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APPLICATION NUMBER:

218158Orig1s000

NON-CLINICAL REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

PHARMACOLOGY/TOXICOLOGY MEMORANDUM

Date:	February 27, 2024
Application number:	218158
Supporting document/s:	1, 20
Applicant's letter date:	SDN 1: 5-4-2023 SDN 20: 2-26-2024
Product:	Clobetasol Propionate Ophthalmic Nanosuspension, 0.05% (APP13007)
Subject:	Updated scientific bridge to support the 505(b)(2) application
Reviewer:	Maria I Rivera, PhD
Supervisor/Team Leader:	Kimberly Hatfield, PhD
Project Manager:	Kalesha Grayson

Memo/ Summary Statement

In the latter part of the review cycle, the 505(b)(2) committee concluded that the initial scientific bridge strategy for this application using a nonclinical bridge to the Listed Drug (LD) Temovate via comparison of APP13007 to the non-US comparator product (b) (4), was unacceptable. As such, the Agency sent an Information Request (e-mail dated 2-22-2024) to the Applicant stating the following:

"Your 505(b)(2) NDA for clobetasol propionate ophthalmic suspension 0.05% relies on FDA's finding of nonclinical safety for Fougera's NDA 19323, Temovate (clobetasol propionate) topical ointment. Temovate topical ointment is listed in FDA's Orange Book as discontinued from marketing (not for reasons of safety and/or effectiveness). To justify reliance of your proposed product on FDA's nonclinical safety findings for Temovate, you conducted a nonclinical relative bioavailability study comparing your product to (b) (4) a non-US-approved topical clobetasol propionate ointment product.

A 505(b)(2) applicant relying on FDA's finding of safety and/or effectiveness for a listed drug must establish that such reliance is scientifically appropriate and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug relied upon. To demonstrate that such reliance is scientifically justified, a 505(b)(2) applicant should establish a "bridge" (e.g., via comparative bioavailability data) using the relied-upon listed drug approved under section 505(c) of the FD&C Act, or a listed drug approved in an abbreviated new drug application (ANDA) under section 505(j) of the FD&C Act that references the relied-upon listed drug. The drug product marketed under the name (b) (4) has not been approved under section 505(c) or (j) of the FD&C Act and is, therefore, not a listed drug within the statutory meaning.

Therefore, the data from the study that compares your ophthalmic drug product to (b) (4) *a non-US-approved product, are not adequate to bridge to and, therefore, justify reliance on FDA's finding of nonclinical safety for Temovate. As such data are not adequate, information to justify reliance of your product on Temovate is needed for approval of your application.*

You may be able to justify reliance on FDA's finding of nonclinical safety for Temovate topical ointment by establishing a scientific bridge based on a comparison of the AUC and Cmax for your proposed product established in your PK study, CPN-102, to the AUC and Cmax identified in the published literature for Temovate topical ointment (e.g., the 2008 publication by Kimball et al)."

Applicant response to the IR

The Applicant response to the IR was received on 2-26-2024 (SDN 20). Based on the Agency's recommendation, the Applicant compared the plasma exposure data of clobetasol propionate obtained from clinical Study CPN-102 following ocular administration of APP13007 (clobetasol propionate ophthalmic suspension 0.05%) to data from the paper by Kimball et al[1] following dermal application of Temovate ointment 0.05%, the LD.

Summary statistics of Cmax and AUC values of clobetasol propionate were compared between APP13007 and the LD (Temovate ointment 0.05%) as shown in Applicant's Table 1 (copied below).

Table 1 Comparison of Summary Statistics of Cmax and AUCs of Clobetasol Propionate between APP13007 and the RLD (Temovate Ointment 0.05%)

	APP13007				TEMOVATE	
	Period 1 (First Dose)		Period 2 (Second Dose)		Day 8 (First Dose)	
Statistics	Cmax (pg/mL)	$AUC_{(0-24)}$ (hr*pg/mL)	Cmax (pg/mL)	$AUC_{(0-12)}$ (hr*pg/mL)	Cmax (pg/mL)	$AUC_{(0-12)}$ (hr*pg/mL)
N	12	12	10	10	16	16
Mean	32.2	56.9	36.5	77.2	188.1	1572.9
SD	43.6	90.1	59.8	143.5	274.2	2436.8
%CV	135.4	158.2	163.7	185.9	145.8	154.9
Min	0	0	0	0	0.0	0.0
Median	0	0	0	0	100.5	796.4
Max	128.0	273.1	182.0	441.6	1104.3	10133.1

Applicant's Conclusions:

- Following ophthalmic administration of APP13007 twice daily, plasma concentrations of clobetasol propionate are mostly non-quantifiable, and if quantifiable they are minimal using a very sensitive bioanalytical method. No

[1] Kimball AB et. al., 2008, *J Am Acad Dermatol* 59(3):448-454.

accumulation of clobetasol propionate concentration in plasma is expected after multiple doses.

- The Cmax and AUC values of clobetasol propionate following ocular administration of APP13007 twice daily are substantially (up to 6- and 23-fold, respectively) lower than those following dermal application of Temovate ointment 0.05% at a clinically relevant dose.
- These clinical pharmacokinetic data justify the reliance on FDA's finding of nonclinical safety for Temovate ointment 0.05% by establishing a scientifically valid bridge.

Reviewer's Conclusions:

- Clinical Pharmacology team confirmed the human PK comparison is acceptable (see Clin Pharm team memo).
- Pharm/Tox team agrees that the updated bridge is acceptable.

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

/s/

MARIA I RIVERA
02/27/2024 04:39:01 PM

KIMBERLY P HATFIELD
02/27/2024 05:01:10 PM
I concur with the review and evaluation of Dr. Rivera.

PHARMACOLOGY/TOXICOLOGY LABELING REVIEW

NDA #:	218158
Supporting Document(s):	1
Submit Date:	5-4-2023
Received Date:	5-4-2023
PDUFA Goal Date:	3-4-2024
Established/Proper Name	Clobetasol Propionate Ophthalmic Nanosuspension, 0.05%
(Proposed) Trade Name	(b) (4) (clobetasol propionate ophthalmic nanosuspension, 0.05%)
Pharmacologic Class	Corticosteroid
Code name	APP13007
Applicant	Formosa Pharmaceuticals Inc. (Formosa Pharma)
Dosage form	Eye-drop of aqueous suspension
Applicant proposed Dosing Regimen	One drop in the affected eye twice daily (BID) beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period
Applicant Proposed Indication(s)/Population(s)	Treatment of post-operative inflammation and pain in patients following ocular surgery

Introduction

Formosa Pharmaceuticals Inc. (Formosa Pharma) has submitted a 505(b)(2) NDA for APP13007 (Clobetasol Propionate Ophthalmic Nanosuspension, 0.05%). Formosa Pharma is seeking FDA's approval for marketing this prescription drug product for the treatment of post-operative inflammation and pain in patients following ocular surgery.

Clobetasol propionate is a synthetic corticosteroid that is FDA approved as a dermal ointment, cream, or shampoo for the treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. However, clobetasol propionate has not been previously approved for ophthalmic use. Temovate® Ointment 0.05%, the listed drug (LD) for this 505(b)(2) NDA, was originally approved in 1985 and remained on the market in the USA until 2015. The product was withdrawn for reasons other than safety or efficacy.

In this NDA, the Applicant has completed two GLP (14-day and 28-day) toxicology studies with ocular administration of APP13007. The Applicant is relying on the existing information in Sections 8.1 Pregnancy, 8.2 Lactation, and 13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility of the LD label.

The nonclinical review of [redacted] was presented in a separate nonclinical review filed in DARRTS on 2-1-2024. The current document is for labeling only.

Labeling Review

The table below presents: 1) the current labeling of the Listed Drug; 2) the Applicant's proposed labeling in PLLR format (Latest version submitted under SDN 1; eCTD 0001), and 3) the Division's proposed labeling for the nonclinical-relevant sections of the Prescribing Information, including the Indications and Usage section in Highlights of Prescribing Information and Sections 8.1, 8.2, 12.1, and 13.

The Division's proposed additions are noted by **bold** text and deletions are noted by ~~strikethrough~~ text. The exposure margin calculations are shown under the table. [redacted].

1) Listed Drug Text	2) Applicant Proposed Labeling:	3) FDA Proposed Edits:
INDICATIONS AND USAGE	[redacted]	
8.1 Pregnancy Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application to laboratory animals. Clobetasol propionate has not been tested for teratogenicity when applied topically; however, it is absorbed percutaneously, and when administered subcutaneously it was a significant teratogen in both the rabbit and mouse. Clobetasol propionate has greater teratogenic potential than steroids that are less potent. Teratogenicity studies in mice using the subcutaneous route		

resulted in fetotoxicity at the highest dose tested (1 mg/kg) and teratogenicity at all dose levels tested down to 0.03 mg/kg. These doses are approximately 1.4 and 0.04 times, respectively, the human topical dose of TEMOVATE Cream and Ointment. Abnormalities seen included cleft palate and skeletal abnormalities. In rabbits, clobetasol propionate was teratogenic at doses of 3 and 10 mcg/kg. These doses are approximately 0.02 and 0.05 times, respectively, the human topical dose of TEMOVATE Cream and Ointment. Abnormalities seen included cleft palate, cranioschisis, and other skeletal abnormalities. There are no adequate and well-controlled studies of the teratogenic potential of clobetasol propionate in pregnant women. TEMOVATE Cream and Ointment should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.		(b) (4)

	(b) (4)
8.2 Lactation Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects, it is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when TEMOVATE Cream or Ointment is administered to a nursing woman.	
12.1 Mechanism of Action Like other topical corticosteroids, clobetasol propionate has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear.	

However, corticosteroids are thought to act by the induction of phospholipase A2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A2.	(b) (4)
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate. Studies in the rat following subcutaneous administration at dosage levels up to 50 mcg/kg per day revealed that the females exhibited an increase in the number of resorbed embryos and a decrease in the number of living fetuses at the highest dose. Clobetasol propionate was non-mutagenic in 3 different test systems: the Ames test, the Saccharomyces cerevisiae gene conversion assay, and the E. coli B WP2 fluctuation test.	

Exposure Margins Calculations

Intended human dose, 0.05% BID

- 0.05% BID = 0.05 mg in the affected eye (i.e., unilateral dosing)
- Based on 60 kg human body weight = 0.00083 mg/kg, unilateral dosing

Section 12.3 Pharmacokinetics of the proposed label states:

PK evaluation in 12 human subjects following a single ocular treatment of 0.05% APP13007 BID (see Table below) showed that APP13007 plasma concentrations of clobetasol propionate were not measurable (below LLOQ of 0.04 ng/mL) in >90% of the plasma samples or were very low (slightly above 0.04 ng/mL) in 3% of the samples. One female subject showed levels up to 0.182 ng/mL which was below LLOQ after 4 hours postdose.

Table 14.2.1
Summary of Plasma Clobetasol Propionate (CP) Concentration (pg/mL)

TRMT 2: 0.05% BID

Site ID	Subject/ Statistics	Pre-Dose	0.25 Hr	0.5 Hr	1 Hr	1.5 Hr	2 Hr	3 Hr	4 Hr	5 Hr	6 Hr	8 Hr	10 Hr	12 Hr	16 Hr	20 Hr	24 Hr
01	(b) (6) [redacted]	BLQ	BLQ	82.5	182	171	134	80.3	53.4	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
		BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
		BLQ	BLQ	BLQ	40.3	BLQ	40.3	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
		BLQ	BLQ	60.4	87.5	81.4	69.0	44.7	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
		BLQ	41.7	55.3	46.5	43.4	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
		BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
		BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
		BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
		BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
		BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	n	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	Mean	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	STD	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Median	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Min	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	Max	BLQ	41.7	82.5	182.0	171.0	134.0	80.3	53.4	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ

Source: Clinical Study Report CPN-102

There is no animal TK data in the LD label to allow for exposure margin calculations. Therefore, the exposure margins were calculated based on dose which assumes 100% systemic absorption. It is recognized that given the low systemic exposure measured in humans, this approach to determine exposure margins is expected to be more conservative.

EFD Studies (Section 8.1)

Mice

- (b) (4) [redacted] mg/kg
  - HED = [redacted] (b) (4) mg/kg
  - Exposure margin: [redacted] (b) (4)
- (b) (4) [redacted] mg/kg
  - HED = [redacted] (b) (4) mg/kg
  - Exposure margin: [redacted] (b) (4)

Rabbits

- (b) (4) [redacted] µg/kg
  - HED = [redacted] (b) (4) µg/kg
  - Exposure margin: [redacted] (b) (4)
- (b) (4) [redacted] µg/kg
  - HED = [redacted] (b) (4) µg/kg
  - Exposure margin: [redacted] (b) (4)

Impairment of Fertility Study (Section 13.1)

Rats

- (b) (4) µg/kg/day
  - HED = (b) (4) µg/kg
  - Exposure margin: (b) (4)

(b) (4)

- The ocular PK studies as well as the 14-day and 28-day ocular toxicity studies in the rabbit showed low systemic exposure after topical ocular instillation. Despite the low systemic exposure across dose levels (C_{max} [male and female combined] of 1.06 to 3.47 ng/mL on Day 13 in the 14-day study and 2.13 to 3.32 ng/mL on Day 28 in the 28-day study), there were systemic findings.
- The systemic findings were for most part consistent with glucocorticoid class effects.
- A systemic NOAEL was not determined.
- The systemic exposure margins at the LOAEL are shown in the table below.

Systemic Exposure Margins Based on LOAEL from Pivotal Toxicology Studies

Nonclinical				Clinical Safety Margins[c] (Based on dose/plasma exposure)		
Species/ Duration	**LOAEL[a]**	**HED (mg/kg)**	**C_{max} (ng/mL)[b]**	**Dose 0.00083 mg/kg/day**	**Exposure at LLOQ (0.04 ng/mL)**	**Max exposure[d] (0.182 ng/mL)**
14-day rabbit study	(b) (4) QD (b) (4) mg/eye (b) (4) mg/kg	(b) (4)	1.06	7.8X	26X	5.8X
28-day rabbit study	(b) (4) % BID (b) (4) mg/eye (b) (4) mg/kg	(b) (4)	2.13	6.5X	53X	11.7X

(a) Estimated rabbit average body weight of 2.5 kg and 3.0 kg for the 14-day and 28-day studies, respectively
(b) Combined male and female mean C_{max}
(c) Proposed maximum human dose = 0.05% APP13007, one 50 µL drop, unilateral, twice daily for 14 days (0.05 mg/eye/day or 0.00083 mg/kg/day for a 60 kg human)
(d) Value in only one sample of a female human subject

- Based on the highest systemic exposure of 0.182 ng/mL observed in one female human subject, exposure margins at the LOAEL were approximately 6X to 12X the intended clinical dose (i.e., 0.05 mg/eye/day).
- Because a NOAEL was not determined in the general toxicity studies, these exposure margins are expected to be lower.
- As explained in Section 11 of the NDA review, the systemic safety profile of APP13007 in humans is not expected to differ from that previously established

for approved dermal products including Temovate® Ointment 0.05%. The animal data following topical ocular administration of Clobetasol Propionate Ophthalmic Nanosuspension, 0.05% does not allow to definitely rule out that exposure in some pregnant women could potentially lead to fetal adverse effects.

- In addition, it is not possible to confirm that the selected assay LLOQ represents a no activity level in the embryonic cell populations, which are often significantly more sensitive than adult cells.

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/s/

MARIA I RIVERA
02/05/2024 02:26:11 PM

KIMBERLY P HATFIELD
02/05/2024 04:41:44 PM
I concur with the review and recommendations of Dr. Rivera.

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:	218158
Supporting document/s:	1
Applicant's letter date:	5-4-2023
CDER stamp date:	5-4-2023
Product:	Clobetasol Propionate Ophthalmic Nanosuspension, 0.05%
Indication:	Treatment of post-operative inflammation and pain following ocular surgery
Applicant:	Formosa Pharmaceuticals Inc. (Formosa Pharma)
Review Division:	Division of Pharm/Tox for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine/ Specialty Medicine (DPT-RPURM/SM) supporting the Division of Ophthalmology (DO)
Reviewer:	María I Rivera, PhD
Supervisor/Team Leader:	Kimberly Hatfield, PhD
Division Director:	(currently vacant)
Project Manager:	Kalesha Grayson

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 218158 are owned by Formosa Pharma or are data for which Formosa Pharma has obtained a written right of reference. Any information or data necessary for approval of NDA 218158 that Formosa Pharma does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 218158.

TABLE OF CONTENTS

Table of Tables

Table of Figures

1 Executive Summary

1.1 Introduction

Formosa Pharmaceuticals Inc. (Formosa Pharma) has submitted an NDA for APP13007 (Clobetasol Propionate Ophthalmic Nanosuspension, 0.05%), in accordance with Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.54. Formosa Pharma is seeking FDA's approval for marketing this prescription drug product for the treatment of post-operative inflammation and pain in patients following ocular surgery. The intended marketing dosing regimen is one drop in the affected eye twice daily (BID) beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

Clobetasol propionate is a synthetic corticosteroid that is FDA approved as a dermal ointment, cream, or shampoo for the treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. However, clobetasol propionate has not been previously approved for ophthalmic use. Temovate® Ointment 0.05%, the listed drug (LD) for this 505(b)(2) NDA, was originally approved in 1985 and remained on the market in the USA until the product was withdrawn in 2015 for reasons other than safety or efficacy.

In this NDA, the Applicant has completed ophthalmological clinical Phase 1, Phase 2, and two well-controlled Phase 3 safety and efficacy studies of APP13007, along with two GLP (14-day and 28-day) toxicology studies with ocular administration of APP13007. Therefore, the safety and efficacy of APP13007 for the proposed indication does not rely on the Agency's prior findings of safety and efficacy of the dermal LD, except when referencing the existing safety information in the LD label on the use in pregnancy and lactation, and carcinogenesis, mutagenesis, and impairment of fertility.

To bridge the data of APP13007 to that of Temovate® Ointment 0.05%, the Applicant conducted a comparative PK study (b) (4) (b) (4) (b) (4) See Section 2.8 below for further details.

1.2 Brief Discussion of Nonclinical Findings

No adverse ocular findings were observed in the pivotal ocular toxicity studies with APP13007 doses up to 0.1% BID (4-week study) and 0.1% QID (2-week study) in albino rabbits. The high doses are the ocular NOAELs which provide exposure margins of 2X

and 4X, respectively. In a non-GLP study with APP13007 doses up to 0.1% 10X/day (0.5 mg/day) for 7 days, no ocular adverse effects were observed. This dose is 10X the intended marketing dose of 0.05 mg/day (0.05% BID), although with the caveat that the study duration was shorter than the 14 days intended for marketing. Overall, the nonclinical data support the ocular safety of the intended marketing dosing regimen.

The ocular PK studies as well as the 14-day and 28-day ocular toxicity studies in the rabbit showed low systemic exposure after topical ocular instillation (C_{max} ≤3.47 ng/mL and $AUC_{0\text{-}8h}$ ≤8.73 ng•hr/mL). Despite the low systemic exposure, there were systemic findings. The systemic findings were for most part consistent with glucocorticoid class effects. Main targets included RBC, WBC, coagulation, liver, kidney, adrenals, spleen, lymph nodes, thymus, and skin, among others. Most findings showed complete or partial reversibility during the recovery period.

A systemic NOAEL was not determined in either the 14-day or 28-day ocular toxicity studies. As such, the lowest dose is the low-observed-adverse-effect level (LOAEL). At the LOAEL, the exposure margins are 7.8 and 6.5X (based on body surface area), 26 and 53X (based on human systemic exposure below LLOQ) and 5.8 and 11.7X (based on highest systemic exposure in one human subject) the intended human topical ocular dose (see Table 26 for further details). As most human PK samples showed levels below LLOQ, the exposure margins are considered supportive of systemic safety.

Several additional observations provide further support for the systemic safety of the intended clinical dose, from the nonclinical perspective. These include:

- The Applicant is relying on FDA's previous findings of safety and efficacy for the referenced dermal product Temovate®. A comparative PK study in the rabbit supports that systemic exposure after ocular administration is expected to be lower than that of the dermal product at clinically relevant doses.
- Following ocular instillation of 0.05% APP13007 BID in humans, clobetasol propionate concentrations in plasma were generally not measurable (< 0.04 ng/mL LLOQ) or very low (≤0.182 ng/mL) and were rapidly eliminated. These concentrations are lower than peak concentrations following application of [redacted](b) (4)Temovate® Ointment 0.05% (overall range of 0.19 to 15.8 ng/mL) per the published information provided on Module 2.7.2.1.2, Summary of Clinical Pharmacology Studies). Therefore, the systemic safety profile of APP13007 in humans is not expected to differ from that previously established for approved dermal products including Temovate® Ointment 0.05%.
- The systemic exposure observed in humans after topical ocular administration of 0.05% APP13007 BID is below the IC_{50} of 3.25 ng/mL for clobetasol propionate binding to the human glucocorticoid receptor. This finding helps mitigate clinical concerns for drug-class related adverse systemic findings.
- Per Summary information in the NDA (Module 2.5 Clinical Overview), there were no clinically noteworthy changes in any of the hematology or clinical chemistry parameters, including renal parameters and serum cortisol, following administration of 0.05% APP13007 BID for 21 days (Phase 2 Study CPN-201).

- The intended ocular dose is 71X lower than the maximal recommended weekly dose (50 g/week) for the approved dermal products, including Temovate® Ointment 0.05%.

In summary, the nonclinical data provides support for the ocular and systemic safety of APP13007 (Clobetasol Propionate Ophthalmic Nanosuspension, 0.05%) in the treatment of post-operative inflammation and pain in patients following ocular surgery at the intended dosing regimen for marketing. The Pharmacology/Toxicology team recommends approval.

1.3 Recommendations

1.3.1 Approvability

Approval is recommended.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

See Pharmacology/Toxicology team recommendations in a separate label review for this NDA.

2 Drug Information

2.1 Drug

CAS Registry Number: 25122-46-7

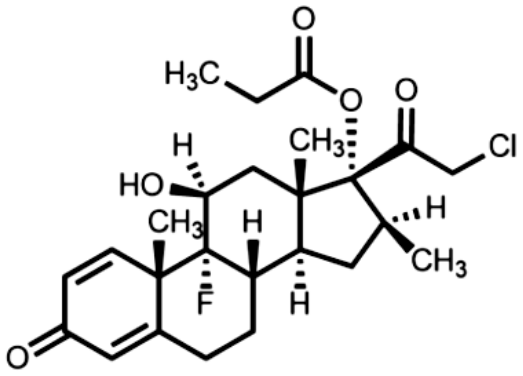
Generic Name: Clobetasol Propionate

Code Name: APP13007

Chemical Name: 21-chloro-9α-fluoro-11β,17α-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-propionate

Molecular Formula/Molecular Weight: $C_{25}H_{32}ClFO_5$/466.97 daltons

Structure or Biochemical Description:



Pharmacologic Class: Corticosteroid

2.2 Relevant INDs, NDAs, BLAs and DMFs

- IND 128133 (APP13007; Clobetasol Propionate Ophthalmic Nanosuspension)
- Temovate® NDAs 019322 (Clobetasol Propionate Cream, 0.05%) and 019323 (Clobetasol Propionate Ointment, 0.05%)
- DMFs (b) (4)

2.3 Drug Formulation

Clobetasol Propionate Ophthalmic Nanosuspension, 0.05% (APP13007) is an eye-drop product of a nanosuspension prepared by dispersing nanomilled particles of clobetasol propionate with excipients in a preserved multi-dose aqueous formulation. The mean particle size distribution of the nanosuspension is in the range of (b) (4) nm.

The composition of Clobetasol Propionate Ophthalmic Nanosuspension, 0.05%, is shown in Table 1.

Table 1: Composition of Clobetasol Propionate Ophthalmic Nanosuspension, 0.05%

Component	Quality Standard	Function	Formulation Composition (%w/v) [a]
Clobetasol Propionate	USP	Active ingredient	0.05 [b]
Sodium Chloride	USP	(b) (4)	
Hydrogenated Soybean Lecithin	NF		
Citric Acid (b) (4)	USP		
Glycerin	USP		
Poloxamer 407	NF		
Polyvinyl Alcohol	USP		
Boric Acid	NF		
Edetate Disodium Dihydrate	USP		
Benzalkonium Chloride	NF	Preservative	0.0036
Methylcellulose	USP	(b) (4)	
Tri-Sodium Citrate (b) (4)	USP		
Water for Injection	USP		

[a] Composition is reported as %w/v for consistency with the intended label strength of the drug product as % w/v. (b) (4) the drug product's specific gravity was determined to be (b) (4)

[b] (b) (4)

Source: NDA Table 3.2.P.1.1, Module 3.2.P.1 Description and Composition of the Drug Product

Except for the 28-day pivotal ocular toxicity study (Study # APP13007-TOX-001), all nonclinical studies were conducted with earlier formulations of AP13007. Study # APP13007-TOX-001 used the proposed clinical formulation. The nonclinical formulations differ in excipient content (Table 2).

Table 2: Formulations of APP13007 Administered in Pharmacokinetics and Ocular Toxicology Nonclinical Studies

Formulation Component	Quality Standard	Study No. SBL245-041 (14-Day GLP Tox)	Study No. SBL245-045 (Ocular vs Dermal PK)	Study No. APP13007-TOX-001 (28-Day GLP Tox)		Study No. APP13007-ADME-001[2] (Ocular PK)
		0.1% APP13007 [Lot No. CPEOS150625]	0.05% APP13007 [Lot No. CPEOS170112]	0.05% APP13007 [Lot No. CPEOS180904] [1]	0.1% APP13007 [Lot No. CPEOS180828] [1]	0.05% APP13007 [Lot No. TR016] [3]
Clobetasol Propionate	USP	0.10%	0.05%	0.05%	0.10%	0.05%
Sodium Chloride	JP, USP	(b) (4)				
Hydrogenated Soybean Lecithin	NF					
(b) (4) Citric Acid	USP					
Glycerin	USP					
Poloxamer 407	NF					
Polyvinyl Alcohol	USP					
Boric Acid	NF					
(b) (4)	JP, USP					
Benzalkonium chloride	NF					(b) (4) 0.0036%
Methylcellulose	USP					(b) (4)
Glycerin	USP					
Sodium Citrate	USP					
Water for Injection	JP					

USP = United States Pharmacopeia, JP = Japanese Pharmacopeia, NF = National Formulary.
% expressed as w/v.
[1]: consistent with Phase 2 clinical formulation. [2]: same composition as Phase 2 and Phase 3 clinical formulation. [3]: Phase 3 clinical batch.

Source: NDA Table 2, Module 2.6.4 Pharmacokinetics Written Summary

2.4 Comments on Novel Excipients

No ophthalmic drug products containing hydrogenated soybean lecithin are listed in the FDA Inactive Ingredient Database. It is listed for otic, IV, oral, and topical use at concentrations up to 1.5% (topical cream) or 213 mg (IV).

The nonclinical formulations used in the pivotal ocular toxicity studies used this excipient at concentrations of (b) (4) (14-day ocular toxicity study, No. (b) (4) 245-041) and (b) (4) (28-day ocular toxicity study, No. APP13007-TOX-001). Both studies evaluated eyes treated with saline and vehicle as controls. No adverse ocular findings were noted for vehicle or test-article treated groups at dosing frequencies of up to 4X (14-day study) and 2X (28-day study). No systemic toxicities were observed in the vehicle-treated groups. Therefore, there are no safety issues with the use of Hydrogen Soybean Lecithin (b) (4) in the clinical formulation at the intended dosing regimen (BID for 14 days).

2.5 Comments on Impurities/Degradants of Concern

No issues have been identified by CMC review that require nonclinical input.

2.6 Proposed Clinical Population and Dosing Regimen

- Clobetasol Propionate Ophthalmic Nanosuspension, 0.05% is indicated for the treatment of post-operative inflammation and pain following ocular surgery.
- The recommended dosing regimen is to instill one drop into the affected eye twice daily (BID) beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

2.7 Regulatory Background

- Pre-IND meeting was held on 1-21-2016 (see meeting minutes filed in DARRTS on 2-12-2016, Germain J, and nonclinical review filed in DARRTS on 1-12-2016, Rivera MI).
    - Pharm/Tox team agreed that the proposed ocular toxicity and ocular PK studies were adequate for IND submission.
    - Pharm/Tox team agreed that the use of only one species was acceptable in this case based on the long history of ocular use of corticosteroids with known safety profile, the intended short-term duration of use, and the topical ocular route of administration.
    - Pharm/Tox team recommended inclusion of a recovery period in the pivotal ocular toxicity study.
    - The standard recommendations for nonclinical requirements for a 505(b)(2) application were conveyed. The Division noted that reliance on the listed drug would be scientifically justified if systemic exposure following APP13007 administration was less than that of the listed drug product.

- Initial IND submitted on 6-10-2019 (see nonclinical review filed in DARRTS on 7-22-2019, Rivera MI).
    - IND was allowed to proceed.

- End-of-Phase 2 meeting was held on 9-2-2020 (see meeting minutes filed in DARRTS on 9-30-20, Almoza LA, and nonclinical review filed in DARRTS on 8-24-2020, Rivera MI).
    - Pharm/Tox team agreed that the battery of nonclinical studies appeared sufficient for NDA submission.

- Pre-NDA meeting was held on 10-31-2022 (see meeting minutes filed in DARRTS on 11-30-2022, Almoza LA)
    - Pharm/Tox team reiterated that the battery of nonclinical studies appeared sufficient for NDA submission.
    - Pharm/Tox team recommended the labeling information be primarily based on information pertinent to the active ingredient (vs. class labeling).

2.8 505(b)(2)

Temovate® Ointment 0.05%, the listed drug (LD) for this 505(b)(2) NDA, was originally approved in 1985 and remained on the market in the USA until the product was withdrawn in 2015 for reasons other than safety or efficacy. To bridge the data of APP13007 to that of Temovate® Ointment 0.05%, the Applicant conducted a comparative PK study (b) (4)

(b) (4)

3 Studies Submitted

3.1 Studies Reviewed

New studies submitted with the NDA

- Affinity of Steroids to Glucocorticoid Receptors (Study # AL-6269)
- Single-Dose Ocular Pharmacokinetics Study in Rabbits with APP13007 (Clobetasol Propionate Ophthalmic Nanosuspension) 0.05% Administered via Ocular Surface Instillation (Study # APP13007-ADME-001)

Reviewed under IND 128133 (30-day safety review, filed in DARRTS on 7-22-2019, Rivera MI)

Pharmacology

- Anti-Inflammatory Effect of APP13007 in Rabbit Paracentesis Model (Study # (b) (4) 15001)
- Anti-Inflammatory Effect of APP13007 in a Rabbit Endotoxin-Induced Uveoretinitis Model (Study # (b) (4) 16001)
- Anti-Inflammatory Effect of APP13007 in a Rabbit Endotoxin-Induced Uveoretinitis Model (Study # (b) (4) 16002)

PK/ADME

- Ocular Instillation of Pharmacokinetics Study-8 of Clobetasol in Rabbits (Study # (b) (4) 245-031)
- Ocular Instillation Pharmacokinetics Study of 0.1% APP13007 in Rabbits (Study # (b) (4) 245-042)

(b) (4)

General Toxicology

- A 4-Week Repeat-Dose Topical Ocular Toxicity Study of APP13007 (Clobetasol Propionate Ophthalmic Nanosuspension) with a 4-Week Recovery Period in New Zealand White Rabbits (Study # APP13007-TOX-001)
- A 2-Week Ocular Toxicity Study of 0.1% APP13007 in Rabbits Followed by a 4-Week Recovery Period (Study # (b) (4) 245-041)
- A 7-Day Ocular Toxicity Study of Clobetasol in Rabbits (Study # (b) (4) 245-032)

3.2 Studies Not Reviewed

- Reports under Module 4.2.2.1 Analytical Methods and Validation Reports

3.3 Previous Reviews Referenced

- IND 128133 (30-day safety review, filed in DARRTS on 7-22-2019, Rivera MI)

4 Pharmacology

Clobetasol propionate, an analog of prednisolone, is a potent corticosteroid that has anti-inflammatory, antipruritic, and vasoconstrictive properties. It is considered to be the most potent corticosteroid compared with other corticosteroids on the market and is classified as a Class 1 - Superpotent corticosteroid in the USA. Clobetasol propionate has a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity.

The mechanism of the anti-inflammatory activity of topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammations such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A2 (Temovate® Package Insert).

4.1 Primary Pharmacology

Affinity of Steroids to Glucocorticoid Receptors (Study No. AL-6269) - The in vitro potency of clobetasol propionate was assessed by its binding affinity to the human recombinant glucocorticoid receptor in comparison to other glucocorticoids. The IC_{50} data (Table 3) show that clobetasol propionate is the most potent corticosteroid of the 4 tested. The IC_{50} value for clobetasol propionate was 6.95×10^{-9} M, equivalent to 3.25 ng/mL.

Table 3: Relative Potency of Corticosteroids as Determined by their IC50 Values to Inhibit a Radioligand Binding to Human Glucocorticoid Receptor

Test Compound	% Inhibition at Each Test Article Concentration (M)						IC_{50} (M)
	1×10^{-11}	1×10^{-10}	1×10^{-9}	1×10^{-8}	1×10^{-7}	1×10^{-6}	
Clobetasol Propionate	0.84	1.87	5.60	63.03	98.74	99.97	6.95×10^{-9}
Difluprednate	0.00	0.53	0.00	20.64	93.08	99.56	2.21×10^{-8}
Prednisolone	3.80	3.97	4.84	17.23	73.26	96.56	4.06×10^{-8}
Dexamethasone	1.88	0.68	7.43	43.97	93.17	99.48	1.05×10^{-8}

Source: Table 3, Module 2.6.2 Pharmacology Written Summary

Pharmacology studies included the evaluation of APP13007 in ocular inflammation models of uveoretinitis and paracentesis in rabbits (Table 4). These studies were reviewed under the initial IND. The paracentesis model is intended to mimic certain aspects of inflammation induced by anterior ocular surgery such as

cataract surgery, while the uveoretinitis model characterizes inflammation in both the anterior and posterior segments.

These primary pharmacology studies demonstrated that APP13007 (at concentrations including 0.05% QD to QID and 0.1% QD to BID) was well tolerated and reduced signs of inflammation with efficacy similar or superior to that observed with Durezol® (difluprednate ophthalmic emulsion) 0.05%.

Table 4: Primary Pharmacology Studies Main Findings

Study Type	Test System	Method of Administration	Treatments	and No. per Group	Noteworthy Findings	Testing Facility	Study Number
Ocular Paracentesis Model	Japanese White Rabbit	Ocular Surface Instillation (Single Administration)	• Saline • Durezol® • 0.002% APP13007 • 0.01% APP13007 • 0.05% APP13007	6 Males per Group	• APP13007 at all strengths significantly reduced protein concentration in aqueous humor, with the 0.05% demonstrating the greatest anti-inflammatory activity among the APP13007 dose groups. • 0.05% APP13007 produced similar reduction of aqueous humor protein concentrations to that seen with Durezol®	(b) (4)	(b) (4) 15001
Endotoxin-Induced Uveoretinitis Model	Japanese White Rabbit	Ocular Surface Instillation (Repeat Administration for 6 Days)	• Saline 4 times daily 3 hrs apart (QID) • Durezol® twice daily 8 hrs apart (BID), and 4 times daily 3 hrs apart (QID) • 0.05% APP13007 once daily (QD), twice daily 8 hrs apart (BID), and 4 times daily 3 hrs apart (QID)	4 or 5 Males per Group	• Durezol® (BID, QID) and 0.05% APP13007 (QD, BID and QID) significantly reduced biomarkers of inflammation (vitreous concentrations of protein and/or PGE2). • Both BID and QID 0.05% APP13007 were superior to BID or QID Durezol® at reducing vitreous concentration of PGE2		(b) (4) 16001

Study Type	Test System	Method of Administration	Treatments	and No. per Group	Noteworthy Findings	Testing Facility	Study Number
Endotoxin-Induced Uveoretinitis Model	Japanese White Rabbit	Ocular Surface Instillation (Repeat Administration for 6 Days)	• Saline twice daily • Durezol® once daily (QD), twice daily 8 hrs apart (BID) • 0.05% APP13007 once daily (QD), twice daily 8 hrs apart (BID), 0.1% APP13007 once daily (QD), twice daily 8 hrs apart (BID)	6-7 Males per Group	• Durezol® BID and APP13007 (0.05% and 0.1%) QD or BID significantly reduced biomarkers of inflammation (vitreous concentrations of protein and PGE2), while Durezol® QD was not effective. • The APP13007 BID groups demonstrated greater effects as compared to the QD groups. • 0.05% and 0.1% APP13007 given QD or BID demonstrated efficacy similar or superior to that seen with BID Durezol®	(b) (4)	(b) (4) 16002

Source: NDA Module 2.6.3, Pharmacology Tabulated Summary

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The ocular tissue and plasma PK of clobetasol propionate were characterized following single ocular instillations of APP13007 in albino rabbits. These studies evaluated the earlier formulations (Studies # (b) (4) 245-031 and (b) (4) 245-042) and clinical/commercial formulation (Study # APP13007-ADME-001) of APP13007. The nanoparticles of clobetasol propionate in APP13007 are expected to efficiently penetrate the target tissues of the eye upon ocular surface instillation. These studies showed that clobetasol propionate distributed to all ocular matrices evaluated with higher concentrations in the cornea, conjunctiva, and iris/ciliary body and lower concentrations in retina/choroid/RPE, optic nerve, and vitreous.

A comparative bridging study of systemic exposure following topical ocular versus dermal application was also conducted (Study # (b) (4) 245-045). This study was used to support reliance on FDA's findings of safety and effectiveness for the listed drug (Temovate®) Ointment 0.05%.

The composition of the earlier 0.05% and 0.1% APP13007 formulations used in these studies is shown in Table 2 above. The earlier formulations differ slightly from the Phase 3/intended commercial formulation of APP13007 in the content of certain excipients such as methylcellulose and benzalkonium chloride, and the addition of (b) (4) (b) (4) in the Phase 3/commercial formulation.

A study comparing each formulation simultaneously was not conducted. However, the studies below show the following:

- The rank order of ocular tissue distribution was comparable between formulations (cornea>conjunctiva>iris/ciliary body>aqueous humor>retina/choroid>plasma>vitreous humor).
- When the earlier and commercial formulation at the same concentration of 0.05% are compared for the matrices commonly evaluated (plasma, conjunctiva [assumed to be bulbar for the earlier formulation], and aqueous humor), the exposure is comparable.
- Plasma concentration was comparable at APP13007 earlier formulation given at 0.1% to one eye and commercial formulation given at 0.05% to each eye.
- Overall, these data support that the results of the bridging study conducted with the earlier formulation are applicable to the commercial formulation.

Single-Dose Ocular Pharmacokinetics Study in Rabbits with APP13007 (Clobetasol Propionate Ophthalmic Nanosuspension) 0.05% Administered via Ocular Surface Instillation (Study # APP13007-ADME-001) – This study evaluated the Phase 3 clinical/commercial formulation. Male New Zealand White rabbits received a single bilateral ocular surface instillation of 0.05% APP13007 (50 µL per eye) and ocular matrices and plasma samples were collected over 24 hours postdose.

Clobetasol propionate was detected in plasma with peak concentrations (T_{max}) observed at the first sampling timepoint of 15 minutes postdose and mean C_{max} of 2.19 ng/mL. By 8 hours postdose, most plasma samples had concentrations close to or below the LLOQ (0.05 ng/mL). Only 2 out of 6 samples still had minimal (close to LLOQ) clobetasol propionate concentrations in plasma at 12 hours postdose.

Clobetasol propionate distributed to all ocular matrices with higher concentrations in the cornea, conjunctiva, and iris/ciliary body and lower concentrations in retina/choroid/RPE, optic nerve, and vitreous. T_{max} was generally observed at 15 to 30 min postdose in all tissues, except for lens at 2-hour postdose. Concentrations of clobetasol propionate were generally measurable up to 12-24 hours postdose in all tissues except for up to 4 hours postdose in the vitreous. Half-lives ($t_{1/2}$) of clobetasol propionate in the ocular tissues ranged from 1.72-5.42 hours, except for the lens with $t_{1/2}$ of 15 hours. In the liquid ocular matrices, $t_{1/2}$ was 1.05 hours in aqueous humor and could not be estimated in vitreous humor due to low concentrations.

The concentration of clobetasol propionate in plasma was lower than that in ocular tissues, except for the vitreous body.

The mean PK parameter estimates of clobetasol propionate in plasma and each of the ocular tissues evaluated are summarized in Table 5.

Table 5: Pharmacokinetic Parameter Estimates of Clobetasol Propionate in Plasma and Ocular Tissues following a Single Bilateral Instillation of 0.05% APP13007 in Rabbits (Commercial Formulation)

Matrix	C_{max} (ng/mL or ng/g)	t_{max} (h)	AUC_{0-t} (h*ng/mL or h*ng/g)	$t_{1/2}$ (h)	t_{last} (h)
Plasma	2.19± 0.0877	0.25	2.36± 0.0807	3.17	12
Cornea	3240± 369	0.25	4240± 237	5.42	24
Palpebral Conjunctiva	1720± 199	0.25	997± 83.3	4.52	24
Bulbar Conjunctiva	1390± 163	0.25	778± 49.3	4.45	24
Sclera	59.2± 6.91	0.25	97.8± 3.53	3.3	24
Aqueous Humor	46.9± 9.77	0.5	68.9± 4.72	1.05	12
Iris/Ciliary Body	117± 13.3	0.5	231± 12.2	1.72	12
Lens	8.05± 0.493	2	86.8± 7.20	15	24
Vitreous Humor	0.0595± 0.0287	0.25	0.0570± 0.0126	NR	4
Retina/Choroid/RPE	6.36± 0.707	0.5	22.6± 0.830	3.65	12
Optic Nerve	5.59± 0.922	0.5	22.6± 4.94	NR	12

Data are presented as either Mean or Mean±SE (C_{max} and AUC_{0-t} only). n = 6 for each eye tissue. n=24 for plasma at 0.25 hr and then reduced by 3 at each subsequent time point; NR – not reported due to R^2 not meeting acceptance criteria (in both instances R^2 < (b) (4)

Source: Table 25, NDA Module 2.6.4, Pharmacokinetics Written Summary

Ocular Instillation of Pharmacokinetics Study-8 of Clobetasol in Rabbits (Study # (b) (4) 245-031) – This study used an earlier formulation and was previously reviewed under initial IND 128133. Male Japanese White rabbits (Kbl:JW) received a single ocular surface instillation of 50 µL of 0.025%, 0.05%, or 0.1% APP13007 into the left eye only. Concentration of clobetasol propionate in plasma, conjunctiva, and aqueous humor were evaluated at 0.25, 0.5, 1, 2, and 3 hours postdose.

Plasma exposure to clobetasol propionate was in the low nanogram/mL range (Table 6), with mean T_{max} observed at 15 minutes postdose (first sampling timepoint) and decreased rapidly over time (mean $t_{1/2}$ of 0.21 to 1.03 hours). The increase in plasma exposure was not dose proportional.

Table 6: Mean Pharmacokinetic Parameters Estimates of Clobetasol Propionate in Rabbit Plasma following a Single Topical Ocular Instillation of Several Concentrations (Earlier Formulation)

Group (Dose Strength)	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (h*ng/mL)	$AUC_{0-\infty}$ (h*ng/mL)	$t_{½}$ (h)
1 (0.025%)	1.76	0.25	0.70	0.74	0.21
2 (0.05%)	2.04	0.25	2.23	2.31	0.54
3 (0.1%)	2.88	0.25	2.85	3.39	1.03

Data are mean in 5 rabbits/group.

Source: Table 17, NDA Module 2.6.4, Pharmacokinetics Written Summary

Aqueous humor concentrations of clobetasol propionate peaked at 30 minutes postdose and were quantifiable in all samples at all timepoints, slowly decreasing over time during the 3-hour study period ($t_{1/2}$ of 1.96 to 2.46 hours) (Table 7). T_{max} occurred at 30 minutes postdose. The increase in aqueous exposure was not dose proportional.

Table 7: Mean Pharmacokinetic Parameter Estimates of Clobetasol Propionate in Rabbit Aqueous Humor following a Single Topical Ocular Instillation of Several Concentrations (Earlier Formulation)

Group (Dose Strength)	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (h*ng/mL)	$AUC_{0-\infty}$ (h*ng/mL)	$t_{½}$ (h)
1 (0.025%)	57.27	0.50	92.59	162.74	1.96
2 (0.05%)	55.43	0.50	98.82	150.31	1.58
3 (0.1%)	47.71	0.50	111.15	204.06	2.46

Data are mean in 5 rabbits/group.

Source: Table 19, NDA Module 2.6.4, Pharmacokinetics Written Summary

Conjunctiva concentrations of clobetasol propionate peaked at 15 minutes postdose and were quantifiable in all samples at all time points, decreasing over time during the 3-hour study period ($t_{1/2}$ of 1.32 to 1.48 hours) (Table 8). T_{max} occurred at 15 minutes postdose. The increase in conjunctival exposure was not dose proportional.

Table 8: Mean Pharmacokinetic Parameter Estimates of Clobetasol Propionate in Rabbit Conjunctiva after a Single Topical Ocular Instillation of Several Concentrations (Earlier Formulation)

Group (Dose Strength)	C_{max} (ng/g)	t_{max} (h)	AUC_{0-t} (h*ng/g)	$AUC_{0-\infty}$ (h*ng/g)	$t_{½}$ (h)
1 (0.025%)	810.0	0.25	623.0	738.1	1.32
2 (0.05%)	970.0	0.25	1074	1252	1.34
3 (0.1%)	2284	0.25	1815	2428	1.48

Data are mean in 5 rabbits/group.

Source: Table 21, NDA Module 2.6.4, Pharmacokinetics Written Summary

Ocular Instillation Pharmacokinetics Study of 0.1% APP13007 in Rabbits (Study # (b) (4) 245-042) - This study used the earlier formulation and was previously reviewed under initial IND 128133. Male Japanese White rabbits (Kbl:JW) received a single ocular surface instillation of 50 µL of 0.1% APP13007 into the left eye only. Concentration of clobetasol in plasma and ocular tissues (aqueous humor, conjunctiva, cornea, iris, ciliary body, vitreous body, and retina and choroid) were evaluated at various timepoints from 0.25 to 24 hours postdose.

The concentration of clobetasol propionate in plasma was lower than in ocular tissues, except for the vitreous body (Table 9). Mean T_{max} was observed at 0.25-hour postdose, and the terminal $t_{1/2}$ was 1.22 hours. Samples were below the lower limit of quantitation (0.1 ng/mL) at 8 hours after dosing.

As noted in pivotal Study # APP13007-ADME-001, CP distributed to all ocular matrices with higher concentrations in the cornea, conjunctiva, and iris+ciliary body, and lower concentrations in retina/choroid and vitreous. The mean T_{max} in these ocular tissues ranged from 15 minutes to 1 hour. Overall, the $t_{1/2}$ ranged from 0.74 to 7.85 hours (lens was not measured).

Table 9: Mean Pharmacokinetic Parameter Estimates of Clobetasol Propionate in Rabbit Ocular Matrices and Plasma following a Single Instillation of 0.1% APP13007 in Rabbits (Earlier Formulation)

Matrix	C_{max} (ng/mL or ng/g)	t_{max} (h)	AUC_{0-t} (h*ng/mL or h*ng/g)	$AUC_{0-\infty}$ (h*ng/mL or h*ng/g)	$t_{½}$ (h)
Cornea	4200	0.5	6979	7083	5.34
Conjunctiva	442.9	0.25	548.3	579.7	7.85
Aqueous Humor	79.32	1.0	141.4	141.8	0.95
Iris	403.9	0.5	699.5	704.8	1.21
Ciliary Body	70.03	1.0	118.0	127.4	0.94
Vitreous Humor	0.371	0.25	0.236	0.429	0.74
Retina/ Choroid	23.33	1.0	52.95	60.21	2.95
Plasma	2.273	0.25	2.958	3.276	1.22

Data are mean in 6 rabbits.

Source: Table 23, NDA Module 2.6.4, Pharmacokinetics Written Summary

(b) (4)

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(b) (4)

6 General Toxicology

6.2 Repeat-Dose Toxicity

Pivotal ocular toxicology studies of 14-day and 28-day duration were conducted in rabbits. The 14-day study used an earlier formulation as described in the study review below. The 28-day study used the Phase 3/commercial formulation. These studies were reviewed at the IND stage. The reviews below generally reflect the assessment conducted under the initial nonclinical review for IND 128133 (Rivera MI, filed in DARRTS on 7-22-2019). The Applicant's tables were updated for the NDA section (source) they were copied from.

Study title: A 2-Week Ocular Toxicity Study of 0.1% APP13007 in Rabbits Followed by a 4-Week Recovery Period

Study no.:	(b) (4) 245-041
Study report location:	Module 4.2.3.2 \\CDSESUB1\EVSPROD\nda218158\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox(b) (4) 245-041\ (b) (4) 245-041.pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 17, 2016
GLP compliance:	Y
QA statement:	Y
Drug, lot #, and % purity:	APP13007 0.1%, lot # CPEOS150625, 100.00% pure

Notes:

- The certificates of analysis are in (b) (4) In Section 7.1.1 "Test Article" of the Study Report, the purity is specified as 100.00%.
- The English translation of the certificate of analysis was submitted to IND 128133 SDN 8 (2-7-2020) under Module 1.11.1. It confirms that the purity of the test article was 100.00%.

- The formulation used in this study is not the commercial formulation.
  - It does not contain [redacted] (b) (4).
  - It differs slightly in the amount of sodium chloride ([redacted] (b) (4) in the clinical formulation), hydrogenated soybean lecithin ([redacted] (b) (4) in the commercial formulation), glycerin [redacted] (b) (4) in the commercial formulation) and BAK [redacted] (b) (4) vs 0.0036% in the commercial formulation).

Key Study Findings

- There were no adverse ocular findings at any dose in any ophthalmic endpoint including ophthalmic exams, ocular histopathology, IOP, and ERG.
- Despite the low systemic exposure (mean C_{max} ranging from 1.038 to 3.467 ng/mL across dose levels on Day 13), a variety of drug class related (glucocorticoid) systemic effects were observed. These included hematological, coagulation, clinical chemistry, and urinalysis changes, organ weight changes, and gross and microscopic findings. Test article-related microscopic findings were observed in the kidneys, liver, skin, thymus, spleen, adrenals, lymph nodes, cecum, pancreas, and uterus.
- The findings were generally reversible or partially reversible.
- The NOAEL for ocular toxicity was the high dose, 0.1% APP13007 QID (0.2 mg/eye/day).
- The NOAEL for systemic toxicity was not established in this study due to the pharmacologic effects observed. The mean C_{max} (males and females combined) at the low dose (0.1% 1X/day) was 1.06 ng/mL.

Methods

Doses:	0 (saline), 0 (placebo vehicle), and 0.1% 1X, 2X, or 4X/day (0, 0.05, 0.1, and 0.2 mg/eye/day, respectively) Placebo, saline (0.9% sodium chloride for injection) and the test article were administered to the left eye only.
Frequency of dosing:	1, 2, or 4x daily for 14 days; 1-hour intervals **Note:** Placebo and saline-treated eyes were administered 4X daily (QID).
Route of administration:	Topical ocular into the conjunctival sac
Dose volume:	50 µL

Formulation/Vehicle:	APP13007 Vehicle
Species/Strain:	Japanese White Rabbit
Number/Sex/Group:	7/sex/group
	Note: Three rabbits/sex/group were maintained for a 4-week recovery period.
Age:	2 to 4 months
Weight:	Males: 2.21 to 2.64 kg; females: 2.40 to 2.86 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	None with an impact on data interpretation

Observations and Results

Mortality (2x/day)

None considered test article related. One high-dose female (# 66) died after the ERG procedure on Day 41 (during recovery). Diffuse hepatocyte vacuolation and splenic congestion were noted by histopathological evaluation. Per information in the Study Report, it was determined that the death resulted from the anesthesia performed for the ERG procedure.

Clinical Signs (2x/day)

No test article-related findings

Body Weights (Pretreatment, Days 3, 6, 10, and 13 of dosing; Days 6, 13, 20, and 27 of recovery)

A statistically significant decrease in mean body weight was observed in all test article-treated groups at ≥ Day 10 (e.g., 8.2 to 12.3% at Day 13, compared to saline), which continued through Day 13 of the recovery period. By the end of the recovery period, there were no significant differences in mean body weight across groups.

Feed Consumption (Pretreatment, Days 5 and 12 of dosing; Days 5, 12, 19, and 26 of recovery)

No test article-related effects

Ophthalmoscopy (Slit lamp biomicroscopy with modified Draize scoring, pretreatment, Days 6 and 12 of dosing [1 to 2 hours after the final dose] and Day 28 of recovery; indirect ophthalmoscopy, pretreatment and Day 12 of dosing and Day 28 of recovery)

No test article-related effects

Corneal Fluorescein Staining (Once pretreatment, Day 12 at ~1 to 2 hours after the final dose and Day 28 of recovery)

No test article-related effects

Tonometry (Pretreatment and once on Day 11 of dosing [after the final dose] and Day 26 of recovery)

No test article-related effects

Full-field Electroretinography (ffERG) (Pretreatment and on Day 10 of dosing and Day 27 of recovery; scotopic; luminescence intensity: (b) (4) (b) (4)

The data showed no test article-related effects in a-wave, b-wave, and oscillatory potentials amplitude and latency. However, the ERG evaluation was limited as only one white light stimuli under dark adaptation was evaluated.

Reviewer's comments: *An Information Request was sent to the Applicant for clarification following review of the Study Report under the initial IND. The response was received under IND 128133 SDN 8, 2-7-2020, Module 1.11.1. The Sponsor did not provide any new details that could help understand or evaluate the adequacy of the ERG assay. However, as no adverse retinal effects were noted microscopically or in any other ocular endpoints, the ERG analysis limitations are not considered to have an impact on risk assessment.*

Hematology and Coagulation (Pretreatment and once on Day 9 of dosing and Day 25 of recovery)

Compared to the saline control, RBC and WBC parameters were affected (Table 11). APTT was decreased at all test article doses. No significant changes were observed between saline and vehicle control.

Table 11: Mean Hematology Changes – 2-Week Ocular Toxicity Rabbit Study

Test Material	Saline QID		Vehicle QID		0.1% APP13007 QD		0.1% APP13007 BID		0.1% APP13007 QID	
Dose (mg/eye/day)	0		0		0.05		0.1		0.2	
Sex	M	F	M	F	M	F	M	F	M	F
Hematology										
Erythrocyte Count (10^6/µL)	6.511	6.347	6.620	6.414	6.527	5.994	6.273	5.734*	5.836**	5.526**
Hemoglobin Concentration (g/dL)	13.71	13.51	14.11	13.87	13.77	12.61	13.01	12.43*	12.69*	11.87**
Hematocrit (%)	41.84	41.76	42.61	42.67	41.83	39.11	40.24	38.64	39.54	36.83**
Leukocyte Count (10^3/µL)	6.327	5.729	6.811	6.964	4.269**	4.316	3.320**	3.411*	3.131**	2.824**
Lymphocyte Count (10^3/µL)	4.497	4.306	5.014	4.984	2.554**	2.533	1.983**	1.929*	1.771**	1.489**
Eosinophil Count (10^3/µL)	0.091	0.103	0.081	0.110	0.044	0.051	0.029**	0.030**	0.023**	0.021**
Basophil Count (10^3/µL)	0.401	0.349	0.333	0.409	0.226**	0.269	0.157**	0.160**	0.159**	0.127**
Mean Corpuscular Volume (fL)	64.29	65.83	64.36	66.53	64.17	65.37	64.20	67.36	67.77**	66.67
Reticulocyte Ratio (%)	4.13	4.16	3.39	4.34	3.91	4.59	4.53	4.71	5.49**	5.64*
Coagulation										
Activated Partial Thromboplastin Time (s)	18.83	20.27	19.17	21.33	14.51**	15.10**	13.93**	16.23**	14.27**	16.91**

Source: Excerpt from NDA Table 2.6.7.7A, Module 2.6.7. Toxicology Tabulated Summary

Statistically significantly low leukocyte count in high-dose females and low lymphocyte counts at all doses in females were still observed on Day 25 of recovery.

Clinical Chemistry (Pretreatment and once on Day 9 of dosing and Day 25 of recovery)

Compared to the saline control, several parameters were affected (Table 12). Statistically significant increases in mean globulin (12% to 17%) and glucose (9% to 12%) were noted in females in all test article-treated groups, without a dose response. In males, mean glucose showed a statistically significant increase in the low-dose (12%) and mid-dose (11%) only. There was a 9% increase in mean glucose at the high dose, without statistical significance. These findings were not considered test article-related in the Study Report. However, despite the lack of a dose response, based on the known effects of glucocorticoids in glucose levels, this reviewer believes that a test-article related effect cannot be totally ruled out. No significant changes were observed between saline and vehicle control in any parameter. The changes were not observed at recovery.

Table 12: Mean Clinical Chemistry Changes – 2-Week Ocular Toxicity Rabbit Study

Test Material	Saline QID		Vehicle QID		0.1% APP13007 QD		0.1% APP13007 BID		0.1% APP13007 QID	
Dose (mg/eye/day)	0		0		0.05		0.1		0.2	
Sex	M	F	M	F	M	F	M	F	M	F
Blood Chemistry										
Alkaline Phosphatase (IU/L)	582.0	504.9	523.9	491.6	246.9**	193.1*	199.7**	176.1**	194.3**	242.9**
Alanine Transaminase (IU/L)	35.9	33.3	40.4	35.7	70.9**	94.9**	37.7	92.9*	53.7	74.9*
Total Protein (g/dL)	5.53	5.34	5.51	5.47	6.44**	6.40**	6.31**	6.27**	6.40**	6.19**
Triglyceride (mg/dL)	41.7	29.9	65.1	35.1	191.3	383.3	410.4**	648.1**	480.7**	848.6**
Total Cholesterol (mg/dL)	27.0	54.6	34.6	46.7	50.7*	59.7	69.0**	65.7	57.1**	75.0
Creatinine (mg/dL)	0.919	1.131	1.014	1.069	0.746*	0.670**	0.689**	0.739**	0.637**	0.627**
Inorganic Phosphorus (mg/dL)	6.623	6.610	6.850	6.673	5.101**	5.329	5.000**	4.879**	4.557**	4.393**
Chloride (mEq/L)	105.4	106.4	105.3	105.4	104.3	102.3**	104.4	103.0*	103.0	102.3**
Albumin Ratio (%)	79.09	79.40	79.31	79.61	79.63	79.69	79.23	79.96	80.40*	80.34
Gamma Globulin Ratio (%)	5.83	6.09	5.79	5.74	5.01*	5.13*	5.06*	5.03**	4.44**	4.33**
Albumin/Globulin	3.803	3.869	3.847	3.916	3.920	3.940	3.836	4.000	4.100*	4.096
Albumin (g/dL)	4.37	4.24	4.37	4.36	5.14**	5.11**	5.01**	5.01**	5.17**	4.96**

Source: Excerpt from NDA Table 2.6.7.7A, Module 2.6.7. Toxicology Tabulated Summary

Urinalysis (Pretreatment, Day 8 of dosing and Day 24 of recovery)

Compared to saline control, mean total excretion of sodium was statistically significantly higher in high-dose males and mid-dose and high-dose females on Day 8 (Table 13). Mean bilirubin and urobilinogen were increased in females in all test article dose groups on Day 8. The findings reversed during recovery. No significant changes were observed between saline and vehicle control.

Table 13: Mean Urinalysis Changes – 2-Week Ocular Toxicity Rabbit Study

Test Material	Saline QID		Vehicle QID		0.1% APP13007 QD		0.1% APP13007 BID		0.1% APP13007 QID	
Dose (mg/eye/day)	0		0		0.05		0.1		0.2	
Sex	M	F	M	F	M	F	M	F	M	F
Urinalysis (Mean)										
Sodium Excretion (mEq)	4.741	6.216	5.509	7.961	8.696	11.44	9.157	12.439*	11.276**	14.806**
Bilirubin (significantly different from saline)	-	-	-	-	*	*	-	*	-	*
Urobilinogen (significantly different from saline)	-	-	-	-	*	*	-	*	-	**

Source: Excerpt from NDA Table 2.6.7.7A, Module 2.6.7. Toxicology Tabulated Summary

Gross Pathology (Day after the end of dosing and recovery periods)

Test article-related changes were observed in the thymus, spleen, adrenal, liver, and kidney in males and/or females in test article-treated groups (Table 14).

Table 14: Necropsy Findings – 2-Week Ocular Toxicity Rabbit Study

Sex	Male					Female				
Group			APP13007_					APP13007_		
	0[1)]	0[2)]	0.1%			0[1)]	0[2)]	0.1%		
Dose (Frequency)	4	4	1	2	4	4	4	1	2	4
No. of animals	4	4	4	4	4	4	4	4	4	4
Spleen										
Small size	0	0	1	2	4	0	0	0	2	3
Thymus										
Small size	0	0	3	4	4	0	0	3	4	3
Liver										
Enlargement	0	0	0	0	0	0	0	0	1	2
Kidney										
Pale brown focus, left	0	0	0	0	1	0	0	0	0	0
Adrenal										
Small size, left/right	0	0	1	2	3	0	0	0	0	1

1) Physiological saline, 2) APP13007_Vehicle

Source: Study Report, page 43

At the end of the recovery period, yellowish brown focus in the liver was observed in 1 high-dose male. Pale brown focus in both kidneys was observed in 1 low-dose and 1 high-dose female.

Organ Weights (Adrenals, brain, epididymides, heart, kidneys, liver, lungs/bronchi, ovaries, pituitary, prostate, seminal vesicles, submandibular glands, spleen, testes, thymus, thyroid/parathyroids, and uterus)

Test article-related effects on organ weights (absolute and relative to body weight) included decreases in mean thymus, spleen, and adrenal weights, and increased mean liver and kidney weights (Table 15).

Table 15: Organ Weight Changes – 2-Week Ocular Toxicity Rabbit Study

Test Material	Saline QID		Vehicle QID		0.1% APP13007 QD		0.1% APP13007 BID		0.1% APP13007 QID	
Dose (mg/eye/day)	0		0		0.05		0.1		0.2	
Sex	M	F	M	F	M	F	M	F	M	F
Organ Weights (Absolute, Mean, g)										
Adrenal (Left)	0.088	0.083	0.088	0.075	0.055**	0.058	0.053**	0.060	0.045**	0.053*
Adrenal (Right)	0.075	0.068	0.080	0.073	0.048	0.053	0.045	0.055	0.040*	0.045*
Thymus	2.88	2.70	3.05	3.25	0.63**	0.65	0.43**	0.48*	0.63**	0.63
Spleen	1.73	1.58	1.35	1.18	0.78	1.00**	0.68	0.68**	0.53**	0.63**
Liver	55.48	55.35	65.18	55.70	71.30	86.05*	90.50**	99.93**	92.95**	111.28**
Kidney (Right and Left)	12.63	12.60	12.50	12.83	12.35	15.98*	14.73	14.28	14.60	14.85

Source: Excerpt from NDA Table 2.6.7.7A, Module 2.6.7. Toxicology Tabulated Summary

The brain showed decreases in mean absolute weight in mid and high-dose males and at all doses in females. No difference was noted when corrected by body weight. There was no histopathological correlate. Therefore, the finding was considered of no toxicological relevance.

All findings were reversible during recovery.

Histopathology

Adequate Battery: Yes

Peer Review: No

Test article-related changes were observed in the lymphatic organs (thymus, spleen, lymph node, lymphatic follicles in the cecum or Peyer's patch [ileum]), liver, kidney adrenals, skin, pancreas, and uterus at all dose levels (Table 16). Incidence and/or severity of changes in these organs were generally dosing frequency dependent.

Table 16: Histopathology Findings at End of Treatment – 2-Week Ocular Toxicity Rabbit Study

Sex	Male					Female				
Group			APP13007_					APP13007_		
	0[1)]	0[2)]	0.1%			0[1)]	0[2)]	0.1%		
Dose (Frequency)	4	4	1	2	4	4	4	1	2	4
No. of animals	4	4	4	4	4	4	4	4	4	4
Spleen										
Decrease, cellularity, lymphocyte, follicle(± - 2+)	0	0	4	4	4	0	0	3	4	4
Thymus										
Atrophy (+ - 2+)	0	0	4	4	4	0	0	4	4	4
Lymph node (mesenteric)										
Increase, cellularity, large lymphocyte (± - 2+)	0	0	4	4	4	0	0	4	4	4
Necrosis, lymphocyte (± - +)	0	0	0	2	4	0	0	1	1	3
Lymph node (submandibular, left)										
Decrease cellularity, lymphocyte (± - +)	0	0	2	3	4	0	0	2	2	3
Peyer's patch (ileum)										
Decrease, cellularity, lymphocyte (± - +)	0	0	3	4	4	0	0	0	2	4
Cecum										
Decrease, cellularity, lymphocyte, aggregated lymphatic follicle (± - +)	0	0	3	4	4	0	0	2	3	4
Liver										
Clear cell change, hepatocyte, centrilobular (± - 2+)	0	2	3	4	4	0	0	2	4	4
Hypertrophy, hepatocyte, centrilobular (± - 2+)	0	0	3	4	4	0	0	2	4	4
Kidney										
Dilatation, renal tubule (± - +)	0	0	1	1	2	1	0	1	2	2
Adrenal										
Atrophy, zona fasciculata/reticularis (± - +)	0	0	4	4	4	0	0	4	4	4
Elongation, cell cord, zona glomerulosa (± - +)	0	0	4	4	4	0	0	4	4	4
Eyelid (including palpebral conjunctiva)										
Thinning, epidermis, skin (±)	0	0	0	1	3	0	0	0	1	4
Skin (abdomen, left)										
Thinning epidermis(±)	0	0	1	2	2	0	0	0	1	2
Skin (back, interscapular)										
Thinning epidermis (±)	0	0	0	0	0	0	0	1	1	1
Pancreas										
Atrophy, acinus, focal (± - +)	0	0	0	1	1	0	0	2	2	2
Uterus (left)										
Hemorrhage, endometrium (± - +)	-	-	-	-	-	0	0	2	2	2

1) Physiological saline 2) APP13007_Vehicle ±: Very slight, +: Slight, 2+: Moderate,

Source: Study Report, page 48

Effects on the spleen, thymus, adrenal glands, pancreas, and uterus were not present at recovery. In general, findings present (Table 17) showed lower incidence and/or severity, indicating partial recovery. Slight hemorrhage in the endometrium was noted in one vehicle control animal at the end of the recovery period.

Table 17: Histopathology Findings at End of Recovery – 2-Week Ocular Toxicity Rabbit Study

Sex	Male					Female				
Group			APP13007_					APP13007_		
	0[1)]	0[2)]	0.1%			0[1)]	0[2)]	0.1%		
Dose (Frequency)	4	4	1	2	4	4	4	1	2	4
No. of animals	3	3	3	3	3	3	3	3	3	2
Lymph node (mesenteric)										
Increase, cellularity large lymphocyte cortex / medullary sinus (±)	0	0	0	0	0	0	0	0	0	1
Lymph node (submandibular, left)										
Decrease cellularity, lymphocyte (±)	0	0	0	0	0	0	0	0	0	1
Peyer's patch (ileum)										
Decrease, cellularity, lymphocyte (±)	0	0	1	0	1	0	0	0	1	0
Cecum										
Decrease, cellularity, lymphocyte, aggregated lymphatic follicle (±)	0	0	0	0	1	0	0	0	0	0
Liver										
Clear cell change, hepatocyte, centrilobular (±)	0	0	0	0	1	0	0	0	0	0
Hypertrophy, hepatocyte, centrilobular (±)	0	0	0	0	1	0	0	0	0	0
Inflammatory cell infiltration, centrilobular (± - +)	0	0	0	0	1	1	0	0	0	0
Necrosis, hepatocyte, centrilobular (± - +)	0	0	0	0	1	1	0	0	0	0
Kidney										
Dilatation, renal tubule (± - +)	0	0	0	0	1	0	0	2	2	1
Eyelid										
Thickning epidermis, skin (±)	0	0	0	0	1	0	0	0	0	0
Skin (abdomen, left)										
Thickenig, epidermis(+)	0	0	0	0	1	0	0	0	0	0
Skin (back, interscapular)										
Thickening epidermis (± - +)	0	0	2	1	3	0	0	1	0	1

1) Physiological saline 2) APP13007_Vehicle ±: Very slight, +: Slight, 2+: Moderate,

Source: Study Report, page 48

As with the clinical pathology findings, these histopathological findings were for the most part suggestive of corticosteroid class effects and generally demonstrated reversibility in this study. The Applicant stated that the observed effects in the pancreas and uterus are not generally expected following corticosteroid administration.

Toxicokinetics (Days 0 and 13; prior to the first dose of the day and then at 0.5, 1, 2, 4, and 8 hours after the last dose of the day)

Clobetasol propionate was present in plasma from all test article-treated groups (Table 18) and at all timepoints. C_{max} and $AUC_{0\text{-}8h}$ increased with increased dosing frequency. The T_{max} was observed at 0.5 hours (1st timepoint evaluated) following the last dose. C_{max} and $AUC_{0\text{-}8h}$ were higher on Day 13 compared to Day 1, i.e., accumulation with repeated dosing was observed. There were no significant sex differences.

Table 18: Mean Toxicokinetic Parameters - 2-Week Ocular Toxicity Rabbit Study

Group/ Treatment	Day	C_{max} (ng/mL)*		t_{max} (h)*		AUC_{0-8h} (h*ng/mL)	
		Male	Female	Male	Female	Male	Female
3 (0.1% APP13007 QD	0	0.3537	0.5870	0.5	0.5	0.3624	0.5480
	13	1.038	1.075	0.5	0.5	2.211	1.907
4 (0.1% APP13007 BID)	0	0.5445	1.081	0.5	0.5	1.504	2.459
	13	1.431	1.340	0.7	0.5	3.783	3.714
5 (0.1% APP13007 QID)	0	2.115	2.573	0.5	0.5	4.960	5.972
	13	3.170	3.467	0.5	0.5	7.603	8.733

*: t_{max} is the first sampling time, i.e., 0.5 hour post dose.

Source: Table 32, Module 2.6.4 Pharmacokinetics Written Summary

Dosing Solution Analysis

The test and vehicle control articles were used as supplied. Dosing solution stability was confirmed for up to 6 months (data submitted to IND 128133 SDN 8, 2-7-2020, Module 1.11.1).

Study title: A 4-Week Repeat-Dose Topical Ocular Toxicity Study of APP13007 (Clobetasol Propionate Ophthalmic Nanosuspension) with a 4-Week Recovery Period in New Zealand White Rabbits

Study no.: APP13007-TOX-001; 74176B

Study report location: Module 4.2.3.2 \\CDSESUB1\EVSPROD\nda218158\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\app13007-tox-001\app13007-tox-001.pdf

Conducting laboratory and location: (b) (4)

Date of study initiation: September 17, 2018

GLP compliance: Y

QA statement: Y

Drug, lot #, and % purity: 0.05% APP13007 (Clobetasol Propionate Ophthalmic Nanosuspension), lot # CPEOS180904, 96.5% pure

0.1% APP13007 (Clobetasol Propionate Ophthalmic Nanosuspension), lot # CPEOS180828, 90.8% pure

The formulation used in this study is consistent with the clinical formulations that were used in the clinical studies, including CPN-201, and the pivotal Phase 3 studies, CPN-301 and CPN-302.

The 0.05% formulation is identical to the commercial formulation except for a glycerin content of (b) (4) in the commercial formulation.

Key Study Findings

- There were no adverse ocular findings at any dose in any ophthalmic endpoint including ophthalmic exams, ocular histopathology, IOP, and ERG.
- Despite the low systemic exposure (C_{max} 0.94 to 3.14 ng/mL), a variety of drug class-related (glucocorticoid) systemic effects were observed.
- These included hematological, clinical chemistry, organ weight changes, and gross and microscopic findings.
- Test article-related microscopic findings were observed in the kidneys, liver, heart, thymus, spleen, adrenals, and mandibular lymph node. The overall severity ranged from minimal to moderate. The findings were mostly reversible.
- The ocular NOAEL was the high dose (0.1% APP13007 BID or 0.1 mg/eye/day).
- A systemic NOAEL was not determined.

Methods

Doses:	0 (placebo vehicle or saline), 0.05% 2X/day and 0.1% 2X/day (0, 0.05 and 0.1 mg/eye/day, respectively) Placebo vehicle and the test article were administered to the left eye only; saline (0.9% sodium chloride for injection) was administered to the right eye of placebo vehicle control animals; the right eye of test article-treated animals was untreated.
Frequency of dosing:	2X daily for 28 days (8 hours ± 30 minutes apart)
Route of administration:	Topical ocular into the conjunctival sac
Dose volume:	50 µL
Formulation/Vehicle:	APP13007 Vehicle
Species/Strain:	New Zealand White Rabbit
Number/Sex/Group:	7/sex/group

	Note: Three rabbits/sex/group were maintained for a 4-week recovery period.
Age:	Approx. 4 months
Weight:	Males: 2.8 to 3.2 kg; females: 2.7 to 3.4 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	None with an impact on data interpretation

Observations and Results

Mortality (2x/day)

None

Clinical Signs (Daily; detailed clinical examination 2x/week)

No test article-related effects

Body Weights (Weekly)

A statistically significant decrease in mean body weight was noted in males at both test article groups (12 to 17% in the low dose; 8 to 11% at the high dose) throughout recovery (Day 35 to Day 56). The decrease was not dose related. Contrary to this observation, there were no significant changes in mean body weight gain during recovery in males. However, the overall body weight gain from treatment Day -1 to 28 was decreased (67% at the high dose [statistically significant] and 33% at the low dose [not statistically significant]) and could have affected body weight during recovery. The Applicant considered the decrease was related to normal variation range. Because the decreased was present at recovery, a definite relationship to the test article is difficult to establish.

Feed Consumption (Daily)

During treatment, food consumption was statistically significantly higher in both test article-treated groups in males and females at multiple timepoints. A dose-relationship was generally observed in females. During recovery, lower mean food consumption was generally observed in males and females in both test article-treated groups with statistical significance observed at some timepoints. This lower mean consumption is consistent with decreased body weights seen at recovery in males. The Applicant considered the values were within normal biological variation.

Ophthalmoscopy (Slit lamp biomicroscopy with Hackett-McDonald scoring and indirect ophthalmoscopy; once pretreatment, and ~2 hours ± 30 minutes post first daily dose on Days 1, 7, 14, 21, 28, 42 and 56)

Minor conjunctival congestion (hyperemia) was observed across groups (saline, placebo vehicle, non-treated, and APP13007 treated eyes). The severity in most eyes was graded very slight or slight. The finding was considered unrelated to the test article.

Corneal Fluorescein Staining (Once pretreatment, and ~2 hours ± 30 minutes post second daily dose on Days 14, 28, and 56)

No test article-related effects

Tonometry (Pretreatment and once prior to the first daily dose on Days 7, 14, 28, 42 and 56)

No test article-related effects

Electroretinography (ERG) (Once pretreatment and towards the end of the treatment [between Day 26 and 27] and recovery period [between Day 53 and 55]; dark-adapted animals)

The data showed no test article-related effects. The presentation of the data was limited to the results from the low intensity (I=5) and high intensity (I=1) stimuli.

Reviewer's comments: *The description of the ERG procedure states: "Animals were dark-adapted for at least 2 hours. Typical unprocessed, dark-adapted ERGs were obtained at up to five stimulus intensities increasing in 1 log unit increments from Intensity 5 (bottom, dimmest) up to Intensity 1 (top, brightest). Stimuli were presented in order of increasing intensity. The ERGs at Intensity 5 and Intensity 1 were designated as the 'standard' responses for quantitative analysis." For both stimuli conditions parameters included a-wave and b-wave amplitude, time to peak, and slope and A/B ratio. However, because only 2 stimuli were analyzed, it was not clear if this was a proper assessment of test article-related effects.*

An Information Request was sent to the Applicant for clarification following review of the Study Report under the initial IND. The response was received under IND 128133 SDN 8, 2-7-2020, Module 1.11.1. The Applicant's electroretinographer explained that all five responses are quantitatively measured but only the data for the lowest and highest intensity values were included in the study report as they have been found to be the most relevant for diagnosis of retinal dysfunction in this protocol.

As no adverse retinal effects were noted microscopically and no other ocular endpoint was affected, the response was considered acceptable. See SDN 8/SDN 13 EoP2 nonclinical review filed in DARRTS on 8-24-2020 (Rivera MI) for further details.

Hematology and Coagulation (Prior to start of treatment [Day -8 to -6] and at the end of treatment period [Day 29] and recovery period [Day 57])

At Day 29, there was a statistically significant decrease in mean erythroid cells (RBC count, hemoglobin, and hematocrit) and leukocytes (WBC count, neutrophils, lymphocytes, and/or monocytes) (Table 19). Males showed the erythroid changes in both test article-treated groups, while females showed the decrease at the high dose only. Decreased lymphocyte counts were observed at both test article dose levels and are consistent with corticosteroid effects on the lymphoid system.

Table 19: Mean Hematological Changes – 4-Week Ocular Toxicity Rabbit Study

Day: 29 Relative to Start Date

Sex: Male		RBC (10^12/L) [g]	HGB (g/L) [g]	HCT (L/L) [g1]
Group 1 0 mg/eye/day	Mean	6.82	141	0.41
	SD	0.299	6.0	0.021
	N	7	7	7
Group 2 0.05 mg/eye/day	Mean	6.07 ***	130 **	0.38 **
	SD	0.255	6.7	0.025
	N	7	7	7
Group 3 0.1 mg/eye/day	Mean	6.03 ***	129 **	0.37 **
	SD	0.387	6.2	0.017
	N	7	7	7

Day: 29 Relative to Start Date

Sex: Male		WBC (10^9/L) [g]	R-NEUT (10^9/L) [g]	R-LYMPH (10^9/L) [g1]	R-MONO (10^9/L) [g2]
Group 1 0 mg/eye/day	Mean	7.00	2.25	4.34	0.41
	SD	1.036	0.375	0.947	0.103
	N	7	7	7	7
Group 2 0.05 mg/eye/day	Mean	4.33 ***	2.54	1.58 ***	0.21 ***
	SD	0.738	0.661	0.248	0.055
	N	7	7	7	7
Group 3 0.1 mg/eye/day	Mean	3.21 ***	2.09	1.00 ***	0.11 ***
	SD	0.667	0.436	0.364	0.020
	N	7	7	7	7

Day: 29 Relative to Start Date

Sex: Female		RBC (10^12/L) [g]	HGB (g/L) [g]	HCT (L/L) [g]
Group 1 0 mg/eye/day	Mean	6.30	132	0.38
	SD	0.328	5.9	0.014
	N	7	7	7
Group 2 0.05 mg/eye/day	Mean	5.87	125	0.36
	SD	0.343	7.8	0.020
	N	7	7	7
Group 3 0.1 mg/eye/day	Mean	5.56 *	119 *	0.34 **
	SD	0.603	9.5	0.028
	N	7	7	7

Day: 29 Relative to Start Date

Sex: Female		WBC (10^9/L) [g]	R-NEUT (10^9/L) [g1]	R-LYMPH (10^9/L) [g]	R-MONO (10^9/L) [g1]
Group 1 0 mg/eye/day	Mean	7.52	2.83	4.40	0.27
	SD	1.442	0.497	1.335	0.055
	N	7	7	7	7
Group 2 0.05 mg/eye/day	Mean	3.41 ***	2.10 *	1.19 ***	0.12 ***
	SD	0.603	0.515	0.500	0.019
	N	7	7	7	7
Group 3 0.1 mg/eye/day	Mean	2.91 ***	2.01 *	0.79 ***	0.11 ***
	SD	0.556	0.468	0.239	0.042
	N	7	7	7	7

[g] - Anova & Dunnett: * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$
[g1] - Kruskal-Wallis & Dunnett on Ranks
[g2] - Anova & Dunnett(Log): *** = $p < 0.001$
Source: Excerpts from Study Report Table 4 Hematology Summary of Means

These changes showed complete or partial reversibility at the end of the 4-week recovery period (Day 57). Mean hemoglobin at both doses in males, mean lymphocytes and monocytes at both doses in females, and mean WBC in high-dose females showed statistically significant lower values. However, the mean values were generally comparable to baseline values.

A statistically significant decrease in mean PT was observed at both the low and high dose in males (16.2% and 11.8%, respectively) and females (11.8% and 14.5%, respectively) on Day 29; mean APTT was increased (35.8%) in females. These changes were reversible (not observed at the end of the recovery period).

Clinical Chemistry (Prior to start of treatment [Day -8 to -6] and at the end of treatment period [Day 29] and recovery period [Day 57])

The mean value of several parameters showed a statistically significant change at both test article dose levels in both males and females (Tables 20 and 21). These changes were reversible (not observed at the end of the recovery period).

Table 20: Mean Clinical Chemistry Changes in Males – 4-Week Ocular Toxicity Rabbit Study

Day: 29 Relative to Start Date

Sex: Male					Clinical Chemistry					
		R-A/G	R-ALB	R-GLOB	ALT	ALP	AST	CA	CL	CHOL
			(g/L)	(g/L)	(U/L)	(U/L)	(U/L)	(mmol/L)	(mmol/L)	(mmol/L)
		[g]	[g1]	[g1]	[g2]	[g1]	[g2]	[g1]	[g1]	[g]
Group 1	Mean	1.0	28	28	36	105	20	3.59	102	1.06
0	SD	0.03	1.0	1.3	13.0	35.9	8.2	0.331	1.4	0.520
mg/eye/day	N	7	7	7	7	7	7	7	7	7
Group 2	Mean	1.0	35 ***	34 ***	70 *	129	39	3.72	99 *	2.53 ***
0.05	SD	0.09	1.9	2.6	25.7	43.8	24.2	0.279	3.5	0.543
mg/eye/day	N	7	7	7	7	7	7	7	7	7
Group 3	Mean	1.1 **	36 ***	33 ***	124 **	111	61 *	3.98	98 *	2.19 **
0.1	SD	0.05	1.7	1.8	112.6	86.1	57.4	0.403	2.8	0.471
mg/eye/day	N	7	7	7	7	7	7	7	7	7

Sex: Male		Clinical Chemistry								
		CK	CRE	GLUC	PHOS	K	NA	T-BIL	TP	TRIG
		(U/L)	(µmol/L)	(mmol/L)	(mmol/L)	(mmol/L)	(mmol/L)	(µmol/L)	(g/L)	(mmol/L)
		[g]	[g1]	[g2]	[g1]	[g1]	[g1]		[g1]	[g]
Group 1	Mean	4256	91	6.5	1.99	4.3	142	1.7	56	0.59
0	SD	4522.6	15.0	0.13	0.239	0.71	1.5	-	2.2	0.136
mg/eye/day	N	7	7	7	7	7	7	1	7	7
Group 2	Mean	2540	58 ***	6.6	1.85	3.9	142	-	69 ***	8.39 ***
0.05	SD	1860.7	7.5	0.51	0.351	0.48	2.7	-	3.4	3.624
mg/eye/day	N	7	7	7	7	7	7	0	7	7
Group 3	Mean	2037	58 ***	7.0 *	1.89	4.2	143	-	69 ***	6.73 ***
0.1	SD	1509.4	6.4	0.36	0.177	0.62	2.6	-	3.1	3.346
mg/eye/day	N	7	7	7	7	7	7	0	7	7

[g] - Kruskal-Wallis & Dunnett on Ranks: ** = $p < 0.01$; *** = $p < 0.001$
[g1] - Anova & Dunnett: * = $p < 0.05$; *** = $p < 0.001$
[g2] - Anova & Dunnett (Log): * = $p < 0.05$; ** = $p < 0.01$
Source: Excerpts from Study Report Table 6 Clinical Chemistry Summary of Means

Table 21: Mean Clinical Chemistry Changes in Females – 4-Week Ocular Toxicity Rabbit Study

Day: 29 Relative to Start Date

Sex: Female					Clinical Chemistry					
		R-A/G	R-ALB (g/L)	R-GLOB (g/L)	ALT (U/L)	ALP (U/L)	AST (U/L)	CA (mmol/L)	CL (mmol/L)	CHOL (mmol/L)
		[g]	[g]	[g]	[g1]	[g1]	[g]	[g2]	[g]	[g1]
Group 1	Mean	1.0	29	28	35	67	18	3.86	102	1.71
0	SD	0.05	1.3	1.2	8.2	19.9	4.5	0.250	1.0	0.219
mg/eye/day	N	7	7	7	7	7	7	7	7	7
Group 2	Mean	1.1	39 ***	36 ***	72 **	88	36 **	4.15	97 ***	1.89
0.05	SD	0.05	1.3	1.7	27.0	71.5	10.8	0.317	2.7	0.741
mg/eye/day	N	7	7	7	7	7	7	7	7	7
Group 3	Mean	1.1	37 ***	35 ***	94 ***	74	33 *	3.89	100	1.39
0.1	SD	0.06	1.3	2.3	42.1	45.9	10.8	0.286	1.6	0.406
mg/eye/day	N	7	7	7	7	7	7	7	7	7

Sex: Female		Clinical Chemistry								
		CK (U/L)	CRE (µmol/L)	GLUC (mmol/L)	PHOS (mmol/L)	K (mmol/L)	NA (mmol/L)	T-BIL (µmol/L)	TP (g/L)	TRIG (mmol/L)
		[g]	[g]	[g1]	[g1]	[g1]	[g1]		[g1]	[g2]
Group 1	Mean	3442	120	6.5	2.02	4.1	143	-	57	0.56
0	SD	3604.4	22.9	0.34	0.382	0.52	2.8	-	2.1	0.123
mg/eye/day	N	7	7	7	7	7	7	0	7	7
Group 2	Mean	2435	77 ***	6.8 *	2.03	4.1	144	-	74 ***	6.82 ***
0.05	SD	1818.2	12.3	0.15	0.412	0.57	2.2	-	2.5	5.186
mg/eye/day	N	7	7	7	7	7	7	0	7	7
Group 3	Mean	2271	61 ***	7.3 ***	1.69	3.9	144	-	73 ***	7.28 ***
0.1	SD	2150.9	6.4	0.26	0.333	0.43	3.0	-	3.2	2.113
mg/eye/day	N	7	7	7	7	7	7	0	7	7

Sex: Female		Clinical Chemistry	
		UREA (mmol/L)	UREAN (mg/dL)
		[g]	[g]
Group 1	Mean	8.9	25
0	SD	3.24	9.1
mg/eye/day	N	7	7
Group 2	Mean	12.9 *	36 *
0.05	SD	3.45	9.7
mg/eye/day	N	7	7
Group 3	Mean	10.5	29
0.1	SD	1.68	4.7
mg/eye/day	N	7	7

[g] - Kruskal-Wallis & Dunnett on Ranks: ** = $p < 0.01$; *** = $p < 0.001$
[g1] - Anova & Dunnett: * = $p < 0.05$; *** = $p < 0.001$
[g2] - Anova & Dunnett(Log): * = $p < 0.05$; ** = $p < 0.01$
Source: Excerpts from Study Report Table 6 Clinical Chemistry Summary of Means

Analytes related to liver function, i.e., alanine aminotransferase (ALT), aspartate aminotransferase (AST), cholesterol (CHOL), triglycerides (TRIG), and glucose (GLUC), showed mild to moderate increases which correlated with the microscopic findings noted in the liver. As noted in the study report, these were considered typical class effects and

generally due to enzyme induction, altered lipid metabolism, and gluconeogenesis/ glycogenolysis.

Gross Pathology (Day 29 [main animals] and Day 57 [recovery animals])

Enlargement and/or pale discoloration of the liver were noted in one low dose male and two high dose females. These findings correlated with increased liver weights and microscopic findings of increased glycogen, consistent with corticosteroid hepatopathy. The findings were not observed in recovery animals.

Organ Weights (Adrenals, brain, eyes [with bulbar conjunctiva and optic nerve], heart, kidneys, liver, lungs [with trachea], ovaries, pituitary, prostate, mandibular salivary gland, spleen, testes, thyroid/parathyroids, and uterus)

Test article-related differences in mean organ weights were observed in kidney, liver, heart, thymus, spleen, and adrenal weights (absolute and relative to body weight) at the low and/or high dose at main necropsy (Table 22 A). At recovery necropsy, statistically significant differences were observed in the liver, heart, and adrenal weights in animals at the low and/or high dose (Table 23 B). There were macroscopic (liver) and/or microscopic correlates for these organ weight changes (see below).

Table 22: Changes in Mean Organ Weight - 4-Week Ocular Toxicity Rabbit Study

A. Main Necropsy (Day 29)

		APP13007					
	Sex	Males			Females		
	Dose Level (% twice daily)	0	0.05	0.1	0	0.05	0.1
Kidney							
	Absolute Weight (g)	15.208	**21.416***	**19.560***	14.656	**17.861**	**16.582**
	Body Weight Ratio (%)	0.4997	**0.6950***	**0.6799***	0.4883	**0.6049**	**0.5333**
Liver							
	Absolute Weight (g)	64.843	**142.138***	**134.350***	59.911	**104.680***	**125.774***
	Body Weight Ratio (%)	2.1266	**4.6347***	**4.6616***	1.9986	**3.5244***	**4.0720***
Heart							
	Absolute Weight (g)	6.697	7.392	**8.146**	6.195	**7.264**	**7.634**
	Body Weight Ratio (%)	0.2199	0.2409	**0.2835***	0.2066	**0.2453**	**0.2473**
Thymus							
	Absolute Weight (g)	2.415	2.713	**1.842**	3.234	**2.033**	**2.813**
	Body Weight Ratio (%)	0.0795	0.0875	**0.0643**	0.1066	**0.0686**	**0.0898**
Spleen							
	Absolute Weight (g)	0.933	0.969	**0.762**	1.282	**0.869**	**0.606***
	Body Weight Ratio (%)	0.0309	0.0321	**0.0265**	0.0428	**0.0293**	**0.0199***
Adrenal							
	Absolute Weight (g)	0.211	0.244	**0.162**	0.252	**0.165***	**0.135***
	Body Weight Ratio (%)	0.0070	0.0081	**0.0056**	0.0084	**0.0056***	**0.0044***

* = Statistically significant difference (absolute or relative) compared to respective control mean value.
Bolded values are considered to be test item-related and different from concurrent controls.

Source: Study Report, page 37

B. Recovery Necropsy (Day 57)

		APP13007					
	Sex	Males			Females		
	Dose Level (% twice daily)	0	0.05	0.1	0	0.05	0.1
Liver							
	Absolute Weight (g)	73.701	67.920	**57.357***	50.553	60.206	68.105
	Body Weight Ratio (%)	2.0690	2.1736	**1.7445**	1.5181	1.8300	1.9930
Heart							
	Absolute Weight (g)	7.308	6.781	**8.047**	6.055	**6.946***	**7.105***
	Body Weight Ratio (%)	0.2048	0.2165	**0.2429**	0.1820	**0.2113**	**0.2108**
Adrenal							
	Absolute Weight (g)	0.431	**0.318**	**0.321**	0.412	**0.219***	**0.248***
	Body Weight Ratio (%)	0.0121	**0.0102**	**0.0097**	0.0123	**0.0066***	**0.0073***

* = Statistically significant difference (absolute or relative) compared to respective control mean value.
Bolded values are considered to be test item-related and different from concurrent controls.

Source: Study Report, page 37

Histopathology

Adequate Battery: Yes

Peer Review: No

Test item-related microscopic findings were observed in the kidneys, liver, heart, thymus, spleen, adrenals, and mandibular lymph node (Table 23).

The microscopic findings were considered related to the pharmacological activity. The following is an excerpt from the Study Report:

"The kidney findings observed were considered adverse, but were due to a unique sensitivity of the rabbit to corticosteroids. Kidney findings were considered adverse because they were indicators of glomerular injury, which is the initial injury associated with corticosteroid nephropathy in rabbits. The increased glycogen in the liver with discoloration, enlargement, and increased weights are typical of a corticosteroid hepatopathy and is a pharmacologic effect of corticosteroid systemic exposure. Similarly, the increased glycogen in the heart was due to accumulation of glycogen in myofibers as a pharmacologic effect of corticosteroid systemic exposure. Thymus and spleen decreased cellularity and decreased weights were consistent with corticosteroid effects on the immune system. The adrenal cortical atrophy and decreased weights were consistent with negative feedback on the pituitary due to systemic corticosteroid exposure and reduced action of adrenocorticotrophic hormone (ACTH) on the adrenal cortex."

Table 23: Microscopic Findings - 4-Week Ocular Toxicity Rabbit Study

A. Main Necropsy (Day 29)

	APP13007					
Sex	Males			Females		
Dose Level (% twice daily)	0	0.05	0.1	0	0.05	0.1
Number Examined	4	4	4	4	4	4
Kidneys						
Casts, protein						
Minimal	0	1	0	0	2	3
Mild	0	0	0	0	0	1
Mineralization, tubular						
Minimal	0	0	0	0	0	2
Mild	0	1	0	0	0	0
Liver (2 lobes)						
Increased glycogen						
Minimal	0	0	1	0	2	0
Mild	0	2	0	0	1	2
Moderate	0	2	1	0	1	1
Marked	0	0	2	0	0	0
Heart						
Increased glycogen						
Minimal	0	1	2	0	2	2
Mild	0	2	1	0	2	0
Thymus						
Cellularity decreased						
Marked	0	4	4	0	4	4
Spleen						
Cellularity decreased, white pulp						
Mild	0	4	4	0	4	3
Adrenals						
Atrophy, cortex						
Minimal	0	1	0	0	2	2
Moderate	0	3	3	0	1	2
Lymph node, mandibular						
Number Examined	4	3	2	4	3	3
Cellularity decreased						
Mild	0	0	1	0	0	0

B. Recovery Necropsy (Day 57)

	APP13007					
Sex	Males			Females		
Dose Level (% twice daily)	0	0.05	0.1	0	0.05	0.1
Number Examined	3	3	3	3	3	3
Kidneys						
Mineralization, tubular						
Minimal	0	0	0	0	0	1
Liver (2 lobes)						
Vacuolation, hepatocellular, midzonal						
Minimal	0	0	0	0	0	1
Mild	0	0	0	0	0	2

Source: Study Report, page 40 and 41

Toxicokinetics (Day 1: 0.25, 0.50, 1, 2, 4 and 8 hours post first daily dose and 0.25-hour post second daily dose; Day 28: predose (prior to first daily dose), 0.25, 0.50, 1, 2, 4 and 8 hours [immediately prior to second dose] post first daily dose and 0.25-hour post daily second dose (i.e., 8.25 hr after the first dose)

Clobetasol propionate was observed in plasma following topical ocular administration at 0.05% BID and 0.1% BID (Table 24). The mean T_{max} value was slightly prolonged on Day 28 compared to Day 1. On Day 1, plasma clobetasol propionate concentrations were quantifiable up to 3.57 and 5.16 hours after the first dose of 0.05% and 0.1% APP13007, respectively. On Day 28, plasma clobetasol propionate concentrations were quantifiable for a slightly longer period than that on Day 1, up to 7.14 and 8.00 hours postdose for the 0.05% and 0.1% dose groups, respectively.

Mean C_{max} values (males and females combined) after the first dose on Day 28 were about 2X and 2.4X higher than that on Day 1 for the low and high dose, respectively. The mean AUC_{0-8h} value on Day 28 was about 3.3 X and 2.7X higher than that on Day 1 for the low and high-dose, respectively. Overall, there was no clear dose-related increase in the systemic exposure (as determined by mean AUC values) to clobetasol propionate on Day 1 or Day 28. There were no apparent sex-related differences.

Table 24: Clobetasol Mean Toxicokinetic Parameters - 4-Week Ocular Toxicity Rabbit Study

Group/ Treatment	Sex	Parameter	t_{max} (h)	C_{max} (ng/mL)	AUC_{0-8h} (h*ng/mL)	C_{max2}[1] (ng/mL)
Day 1						
2 (0.05% BID)	M+F	Mean	0.86	1.04	1.66	0.94
		SD	1.34	0.23	1.02	0.32
		n	14	14	13	14
3 (0.1% BID)	M+F	Mean	0.36	1.29	1.93	1.03
		SD	0.15	0.44	0.67	0.96
		n	14	14	12	14
Day 28						
2 (0.05% BID)	M+F	Mean	1.11	2.13	5.45	1.19
		SD	1.57	1.11	4.11	0.52
		n	14	14	12	14
3 (0.1% BID)	M+F	Mean	0.66	3.14	5.29	1.63
		SD	1.07	2.04	1.73	0.38
		n	14	14	14	14

[1] $C_{max,2}$ after the second dose of the day.

Source: Table 36, Module 2.6.4 Pharmacokinetics Written Summary

A 7-Day Ocular Toxicity Study of Clobetasol in Rabbits (Study # (b) (4) 245-032; Non-GLP; Module 4.2.3.2)

Reviewer's comments: *This non-GLP study shows that doses up to 0.1% 10X/day (0.5 mg/day) for 7 days were well tolerated. This dose is 10X the intended marketing dose of 0.05 mg/day (0.05% BID), although with the caveat that the study duration was shorter than that intended for marketing. The study was reviewed under the initial IND.*

Japanese white rabbits (Kbl:JW), 3 males per group, received daily ocular surface instillation of 50 µL of 0.025%, 0.05%, or 0.1% APP13007 to the left eye only at a frequency of 10X daily (~ 30 min apart) for 7 days. Physiological saline or APP13007 vehicle control animals received daily ocular surface instillation of 50 µL to the left eye 10X daily. A separate set of animals (including all dose levels) was designated for assessment of changes in IOP only. Ocular toxicity endpoints included slit lamp biomicroscopy with Draize scoring and corneal fluorescein staining, assessment of nictitation frequency, and IOP (prior to the start of dosing, and then twice daily [before the first and after the last administration]). Clinical signs and effects on body weight were also evaluated.

Main Findings:

- No adverse test article-related effects were observed in any ocular parameter, clinical signs, or body weight.
- The ocular NOAEL was 0.1% 10X/day.
- The systemic NOAEL was not determined; limited systemic toxicity parameters (i.e., body weight and clinical signs) were included precluding adequate safety assessment.

7 Genetic Toxicology

No genotoxicity studies were conducted by the Applicant. The Applicant is relying on the mutagenicity information reported in the label for the LD (Temovate® Ointment, 0.05%).

8 Carcinogenicity

No carcinogenicity studies were conducted by the Applicant. The Applicant is relying on the label information from the LD (Temovate® Ointment, 0.05%).

As noted by the Applicant, APP13007 is unlikely to pose a carcinogenic risk to human subjects because it does not pose a genotoxic hazard, patients will use APP13007 for only 14 days, and systemic concentrations of clobetasol propionate are low following topical ocular administration of APP13007.

9 Reproductive and Developmental Toxicology

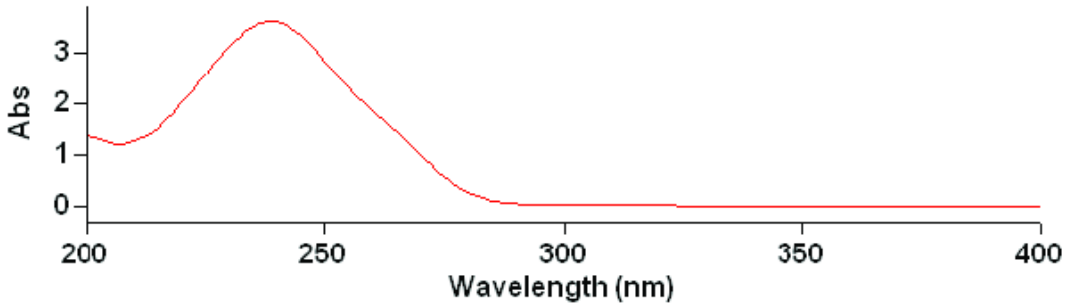
No reproductive and developmental toxicity studies were conducted by the Applicant. The Applicant is relying on the label information from the LD (Temovate® Ointment, 0.05%).

10 Special Toxicology Studies

No phototoxicity studies of APP13007 were conducted by the Applicant. The Applicant stated that the phototoxic potential of clobetasol propionate is not described in the literature or in the package insert for Temovate® or other clobetasol propionate containing products. The Applicant also stated that the phototoxicity potential of APP13007 is not expected to differ from that of the LD.

Per information found online by this reviewer, clobetasol propionate maximum absorption occurs at 239 nm in ethanol[1] and 240 nm in distilled water[2]. The absorption spectra in ethanol and water are shown in the figures below. The molar absorptivity is above 1,000 L mol^{-1} cm^{-1} (i.e., 1.35 X 10^4 L mol^{-1} cm^{-1}). The cornea absorbs wavelengths of < 300 nM before it reaches the lens. Based on clobetasol absorption spectrum, the main target of clobetasol is expected to be the cornea. Findings consistent with phototoxicity were not observed in the ocular toxicology studies or reported in the clinical trials conducted for the current NDA.

Figure 2: Absorption Spectrum of Clobetasol Propionate in Ethanol[4]

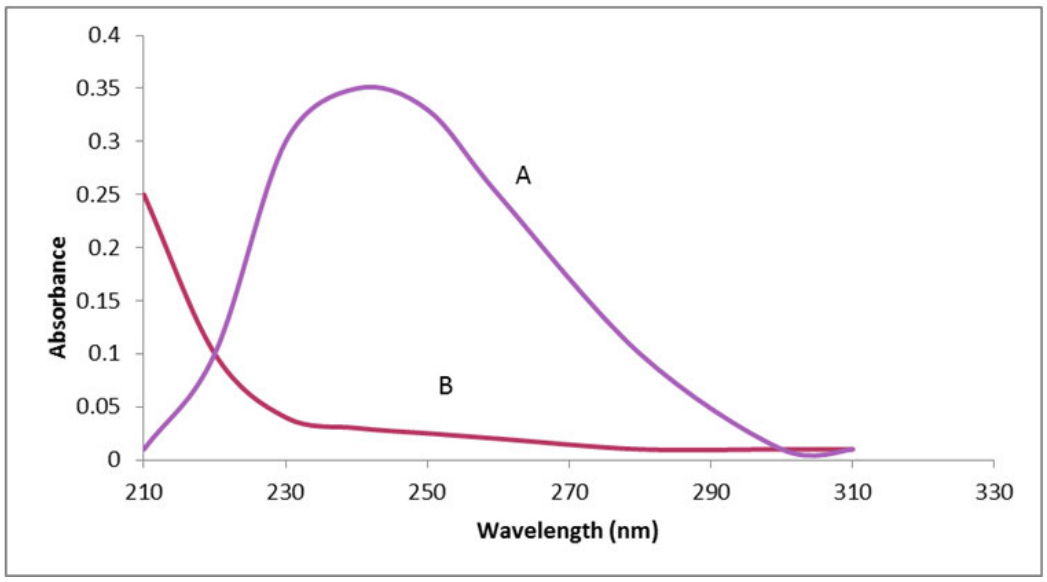


100 µg/mL clobetasol propionate against ethanol as a blank

[1] https://www.researchgate.net/publication/315014262_Development_and_Validation_of_UV_Spectrophotometric_Method_for_Quantitative_Estimation_of_Clobetasol_17-Propionate

[2] https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwjXm8jeoIqDAxV5FFkFHSi7ChEQFnoECBIQAQ&url=https%3A%2F%2Fjournals.indexcopernicus.com%2Fapi%2Ffile%2FviewByFileId%2F695580.pdf&usg=AOvVaw2eHBZlMdhBQELr9rvownbL&opi=89978449

Figure 3: Absorption Spectrum of Clobetasol Propionate in Water[5]



(A)10 µg/mL clobetasol propionate against blank (80:20 methanol: water)
(B) Blank against distilled water

11 Integrated Summary and Safety Evaluation

APP13007 (Clobetasol Propionate Ophthalmic Nanosuspension, 0.05%) contains the active compound clobetasol propionate, and is an eye-drop product of a nanosuspension (b) (4) nm particle size) prepared by dispersing nanomilled particles of clobetasol propionate with excipients in a preserved multi-dose aqueous formulation. The nanoparticles of clobetasol propionate in APP13007 are expected to efficiently penetrate the target tissues of the eye upon ocular surface instillation.

The ocular tissue distribution studies in rabbits showed good penetration of clobetasol propionate in the eye following ocular instillation of 1 drop of APP13007. The highest concentrations were observed in the cornea (mean C_{max} = 3240 ng/g), conjunctiva and iris/ciliary body and much lower concentrations in the lens, and posterior segment of the eye (retina/choroid/RPE, optic nerve, and vitreous).

Local ocular toxicity and systemic toxicity of APP13007 following ocular instillation were evaluated in the 2-week and 4-week GLP toxicology studies in albino rabbits. The clinical/Phase 3 formulation was used in the pivotal 4-week ocular toxicity study. An earlier formulation was used in the 2-week ocular toxicity study. Both nonclinical formulations differ in excipient content (Table 2).

No adverse ocular findings were observed in the pivotal rabbit ocular toxicity studies at APP13007 doses up to 0.1% BID (4-week study) and 0.1% QID (2-week study). In a non-GLP study, no adverse ocular effects were noted at doses up to 0.1% 10X/day (0.5 mg/day) for 7 days, with the caveat that the study duration was shorter than that intended for marketing. The ocular NOAEL was the high dose in all studies. Overall, the

ocular NOAEL provides adequate exposure margins to support the human safety of the intended (marketing) dosing regimen of 0.05% BID for 14 days (Table 25).

Table 25: Ocular Exposure Margins Based on NOAEL from Ocular Toxicology Studies

The ocular PK studies as well as the 14-day and 28-day ocular toxicity studies in the rabbit showed low systemic exposure after topical ocular instillation. Despite the low systemic exposure (C_{max} ≤3.47 ng/mL and $AUC_{0\text{-}8h}$ ≤8.73 ng•hr/mL on Day 13 in the 14-day study; C_{max} ≤3.17 ng/mL and $AUC_{0\text{-}8h}$ ≤5.58 ng•hr/mL on Day 28 in the 28-day study), there were systemic findings. The systemic findings were for the most part consistent with glucocorticoid class effects, and though adverse, were considered by the Applicant to be "*due to a unique sensitivity of the rabbit to corticosteroids*". Most findings showed complete or partial reversibility during the recovery period. A systemic NOAEL was not determined.

The key findings included the following:

- 14-day study: changes in hematology (decreased RBC and WBC parameters), coagulation (decreased activated partial thromboplastin time [APTT]), changes in clinical chemistry (increased globulin, glucose, alanine aminotransferase [ALT], total protein, cholesterol, triglyceride; decreased creatinine, inorganic phosphorous, and chloride, among others), and urinalysis (increased sodium excretion); effects in organ weights (decreased thymus, spleen and adrenal weights, and increased liver and kidney weights); histopathology findings of decreased cellularity in the lymph node (submandibular), spleen, Payer's patch (ileum), and cecum, atrophy in the adrenals, pancreas, and thymus, hepatocyte centrilobular hypertrophy, tubule dilation in the kidney, thinning of the skin, and hemorrhage in the uterus with severity ranging from minimal to moderate
- 28-day study: changes in hematology (decreased RBC and WBC parameters), coagulation (decreased prothrombin time and prolonged APTT), and clinical chemistry (increased albumin, globulin, total protein,

ALT, aspartate aminotransferase [AST], cholesterol, triglycerides, and glucose); effects in organ weights (increased kidney, liver, and heart weights, and decreased spleen and adrenal weights; histopathology findings in the kidneys (minimal to mild protein casts and tubular mineralization), liver (minimal to marked increased glycogen), heart (minimal to mild increased glycogen), thymus (decreased cellularity), spleen (decreased cellularity of the white pulp), adrenals (minimal to moderate atrophy of the adrenal cortex), and mandibular lymph node (mild decreased cellularity).

- In the 4-week study, minimal to mild protein casts and tubular mineralization were observed in the kidneys of low- and high-dose females, and low-dose (but not high-dose) male rabbits. The Applicant noted that these findings are consistent with the very early stages of corticosteroid-induced nephropathy, for which the rabbit is a uniquely sensitive species (Ogilvie 1965, Libretto 1995, Behrend 1997). However, the references cited do not particularly support the "unique renal sensitivity" statement.

The systemic exposure margins at the **low-observed-adverse-effect level (LOAEL)** are shown in the table below. As most human PK samples showed levels below LLOQ, the exposure margins are considered supportive of systemic safety.

Table 26: Systemic Exposure Margins Based on LOAEL from Pivotal Toxicology Studies

Nonclinical				Clinical Safety Margins[c] (Based on dose/plasma exposure)		
Species/ Duration	**LOAEL[a]**	**HED (mg/kg)**	**C_{max} (ng/mL)[b]**	**Dose 0.00083 mg/kg/day**	**Exposure at LLOQ (0.04 ng/mL)**	**Max exposure[d] (0.182 ng/mL)**
14-day rabbit study	(b) (4) QD (b) (4) mg/eye (b) (4) mg/kg	(b) (4)	1.057	7.8X	26X	5.8X
28-day rabbit study	(b) (4) BID (b) (4) mg/eye (b) (4) mg/kg	(b) (4)	2.13	6.5X	53X	11.7X

(a) Estimated rabbit average body weight of 2.5 kg and 3.0 kg for the 14-day and 28-day studies, respectively
(b) Combined male and female mean C_{max}
(c)Proposed maximum human dose = 0.05% APP13007, one 50 µL drop, unilateral, twice daily for 14 days (0.05 mg/eye/day or 0.00083 mg/kg/day for a 60 kg human)
(d)Value in only one sample of a female human subject

Although a systemic NOAEL was not determined, the following observations provide further support for the safety of the intended dosing regimen, from the nonclinical perspective.

- [redacted] A comparative PK study in the rabbit (Study # [redacted]245-045) supports that systemic exposure after ocular administration is expected to be lower than that of the Temovate® Ointment (as [redacted] at a clinically relevant dose.
- Following ocular instillation of 0.05% APP13007 BID in humans, clobetasol propionate concentrations in plasma were generally not measurable (< 0.04 ng/mL LLOQ) or very low (≤0.182 ng/mL) and were rapidly eliminated. These concentrations are lower than peak concentrations following application of [redacted]Temovate® Ointment 0.05% (overall range of 0.19 to 15.8 ng/mL) per the published information provided in Module 2.7.2.1.2, Summary of Clinical Pharmacology Studies). As such, the systemic safety profile of APP13007 in humans is not expected to differ from that previously established for approved dermal products including Temovate® Ointment 0.05%.
- The exposure observed in humans is below the IC_{50} of 3.25 ng/mL for clobetasol propionate binding to the human glucocorticoid receptor. This finding helps mitigate clinical concerns for drug-class related adverse systemic findings.
- Per Summary information in the NDA (Module 2.5 Clinical Overview), there were no clinically noteworthy changes from baseline in any of the hematology or clinical chemistry parameters, including renal parameters and serum cortisol, and there were no patterns suggestive of study drug-related effects following administration of 0.05% APP13007 BID for 21 days (Phase 2 Study CPN-201).
- The total ocular dose at the maximal proposed dosing regimen of 0.05% BID for 2 weeks is 0.35 mg/week (unilateral treatment). The intended ocular dose is 71X lower than the maximal recommended weekly dose (50 g/week) for the approved dermal products.

Regarding genotoxicity, carcinogenicity, reproductive and developmental toxicity assessment, no studies were performed for APP13007. The Applicant is relying on the FDA's prior findings for the LD, Temovate® Ointment 0.05%, as communicated in the approved label. As noted by the Applicant:

- APP13007 is unlikely to pose a carcinogenic risk to human subjects because clobetasol propionate is not genotoxic or carcinogenic (Temovate® PI, Clobex® PI, Impeklo™ PI); patients will use APP13007 for only 14 days and systemic concentrations of clobetasol propionate are low following ocular administration of APP13007.
- APP13007 has the potential to adversely affect reproductive function in men and women and adversely affect embryofetal development. Like other corticosteroids, clobetasol propionate is a significant teratogen in the rabbit, rat and mouse when absorbed percutaneously (Temovate® PI, Impeklo™ PI) and dermal exposure may be associated with low-birth-weight infants when large areas of the body are treated over long periods of time (Impeklo™ PI). However, the risks during pregnancy are mitigated by the low systemic concentrations of clobetasol propionate observed in humans after ocular administration of APP13007, [redacted]

(b) (4)

(b) (4)

Conclusion and Recommendations:

The nonclinical data provides support for the ocular and systemic safety of APP13007 (Clobetasol Propionate Ophthalmic Nanosuspension, 0.05%) in the treatment of post-operative inflammation and pain in patients following ocular surgery at the intended dosing regimen for marketing. Pharmacology/Toxicology team recommends approval.

For final nonclinical labeling recommendations, see separate label review for this NDA.

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/s/

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02/01/2024 01:34:13 PM

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02/01/2024 03:17:33 PM
I concur with the review and recommendations of Dr. Rivera.