
 - a qualification threshold of “1.0% or 50 µg TDI, (whichever is lower)”
 - A draft rule-of-thumb for ophthalmology products is (b) (4) %.

Table 18: Calculated exposures to degradation products (b) (4)

Ingredient	As formulated (% dry basis) of OTX-DP	Theoretical composition (mg, dry basis) of OTX-DP	% formulated for the placebo plug	threshold*	(b) (4) threshold*
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(b) (4)

*The percentage in parentheses represents the % of the total impurities arising from this ingredient eluting per day from the placebo plug that would still be below the threshold. Exposures to impurities from the dexamethasone plug would be proportionally lower.

Table 18 is intended to support this reviewer's conclusion that any impurities that might arise from the (b) (4) are below the ICH threshold (but not necessarily below the more protective rule-of-thumb threshold desired for impurities in ophthalmology products).

The sponsor expects that the (b) (4) Considered from a different perspective, the sponsor is essentially predicting that the (b) (4).

This reviewer considers this prediction reasonable.

Note: Figure 16 is not a starting material; the (b) (4) degradant (b) (4) product (b) (4). Structure noted as a reviewer aid (copied from the (b) (4) catalog).

Figure 16: Structure of (b) (4)

Additional notes

Based on an informal communication (Nevitt/McDougal, personal communication 9/05/2012):

- Although this reviewer did not find details regarding the punctum dilator to be used, they are common devices and multiple dilators have been approved; unlikely that an unapproved device would be used
- Generally expect that pain from this type of cataract surgery will resolve by approximately day 15 (with or without dexamethasone therapy)
- Regarding the potential ethical issues for using a placebo (a potentially ineffective investigational agent) on a pain trial, patients will have the option of rescue (escape) therapy and will be monitored frequently

- Regarding the nonclinical findings (eye discharge and infection), these risks are considered well characterized, predictable, monitorable, and treatable (to the extent treatment is appropriate)
- The plugs will be inserted into the lower punctum if feasible; the upper punctum is the alternate location. Regarding the potential effects of punctum location on PK – most plugs will be inserted into the lower punctum; the infrequent use of the upper punctum will have only a slight effect on PK; analysis of the plug location might be necessary for the pivotal trials, but no changes to the inclusion/exclusion criteria or pre-hoc stratification are needed.

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

/s/

ANDREW J MCDOUGAL
09/19/2012

LORI E KOTCH
09/19/2012