

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-315

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	22-315
Submission Date(s):	23DEC2008
Brand Name	POSURDEX®
Generic Name	DEX PS DDS Applicator System
Primary Reviewer	Kimberly L. Bergman, Pharm.D.
Team Leader	Charles Bonapace, Pharm.D.
OCP Division	DCP4
OND Division	DAIOP
Applicant	Allergan, Inc.
Relevant IND(s)	IND 58,663
Submission Type; Code	Original NDA; 505(b)(1) application
Formulation; Strength(s)	DEX PS DDS Applicator System 0.35% and 0.7%
Indication	Treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO)

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1. EXECUTIVE SUMMARY

POSURDEX® (Dexamethasone Posterior Segment Drug Delivery System or DEX PS DDS Applicator System) is an intraocular drug delivery system containing the active ingredient dexamethasone, a potent corticosteroid with marked anti-inflammatory activity. Dexamethasone is combined with biodegradable polymers and extruded into a small implant for delivery into the posterior segment of the eye through a specifically designed applicator. POSURDEX® is proposed for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). The proposed dosage and route of administration for POSURDEX® is as follows: an intravitreal dose of the NOVADUR™ solid polymer drug delivery system containing dexamethasone 0.7 mg is recommended when there is evidence of macular edema or vascular leakage in the macula. Fast Track Designation for DEX PS DDS was granted by the United States Food and Drug Administration (FDA) on January 10, 2005. To support product approval, the clinical development program for POSURDEX® included initial phase 1 emergency and compassionate use studies, phase 1 and 2 dose-ranging trials, and two Phase 3 multicenter, masked, randomized, sham-controlled, safety and efficacy studies in patients with macular edema following CRVO or BRVO.

Based on the assessment of systemic exposure information from the Phase 3 multicenter, masked, randomized, sham-controlled, safety and efficacy studies in patients with macular edema following CRVO or BRVO, the regulatory requirement for submission of in vivo bioavailability data has been addressed.

1.1. Recommendation

The Clinical Pharmacology information provided by the Applicant is acceptable.

1.2. Phase IV Commitments

No phase IV commitments are recommended.

1.3. Summary of Important Clinical Pharmacology Findings

POSURDEX® (DEX PS DDS Applicator System) is an intraocular drug delivery system containing the active ingredient dexamethasone intended for intravitreal injection. POSURDEX® is proposed for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). To support product approval, the clinical development program for POSURDEX® included initial phase 1 emergency and compassionate use studies, phase 1 and 2 dose-ranging trials, and two Phase 3 multicenter, masked, randomized sham-controlled, safety and efficacy studies in patients with macular edema following CRVO or BRVO. The Clinical Pharmacology findings from these studies are summarized as follows:

- A dose-response relationship was suggested in both the phase 2 study and the pooled analysis of the two phase 3 trials. In the phase 3 studies 008 and 009, patients treated with either DEX PS DDS containing 700 µg of dexamethasone (DEX 700) or DEX PS DDS containing 350 µg of dexamethasone (DEX 350) experienced better visual acuity based on multiple measures, including time to achieve ≥ 15 letters improvement in BCVA and percent of patients with ≥ 15 letter BCVA improvements. The data presented suggests DEX 700 demonstrated greater efficacy and with a longer duration of effect than DEX 350.

- No dose-response relationship for safety was observed in the pooled phase 3 studies between DEX 700 and DEX 350. The overall incidence of adverse events in the initial treatment period for the pooled phase 3 studies was significantly higher in the DEX 700 group (72.4%) and DEX 350 group (71.8%) compared to sham (57.0%), and there was no significant difference between the 700 and 350 doses of DEX PS DDS.
- The extent of systemic exposure to dexamethasone resulting from delivery of DEX 350 or DEX 700 into the posterior segment of the eye was determined from plasma samples obtained from selected patients in phase 3 studies. In both studies (206207-008 and 206207-009), the majority of plasma dexamethasone concentrations were BLQ (LLOQ = 0.05 ng/mL). Plasma dexamethasone concentrations from 10 of 73 samples in the DEX 700 group and from 2 of 42 samples in the DEX 350 group were above the LLOQ, ranging from 0.0521 ng/mL to 0.0940 ng/mL. Systemic exposure of dexamethasone appears to be minimal but dose dependent following administration of 700 µg DEX PS DDS and 350 µg DEX PS DDS.

Based on the assessment of systemic exposure information from the Phase 3 multicenter, masked, randomized, sham-controlled, safety and efficacy studies in patients with macular edema following CRVO or BRVO, the regulatory requirement for submission of in vivo bioavailability data has been addressed.

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cc:
Division File: NDA 22-315
HFD-520 (CSO/Rodriguez)
HFD-520 (MO/Nevitt)
HFD-520 (Chambers, Boyd)
HFD-880 (Lazor, Reynolds, Bonapace)

2. QUESTION BASED REVIEW

Since this submission is an NDA for a locally administered ophthalmic drug product, only relevant questions from the OCP question-based review (QBR) format are addressed below.

2.1. General Attributes of the Drug

2.1.1. *What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?*

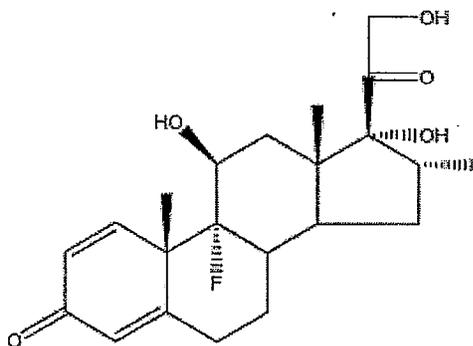
POSURDEX® (DEX PS DDS Applicator System) is an intraocular drug delivery system containing the active ingredient dexamethasone intended for intravitreal injection only. It is a drug-device combination product comprising a biodegradable sustained delivery intravitreal implant for the treatment of macular edema due to retinal vein occlusion. POSURDEX is formulated in two dosage strengths, 0.35 mg (DEX 350) and 0.7 mg (DEX 700). The drug component is the drug substance dexamethasone USP/Ph Eur, dispersed in a poly (D,L-lactide-co-glycolide) (PLGA) biodegradable polymer matrix formed into a rod-shaped implant, which is _____mm in diameter and approximately _____mm (DEX 350) to _____mm (DEX 700) in length. The polymer matrix consists of two different PLGA polymers. The product _____ DEX PS DDS for the different doses.

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The chemical structure and physical-chemical properties of the active ingredient dexamethasone are as follows:

Structural Formula: $C_{28}H_{29}FO_5$

Chemical Structure:



Chemical Name:

Pregna-1,4-diene-3,20-dione-9-fluoro-11,17,21-trihydroxy-16-methyl-, (11 β ,16 α)

IUPAC: 9 α -Fluoro-11 β ,17,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione

CAS: (11 β , 16 α)-9-Fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione

Compendial Name: Dexamethasone (USP, Ph Eur, JP)

International Nonproprietary Name (INN): Dexamethasone

Company Laboratory Code: AGN-206207

Chemical Abstract Service (CAS) Registry Number: 50-02-2

Molecular Weight: 392.47

The qualitative and quantitative composition of the proposed POSURDEX® (DEX PS DDS Applicator System) drug product is shown in Table 2.2-1.

Table 2.2-1 Composition of POSURDEX® (DEX PS DDS Applicator System)

Ingredient	Quality Standard	Function	%, w/w	mg/g	0.35 mg Dose, µg	0.70 mg Dose, µg
Dexamethasone	Ph Eur, USP	Active drug substance	—		350	700
Poly (D,L-lactide-co-glycolide), PLGA ester	In house	Biodegradable extended release polymer matrix	—			
Poly (D,L-lactide-co-glycolide), PLGA acid	In house	Biodegradable extended release polymer matrix	—			

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Source: Section 2.3.P.1

The device component is a single-use applicator designed specifically to deliver the rod-shaped implant, (Dexamethasone Posterior Segment Drug Delivery System, DEX PS DDS), directly into the posterior segment of eye. The DEX PS DDS implant is loaded and retained within the needle of the applicator (DEX PS DDS Applicator System).

2.1.2. What is the proposed mechanism of drug action and therapeutic indication?

Dexamethasone, a potent 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. Vascular endothelial growth factor (VEGF) is a cytokine which is expressed at increased concentrations in the setting of macular edema. It is a potent promoter of vascular permeability. Corticosteroids have been shown to inhibit the expression of VEGF. Additionally, corticosteroids prevent the release of prostaglandins, some of which have been identified as mediators of cystoid macular edema.

POSURDEX® is proposed for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

2.1.3. What is the proposed dosage and route of administration?

The proposed dosage and route of administration for POSURDEX® is as follows: an intravitreal dose of the NOVADUR™ solid polymer drug delivery system containing dexamethasone 0.7 mg is recommended when there is evidence of macular edema or vascular leakage in the macula.

2.2. General Clinical Pharmacology

2.2.1. *What are the design features of the clinical pharmacology and clinical studies used to support dosing claims?*

The following seven studies have been completed to date evaluating the use of DEX PS DDS:

- phase 1 emergency and compassionate use studies with tableted DEX PS DDS (DC103-02, DC103-03, and DC103-04)
- phase 1/2 dose-ranging study with tableted DEX PS DDS in patients post-vitreotomy (DC103-05; terminated early due to slow enrollment)
- phase 2 dose-ranging study with tableted DEX PS DDS in patients with persistent macular edema (DC103-06)
- phase 2 study to test the safety and applicator performance of the DEX PS DDS applicator system compared to with tableted DEX PS DDS in patients with persistent macular edema (DC103-07)
- phase 3 study with DEX PS DDS applicator system in patients with retinal vein occlusion (206207-009)
- phase 3 study with DEX PS DDS applicator system in patients with retinal vein occlusion (206207-008)
- phase 3 study with DEX PS DDS applicator system in anterior uveitis; terminated early due to slow enrollment (206207-015)

The 3 studies of DEX PS DDS 350 µg and 700 µg in patients with macular edema (DC103-06, 206207-008, and 206207-009) are used for the analysis of efficacy. Studies DC103-04, DC103-05, and 206207-015 are not included in the efficacy summary as these trials evaluated patients with macular edema due to diseases other than retinal vein occlusion. Study DC103-07 did enroll patients with macular edema; however efficacy was not assessed (only applicator performance). Data from ongoing studies in other indications are not included in this submission. Design features of the three studies supporting safety and efficacy of DEX PS DDS (DC103-06, 206207-008, and 206207-009) are presented in Table 2.2.1-1.

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Table 2.2.1-1 Clinical Studies Supporting the Efficacy and Safety of POSURDEX®

Study Objective	Design Control Type	Test Product(s), Dosage Regimen, Route	Duration of Treatment	Population	# Subjects
Study DC103-06: A Phase 2 Randomized, Multicenter, Dose-Ranging, Controlled, Parallel-Group Trial to Assess the Safety and Efficacy of Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS®) in the Treatment of Persistent Macular Edema	randomized, examiner-masked, multicenter, observation control	DEX PS DDS (350 or 700 µg dexamethasone) inserted through the pars plana	6 months (plus every 3 months until exit if DDS at Day 180)	patients with persistent macular edema	315
Study 206207-008: A Six-Month, Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial (with Six-Month Open-Label Extension) to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Macular Edema Following Central Retinal Vein Occlusion or Branch Retinal Vein Occlusion	initial treatment: randomized, examiner-masked, multicenter, sham control; extension: non-randomized open-label, multicenter, no control	DEX PS DDS (350 or 700 µg dexamethasone); Sham (needleless DDS applicator without study medication); inserted thru the pars plana using applicator system	6-month masked initial treatment followed by 6-month open-label extension	patients with macular edema due to branch or central retinal vein occlusion	599
Study 206207-009: A Six-Month, Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial (with Six-Month Open-Label Extension) to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Macular Edema Following Central Retinal Vein Occlusion or Branch Retinal Vein Occlusion	initial treatment: randomized, examiner-masked, multicenter, sham control; extension: non-randomized open-label, multicenter, no control	DEX PS DDS (350 or 700 µg dexamethasone); Sham (needleless DDS applicator without study medication); inserted thru the pars plana using applicator system	6-month masked initial treatment followed by 6-month open-label extension	patients with macular edema due to branch or central retinal vein occlusion	668

Source: 5.2 Tabular Listing of All Clinical Studies

2.2.2. *What is the basis for selecting the response endpoints (i.e. clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?*

The primary efficacy variable across studies was consistently best-corrected visual acuity (BCVA) in the study eye measured using the ETDRS method. In the phase 2 study DC103-06, the percent of patients achieving a 2-line improvement in BCVA was the primary endpoint; the percent of patients achieving a 3-line improvement was analyzed as a secondary endpoint. In both phase 3 studies, the primary endpoint was based on a 3-line improvement in BCVA. A 3-line worsening of visual acuity is equivalent to a doubling of the visual angle. This translates to a 15-letter change, which is considered clinically significant and reflects a true alteration in visual acuity.

Following recommendations from the FDA, the Phase 3 trial designs included more than one dose strength (DEX 350 and DEX 700) along with Sham control. Based on phase 2 data showing that DEX 700 had better efficacy and similar safety to DEX 350 and upon agreement with the FDA, the primary efficacy comparison in the Phase 3 trials was DEX 700 versus Sham.

2.2.3. *Are the active moieties in the biological fluid appropriately identified and measured to assess pharmacokinetic parameters?*

The active moiety dexamethasone was appropriately identified and measured in plasma for purposes of assessment of systemic exposure following ocular administration. Refer to Section 2.6 for further details regarding analytical methodology and performance.

2.2.4. *Exposure-Response*

2.2.4.1. *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?*

In Study DC103-06, treatment with DEX PS DDS containing 700 µg of dexamethasone had a statistically and clinically significant improvement in BCVA and other measures associated with persistent macular edema (PME). In general, improvements in the DEX 350 group were numerically greater than Observation alone and lower than with DEX 700, suggesting a dose-response effect. Statistical significance for the primary endpoint, an improvement of 2 or more lines in the last observation carried forward (LOCF) analysis of best-corrected visual acuity (BCVA) at day 90, was observed for the DEX 700 group versus the Observation group as presented in Table 2.2.4.1-1. The improvement rate was likewise numerically higher with DEX 350 versus Observation, although the difference was not statistically significant.

Table 2.2.4.1-1. Patients with 2 or More Lines Improvement in Best-Corrected Visual Acuity from Baseline (ITT Population)

Change from baseline in BCVA at Day 90	DEX PS DDS 350 µg (N = 100)	DEX PS DDS 700 µg (N = 101)	Observation (control) (N = 105)	Difference/P-value ^a	
				350 v Obs	700 v Obs
≥ 2 lines improvement ^b	26.1% (24/92)	36.7% (36/98)	19.0% (19/100)	7.1% P = 0.238	17.7% P = 0.005
Otherwise	73.9% (68/92)	63.3% (62/98)	81.0% (81/100)		

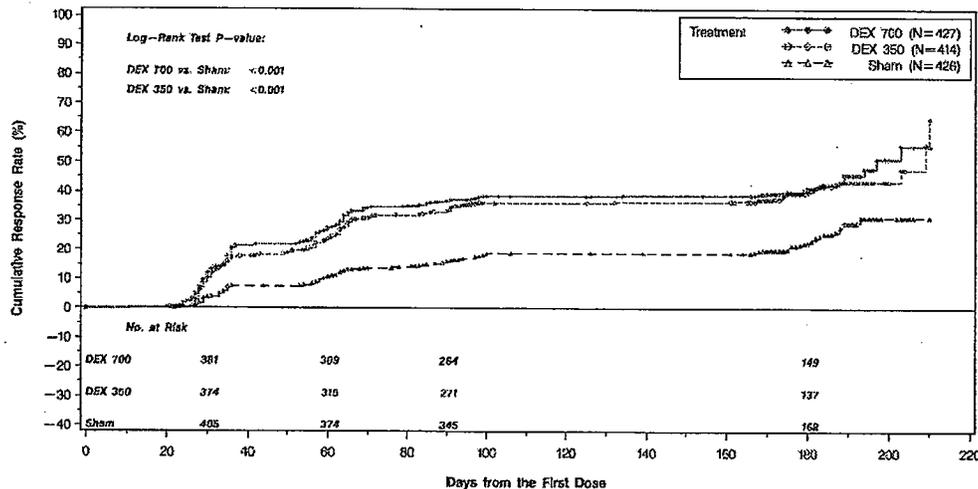
a P-value based on the Z-test for 2 proportions, DEX PS DDS versus Observation

b ≥ 2 lines better in BCVA means that the change in LogMAR was ≤ -0.20

Source: CSR DCI03-06, Table 11.4-1

In the pooled analysis of studies 009 and 008, the cumulative response rates (cumulative probability of response over time as estimated by Kaplan-Meier method) were significantly different for DEX 700 and DEX 350 compared to the sham group ($p < 0.001$). Response rates were higher with DEX 700 and DEX 350 than with sham, with separation of curves as early as day 30 and no crossover during the initial treatment period, as shown in Figure 2.2.4.1-1 Rates were numerically lower with DEX 350 compared to DEX 700, although the difference between the 2 doses was not statistically significant. Results were similar in the PP population pooled across studies 008 and 009.

Figure 2.2.4.1-1. Time to Achieve 15 or More Letters Improvement from Baseline Best-Corrected Visual Acuity (Studies 009 and 008, ITT Population)



Source: 2.7.3 Summary of Clinical Efficacy

In the pooled analysis of studies 009 and 008, the proportion of patients with 15 or more letters improvement from baseline were consistently and significantly higher with DEX 700 and DEX 350 compared to sham at days 30, 60, and 90, as displayed in Table 2.2.4.1-2. At day 180, the response rate was similar to the day 90 findings for the patients receiving DEX 700 and statistically significantly better than sham; there was a slight decrease in response for patients receiving DEX 350 and an increase in patients receiving sham.

Table 2.2.4.1-2. Proportion of Patients with 15 or More Letters Improvement from Baseline Best Corrected Visual Acuity in the Study Eye (Studies 009 and 008 pooled, ITT Population)

Visit	DEX 700 (N = 427)	DEX 350 (N = 414)	Sham (N = 426)
Day 30	21.3% [†]	17.9% [†]	7.5%
Day 60	29.3% [†]	28.5% [†]	11.3%
Day 90	21.8% [†]	23.4% [†]	13.1%
Day 180	21.5% [†]	19.3%	17.6%

[†] Proportion significantly higher with DEX compared to Sham (p < 0.001)

Source: 2.7.3 Summary of Clinical Efficacy

In summary, a dose-response relationship was suggested in both the phase 2 study and the pooled analysis of the two phase 3 trials. In the phase 3 studies 008 and 009, patients treated with either DEX 700 or DEX 350 experienced better visual acuity based on multiple measures, including time to achieve ≥ 15 letters improvement in BCVA and percent of patients with ≥ 15 letter BCVA improvements. The data presented suggests DEX 700 demonstrated greater efficacy and with a longer duration of effect than DEX 350. In the current application, the Applicant has proposed the 700 μg dose strength of DEX PS DDS for approval. Based on the Applicant's analysis of 15-letter improvement rates, the proposal to seek approval of the 700 μg dose strength of DEX PS DDS is acceptable from a Clinical Pharmacology perspective. For further discussion of the efficacy comparison of the two POSURDEX® doses, refer to the Medical Officer's review of NDA 22-315.

2.2.4.2. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

The overall incidence of adverse events in the initial treatment period for the pooled phase 3 studies 008 and 009 was significantly higher in the DEX 700 group (72.4%) and DEX 350 group (71.8%) compared to sham (57.0%). There was no significant difference between the 700 and 350 doses of DEX, as presented in Table 2.2.4.2-1. Ocular adverse events were likewise more commonly reported with DEX 700 (64.1%) and DEX 350 (64.6%) than with Sham (45.4%). The rate of non-ocular events was similar among the 3 treatment groups. The same patterns were observed for treatment-related events. There were no notable differences in the adverse event profile between the 2 studies. There was 1 death during the initial treatment period in study 009 and 3 deaths during the initial treatment period in study 008. None of the deaths were considered to be related to study treatment. The overall incidence of serious adverse events in the initial treatment period for the pooled phase 3 studies was 5.0% (21/421) in the DEX 700 group, 6.6% (27/412) in the DEX 350 group, and 5.9% (25/423) in the Sham group. The serious adverse event profile was similar between the 3 treatment groups.

Table 2.2.4.2-2. Adverse Events in POSURDEX® Phase 3 Studies (Studies 009 and 008, Safety Population)

Events/Relationship	DEX 700 (N = 421)	DEX 350 (N = 412)	Sham (N = 423)
All Adverse Events	305 (72.4%)	296 (71.8%)	241 (57.0%)
<i>Ocular</i>	270 (64.1%)	266 (64.6%)	192 (45.4%)
<i>Non-Ocular</i>	126 (29.9%)	119 (28.9%)	131 (31.0%)
Treatment-Related	199 (47.3%)	192 (46.6%)	74 (17.5%)
<i>Ocular</i>	199 (47.3%)	191 (46.4%)	74 (17.5%)
<i>Non-Ocular</i>	4 (1.0%)	3 (0.7%)	1 (0.2%)

Source: 5.3.5.3 Integrated Summary of Safety

In summary, no dose-response relationship for safety was observed in the pooled phase 3 studies between DEX 700 and DEX 350. From a Clinical Pharmacology perspective, this finding supports the Applicant's proposal to seek approval of only the 700 µg dose strength of DEX PS DDS. For further discussion of the safety comparison of the two POSURDEX® doses, refer to the Medical Officer's review of NDA 22-315.

2.2.5. What are the PK characteristics of the drug and its major metabolite?

2.2.5.1. Systemic Exposure Following Ocular Administration

The extent of systemic exposure to dexamethasone resulting from delivery of 350 µg or 700 µg DEX PS DDS into the posterior segment of the eye was determined from plasma samples obtained from selected patients in the phase 3 studies 206207-008 and 206207-009. These studies were 6-month, multicenter, masked, randomized, sham-controlled safety and efficacy studies in patients with macular edema following central retinal vein occlusion or branch retinal vein occlusion. Patients were randomized in a 1:1:1 ratio to receive a single 700 µg DEX PS DDS applicator system, 350 µg DEX PS DDS applicator system, or Sham DEX PS DDS applicator system (needleless DDS applicator, henceforth referred to as Sham) and were followed for the first 6 months. In studies 206207-008 and 206207-009, it was planned to obtain plasma samples from approximately 15 patients in each study. Plasma samples for pharmacokinetic analysis were obtained from participating patients at the following visits: predose, initial treatment days 1, 7, 30, 60, and 90, and early exit when applicable.

In both studies (206207-008 and 206207-009), the majority of plasma dexamethasone concentrations were BLQ. In both studies combined, plasma dexamethasone concentrations from 13.7% of samples (10/73 samples) in the DEX 700 group and from 4.8% of samples (2/42 samples) in the DEX 350 group were above the LLOQ, ranging from 0.0521 ng/mL to 0.0940 ng/mL. There were no apparent correlations between plasma dexamethasone concentration and age, body weight, or gender.

Systemic exposure of dexamethasone appears to be minimal but dose dependent following administration of 700 µg DEX PS DDS and 350 µg DEX PS DDS. In addition, the active component of POSURDEX® is available in many currently marketed systemic and ophthalmic products in the US. The safety of doses much greater than those examined in these efficacy studies for POSURDEX® has been well established.

2.3. Intrinsic Factors

Not applicable.

Table 2.3.3.3-1 Accuracy and Precision for Dexamethasone in Plasma

Intraday and Interday Precision and Accuracy				
Human Plasma QC Samples				
Nominal Conc. (ng/mL)	Intraday		Interday	
	Accuracy (mean %)	Precision (CV %)	Accuracy (mean %)	Precision (CV %)
0.05 (LLOQ)	102	3.20	96.0	6.56
0.15 (LQC)	89.4	4.43	90.1	4.50
2.5 (MQC)	86.3	0.912	89.2	3.00
7.5 (HQC)	87.6	1.90	90.0	2.62

Source: Report PK-04-155

In addition, the results showed that no interfering peaks were observed at the retention time of analyte and internal standard in chromatograms from 6 lots of EDTA-treated human plasma.

The accuracy, precision and selectivity of the bioanalytical method are acceptable for the intended purpose.

2.6.3.4. *What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?*

Dexamethasone was stable in human plasma for at least 24 hours at room temperature. Stability was also demonstrated for dexamethasone human plasma samples that went through three freeze/thaw cycles. For processed plasma samples, stability was demonstrated for up to 48 hours in the dried extract state and up to 48 hours in the injection solvent. Dilution integrity was demonstrated for up to a 10-fold dilution.

2.6.3.5. *What is the QC sample plan?*

QC samples at four concentrations (— [LLOQ], — [low QC], — [medium QC], and — [high QC] ng/mL; n = 6 at each concentration) within the calibration curve concentration range were measured. For run acceptance, samples had to assay within —% of nominal concentration. All but one QC met acceptance criteria.

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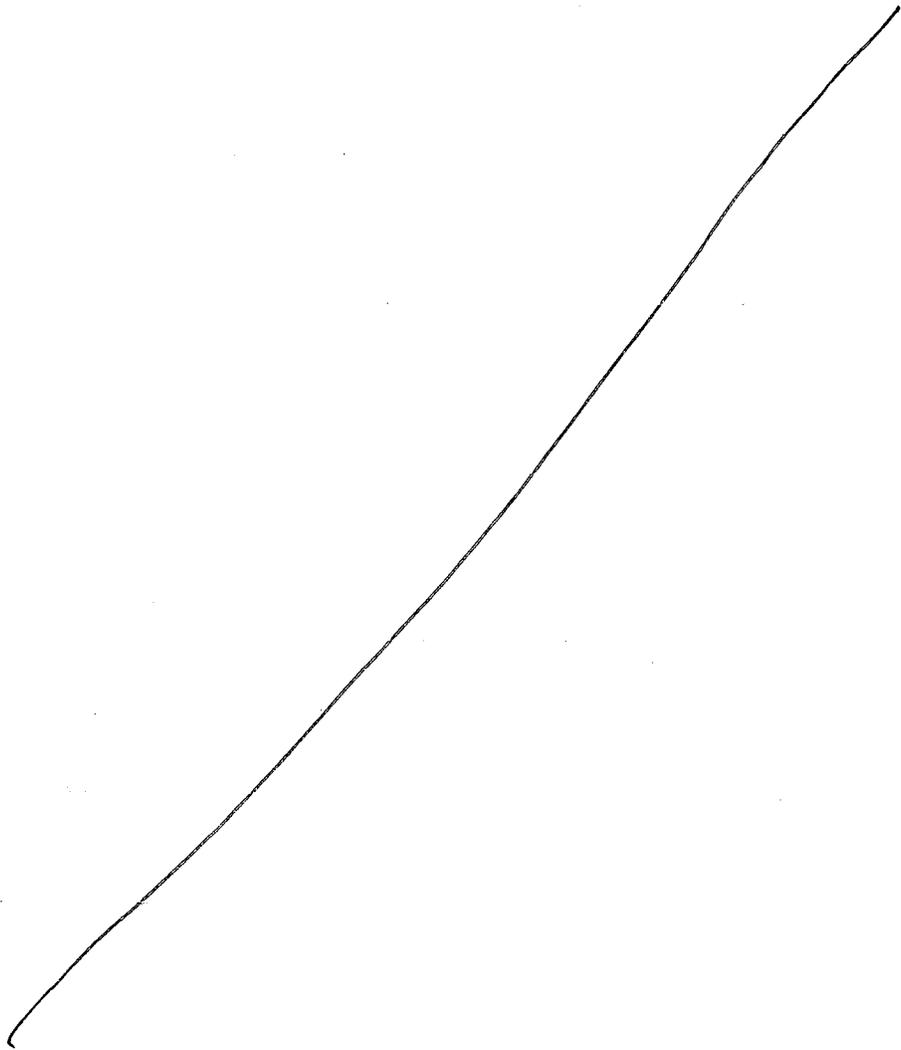
3. LABELING RECOMMENDATIONS

The following changes reflect Clinical Pharmacology Reviewer recommendations to the proposed labeling (recommendations appear in *bold italicized underlined type*).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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4. APPENDICES

4.1. Individual Study Reviews

4.1.1. Study 206207-008

TITLE:

A Six-Month, Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial (with Six-Month Open-Label Extension) to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Macular Edema Following Central Retinal Vein Occlusion or Branch Retinal Vein Occlusion

Principal Investigator: Mark Blumenkranz, MD, MMS, California VitreoRetinal Center
Stanford University

Study Initiation: 22 October 2004

Study Completion: 31 March 2008

OBJECTIVES:

- To evaluate the safety and efficacy of the 700 µg DEX PS DDS Applicator System (700 µg dexamethasone) and 350 µg DEX PS DDS Applicator System (350 µg dexamethasone) compared with a Sham DEX PS DDS Applicator System (needle-less applicator) in patients with macular edema due to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO),
- To evaluate safety and efficacy of the 700 µg DEX PS DDS Applicator System (700 µg dexamethasone) compared with the 350 µg DEX PS DDS Applicator System (350 µg dexamethasone) in patients with macular edema due to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO), and
- To assess the safety of the 700 µg DEX PS DDS Applicator System for an additional 6 months in patients who qualify for treatment in an open-label extension.

STUDY DESIGN:

This was a 6-month, multicenter, masked, randomized, sham-controlled, safety and efficacy study followed by a 6-month open-label extension. Approximately 550 patients were to be randomized in a 1:1:1 ratio to 700 µg DEX PS DDS Applicator System (700 µg dexamethasone): 350 µg DEX PS DDS Applicator System (350 µg dexamethasone): Sham DEX PS DDS Applicator System (needle-less DDS applicator) for the first 6 months. While remaining masked to the initial randomized treatment, at initial treatment day 180 (month 6), qualified patients were to receive an open-label dose of 700 µg DEX PS DDS Applicator System (700 µg dexamethasone) if the following criteria were met: 1) Best-Corrected Visual Acuity (BCVA) was < 84 letters (approximately 20/20 Snellen equivalent) or retinal thickness by Optical Coherence Tomography (OCT) was > 250 µm (determined by the site) in the central 1 mm macular subfield; and 2) in the investigator's opinion, the procedure would not put the patient at significant risk. All patients (whether they received the open-label treatment or not) were to be followed up for safety for an additional 6 months following the initial treatment day 180 visit. A patient was to be considered exited from the study upon completion of open-label extension day 180 or upon early study discontinuation.

FORMULATIONS:**700 µg dexamethasone intravitreal delivery system (formulation number 9632X):**

The 700 µg DEX PS DDS applicator system contained an extruded dosage form of 700 µg dexamethasone (lot numbers 03H005, 03J002, 03K001, 12484A1, 12500A1, 12587A1, 12594A1, 12597A1, and 12777A1) in an inactive biodegradable polymer matrix of poly [lactic-glycolic] acid (PLGA) (— drug/polymer ratio). The extruded DEX PS DDS was composed of a biodegradable copolymer (PLGA) containing —————

350 µg dexamethasone intravitreal delivery system (formulation number 9635X):

The 350 µg DEX PS DDS applicator system contained an extruded dosage form of 350 µg dexamethasone (lot numbers 03L001, 12495A1, 12501A1, 12598A1, 12662A1, and 12687A1), in an inactive biodegradable polymer matrix of PLGA (— drug/polymer ratio). The extruded DEX PS DDS was composed of a biodegradable copolymer (PLGA) containing —————

Both the extruded 700 µg and 350 µg DEX PS DDS were loaded in the applicator during manufacturing and provided as a sterile finished product.

Sham DEX PS DDS applicator system:

The Sham DEX PS DDS applicator system consisted of a needleless DDS applicator without study medication and was provided as a sterile finished product.

PHARMACOKINETIC ASSESSMENTS:

Blood sample(s) from approximately 15 patients were to be collected at selected sites to determine plasma dexamethasone concentrations at each of the following visits: pre-dose, Days 1, 7, 30, 60, and 90, and early exit when applicable.

BIOANALYTICAL METHODOLOGY

Plasma concentrations of dexamethasone were measured using a validated liquid chromatography tandem mass spectrometry method (LC-MS/MS) with a lower limit of quantitation (LLOQ) of 0.05 ng/mL for dexamethasone. The bioanalysis of dexamethasone was conducted at Allergan (Irvine, CA). The LC-MS/MS method showed acceptable interday accuracy and precision for QCs, with precision values (CV%) less than — % and accuracy values within — % from nominal value. Assay linearity was demonstrated for dexamethasone from 0.05 to 10 ng/mL in human plasma.

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PHARMACOKINETIC/STATISTICAL ANALYSIS:

Descriptive statistics (n, mean, standard deviation, etc) were to be calculated for plasma dexamethasone concentrations by treatment and by visit day where applicable.

RESULTS:

Pharmacokinetic blood samples were to be collected from 16 patients, including 6 patients who had received the Sham treatment. Data from 10 patients (6 patients who had received 700 µg DEX PS DDS Applicator System treatment and 4 patients who had received 350 µg DEX PS DDS Applicator System) were included in the pharmacokinetic data analysis. Three samples from patients (one from patient 0733 at Day 60, two from patient 0799 at Day 30 and Day 90) who had received 700 µg DEX PS DDS were reported as missing. Five samples from patients (two from patient 0594 at Day 60 and Day 90, two from patient 0734 at Day 1 and Day 90, and one from patient 0777 at Day 60) who had received 350 µg DEX PS DDS were also reported as missing. For Patient 0274 who had received the Sham treatment, one sample collected at Day 1

had a plasma dexamethasone concentration that was substantially higher than concentrations obtained from patients receiving active drug (a concentration of 1.78 ng/mL). After both bioanalytical and clinical investigation, the exact cause could not be determined. There was no other outlier concentration value identified in this study. Since this outlier occurred in the Sham treatment group, the applicant deemed the PK conclusion of this study was not affected by this outlier.

Plasma dexamethasone concentrations in patients who received 700 µg and 350 µg DEX PS DDS are listed and summarized in Tables 4.1.1-1 and 4.1.1-2, respectively. In 4 out of 6 patients who had received 700 µg DEX PS DDS, the plasma concentrations from 5 of the 33 samples collected over time were above the LLOQ, ranging from 0.0558 to 0.0810 ng/mL. Three of these five samples were collected on Day 7, and two were collected on Day 60. In 1 of 4 patients who had received 350 µg DEX PS DDS, the plasma concentrations from 2 of the 19 samples collected over time were both 0.0647 ng/mL. One was collected on Day 7 and the other was collected on Day 30. Mean plasma dexamethasone concentrations were not calculated since > 50% of plasma concentrations were below the LLOQ. There were no apparent correlations between measurable plasma dexamethasone concentrations and patient age or body weight.

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Table 4.1.1-1.

Dexamethasone Plasma Concentrations (ng/mL) in Patients Who Received 700 µg DEX PS DDS in Study 206207-008

Patient Number	Weight (kg)	Age (Year)	Gender	Blood Sampling Day					
				Pre-Dosing	Day 1	Day 7	Day 30	Day 60	Day 90
0085	63.5	75	Female	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
0231	90.8	61	Male	BLQ	BLQ	BLQ	BLQ	0.0613	BLQ
0593	87.1	74	Female	BLQ	BLQ	0.0810	BLQ	BLQ	BLQ
0733	49.9	89	Female	BLQ	BLQ	0.0558	BLQ	NA	BLQ
0739	78.0	50	Male	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
0799	77.1	50	Female	BLQ	BLQ	0.0584	NA	0.0589	NA
Mean				NC	NC	NC	NC	NC	NC
SD				NC	NC	NC	NC	NC	NC

Table 4.1.1-2.

Dexamethasone Plasma Concentrations (ng/mL) in Patients Who Received 350 µg DEX PS DDS in Study 206207-008

Patient Number	Weight (kg)	Age (Year)	Gender	Blood Sampling Day					
				Pre-Dosing	Day 1	Day 7	Day 30	Day 60	Day 90
0594	56.7	75	Female	BLQ	BLQ	0.0647	0.0647	NA	NA
0734	112	63	Male	BLQ	NA	BLQ	BLQ	BLQ	NA
0741	73.5	76	Female	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
0777	72.6	80	Male	BLQ	BLQ	BLQ	BLQ	NA	BLQ
Mean				NC	NC	NC	NC	NC	NC
SD				NC	NC	NC	NC	NC	NC

BLQ, below the limit of quantitation
 NC, not calculated since more than 50% of drug concentrations were BLQs, or the mean value is BLQ
 NA, blood samples were not collected or reported as missing

APPLICANT'S CONCLUSIONS:

These results indicate that systemic exposure of dexamethasone was minimal in patients who had received one 700 µg DEX PS DDS Applicator System (700 µg dexamethasone) or one 350 µg DEX PS DDS Applicator System (350 µg dexamethasone).

REVIEWER ASSESSMENT:

The Applicant's conclusions regarding systemic exposure to dexamethasone following 700 µg DEX PS DDS or 350 µg DEX PS DDS are acceptable from a Clinical Pharmacology perspective. Dexamethasone concentrations obtained from patients in Study 206207-008 were generally below the lower limit of quantitation (0.05 ng/mL) and much lower than concentrations following administration of approved systemic dexamethasone products.

*4.1.2. Study 206207-009***TITLE:**

A Six-Month, Phase 3, Multicenter, Masked, Randomized, Sham-Controlled Trial (with Six-Month Open-Label Extension) to Assess the Safety and Efficacy of 700 µg and 350 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) Applicator System in the Treatment of Patients with Macular Edema Following Central Retinal Vein Occlusion or Branch Retinal Vein Occlusion

Principal Investigator: Jeff Heier, MD, Ophthalmic Consultants of Boston
Study Initiation: 18 November 2004
Study Completion: 3 March 2008

OBJECTIVES:

- To evaluate the safety and efficacy of the 700 µg DEX PS DDS Applicator System (700 µg dexamethasone) and 350 µg DEX PS DDS Applicator System (350 µg dexamethasone) compared with a Sham DEX PS DDS Applicator System (needle-less applicator) in patients with macular edema due to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO)
- To evaluate safety and efficacy of the 700 µg DEX PS DDS Applicator System (700 µg dexamethasone) compared with the 350 µg DEX PS DDS Applicator System (350 µg dexamethasone) in patients with macular edema due to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO)
- To assess the safety of the 700 µg DEX PS DDS Applicator System for an additional 6 months in patients who qualify for treatment in an open-label extension

STUDY DESIGN:

This was a 6-month, multicenter, masked, randomized, sham-controlled, safety and efficacy study followed by a 6-month open-label extension. Approximately 550 patients were to be randomized in a 1:1:1 ratio to 700 µg DEX PS DDS Applicator System (700 µg dexamethasone): 350 µg DEX PS DDS Applicator System (350 µg dexamethasone): Sham DEX PS DDS Applicator System (needle-less DDS applicator) for the first 6 months. While remaining masked to the initial randomized treatment, at initial treatment day 180 (month 6), qualified patients were to receive an open-label dose of 700 µg DEX PS DDS Applicator System (700 µg dexamethasone) if the following criteria were met: 1) Best-Corrected Visual Acuity (BCVA) was < 84 letters (approximately 20/20 Snellen equivalent) or retinal thickness by Optical Coherence Tomography (OCT) was > 250 µm (determined by the site) in the central 1 mm macular subfield; and 2) in the investigator's opinion, the procedure would not put the patient at significant risk. All patients

(whether they received the open-label treatment or not) were to be followed up for safety for an additional 6 months following the initial treatment day 180 visit. A patient was to be considered exited from the study upon completion of open-label extension day 180 or upon early study discontinuation.

FORMULATIONS:

700 µg dexamethasone intravitreal delivery system (formulation number 9632X):

The 700 µg DEX PS DDS applicator system contained an extruded dosage form of 700 µg dexamethasone (lot numbers 03H005, 12484A1, 12500A1, and 12597A1) in an inactive biodegradable polymer matrix of poly [lactic-glycolic] acid (PLGA) (— drug/polymer ratio). The extruded DEX PS DDS was composed of a biodegradable copolymer (PLGA) containing

350 µg dexamethasone intravitreal delivery system (formulation number 9635X):

The 350 µg DEX PS DDS applicator system contained an extruded dosage form of 350 µg dexamethasone (lot numbers 03L001, 12495A1, 12501A1, 12640A1, and 12662A1), in an inactive biodegradable polymer matrix of PLGA (— drug/polymer ratio). The extruded DEX PS DDS was composed of a biodegradable copolymer (PLGA) containing

Both the extruded 700 µg and 350 µg DEX PS DDS were loaded in the applicator during manufacturing and provided as a sterile finished product.

Sham DEX PS DDS applicator system:

The Sham DEX PS DDS applicator system consisted of a needleless DDS applicator without study medication and was provided as a sterile finished product.

PHARMACOKINETIC ASSESSMENTS:

Blood sample(s) from approximately 15 patients were to be collected at selected sites to determine plasma dexamethasone concentrations at each of the following visits: pre-dose, Days 1, 7, 30, 60, and 90, and early exit when applicable.

BIOANALYTICAL METHODOLOGY

Plasma concentrations of dexamethasone were measured using a validated liquid chromatography tandem mass spectrometry method (LC-MS/MS) with a lower limit of quantitation (LLOQ) of 0.05 ng/mL for dexamethasone. The bioanalysis of dexamethasone was conducted at Allergan (Irvine, CA). The LC-MS/MS method showed acceptable interday accuracy and precision for QCs, with precision values (CV%) less than — , and accuracy values within — % from nominal value. Assay linearity was demonstrated for dexamethasone from 0.05 to 10 ng/mL in human plasma.

b(4)

PHARMACOKINETIC/STATISTICAL ANALYSIS:

Descriptive statistics (n, mean, standard deviation, etc.) were to be calculated for plasma dexamethasone concentrations by treatment and by visit day where applicable.

RESULTS:

Pharmacokinetic blood samples were collected from 17 patients including 6 patients who received the Sham treatment. Data from 11 patients (7 patients who had received 700 µg DEX PS DDS Applicator System treatment and 4 patients who had received 350 µg DEX PS DDS Applicator System) were included in the pharmacokinetic data analysis. All plasma dexamethasone concentrations were below the lower limit of quantitation (LLOQ) of 0.05 ng/mL.

from patients who had received 350 µg DEX PS DDS or the Sham treatment. Plasma dexamethasone concentrations in patients who received 700 µg DEX PS DDS are listed and summarized in Table 4.1.2-1. Five of the 40 samples concentrations were above LLOQ, ranging from 0.0521 to 0.094 ng/mL from four different patients who had received 700 µg DEX PS DDS, as presented in Table 4.1.2-1. Four of these five samples were collected on Day 60 including the highest concentration of 0.094 ng/mL. The fifth one was collected on Day 7 and the concentration was 0.054 ng/mL. There were no apparent correlations among plasma dexamethasone concentrations, age, body weight, and gender. Mean plasma dexamethasone concentrations were not calculated since > 50% of plasma concentrations were below the LLOQ.

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Table 4.1.2-1. Dexamethasone Plasma Concentrations (ng/mL) in Patients Who Received 700 µg DEX PS DDS in Study 206207-009

Patient Number	Weight (kg)	Age (year)	Gender	Blood Sampling Day						
				Pre-Dosing	Day 1	Day 7	Day 30	Day 60	Day 90	
2060	42.2	69	Female	BLQ	BLQ	BLQ	BLQ	0.0760	BLQ	
2122	53.5	89	Female	BLQ	BLQ	BLQ	BLQ	0.0521	BLQ	
2206	71.2	69	Male	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	
2208	91.2	83	Male	BLQ	BLQ	0.0540	BLQ	0.0940	BLQ	
2423	87.5	73	Male	BLQ	BLQ	NA	BLQ	0.0781	BLQ	
2637	51.7	51	Female	BLQ	BLQ	BLQ	NA	BLQ	BLQ	
2647	88.5	79	Female	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	
Mean				NC	NC	NC	NC	NC	NC	
SD				NC	NC	NC	NC	NC	NC	

BLQ, below the limit of quantitation
 NC, not calculated since more than 50% of drug concentrations were BLQs, or the mean value is BLQ
 NA, blood samples were not collected or reported as missing

APPLICANT'S CONCLUSIONS:

These results indicate that systemic exposure of dexamethasone was minimal but dose dependent in patients who had received one 700 µg DEX PS DDS Applicator System (700 µg dexamethasone) versus those who had received one 350 µg DEX PS DDS Applicator System (350 µg dexamethasone).

REVIEWER ASSESSMENT:

The Applicant's conclusions regarding systemic exposure to dexamethasone following 700 µg DEX PS DDS or 350 µg DEX PS DDS are acceptable from a Clinical Pharmacology perspective. Dexamethasone concentrations obtained from patients in Study 206207-009 were generally below the lower limit of quantitation (0.05 ng/mL) and much lower than concentrations following administration of approved systemic dexamethasone products.

4.1.3. Study PK-07-108

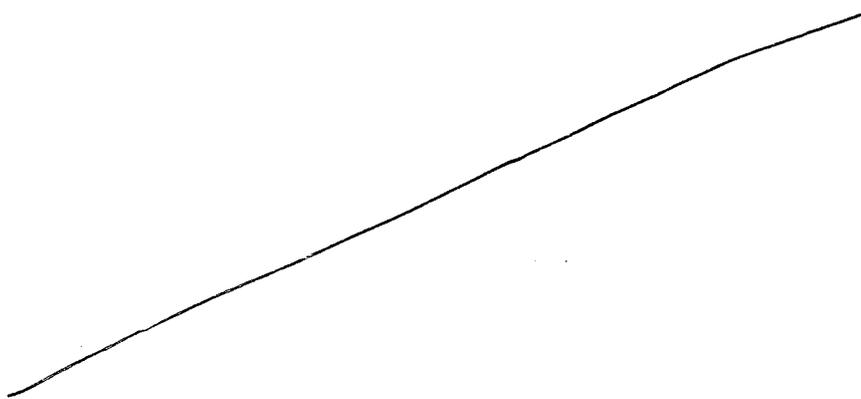
TITLE:

In Vitro Metabolic Profile of Dexamethasone in Human Ocular Tissues

OBJECTIVES:

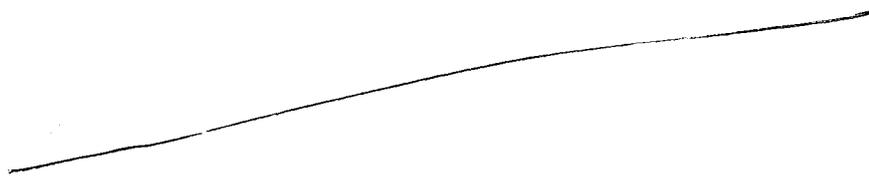
- To investigate the in vitro metabolic profile of dexamethasone after incubation with human ocular tissues.

METHODS:



b(4)

MATERIALS:



b(4)

b(4)

PROTOCOL DEVIATIONS:

The following six deviations were deemed by the applicant as having no impact on the integrity of this study: (1) since there were no metabolites detected in the ocular samples and the parent compound was known to be stable at room temperature, no stability assessment was performed with ocular samples; (2) since there was no metabolite detected by _____ the metabolite characterization was not performed by LC/MS/MS; (3) biological samples were stored at -30°C not -20°C; (4) _____ was used in the extraction of the tissue samples; (5) the ¹⁴C/¹²C Dexamethasone ratio was not determined by LC-MS/MS since metabolism was not observed. Instead, the ¹⁴C/¹²C Dexamethasone ratio was calculated from the concentration of ¹²C Dexamethasone used in the test formulation and its volume ¹⁴C activity; (6) the human eyes were enucleated within 3 to 7 hours of removal, not less than four hours as stated in the protocol.

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RESULTS/CONCLUSION:

Following the incubation of [¹⁴C]-dexamethasone in Waymouth media with human ocular tissues for up to 18 hours, no metabolite was observed by _____

REVIEWER ASSESSMENT:

Based on the results of Study PK-07-108, the Applicant's conclusions are acceptable.

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this page is the manifestation of the electronic signature.**

/s/

Kimberly Bergman
5/1/2009 10:18:32 AM
BIOPHARMACEUTICS

Charles Bonapace
5/1/2009 10:21:22 AM
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