CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218158Orig1s000

SUMMARY REVIEW

Summary Review of NDA 218158

Cross Discipline Team Leader, Deputy Division Director Review

Review Completion Date	See DARRTS Stamp Date
From	Rhea Lloyd, MD, William Boyd, MD
Subject	Summary Review
NDA #	218158
Applicant	Formosa Pharmaceutical, Inc.
Received Date(s)	May 4, 2023
PDUFA Goal Date	March 4, 2024
Proprietary Name	No proprietary name
Established Name	clobetasol propionate ophthalmic suspension 0.05%
Dosage Form(s)	Topical ophthalmic suspension
Applicant Proposed Indication(s)/Population(s)	Treatment of post-operative pain and inflammation following ocular surgery
Applicant Proposed Dosing Regimen	Instill one drop into the affected eye twice daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.
Regulatory Action	**APPROVAL**

NDA 218158 Review Team Role	**Reviewer**
OND RPM	Kalesha Grayson
CDTL	Rhea Lloyd
Clinical Reviewer	Sonal Wadhwa
Pharmacology/Toxicology Reviewer	Maria Rivera / Kim Hatfield
Statistical Reviewer	Yunfan Deng
Clinical Pharmacology Reviewer	Hyewon Kim / Ping Ji
OND Labeling Reviewer	Derek Alberding
Application Technical Lead	Chunchun Zhang
Drug Substance	Stephanie Springer
Drug Product	Elise Luong
Manufacturing	Sureshbabu Dadiboyena
Biopharm	Rajesh Savkur
Microbiology	David Bateman
DMEPA Team Lead / Reviewer	Valerie Vaughn / Deborah Myers
DPV Team Lead / Reviewer	Rachna Kapoor / Paula Gish
OSI CSO	Roy Blay
OPDP Reviewer	Carrie Newcomer
Deputy Division Director	William Boyd

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
IOP	intraocular pressure
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert

PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

Summary

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. The clobetasol propionate ophthalmic suspension 0.05% was also referred to as APP13007 during product development.

NDA 218158 is recommended for APPROVAL. The clinical studies contained in this submission support the safety and efficacy of clobetasol propionate ophthalmic suspension, 0.05% for the treatment of post-operative pain and inflammation following ocular surgery.

Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The data contained in this submission establishes the safety and efficacy of clobetasol propionate ophthalmic suspension, 0.05% for the treatment of post-operative pain and inflammation following ocular surgery. Studies CPN-301 and CPN-302 demonstrate that clobetasol propionate ophthalmic suspension, 0.05% administered BID in the affected eye beginning the day after surgery and continuing twice daily for 14 days improved post-operative pain and inflammation in adults undergoing cataract surgery by a statistically significant and clinically relevant margin. The most common ocular adverse events reported for clobetasol propionate ophthalmic suspension, 0.05% are eye inflammation (2%), corneal edema (2%), intraocular pressure elevation (1%), anterior chamber inflammation (2%), cystoid macular edema (2%), photophobia (1%) and vitreous detachment (1%). The benefits of using this drug product outweigh the risks for the above indication.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Post-operative inflammation is expected after cataract surgery and can lead to permanent damage to the anterior	Treatment of post-operative inflammation will decrease incidence of hyperemia, corneal edema, and increased anterior chamber cells and flare, elevations in IOP, and CME.
Current Treatment Options	• There are many treatment options currently available for postoperative pain and inflammation including topical steroids and topical nonsteroidal anti-inflammatory NSAIDs).	This product if approved would be an ophthalmic formulation of an already approved corticosteroid administered to the affected eye twice per for 14 days during the post-operative period.
Benefit	• Treatment of post-operative inflammation and pain	Studies CPN-301 and CPN-302 demonstrated that treatment with APP13007 administered BID in the affected eye beginning the day after cataract surgery and continuing twice daily for 14 days after was statistically significantly and clinically superior to vehicle in achieving the resolution of anterior chamber cells (ACC=0) and ocular pain at postop day 8 maintained through postop day 15.
Risk and Risk Management	• Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Use of steroids is also associated with increased risk of posterior subcapsular cataract formation. Prolonged topical use may also suppress the host immune response and increase the hazard of secondary ocular infections.	The clinical trials contained in this application demonstrated that the potential adverse events associated with the use of corticosteroids could be monitored. The observed rates with the use of this product were consistent with rates expected for corticosteroids.

Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		Section 8 Study Endpoints
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
☐	Patient experience data was not submitted as part of this application.			

Product Quality

From the Integrated Quality Review finalized on December 21, 2023:

Composition of APP13007 (Clobetasol Propionate Ophthalmic Suspension, 0.05%)

Component	Quality Standard	Function	Formulation Composition (%w/v)[a]	Formulation Composition (mg/mL)	Amount Per Drop (mg)[c]
Clobetasol Propionate	USP	Active ingredient	0.05[b]	0.5	(b) (4)
Sodium Chloride	USP				(b) (4)
Hydrogenated Soybean Lecithin	NF				
Citric Acid (b) (4)	USP				

Component	Quality Standard	Function	Formulation Composition (%w/v)[a]	Formulation Composition (mg/mL)	Amount Per Drop (mg)[c]
Glycerin	USP				(b) (4)
Poloxamer 407	NF				
Polyvinyl Alcohol	USP				
Boric Acid	NF				
Edetate Disodium Dihydratc	USP				
Benzalkonium Chloride	NF	Preservative	0.0036	0.036	(b) (4)
Methylcellulose	USP				(b) (4)
Tri-Sodium Citrate (b) (4)	USP				
Water for Injection	USP				

(b) (4)

Specifications for Clobetasol Propionate Ophthalmic Suspension, 0.05 % w/v

Test Parameter	Method	Acceptance Criteria
Appearance	Visual Inspection (Doc. TS-1508 Item1)	Opalescent liquid; free of visible particles
Clobetasol Propionate Identification	In-house method (HPLC-DAD) (Doc. TS-1508, Item 2)	(1) HPLC retention time (RT) of main peak in sample matches the RT of clobetasol propionate (CP) reference standard, (b) (4) (2) UV absorbance spectrum of main peak at (b) (4) in sample matches that in CP reference standard
Clobetasol Propionate Assay	In-house method (HPLC-UV) (Doc. TS-1508, Item 3)	(b) (4) of the labeled claim (0.05% (b) (4)
Clobetasol Propionate Related Substances	In-house method (HPLC-UV) (Doc. TS-1508, Item 4)	(b) (4) Individual impurity: NMT (b) (4) (Report RRT > (b) (4) Total Impurities: NMT (b) (4)
Benzalkonium Chloride Content	In-house method (HPLC-UV) (Doc. TS-1508, Item 5)	(b) (4)
pH	USP <791> (Doc. TS-1508, Item 6)	(b) (4)
Osmolality	USP <785> (Doc. TS-1508, Item 7)	
Particle Size Distribution	Dynan1ic Light Scattering (Doc. TS-1508, Item 8)	Mean: (b) (4) D90: NMT (b) (4) D50: NMT D10: NMT

Test Parameter	Method	Acceptance Criteria
Viscosity	USP <912> (Doc. TS-1508, Item 10)	(b) (4)
Particulate Matter	USP <788> (Doc. TS-1508, Item 11)	(b) (4)
Elemental impurities (b) (4) [c]	USP <232> (ICP-MS) (Doc. TS-1508, Item 12)	(b) (4)
Elemental impurities (b) (4)	USP <232> (ICP-MS) (Doc. TS-1508, Item 13)	
Sterility	USP <71> (Doc. TM-20034)	No growth
Antimicrobial Effectiveness[d]	USP<51> (Doc. TM-20009)	Complies with USP<51>, Category 1 Log reduction For Bacteria: (b) (4) For Yeast and Molds: No increase from the initial calculated count on (b) (4) (b) (4)
(b) (4)		

cP = centipoise; HPLC = high-performance liquid chromatography; ICP-MS: Inductively Coupled Plasma Mass Spectrometry; NLT: not less than; NMT: not more than; USP: United States Pharmacopeia; UV= ultraviolet spectrometry

a (b) (4)

b D l0, D50, and D90 of PSD statistics to be monitored on annual stability.

c Test conducted upon drug product release for one batch annually.

d No test at release, test to be performed during annual stability monitoring.

Container – Closure System

Primary Container Closure System

APP13007 (Clobetasol Propionate Ophthalmic Suspension 0.05% (w/v)) is filled into a sterile, 5-mL multi-dose container closure system consisting of a white low-density polyethylene (LDPE) bottle equipped with a white LDPE nozzle and tightly closed with a pink high-density polyethylene (HDPE) cap. All these primary packaging components are manufactured by (b) (4)

(b) (4). The materials for the primary packaging components to be used for the commercial drug product are the same as those used for the Phase 3 clinical trial and registration stability batches.

Table 3.2.P.7.1 Components of the Primary Container Closure System

Component	Description	Supplier	Material of Construction			
			Component	Supplier	DMF	Regulatory Status
Bottle	Round Eyedropper LDPE Bottle 5 mL, white color	(b) (4)				
Nozzle	LDPE Nozzle for 5 mL Eyedropper Bottle, white color					
Cap	HDPE Cap for 5 mL Eyedropper Bottle, pink color (b) (4)					

LDPE = Low-Density Polyethylene; HDPE = High-Density Polyethylene; NA= Not applicable

Facilities

Facility name and address	FEI	Responsibilities and profile code(s)	Status
Formosa Laboratories, Inc. No. 36 Hoping Street, Taoyuan City, Louchu District, Taiwan, R.O.C., 338002	3003420376	Manufacturing Clobetasol Propionate Nanomixture including all in-coming materials testing; release testing of the Nanomixture; packaging Nanomixture. Release Nanomixture. Drug product testing including appearance, identification, assay (b) (4) related substances, benzalkonium chloride content, pH, osmolality, particle size distribution,	Approve – Based on Previous History

		viscosity, and elemental impurities. || 356h Status: Pending NEC	
(b) (4)			Approve - Based on Previous History
			No Evaluation Necessary
			No Evaluation Necessary
			No Evaluation Necessary
			No Evaluation Necessary
			Approve - Based on Previous History
			Approve - Based on Previous History

CMC Recommendations:
Satisfactory information and responses have been submitted to support the drug substance, drug product, manufacturing process, biopharmaceutics and quality microbiology aspects.

The product is regulated as a drug and device combination product per the Genus decision. However multi-dose eyedroppers are considered low risk; and CDRH confirmed that a CDRH consult review is not necessary on 5/12/2023.

All the manufacturing facilities are acceptable based on the profile review and inspectional history. OPMA issued an overall recommendation of "approval" on Jul 21, 2023. Therefore, NDA 218158 is recommended Approval from Product Quality perspective.

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling discussion.

Nonclinical Pharmacology/Toxicology

From the Nonclinical Pharmacology/ Toxicology review finalized on February 1, 2024:

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 (b) (4)

(b) (4)

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 (Cmax ≤3.47 ng/mL and AUC0-8h ≤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 (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.

From the Pharmacology Toxicology Memo finalized on February 27, 2024:

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 [redacted] 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, [redacted]

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. [redacted]

Therefore, the data from the study [redacted] 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 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.

Clinical Pharmacology

From the Clinical Pharmacology review finalized on January 10, 2024:

The Applicant, Formosa Pharmaceuticals Inc., has submitted a 505(b)(2) for APP13007 (a clobetasol propionate ophthalmic nanosuspension 0.05%), a synthetic corticosteroid, for the treatment of post-operative inflammation and pain in adult patients following ocular surgery. The proposed dosing regimen is one drop in the conjunctival sac of the operated eye twice daily (BID) for 2 weeks. TEMOVATE® 0.05% (NDAs 019322, 019323, 019966, and 020337) is used as the Reference Drug (RD) in this submission.

In this application, the Applicant completed one clinical PK phase 1 trial (CPN-102), one phase 2 dose-selection trial (CPN-201), and two pivotal phase 3 efficacy and safety trials of APP13007 (CPN-301 and CPN-302). No PK sample was collected in the phase 2 and phase 3 trials, CPN- 201, CPN-3 1, and CPN-302. Therefore, this clinical pharmacology review focused on the phase 1 PK study.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Primary evidence of effectiveness is based on two randomized, double-masked, placebo-controlled phase 3 trials (Studies CPN-301 and CPN-302) in adult patients following ocular surgery. Phase 2 dose-ranging trial provides supportive evidence for its efficacy of APP13007 0.05%.
General dosing instructions	One drop of clobetasol propionate ophthalmic nanosuspension 0.05% into the affected eye twice daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.
Dosing in patients (intrinsic and extrinsic factors)	No dose adjustment is recommended for patients based on intrinsic and extrinsic factors.
Labeling	See Section 2.2.4
Bridge between the to-be-marketed and clinical trial formulations	Not applicable. To-be-marketed formulation of APP13007 0.05% was used in the phase 1 PK, phase 2 dose-selection, and pivotal phase 3 trials.

The Office of Clinical Pharmacology/Division of Inflammation and Immune Pharmacology (OCP/DIIP) has reviewed the clinical pharmacology data submitted in support of NDA 218158 for the proposed clobetasol propionate ophthalmic nanosuspension 0.05% and found the application acceptable to support approval from a clinical pharmacology perspective.

From the Clinical Pharmacology Memo finalized on February 28, 2024:

NDA 218148 for APP13007 (clobetasol propionate ophthalmic suspension 0.05%) was submitted under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act and 21 CRF 314.54 with Temovate ointment 0.05% (NDAs 019322, 019323, 019966, 020337) as a listed drug. The clinical pharmacology review of this NDA was completed and filed in DARRTS on January 10, 2024.

On February 22, 2024, the Agency requested information 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 APP13007 established in the PK study, CPN-102, to the AUC and Cmax, respectively, identified in the published literature for Temovate topical ointment (e.g., the 2008 publication by Kimball AB *et al*.).

On February 26, 2024, the Applicant submitted response to the information request. The Applicant compared the observed Cmax and AUC0-12 of APP13007 from Study CPN-102 to those following Temovate administration in the literature, Kimball AB *et al.*, 2008.

This memo is to review the pharmacokinetic data in the Applicant's response to the information request.

Data Submitted by the Applicant

Data source:

APP13007: An Open-Label, Sequential Dosing Study to Evaluate Systemic Drug Exposure following Ocular Instillation of 0.05% APP13007 in Healthy Subjects (Clinical Study Report CPN-102).

Temovate ointment 0.05%: Clobetasol Propionate Emulsion Formulation Foam 0.05%: Review of Phase II Open-Label and Phase III Randomized Controlled Trials in Steroid- Response Dermatoses in Adults and Adolescents. Kimball AB et. al., 2008, J Am Acad Dermatol 59(3):448-454.

PK exposure:

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

Source: Sponsor's response to the information request dated February 26th, 2024.

Reviewer's Analysis

In Study CPN-102, there were four subjects who had at least two clobetasol propionate concentrations above lower limit of quantification (LLOQ, 0.04 ng/mL). PK samples were collected up to 24 hours post-dose. However, clobetasol propionate concentrations were all below LLOQ after 4 hours post-dose.

Table 2 Concentrations and AUC0-12 Following the First Dose of APP13007 0.05%

Time	0 hour	0.25 hour	0.5 hour	1 hour	1.5 hour	2 hour	3 hour	4 hour	AUC_{0-12}
(b) (6)	0	0	64.4	**128**	105	94.8	61.3	0	273.1
	0	0	0	60	68.8	58.5	42	0	150.3
	0	43.7	74.1	75.1	64.6	55	0	0	149.8
	0	0	0	62.3	51.7	44.6	0	0	90.5

Concentrations in pg/mL; AUC in pg·h/mL

Source: Reviewer's independent analysis using Table 14.2.1 in Clinical Study Report CPN 102

Table 3 Concentrations and AUC_{0-12} Following the Second Dose of APP13007 0.05%

Time	0 hour	0.25 hour	0.5 hour	1 hour	1.5 hour	2 hour	3 hour	4 hour	AUC_{0-12}
(b) (6)	0	0	82.5	**182**	171	134	80.3	53.4	441.6
	0	0	0	40.3	0	40.3	0	0	50.4
	0	0	60.4	87.5	81.4	69	44.7	0	203.6
	0	41.7	55.3	46.5	43.4	0	0	0	76.1

Concentrations in pg/mL; AUC in pg·h/mL

Source: Reviewer's independent analysis using Table 14.2.1 in Clinical Study Report CPN 102

The C_{max} and AUC_{0-12} of clobetasol propionate following one time and two times ocular administrations of APP13007 are lower than those following dermal application of Temovate® ointment 0.05% at a clinically relevant dose.

Reviewer's Conclusion: A scientific "bridge" is acceptable between APP13007 and Temovate ointment 0.05%.

Clinical Efficacy

Clinical data for the two Phase 3 studies CPN-301 and CPN-302 support the safety and efficacy of the product. The trials were performed under similar protocols.

Primary Endpoint Efficacy Results

Study CPN-301: Absence of Anterior Chamber Cells (ACC Count=0) at Day 8 and Maintained Through Day 15 (ITT Population)

	APP13007 N=181	**Vehicle N=197**	**P-value**
Absence of Anterior Chamber Cells at Day 8-Yes	48 (26.5%)	10 (5.1%)	<0.001
95% CI	(20.2%, 33.6%)	(2.5%, 9.1%)	
Yes-Without Imputed Data	47	10	
Yes-With Imputed Data	1	0	
Absence of Anterior Chamber Cells at Day 8-No (Non-responder)	133 (73.5%)	187 (94.9%)	
No-Rescue Medication Use	10	100	
No-Without Imputed Data	121	87	
No-With Imputed Data	2	0	

* The LOCF approach was used to impute missing data for subjects who had any missing data prior to the POD15 assessment without rescue medication use.
** Subjects who were rescued at any time after the first dose of study drug and before the efficacy assessments at POD15 were considered as treatment failures (Non-responders).

Study CPN-302: Absence of Anterior Chamber Cells (ACC Count=0) at Day 8 and Maintained Through Day 15 (ITT Population)

	APP13007 N=185	**Vehicle N=185**	**P-value**
Absence of Anterior Chamber Cells at Day 8-Yes	48 (26.5%)	16 (8.6%)	<0.001
95% CI	(20.3%, 33.5%)	(5.0%, 13.7%)	
Yes-Without Imputed Data	49	16	
Yes-With Imputed Data	0	0	

	APP13007 N=185	Vehicle N=185	P-value
Absence of Anterior Chamber Cells at Day 8-No (Non-responder)	136 (73.5%)	169 (91.4%)	
No-Rescue Medication Use	13	72	
No-Without Imputed Data	119	91	
No-With Imputed Data	4	6	

* The LOCF approach was used to impute missing data for subjects who had any missing data prior to the POD15 assessment without rescue medication use.
** Subjects who were rescued at any time after the first dose of study drug and before the efficacy assessments at POD15 were considered as treatment failures (Non-responders).

Reviewer's Comment:

CPH-301: The proportion of subjects who showed a sustained ACC count=0 from POD8 through to POD15 (i.e., responders) was statistically significantly greater in the APP13007 group compared with the placebo group (26.5% vs 5.1%, p<0.001).

CPN-302: The proportion of subjects who showed a sustained ACC count=0 from POD8 through to POD15 (i.e., responders) was statistically significantly greater in the APP13007 group compared with the placebo group (26.5% vs 8.6%, p<0.001).

Study CPN-301: Absence of Ocular Pain (Grade=0) at POD4 and Maintained Through Day 15 (ITT Population)

	APP13007 N=181	Vehicle N=197	P-value
Absence of Pain at Day 8-Yes	123 (68.0%)	46 (23.4%)	<0.001
95% CI	(60.6%, 74.7%)	(17.6%, 29.9%)	
Yes-Without Imputed Data	119	45	
Yes-With Imputed Data	4	1	
Absence of Pain at Day 8-No (Non-responder)	58 (32.0%)	151 (76.6%)	
No-Rescue Medication Use	10	100	
No-Without Imputed Data	48	51	
No-With Imputed Data	0	0	

* The LOCF approach was used to impute missing data for subjects who had any missing data prior to the POD15 assessment without rescue medication use.
** Subjects who were rescued at any time after the first dose of study drug and before the efficacy assessments at POD15 were considered as treatment failures (Non-responders).

Study CPN-302: Absence of Ocular Pain (Grade=0) at POD4 and Maintained Through Day 15 (ITT Population)

	APP13007 N=185	Vehicle N=185	P-value
Absence of Pain at Day 8-Yes	139 (75.1%)	60 (32.4%)	<0.001
95% CI	(68.3%, 81.2%)	(25.7%, 39.7%)	

	APP13007 N=185	Vehicle N=185	P-value
Yes-Without Imputed Data	138	60	
Yes-With Imputed Data	1	0	
Absence of Pain at Day 8-No (Non-responder)	46 (24.9%)	125 (67.6%)	
No-Rescue Medication Use	13	72	
No-Without Imputed Data	28	46	
No-With Imputed Data	5	7	

* The LOCF approach was used to impute missing data for subjects who had any missing data prior to the POD15 assessment without rescue medication use.
** Subjects who were rescued at any time after the first dose of study drug and before the efficacy assessments at POD15 were considered as treatment failures (Non-responders).

Reviewer's Comment:

CPN-301: The proportion of subjects who showed a sustained ocular pain grade=0 (pain free) from POD4 through to POD15 (i.e., responders) was statistically significantly greater in the APP13007 group compared with the placebo group (68.0% vs 23.4%, p<0.001).

CPN-302: The proportion of subjects who showed a sustained ocular pain grade=0 (pain free) from POD4 through to POD15 (i.e., responders) was statistically significantly greater in the APP13007 group compared with the placebo group (75.1% vs 32.4%, p<0.001).

Secondary Efficacy Endpoints

Study CPN-301: Proportion of Patients With Anterior Chamber Cells (ACC Count=0) at Days 4, 8, and 15 (ITT Population)

	APP13007 N=181	Vehicle N=197	P-value
Absence of Anterior Chamber Cells at Day 4-Yes (Responder)	9 (5.0%)	13 (6.6%)	0.500
Absence of Anterior Chamber Cells at Day 8-Yes (Responder)	59 (32.6%)	23 (11.7%)	<0.001
Absence of Anterior Chamber Cells at Day 15-Yes (Responder)	106 (58.6%)	31 (15.7%)	<0.001

Reviewer's Comment:

The proportion of subjects with ACC count=0 was statistically significantly greater in the APP13007 group compared with the placebo group at POD8 (32.6% vs 11.7%) and then at POD15 (58.6% vs. 15.7%). The difference between the two treatment groups in favor of APP13007 in the proportion of subjects with ACC count=0 increased with time on treatment, at POD8 the difference was 20.9% and at POD15 the difference was 42.9%.

Study CPN-302: Proportion of Patients With Anterior Chamber Cells (ACC Count=0) at Days 4, 8, and 15 (ITT Population)

	APP13007 N=185	**Vehicle N=185**	**P-value**
Absence of Anterior Chamber Cells at Day 4-Yes (Responder)	18 (9.7%)	11 (5.9%)	0.176
Absence of Anterior Chamber Cells at Day 8-Yes (Responder)	55 (29.7%)	24 (13.0%)	<0.001
Absence of Anterior Chamber Cells at Day 15-Yes (Responder)	107 (57.8%)	35 (18.9%)	<0.001

Reviewer's Comment:

The proportion of subjects with ACC count=0 was statistically significantly greater in the APP13007 group compared with the placebo group as early as at POD8 (29.7% vs 13.0%) and then at POD15 (57.8% vs. 18.9%). The difference between the two treatment groups in favor of APP13007 in the proportion of subjects with ACC count=0 increased with time on treatment, at POD8 the difference was 16.7% and at POD15 the difference was 38.9%.

Study CPN-301: Proportion of Patients With Ocular Pain Grade=0 at Days 4, 8, and 15 (ITT Population)

	APP13007 N=181	**Vehicle N=197**	**P-value**
Absence of Anterior Chamber Cells at Day 4-Yes (Responder)	140 (77.3%)	86 (43.7%)	<0.001
Absence of Anterior Chamber Cells at Day 8-Yes (Responder)	149 (82.3%)	84 (42.6%)	<0.001
Absence of Anterior Chamber Cells at Day 15-Yes (Responder)	164 (90.6%)	83 (42.1%)	<0.001

Reviewer's Comment:

The proportion of subjects with ocular pain grade=0 was statistically significantly greater in the APP13007 group compared with the placebo group at POD4 (77.3% vs 43.7%) and then also at POD8 (82.3% vs. 42.6%) and POD15 (90.6% vs. 42.1%). The difference between the two treatment groups in favor of APP13007 in the proportion of subjects with ocular pain grade=0 increased with time on treatment (ie. at POD4 the difference was 33.6%, at POD8 the difference was 39.7%, and at POD15 the difference was 48.5%).

Study CPN-302: Proportion of Patients With Ocular Pain Grade=0 at Days 4, 8, and 15 (ITT Population)

	APP13007 N=185	**Vehicle N=185**	**P-value**
Absence of Anterior Chamber Cells at Day 4-Yes (Responder)	158 (85.4%)	95 (51.4%)	<0.001

	APP13007 N=185	Vehicle N=185	P-value
Absence of Anterior Chamber Cells at Day 8-Yes (Responder)	161 (87.0%)	86 (46.5%)	<0.001
Absence of Anterior Chamber Cells at Day 15-Yes (Responder)	160 (86.5%)	92 (49.7%)	<0.001

Reviewer's Comment:

The proportion of subjects with ocular pain grade=0 was statistically significantly greater in the APP13007 group compared with the placebo group as early as at POD4 (85.4% vs 51.4%) and then also at POD8 (87.0% vs. 46.5%) and POD15 (86.5% vs 49.7%). The difference between the two treatment groups in favor of APP13007 in the proportion of subjects with ocular pain grade=0 increased with time on treatment (ie. at POD4 the difference was 34.0% and at POD15 the difference was 36.8%.

Subpopulations

Efficacy results were analyzed by gender, age, race and ethnicity. The results in each subgroup were consistent with the overall results.

Safety

Extent of Exposure - Safety Population

CPN-301: Summary of Exposure to Study Drug (Safety Population)

	AP13007 N=181	Vehicle N=197
Treatment duration		
Mean (sd)	13.7 (2.2)	9.7 (4.6)
Min, Max	3, 21	1, 18
Duration		
1-4 days	4	36
5-8 days	4	59
9-13 days	2	6
>=14 days	171	96
Number of doses received		
Mean (sd)	27.4 (4.7)	19.2 (9.8)
Min, max	5, 43	2, 37

CPN-302: Summary of Exposure to Study Drug (Safety Population)

	AP13007 N=184	Vehicle N=185
Treatment duration		
Mean (sd)	13.6 (2.4)	10.6 (4.6)
Min, Max	1, 22	1, 22
Duration		
1-4 days	3	30

5-8 days	10	41
9-13 days	4	10
>=14 days	167	104
Number of doses received		
Mean (sd)	27.0 (5.1)	20.8 (9.8)
Min, max	1, 44	1, 43

Reviewer's comments: *There was adequate exposure for this indication.*

Deaths
No deaths were reported during the conduct of either the CBN-301 or the CPN-302 study.

Serious Adverse Events
CPN-301: There were no SAEs reported during this study.

CPN-302: Five subjects had treatment emergent SAEs, 1 subject in the APP13007 group (mild cystoid macular edema (CME)) and 4 subjects in the placebo group (3 patients with mild CME, congestive heart failure, and syncope).

Reviewer's comments:
For the indication and population studied, the adverse events were within the expected.

Studies CPN-301 and CPN-302: Treatment Emergent Ocular AE in the Study Eye in >=1% of Subjects (Safety Population)

	AP13007 N=365	**Vehicle N=382**
Subjects with >=1% Ocular AE	67	76
AC inflammation[1]	19	27
Corneal edema	8	5
IOP increased	8	1
Cystoid macular edema	7	5
Vitreous floaters	4	4
Photophobia	3	5
Vitreous detachment	3	2
Conjunctival hyperemia	2	1
Eye pain	2	6
Dry eye	1	2
Foreign body sensation	1	4
Retinal hemorrhage	0	2

1 Anterior chamber inflammation includes terms AC cell, AC fibrin, AC inflammation, eye inflammation, iridocyclitis and iritis.

Reviewer's Comment:
The most common ocular adverse event reported in the study eye in the APP13007 group were anterior chamber inflammation (5%), corneal edema (2%), intraocular pressure increased (2%), cystoid macular edema (2%); vitreous floaters, photophobia, and vitreous detachment occurred at 1%.

Study CPN-301: Treatment Emergent Non-Ocular AEs (Safety Population)

	AP13007 N=181	**Vehicle N=197**
Any Non-Ocular AE	9	8
GI disorders		
Diarrhea	1	0
Nausea	1	1
Vomiting	1	0
Infections		
Covid-19	2	0
Infection	0	1
Sinusitis bacterial	0	1
UTI	0	1
Nervous system disorder		
Dizziness	1	0
Dysgeusia	1	0
Sciatica	1	0
Headache	0	3
Musculoskeletal disorders		
Arthralgia	1	0
Vascular disorders	1	0
HTN	1	0
Immune system disorders		
Seasonal allergy	0	1
Respiratory disorders		
Cough	0	1

Study CPN-302: Treatment Emergent Non-Ocular AEs (Safety Population)

	AP13007 N=184	**Vehicle N=185**
Any Non-Ocular AE	5	6
Infections		
UTI	2	0
Cellulitis	1	0
GI disorders		
Dyspepsia	1	0
Nervous system disorder		
Dysgeusia	1	0
Headache	0	4
Syncope	0	1
Vascular disorders		
HTN	1	0

	AP13007 N=184	Vehicle N=185
Cardiac disorders		
CHF	0	1
Injury		
Alcohol poisoning	0	1
Joint injury	0	1
Musculoskeletal disorders		
Neck pain	0	1
Psychiatric disorders		
Alcohol abuse	0	1
Skin disorders		
Eczema	0	1

Reviewer's Comment: *The reported non-ocular adverse events did not raise any safety concerns.*

Advisory Committee Meeting

There were no issues raised during the review of this application that were thought to benefit from an Advisory Committee meeting.

Pediatrics

This application triggers PREA as a new active ingredient. The initial Pediatric Study Plan (iPSP) was submitted to IND 128,133 (2/16/20) followed by a meeting with the FDA on 3/26/21. An amendment to the iPSP requesting a full pediatric waiver was then submitted (7/19/21). The Agreed iPSP was issued by the FDA on 9/29/2021.

The Applicant requested a drug-specific waiver for all pediatric age groups for APP13007. On the basis that the corticosteroid in APP13007 will not contribute a more meaningful benefit to pediatric patients over the benefits already provided by corticosteroid products that are approved for use in pediatric patients for this indication (i.e., Pred Forte, Durezol, and Lotemax Gel) or that are approved for use in children to treat inflammatory conditions of the eye (Maxidex and prednisolone acetate eyedrops).

On December 12, 2023, the PeRC agreed with granting full waiver for all pediatric age groups on the basis that the product fails to represent a meaningful therapeutic benefit over existing therapies and is unlikely to be used in this population because in clinical practice the stronger steroid drops (previously approved) are preferred for use in pediatric patients over the weaker products.

Biostatistics

From the Statistical Review finalized on 2/29/2024:

The applicant conducted two similarly designed Phase 3 studies (Study CPN-301, referred to as Study 301; and Study CPN-302, referred to as Study 302) to evaluate efficacy and safety of Clobetasol Propionate Ophthalmic Suspension, 0.05%, (also known as APP13007 throughout this review). Both

studies were multicenter, randomized, double-masked, placebo-controlled, parallel-group studies, evaluating the efficacy and safety of APP13007 (0.05%) 1 drop instilled twice daily (BID) in the study eye for 14 days in approximately 370 subjects per study following routine uncomplicated unilateral cataract surgery. The co-primary efficacy endpoints for both studies were:

- The proportion of subjects with Anterior Chamber Cell (ACC) Count = 0 [ACC Grade = 0] at post-operative day 8 (POD8), maintained through POD15
- The proportion of subjects with Ocular Pain Grade = 0 at POD4, maintained through POD15

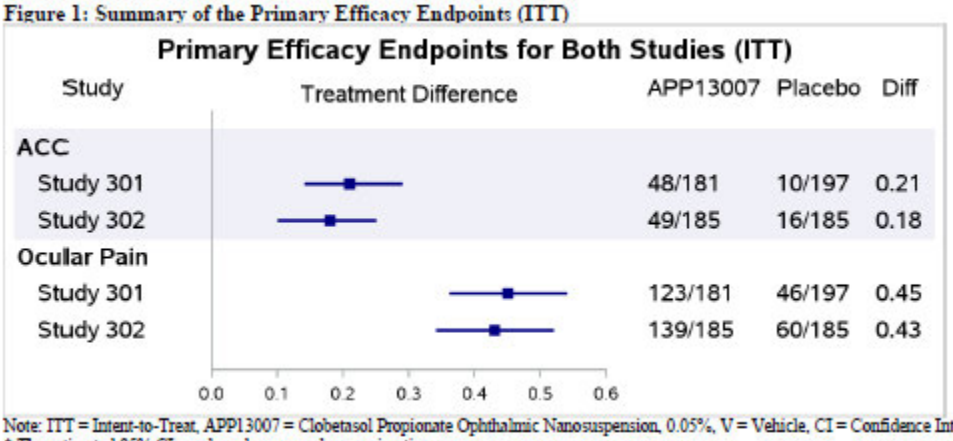
Both studies demonstrated superiority of APP13007 to the vehicle for both primary endpoints (Table 1 and Figure 1). Therefore, the statistical reviewer recommends the approval of clobetasol propionate ophthalmic nanosuspension, 0.05% for the treatment of post-operative inflammation and pain following ocular surgery.

Table 1: Summary of the Primary Efficacy Results (ITT)

		Study 301			Study 302		
		APP13007 (N=181)	**Placebo (N=197)**	**Difference (95% CI)**	**APP13007 (N=185)**	**Placebo (N=185)**	**Difference (95% CI)**
ACC	**Responders (%)**	48 (26.5%)	10 (5.1%)	21.4% (14.3%, 28.6%)	49 (26.5%)	16 (8.6%)	17.8% (10.3%, 25.4%)
	p-value			<0.001			<0.001
Ocular Pain	**Responders (%)**	123 (68.0%)	46 (23.4%)	44.6% (35.6%, 53.6%)	139 (75.1%)	60 (32.4%)	42.7% (33.5%, 51.9%)
	p-value			<0.001			<0.001

Note: ITT = Intent-to-Treat, APP13007 = Clobetasol Propionate Ophthalmic Nanosuspension, 0.05%, V = Vehicle, CI = Confidence Interval
* p-value was from the Pearson's Chi-Square test to compare treatment groups. The estimated 95% CI was based on normal approximation. Source: Tables 13 and 14 of Study 301 Clinical Study Report (CSR), Tables 13 and 14 of Study 302 CSR, and the reviewer's calculation.

Figure 1: Summary of the Primary Efficacy Endpoints (ITT)



Note: ITT = Intent-to-Treat, APP13007 = Clobetasol Propionate Ophthalmic Nanosuspension, 0.05%, V = Vehicle, CI = Confidence Interval
* The estimated 95% CI was based on normal approximation.
Source: Tables 13 and 14 of Study 301 Clinical Study Report (CSR), Tables 13 and 14 of Study 302 CSR, and the reviewer's calculation

ACC Grade

The applicant analyzed the proportion (%) of subjects with ACC Count = 0 (ACC Grade = 0) on each individual visit at PODs 4, 8 and 15. As demonstrated in the table below, starting from POD 8, the APP13007 group had more subjects with ACC grade = 0 comparing with the placebo group.

Table 6: Proportion (%) of Subjects with ACC Count = 0 (ACC Grade = 0) at PODs 4, 8 and 15 (ITT Population)

	Study 301			Study 302		
Post Operative Day (POD)	**APP13007 (N=181)**	**Placebo (N=197)**	**Diff (95% CI)**	**APP13007 (N=185)**	**Placebo (N=185)**	**Diff (95% CI)**
4	9 (5.0%)	13 (6.6%)	-1.6% (-6.3%, 3.1%)	18 (9.7%)	11 (5.9%)	3.8% (-1.7%, 9.3%)
8	59 (32.6%)	23 (11.7%)	20.9% (12.8%, 29.1%)	55 (29.7%)	24 (13.0%)	16.8% (8.6%, 24.9%)
15	106 (58.6%)	31 (15.7%)	42.8% (34.0%, 51.6%)	107 (57.8%)	35 (18.9%)	38.9% (29.8%, 48.0%)

* The estimated 95% CI was based on normal approximation.
Source: Table 14.2.3 of Study 301 CSR, and Table 14.2.3 of Study 302 CSR.

In addition, the Applicant also analyzed the change from baseline of the ACC grade on each individual day at PODs 4, 8 and 15. At each of the PODs 4, 8, and 15 in both studies, the mean change from baseline of the ACC grade for the APP13007 group was greater than the placebo group (Table 7).

Table 7: Analysis of ACC Grade Change from Baseline at PODs 4, 8 and 15 (ITT Population)

	Study 301			Study 302		
Post Operative Day (POD)	**APP13007 (N=181)**	**Placebo (N=197)**	**Diff (95% CI)**	**APP13007 (N=185)**	**Placebo (N=185)**	**Diff (95% CI)**
Baseline	2.6 (0.6)	2.8 (0.7)	N/A	2.7 (0.8)	2.8 (0.8)	N/A
4	-0.9 (0.8)	-0.3 (1.2)	-0.5 (-0.7, -0.3)	-1.1 (1.1)	-0.7 (1.1)	-0.5 (-0.7, -0.3)
8	-1.7 (1.0)	-0.5 (1.3)	-0.9 (-1.1, -0.7)	-1.7 (1.1)	-0.9 (1.2)	-0.9 (-1.1, -0.7)
15	-2.1 (1.0)	-0.6 (1.5)	-1.2 (-1.4, -1.0)	-2.1 (1.1)	-1.0 (1.3)	-1.2 (-1.4, -1.0)

(1) Difference and 95% CI is estimated from an analysis of covariance model that included treatment as a fixed effect and baseline as a covariate. Source: Table 14.2.7 of Study 301 CSR, and Table 14.2.7 of Study 302 CSR.

For the primary efficacy endpoint of the proportion (%) of subjects with ACC Count = 0 (ACC grade=0) at POD8 maintained through POD15, the APP13007 group demonstrated statistically significant comparing with placebo in both Study 301 and Study 302 (Table 8):

- In Study 301, the proportion of subjects with ACC Count = 0 (ACC grade=0) at POD8 maintained through POD15 in the APP13007 group was 26.5% (48/181) vs. 5.1% (10/197) in the placebo group. The treatment difference was 21.4% with the 95% CI of (14.3%, 28.6%), p-value < 0.001.
- In Study 302, the proportion of subjects with ACC Count = 0 (ACC grade=0) at POD8 maintained through POD15 in the APP13007 group was 26.5% (49/185) vs. 8.6% (16/185) in the placebo group. The treatment difference was 17.8% with the 95% CI of (10.3%, 25.4%), p-value < 0.001.
- The treatment effect in both studies is relatively consistent.

Table 8: Primary Efficacy Endpoint – Proportion (%) of Subjects with ACC Count = 0 (ACC grade=0) at POD8 maintained through POD15 (ITT Population)

	Study 301			Study 302		
	APP13007 (N=181)	**Placebo (N=197)**	**Diff (95% CI)**	**APP13007 (N=185)**	**Placebo (N=185)**	**Diff (95% CI)**
Responders (%)	48 (26.5%)	10 (5.1%)	21.4% (14.3%, 28.6%)	49 (26.5%)	16 (8.6%)	17.8% (10.3%, 25.4%)
p-value			<0.001			<0.001

* The estimated 95% CI was based on normal approximation. Source: Table 13 of Study 301 CSR, and Table 13 of Study 302 CSR.

Ocular Pain Grade

The applicant analyzed the proportion (%) of subjects with Ocular Pain Grade = 0 at each individual visit on PODs 4, 8 and 15. As demonstrated in the table below, starting from POD4, the APP13007 group had more subjects with Ocular Pain Grade = 0 comparing with the placebo group, and the treatment difference appeared to be increasing over time.

Table 9: Proportion (%) of Subjects with Ocular Pain Grade = 0 at PODs 4, 8 and 15 (ITT Population)

	Study 301			Study 302		
Post Operative Day (POD)	**APP13007 (N=181)**	**Placebo (N=197)**	**Diff (95% CI)**	**APP13007 (N=185)**	**Placebo (N=185)**	**Diff (95% CI)**
4	140 (77.3%)	86 (43.7%)	33.7% (24.6%, 42.9%)	158 (85.4%)	95 (51.4%)	34.1% (25.2%, 42.9%)
8	149 (82.3%)	84 (42.6%)	39.7% (30.8%, 48.6%)	161 (87.0%)	86 (46.5%)	40.5% (31.9%, 49.2%)
15	164 (90.6%)	83 (42.1%)	48.5% (40.4%, 56.6%)	160 (86.5%)	92 (49.7%)	36.8% (28.0%, 45.5%)

* The estimated 95% CI was based on normal approximation.
Source: Table 14.2.3 of Study 301 CSR, and Table 14.2.3 of Study 302 CSR, and the statistical reviewer's calculation.

In addition, the Applicant also analyzed the change from baseline of the ocular pain grade on each individual day at PODs 4, 8 and 15. At each of the PODs 4, 8, and 15 in both studies, the mean change from baseline of the ocular pain grade for the APP13007 group was greater than the placebo group at all the PODs (Table 10).

Table 10: Analysis of Ocular Pain Grade Change from Baseline at PODs 4, 8 and 15 (ITT Population)

	Study 301			Study 302		
Post Operative Day (POD)	**APP13007 (N=181)**	**Placebo (N=197)**	**Diff (95% CI)**	**APP13007 (N=185)**	**Placebo (N=185)**	**Diff (95% CI)**
Baseline	1.2 (1.0)	1.2 (1.0)	N/A	2.7 (0.8)	2.8 (0.8)	N/A
4	-0.9 (0.9)	-0.2 (1.1)	-0.6 (-0.8, -0.5)	-0.5 (0.8)	-0.2 (1.0)	-0.5 (-0.6, -0.4)
8	-1.0 (1.0)	-0.3 (1.3)	-0.7 (-0.8, -0.5)	-0.5 (1.0)	-0.1 (1.3)	-0.6 (-0.7, -0.4)
15	-1.1 (1.1)	-0.3 (1.3)	-0.7 (-0.9, -0.6)	-0.6 (1.0)	-0.2 (1.3)	-0.5 (-0.7, -0.3)

(1) Difference and 95% CI is estimated from an analysis of covariance model that included treatment as a fixed effect and baseline as a covariate. Source: Table 14.2.7 of Study 301 CSR, and Table 14.2.7 of Study 302 CSR.

For the primary efficacy endpoint of the proportion (%) of subjects with ocular pain grade = 0 at POD4 maintained through POD15, the APP13007 group demonstrated statistically significant comparing with placebo in both Study 301 and Study 302 (Table 11):

- In Study 301, the proportion of subjects with ocular pain grade = 0 at POD4 maintained through POD15 in the APP13007 group was 68.0% (123/181) vs. 23.4% (46/197) in the placebo group. The treatment difference was 44.6% with the 95% CI of (35.6%, 53.6%), p-value < 0.001.
- In Study 302, the proportion of subjects with ocular pain grade = 0 at POD4 maintained through POD15 in the APP13007 group was 75.1% (139/185) vs. 32.4% (60/185) in the placebo group. The treatment difference was 42.7% with the 95% CI of (33.5%, 51.9%), p-value < 0.001.
- The treatment effect in both studies is consistent.

ble 11: Primary Efficacy Endpoint – Proportion (%) of Subjects of subjects with Ocular Pain Grade = 0 at POD4 maintained through POD15 (ITT Population)

	Study 301			Study 302		
	APP13007 (N=181)	**Placebo (N=197)**	**Diff (95% CI)**	**APP13007 (N=185)**	**Placebo (N=185)**	**Diff (95% CI)**
Responders (%)	123 (68.0%)	46 (23.4%)	44.6% (35.6%, 53.6%)	139 (75.1%)	60 (32.4%)	42.7% (33.5%, 51.9%)
p-value			<0.001			<0.001

* The estimated 95% CI was based on normal approximation.
Source: Table 14 of Study 301 CSR, Table 14 of Study 302 CSR, and the statistical reviewer's calculation.

3.2.4.3 Sensitivity Analyses of the Primary Efficacy Endpoints

The Applicant's analyses of the primary endpoints (ACC Grade = 0 at POD8 and Maintained through POD15, and Ocular Pain Grade = 0 at POD4 and Maintained through POD15) in the different analysis sets and/or using different methods for missing data yielded similar results.

Financial Disclosure

The Form 3454 was submitted in an amendment on 6/13/23 (SDN-2).

Covered Clinical Study (Name and/or Number): CPN-301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 27		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements: N/A	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: N/A	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): CPN-302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 29		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements: N/A	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: N/A	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

Study Integrity

From the OSI Clinical Investigation Summary finalized December 20, 2023:

Clinical data from Protocols CPN-301 and CPN-302 were submitted to the Agency in support of NDA 218158 for the use of Clobetasol Propionate Ophthalmic Suspension 0.05% for the treatment of post-operative inflammation and pain following ocular surgery. Three clinical investigators, Drs. Korenfeld, Levenson, and Sadri, were inspected in support of this NDA.

Based on the results of these inspections, Protocols CPN-301 and CPN-302 appear to have been conducted adequately and the data generated by these sites appear acceptable in support of the respective indication.

DMEPA

The Division of Medication Error Prevention and Analysis 1 (DMEPA) completed a review dated August 16, 2023. Revisions were proposed for the draft prescribing information (PI), professional sample and trade container labels and carton labeling.

The Office of Prescription Drug Promotion (OPDP) completed a review of the package insert and carton/ container labeling on 2/14/24. Their comments were noted. One contains true statements regarding the 12.1 Mechanism of Action and one concerns promotional language in 14 Clinical Studies which has since been revised.

Post-marking Risk Management

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

Regulatory Action

NDA 218158 will be approved for the treatment of pain and inflammation after ocular surgery.

Labeling

Attached is the agreed-upon labeling for NDA 218158 Clobetasol Propionate Ophthalmic Suspension, 0.05% for the treatment of pain and inflammation following ocular surgery.

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

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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/

RHEA A LLOYD
03/04/2024 11:45:12 AM

WILLIAM M BOYD
03/04/2024 11:47:20 AM