CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218158Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	218158
Priority or Standard	Standard
Submit Date(s)	5/4/23
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Division/Office	Division of Ophthalmology/Office of Specialty Medicine (DO/OSM)
Reviewer Name(s)	Sonal D. Wadhwa, MD
Review Completion Date	1/4/24
Established/Proper Name	clobetasol propionate ophthalmic suspension. 0.05%
(Proposed) Trade Name	Clobetasol Propionate Ophthalmic Suspension. 0.05%
Applicant	Formosa Pharmaceutical, Inc.
Dosage Form(s)	Topical suspension
Applicant Proposed Dosing Regimen(s)	1 drop BID for 2 weeks
Applicant Proposed Indication(s)/Population(s)	Treatment of post-operative pain and inflammation following ocular surgery
Recommendation on Regulatory Action	Recommend Approval
Recommended Indication(s)/Population(s) (if applicable)	Patients with ocular pain and inflammation following ocular surgery

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Glossary

AC	advisory committee
AE	adverse event
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
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
GCP	good clinical practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NME	new molecular entity
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
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
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment emergent adverse event

Executive Summary

1.1. Product Introduction

Clobetasol Propionate Ophthalmic Suspension, 0.05% is synthetic corticosteroid, an analog of prednisolone, that has potent anti-inflammatory, antipruritic, and vasoconstrictive properties. During clinical development is has also been called APP13007 which is prepared by dispersing milled particles of clobetasol propionate with excipients in a preserved multi-dose aqueous formulation.

The application for clobetasol propionate ophthalmic suspension is submitted as a 505(b)(2) application listing NDAs 019322 and 019323 for TEMOVATE (clobetasol propionate) Ointment as the reference drug product.

1.2. Conclusions on the Substantial Evidence of Effectiveness

NDA 218158 is recommended for approval with the revised labeling identified in the CDTL review. The clinical studies contained in this submission support the use of clobetasol propionate ophthalmic suspension for the treatment of post-operative pain and inflammation following ocular surgery.

1.3. 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 significantly superior to the matching placebo in the proportion of subjects

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		with ACC count = 0 (ACC grade = 0) at POD8 maintained through POD15 and the proportion of subjects with Ocular Pain Grade = 0 at POD4 maintained through POD15.
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.

1.4. 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 6.1 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	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Despite advances in surgical technique, trauma that occurs during cataract removal and intraocular lens (IOL) placement regularly leads to some degree of inflammation. The cellular damage on the surface of the cornea activates an inflammatory process that manifests initially as hyperemia, corneal edema, and increased anterior chamber cells and flare. More serious complications such as increases in intraocular pressure (IOP), cystoid macular edema, and posterior capsule opacification may result if the inflammatory process is not managed appropriately. For this purpose, a post-cataract surgery regimen of anti-inflammatory agents (such as corticosteroids) is typically prescribed because it reverses inflammation, pain and discomfort, and reduces the risk of further complications.

2.2. Analysis of Current Treatment Options

NDA	Drug	Indication
22-212	Difluprednate ophthalmic emulsion 0.05% (Durezol)	DUREZOL is a topical corticosteroid that is indicated for the treatment of inflammation and pain associated with ocular surgery. DUREZOL is also indicated for the treatment of endogenous anterior uveitis.
202-872	Loteprednol etabonate ophthalmic gel 0.5% (Lotemax)	LOTEMAX is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.
20-474	Rimexelone ophthalmic suspension 1% (Vexol)	Treatment of post-operative inflammation following ocular surgery and in the treatment of anterior uveitis.
203-168	Bromfenac ophthalmic solution 0.07% (Prolensa)	PROLENSA is a NSAID indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.
21-664	Bromfenac sodium ophthalmic solution 0.09% (Xibrom)	XIBROM is a NSAID indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.
21-664 201-211 202-030 203-395	Bromfenac sodium ophthalmic solution 0.09% (Bromday)	BROMDAY is a NSAID indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.
21-862	Nepafenac ophthalmic suspension 0.1% (Nevanac)	NEVANAC ophthalmic suspension is a NSAID indicated for the treatment of pain and inflammation associated with cataract surgery.
203-491	Nepafenac ophthalmic suspension 0.3% (Ilevro)	ILEVRO (nepafenac ophthalmic suspension), 0.3% is a NSAID indicated for the treatment of pain and inflammation associated with cataract surgery.
22-427	Ketorolac tromethamine ophthalmic solution 0.45% (Acuvail)	ACUVAIL ophthalmic solution is a NSAID indicated for the treatment of pain and inflammation following cataract surgery.
20-037	Diclofenac sodium ophthalmic solution 0.1% (Voltaren Ophthalmic)	VOLTAREN ophthalmic is indicated for the treatment of post-operative inflammation in patients who have undergone cataract extraction and for the temporary relief of pain and photophobia in patients undergoing corneal refractive surgery.

NDA	Drug	Indication
206-911	BromSite (bromfenac ophthalmic solution) 0.075%	Treatment of post-operative inflammation and prevention of ocular pain in patients undergoing cataract surgery

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Clobetasol propionate has been approved for use in dermatological products for more than 30 years in the US, Europe, and Japan to treat the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses. TEMOVATE Ointment the reference listed drug (RLD) for this 505(b)(2) NDA, was originally approved in 1985 and remained on the market in the US until the product was withdrawn from the market in 2015 for reasons other than safety or efficacy.

3.2. Summary of Presubmission/Submission Regulatory Activity

Three meetings were held in advance of the submission of this NDA:

PIND meeting	1/21/16
EOP2 meeting	9/2/20
Pre-NDA meeting	10/31/22

3.3. Foreign Regulatory Actions and Marketing History

Clobetasol propionate has been approved for use in dermatological products for more than 30 years in the US, Europe, and Japan to treat the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses. Clobetasol propionate ophthalmic suspension 0.05% has not yet been approved for marketing.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The OSI review dated 12/20/23 states that 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.

4.2. Product Quality

The 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				
Glycerin	USP				
Poloxamer 407	NF				
Polyvinyl Alcohol	USP				
Boric Acid	NF				
Edetate Disodium Dihydrate	USP				
Benzalkonium Chloride	NF	Preservative	0.0036	0.036	
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)

[c] (b) (4)

Proposed Drug Product Specifications for APP13007 (Clobetasol Propionate Ophthalmic Suspension, 0.05%)

Test Parameter	Method	Acceptance Criteria
Appearance	Visual Inspection (Doc. TS-1508 Item 1)	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% w/v)
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)	(b) (4)
Particle Size Distribution	Dynamic Light Scattering (Doc. TS-1508, Item 8)	Mean: (b) (4) D90: NMT (b) (4) D50: NMT D10: NMT (b) (4)
Viscosity	USP <912> (Doc. TS-1508, Item 10)	(b) (4)
Particulate Matter	USP <788> (Doc. TS-1508, Item 11)	(b) (4)

Test Parameter	Method	Acceptance Criteria

Elemental impurities (b) (4)	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>, (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 D10, 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.

4.3. Clinical Microbiology

This product is not an anti-infective.

4.4. 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 conducted a comparative PK study in rabbits which showed that systemic exposure to clobetasol propionate following ocular instillation of APP13007 was lower than that observed following a dermal application (b) (4) at a clinically relevant dose. (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 (b) (4) (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). (b) (4) (b) (4)

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. (b) (4)

> *Therefore, (b) (4) (b) (4) (b) (4) 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 al1 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.

4.5. 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 (b) (4) 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) (4), (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) (4), (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%.

4.6. Devices and Companion Diagnostic Issues

Based on the Genus decision, the Agency determined that the language in 21 CFR 200.50(c) indicating that eye cups, eye droppers, and ophthalmic dispensers are regulated as drugs when packaged with other drugs is now obsolete, as these articles meet the "device" definition. The Agency is now regulating these products including the one which is the subject of this review as drug-led combination products composed of a drug constituent part that provides the primary mode of action (PMOA) and a device constituent part (dispenser). As the drug constituent part provides the PMOA, CDER has primary jurisdiction over these products.

However, no CDRH consult was necessary for this NDA per email from Shazma Aftab OPQ on 5/10/23.

4.7. Consumer Study Reviews

Not applicable. No consumer studies were conducted.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Study Name	Study Design/ Study Objectives	Dose, Regimen, Duration	Study Population Number of Subjects	Study Results
CPN-102	Phase 1, single-center, open label, 2-period, sequential dosing study Primary: To evaluate the systemic exposure to clobetasol propionate based on plasma concentrations following ocular instillation of 1 drop and 2 separate drops (12 hours apart) of APP13007 0.05%, respectively, on 2 separate occasions.	2 treatments over 2 dose periods with a minimum 6-day washout interval between treatments: Treatment 1: 1 drop of APP13007 0.05% Treatment 2: 2 separate drops of APP13007 0.05% instilled approximately 12 hours apart Duration: 1 day	Healthy adult subjects 12 entered/ 12 completed	Plasma concentrations of clobetasol propionate were mostly not measurable or very low and there was no evidence of accumulation. APP13007 was well-tolerated and there were no APP13007-related AEs.

Study Name	Study Design/ Study Objectives	Dose, Regimen, Duration	Study Population Number of Subjects	Study Results
CPN-201 US/ 9 centers	Phase 2, randomized double-masked, placebo controlled, 2-part study (designated as Parts A and B) Primary Objectives: • To investigate the safety and tolerability of APP13007 versus vehicle for the treatment of inflammation and pain through post-operative day (POD) 22 in Part A and POD15 in Part B after cataract surgery. • To investigate the preliminary efficacy of APP13007 versus vehicle for the treatment of inflammation and pain through POD15 after cataract surgery.	Part A 1 drop 0.05% APP13007 (22 patients) or placebo (23 patients) BID for 21 days instilled to the operated study eye starting the day after cataract surgery Part B 1 drop 0.05% APP13007 (22 patients) or placebo (22 patients) BID for 3 days followed by 1 drop 0.05% APP13007 QD for 11 days instilled to the operated study eye starting the day after cataract surgery OR 1 drop 0.1% APP13007 (22 patients) or placebo (21 patients) BID for 3 days followed by 1 drop 0.1% APP13007 QD for 11 days instilled to the operated study eye starting the day after cataract surgery	Subjects post uncomplicated cataract surgery 132 patients	0.05% APP13007 BID for 21 days was safe and more effective than placebo and the 0.05% BID/QD and 0.1% BID/QD regimens at reducing inflammation and ocular pain after cataract surgery. The efficacy after 14 days of dosing was comparable to that after 21 days of dosing. All APP13007 dosing regimens were well-tolerated with safety profiles similar to the matching placebos.
CPN-301 US/ 27 centers	Phase 3, multicenter, randomized, double-masked, placebo controlled, parallel-group study	1 drop APP13007 0.05% BID for 14 days instilled to the operated study eye starting the day after cataract surgery (181 patients) OR 1 drop Placebo BID for 14 days instilled to the operated study eye starting the day after cataract surgery (197 patients) Duration: 22 days	Subjects post uncomplicated cataract surgery 378 patients	The primary efficacy endpoint was met. The proportions of subjects with ACC count =0, ACF grade =0 and ocular pain grade =0 were SS greater in the APP13007 group compared with the Placebo group.

Study Name	Study Design/ Study Objectives	Dose, Regimen, Duration	Study Population Number of Subjects	Study Results
CPN-302 US/ 29 centers	Phase 3, multicenter, randomized, double-masked, placebo controlled, parallel-group study	1 drop APP13007 0.05% BID for 14 days instilled to the operated study eye starting the day after cataract surgery (185 patients) OR 1 drop Placebo BID for 14 days instilled to the operated study eye starting the day after cataract surgery (185 patients) Duration: 85 days	Subjects post uncomplicated cataract surgery 370 patients	The primary efficacy endpoint was met. The proportions of subjects with ACC count =0, ACF grade =0 and ocular pain grade =0 were SS greater in the APP13007 group compared with the Placebo group.

5.2. Review Strategy

The sources of clinical data utilized in this review include the studies listed in Section 5.1. The two studies which provide the main support for safety and efficacy were: CPN-301 and CPN-302.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. CPN-301: A Multicenter, Randomized, Double-Masked, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of APP13007 for the Treatment of Inflammation and Pain after Cataract Surgery

6.1.1. Study Design

Overview and Objective

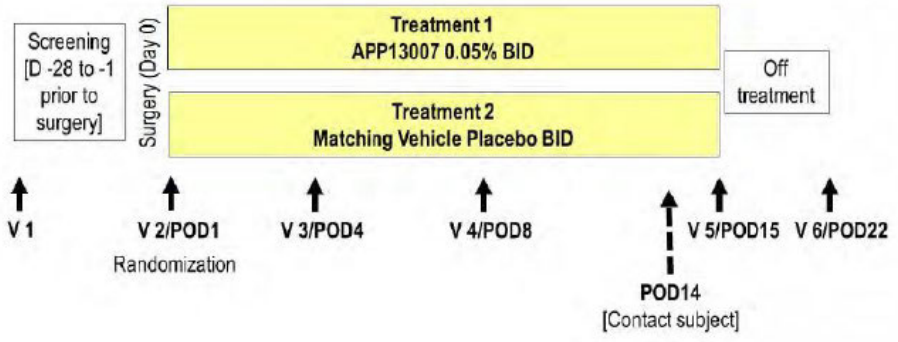
The primary efficacy objective was to investigate the efficacy of APP13007 versus matching vehicle placebo for the treatment of inflammation and pain through post-operative day (POD) 15 after cataract surgery in the study eye.

Trial Design

This was a Phase 3, multicenter, randomized, double-masked, placebo-controlled, parallel-group study in subjects experiencing ocular inflammation and pain following routine cataract surgery without complications. Approximately 370 subjects were planned to be randomized

(approximately 185 subjects per treatment group) across multiple sites in the US. At Visit 2 (Baseline; Randomization; POD1), subjects who continued to meet all inclusion criteria and who did not meet any of the exclusion criteria were eligible for randomization to APP13007 or matching vehicle placebo via the electronic data capturing (EDC)/Interactive Web based Response (IWRS) system. Women of childbearing potential (WOCBP) had a urine pregnancy test at the POD1 visit prior to randomization. Randomized subjects received the first dose of the study drug at the study site and then returned for ocular assessments of the operated study eye on Visit 3 (POD4; ±1 day), Visit 4 (POD8; ±1 day), and Visit 5 (POD15; +1 day).

Figure 1: Schematic Diagram of the Study Design for CPN-301



BID=twice daily; D=Day; POD=post-operative day; V=visit

Eligible subjects were randomized to one of the following 2 treatment groups in a 1:1 ratio:

- Treatment Group 1: 1 drop APP13007 BID for 14 days instilled to the operated study eye
- Treatment Group 2: 1 drop matching vehicle placebo BID for 14 days instilled to the operated study eye

Randomized subjects returned for the POD15 visit for ocular assessments on the study eye. The study drug bottle and dosing diary were collected from subjects during the POD15 visit. WOCBP had a urine pregnancy test at the POD15 visit. Subjects were instructed to return for the POD22 visit after the POD15 visit assessments had been completed. Subjects returned for a final clinic visit on POD22 (Visit 6; POD22 or Early Termination/Withdrawal; ±2 days). Subjects who were discontinued from the study early or who withdrew from the study were required to complete POD22 assessments and a urine pregnancy test (only for WOCBP) at the time of early termination/withdrawal, or as soon as possible thereafter. Visit 6 (POD22) served as an End of Study (EOS) visit for subjects.

Inclusion Criteria

- Provided signed and dated informed consent
- Age ≥ 18 years at time of informed consent

- Males or females of non-childbearing potential. Females of non-childbearing potential were defined as women who have been permanently sterilized or are postmenopausal. Postmenopausal was defined as amenorrhea for a minimum of 12 months (without an alternative medical cause). Note: Pregnant women or nursing (breast-feeding) mothers were excluded from the study
- WOCBP were eligible for enrollment if they had a negative urine pregnancy test on Visit 2 (POD1) prior to Randomization and they agreed to abstain from sexual activity or use a highly effective contraceptive such as occlusive cap (diaphragm or cervical/vault cap) plus spermicidal agent (foam/gel/film/cream/suppository), oral contraceptive, injectable progesterone, implant of etonogestrel or levonorgestrel, estrogenic vaginal, percutaneous contraceptive patches, or intrauterine device from Visit 2 (POD1) to Visit 6 (POD22)
- Expected to undergo unilateral uncomplicated cataract extraction via phacoemulsification and posterior chamber intraocular lens implantation in one eye
- Had a pinhole corrected visual acuity without other correction of ≤ 1.3 logMAR in the study eye to be operated and contralateral eye as measured using an ETDRS chart at Visit 1. Subjects who were unable to read the lines in an ETDRS chart because of the density of the cataract in the study eye could be enrolled if, in the opinion of the Investigator, there was no other significant ocular pathology that would account for the low visual acuity
- Willing and able to comply with study requirements and visit schedule; able to either self-administer study medication or have someone available (ie. spouse or caregiver) who could administer study medication according to the study schedule and instructions. Had undergone unilateral cataract extraction via phacoemulsification and posterior chamber intraocular lens implantation in the study eye without any additional procedures or complications that would, in the opinion of the Investigator, interfere with study procedures or confound study objectives
- No significant ocular pathology affecting visual acuity that was identified after posterior chamber intraocular lens implantation in the study eye
- Had ≥ 10 cells in the anterior chamber (excluding red blood and pigment cells)
- Had an IOP ≤ 30 mmHg. Note: If the IOP was elevated post-surgery, the Investigator was permitted to use non-prostaglandin based IOP-lowering medication(s) at their discretion on the day of surgery (Day 0) only. The IOP was measured and recorded on POD1 to determine eligibility for Randomization

<u>Exclusion Criteria</u>

- Had a known sensitivity or allergy to clobetasol propionate, corticosteroids, or any of the study medication's components including benzalkonium chloride and soybean lecithin or any routine medication required during cataract surgery or for the conduct of study procedures
- Had an ACC count > 0 or any evidence of intraocular inflammation in either eye at the Screening visit

- Had a Grade > 0 on the Ocular Pain Assessment in either eye at the Screening visit
- Had an immunosuppressive or autoimmune disease that in the opinion of the Investigator could affect intraocular inflammation or the normal healing process of the eye
- Had active or chronic/recurrent ocular or systemic disease that was uncontrolled and could affect wound healing and/or resolution of inflammation after cataract surgery
- Suspected or known malignancy or was currently receiving antineoplastic therapy. Note: subjects with basal cell carcinoma were not excluded unless the Investigator believed that the condition had the potential to interfere with study procedures or analysis of results.
- Were using certain medications, namely:
    - Subjects receiving therapy for macular degeneration (in either eye) with Eylea (aflibercept), Avastin (bevacizumab), Lucentis (ranibizumab), Beovu (brolucizumab-dbll) or Visudyne (verteporfin) were excluded.
    - Prokera (preserved amniotic membrane) was excluded from 1 year prior to Visit 1 (Screening) through Visit 6 (POD22; Early Termination/Withdrawal).
    - Anti-inflammatory agents, analgesics [including opioids, narcotics, NSAIDs, aspirin, acetaminophen and other pain medications] or immune-modulating agents systemically or in either eye were excluded from the beginning of the 'Washout' period in the "List of Prohibited Medications" until after Visit 5 (POD15) assessments, but preferably until after Visit 6 (POD22) assessments
    - Use of any of the prohibited medications in the "List of Prohibited Medications" within a time period prior to surgery that was less than the minimum 'washout' period noted in the table below. NOTE: (i) These medications were not to be used from the beginning of the 'Washout' period in "List of Prohibited Medications" until after Visit 5 (POD15) assessments, but preferably until after Visit 6 (POD22) assessments; (ii) Medications for anesthesia related to cataract surgery, ocular pain control and non-prostaglandin-based therapy for the treatment of raised IOP were allowed on the day of surgery only
- Non-approved drugs or investigational products other than the study drug in this study were prohibited from 28 days before surgery until after the subject has been released from the study
- Had an IOP < 5 mmHg or > 22 mmHg in either eye or a difference of > 5 mmHg between the eyes at Visit 1 (Screening)
- Had a history of documented and repeated elevated IOP or glaucoma
- History of herpes keratitis in the study eye
- Had active corneal abrasions or ulcers in the study eye
- Had active or a history of chronic or recurrent inflammatory eye disease (ie. iritis, scleritis, uveitis, iridocyclitis, rubeosis iridis) in the study eye
- Had evidence of acute external ocular infections (bacterial, viral and/or fungal infections including vaccinia, varicella and other viral diseases of the cornea and conjunctiva);

tuberculosis of the eye; intraocular infections, active chalazion, or uncontrolled severe blepharitis in the study eye

- Had corneal dystrophies, including corneal guttae and Fuchs' dystrophy, or dysthyroid ophthalmopathy in the study eye
- Had uncontrolled and clinically significant dry eye syndrome in the study eye (mild dry eye with the use of artificial tears was allowed)
- Had PDR, significantly compromised macular function, significant macular disease, had clinically-significant macular edema or a history of cystoid macular edema in the study eye; had c/d ratio > 0.8
- Had corneal or retinal surgery (laser or incisional) in the study eye within 6 months of Visit 1 (Screening), or were planning to have laser or incisional surgery during the study period in the study eye (other than cataract surgery)
- Had ocular surgery planned, scheduled or performed on the contralateral eye within the 2 months prior to the surgery on the study eye
- Had previous ocular trauma with visible scarring or any deformities due to the trauma in the study eye that in the opinion of the Investigator may affect the pharmacokinetics of the study drug, or post-surgical outcome (including, but not limited to intraocular inflammation, IOP or the normal healing process)
- Required the use of a contact lens or a collagen shield within 72 hours prior to cataract surgery or for the remainder of the study period in either eye
- Required use of non-diagnostic topical ophthalmic medications in either eye for the duration of the study with the exception of the following which were allowed: mydriatics, anesthetics, antiseptics, balanced salt solution, viscoelastics, osmotic agents (i.e., Muro 128), prophylactic antibiotics, nonprostaglandin analog IOP-lowering agents for IOP increases on the day of cataract surgery, lid scrubs for mild blepharitis, or artificial tears for the management of mild dry eye.
- In the opinion of the Investigator, had the potential for ocular hemorrhage in the study eye that could interfere with evaluation of post-surgery inflammation
- Had a planned use of or used femtosecond laser or any other ophthalmic surgical procedure (ie. vitrectomy, relaxing incisions, iridectomy, conjunctival excisions, use of iris hooks or other iris dilators, etc.) in addition to the cataract extraction procedure via phacoemulsification and PCIOL implantation in the study eye
- Had a planned use of or used anterior capsule staining for capsulorhexis (i.e., trypan blue) during cataract surgery
- Had planned to participate in another clinical trial during the duration of this study
- Had participated in another clinical study or received any investigational product within the past 28 days prior to Visit 1 (Screening). Subjects who previously participated in Study CPN-201 were eligible if the planned cataract surgery was for the eye that was the 'non-study' eye in that study. Had any other condition that the Investigator determined should exclude the subject from the trial

- Were an employee of a clinical site that was directly involved in the management, administration, or support of this study or were an immediate family member of the same

Treatments Administered

Subjects were randomized to receive APP13007 or matching vehicle placebo. Subjects administered double-masked study drug BID into the study eye for a period of 14 days, starting at Visit 2 (POD1) and ending on POD14. The first dose of double-masked study drug was self-administered onsite at the clinic by the subject under the supervision of clinic staff. The dose instilled onsite during the POD1 visit was considered the morning dose of study drug in the BID schedule. The second dose of the study drug on POD1 was administered by the subject at >=6 hours after the first dose outside the clinic.

Investigational Product

APP13007 is a sterile, opalescent, ophthalmic aqueous nanosuspension of the active ingredient, clobetasol propionate 0.05%, developed for topical ophthalmic use and administered as eyedrops. The matching vehicle placebo in this study had an identical appearance and formulation composition of the excipients to APP13007, with the exception that the matching vehicle placebo did not contain the active ingredient. A single batch of APP13007 and a single batch of the matching placebo were used in this study. The batch number for the APP13007 used in this study was TR016. The batch number for the matching vehicle placebo used in this study was TR015. If required replacement bottles of study drug were prior to POD15 was queried and the replacement was documented in the eCRF. Both APP13007 and its matching placebo were formulated as preserved (with benzalkonium chloride) eye drops and packaged in opaque low-density polyethylene (LDPE) 5 mL round dropper bottles with a LDPE tip (nozzle) and tightly closed with a pink cap made with high density polyethylene (HDPE).

Rescue Medication

Any subjects who had evidence of persistent or worsening post-operative inflammation were eligible to be rescued and placed on appropriate alternate therapy selected at the Investigator's discretion. The need for rescue was not considered an AE. Rescued subjects were considered treatment failures and stopped administration of the study drug. Rescued subjects placed on an alternate therapy were not withdrawn from the study and were asked to continue attending each subsequent visit after rescue medication was started, if possible, through completion of the Visit 6 (POD22).

Study Flow Chart

Table 4 Schedule of Events

PROCEDURE/ASSESSMENTS [1]	Visit 1 Screening (Day -28 to -1)	Surgery [2] Day 0	Visit 2 POD1 [3]	Visit 3 POD4 (±1 Day)	Visit 4 POD8 (±1 Day)	Contact POD14	Visit 5 POD15 (+1 Day) [4]	Visit 6 POD22 (±2 Days) [5]
ICF, Demography, Medical History	X							
Determine Eligibility, Review Inclusion/Exclusion Criteria	X		X					
Urine pregnancy test only for WOCBP			X				X	
Ocular Symptoms Assessment [6]	X		X	X	X		X	X
ETDRS Visual Acuity	X		X	X	X		X	X
Slit-lamp Biomicroscopy [7]	X		X	X	X		X	X
Indirect Ophthalmoscopy (dilated)	X							X
IOP (Goldmann applanation tonometry) [8]	X		X	X	X		X	X
Randomization			X					
Dispense Study Drug			X					
Study Drug Dosing BID for 14 days (POD1 to POD14) [9]			X	X	X	X		
Dispense Diary Card (with instructions for completion)			X	X	X			
Contact Subject [10]						X		
Collect Study Drug							X	
Collect and Check Diary Cards for Accuracy and Compliance				X	X		X	
AEs [7] and Concomitant Medications [11]	X	X [12]	X	X	X	X [13]	X	X

[1] Ophthalmic assessments were performed in the study eye only at Visits 2-5 and were performed on both eyes at Visit 1 (Screening) and at Visit 6 (POD22), or at subject Early Termination/Withdrawal.
[2] Surgery occurred between 1 to 28 days after Visit 1 (Screening), preferably in the morning. If, due to unexpected events, surgery was postponed and would occur > 28 days past the Screening visit, the Study Medical Monitor was contacted to discuss which, if any, of the screening procedures should be repeated. Subjects were determined to be a suitable candidate for surgery during a pre-surgery medical assessment, where the routine medication list prescribed by the cataract surgeon was reviewed to rule out prohibited medications.
[3] Visit 2 (POD1) was scheduled between 18 to 34 hours following conclusion of surgery on Day 0. All assessments done on POD1 were done prior to Randomization to ensure eligibility. Note: Women-of-childbearing-potential (WOCBP) were eligible for enrollment if they had a negative urine pregnancy test on POD1 prior to Randomization and they agreed to abstinence from sexual activity or use of highly effective method of contraception.
[4] Visit 5 (POD15) occurred on the day after the subject completed the study drug administration for 14 days. Women-of-childbearing-potential had a urine pregnancy test.
[5] Visit 6 (POD22) was the last visit for subjects who completed the study. Subjects who were withdrawn early had the Visit 6 assessments and a urine pregnancy test performed prior to their release from the study.
[6] Included assessments of ocular pain and irritation.
[7] Ocular inflammation assessment using ACC count, anterior chamber flare grade, bulbar conjunctival injection, sclera - ciliary flush and corneal edema.
[8] IOP was assessed at each visit, when possible, within ± 2 hours of the IOP assessment time at Visit 1.
[9] The first dose of study drug was instilled into the study eye at the clinic visit under supervision of clinic staff. The second dose on POD1 could be administered at home. Subjects who were rescued did not continue to instill study drug or receive further diary cards but remained in the study to complete the procedures/assessments through Visit 6 (POD22).
[10] The site contacted the subject via the subject's preferred method on POD14 to remind him/her not to instill study drug on POD15 and to bring the bottle of study drug and the dosing diary back to the site at the POD15 visit.
[11] Concomitant medications used for rescue were reported in the eCRF.
[12] AEs and Concomitant Medications were only recorded on Day 0 if they resulted in disqualification (i.e., screen failure) of the subject; otherwise, the AEs and Concomitant Medications applicable to Day 0 were recorded when the subject returned for Visit 2 (POD1).
[13] Any AEs reported to the site during the POD14 contact were recorded in the source documents. Further assessment of any reported AEs could require an Unscheduled Visit on POD14 if medically significant or they could be assessed, as appropriate, during Visit 5 (POD15).

List of Investigators

Study CPN-301: List of Investigators

Study Center	Investigator	Number of Patients Enrolled
101	Thomas Richard Walters, MD 5717 Balcones Drive Austin, TX 78731	26
102	Joseph Martel, MD 11216 Trinity River Drive Rancho Cordova, CA 95670	23
103	Blair Boehmer, MD 10300N. Illinois Street Suite 1020 Carmel, IN 46290	1
106	Alice T. Epitropoulos, MD 262 Neil Avenue Suite 430 Columbus, OH 43215	5
107	Anna F. Fakadej, MD 2170 Midland Road Southern Pines, NC 28387	5
108	Raymond Fong, MD 109 Lafayette Street	18

Study Center	Investigator	Number of Patients Enrolled
	4th Floor New York, NY 10013	
109	Joseph Gira, MD 12990 Manchester Road Suite 201 St. Louis, MO 63131	3
110	Mohammad Ali Haider, DO 2932 Breckenridge Lane Suite 5 Louisville, KY 40220	12
112	Michael Korenfeld, MD 901 East Third Street Washington, MO 63090	36
113	Eva Liang, MD 330 S. Rampart Blvd. Suite 360 Las Vegas, NV 89145	25
115	Susanne Hewitt, MD 11205 Alpharetta Highway Suite J3 Roswell, GA 30076	2
116	Thomas LoBue, MD 40700 California Oaks Road Suite 106 Murrieta, CA 92562	29
117	Theodore Pasquali, MD 3300 E. South Street Suites 100 and 105 Long Beach, CA 90805	10
118	Robert Pendleton, MD 3637 Vista Way Oceanside, CA 92056	11
119	Mark Rubin, MD 1545 Hand Ave Suite B3 Ormond Beach, FL 32174	5
120	Kyle Rhodes, MD 3503 Wild Cherry Drive Bldg. 3 Lakeway, TX 78738	3
122	Charles Reilly, MD 5430 Fredericksburg Road Suite 100 San Antonio, TX 78229	7
123	Robert Sorenson, MD 3953 W. Stetson Ave. Hemet, CA 92545	9
124	Steven M. Silverstein, MD 4240 Blue Ridge Blvd.	21

Study Center	Investigator	Number of Patients Enrolled
	Suite 1000 Kansas City, MO 64133	
125	Da-Thuy Van, DO 6151 NW Loop 410 Suite 200 San Antonio, TX 78238	19
126	James A. Fox, MD 1000 Wellington Avenue Grand Junction, CO 81501	31
127	Kevin Y. Jong, MD 1415 North Loop West Suite 400 Houston, TX 77008	33
128	Robert John Smyth-Medina, MD 11550 Indian Hills Road Suite 341 Mission Hills, CA 91345	5
131	Ian K. Piovanetti Perez, MD 1250 Jesus T Pinero Avenue San Juan, Puerto Rico 00921	10
132	Peter DeBry, MD 2390 W Horizon Ridge Parkway Suite 100 Henderson, NV 89052	2
133	Bruce Silverstein, MD 900 Butte St Redding, CA 96001	7
135	Jeffrey Levenson, MD 751 Oak Street Suite 200 Jacksonville, FL 32204	20

Study Endpoints

Primary Efficacy Endpoint

ACC count was assessed by the Investigator using a slit-lamp biomicroscope and then graded on a 5-point numeric rating scale from 0 (0 cell) to 4 (> 30 cells).

Grade	0	1	2	3	4
ACC Count	0 cell	1-5 cells	6-15 cells	16-30 cells	> 30 cells

The first primary efficacy variable was the proportion of subjects with ACC count = 0 (ACC grade = 0) at POD8 maintained through POD15.

The second primary efficacy variable was the proportion of subjects with Ocular Pain Grade = 0 at POD4 maintained through POD15.

Secondary Efficacy Endpoints

- Proportion of subjects with ACC count = 0 [ACC Grade = 0] at PODs 4, 8 and 15
- Proportion of subjects with Ocular Pain Grade = 0 at PODs 4, 8 and 15
- Proportion of subjects with ACF Grade = 0 at POD8 maintained through POD15
- Proportion of subjects with ACF Grade = 0 at PODs 4, 8 and 15
- Mean change-from-baseline in ACC Grade at PODs 4, 8, and 15
- Mean change-from-baseline in Ocular Pain Grade at PODs 4, 8 and 15
- Mean change-from-baseline in ACF Grade on PODs 4, 8 and 15
- Number of subjects rescued on or prior to each visit and overall
- Mean change-from-baseline in BCVA assessed by pinhole method using an ETDRS chart at PODs 4, 8 and 15

Analysis Populations

The Intent-to-Treat (ITT) population consisted of all subjects who were randomized to the study drug. Subjects were analyzed according to the treatment assignment at randomization.

The Per-Protocol (PP) population consisted of all subjects in the ITT population who received at least 1 dose of study drug, did not have major protocol deviations that would impact the evaluation of efficacy, and had at least 80% overall treatment compliance. Subjects to be excluded from the PP population were identified prior to database lock and unmasking of the treatment assignment, and the reason for exclusion was documented and listed.

The safety population consisted of all randomized subjects who received at least 1 dose of study drug. Subjects were analyzed in the safety analysis according to the study drug treatment received.

Primary Efficacy Analysis

All efficacy analyses were performed using the ITT population. Primary efficacy analyses were also performed using the PP population as a sensitivity analysis.

The Pearson's Chi-square test was used to test the null hypothesis that there was no difference between treatment groups for the primary efficacy endpoints:

- The proportion of subjects with ACC count = 0 [ACC Grade = 0] at POD8 maintained through POD15
- The proportion of subjects with Ocular Pain Grade = 0 at POD4 maintained through POD15

The treatment comparisons of the primary efficacy endpoints were tested in a sequential order. The fixed-sequence hierarchical testing approach was used to adjust for multiple comparisons. The primary analysis first compared the proportion of subjects with ACC count = 0 (ACC grade = 0) at POD8, maintained through POD15, between APP13007 and the matching vehicle placebo.

If the test was statistically significant at the 2-sided $\alpha = 0.05$ level in favor of APP13007, the comparison of the proportion of subjects with Ocular Pain Grade = 0 at POD4, maintained through POD15, between APP13007 and matching vehicle placebo was then tested at the two sided $\alpha = 0.05$ level. Under the hierarchical testing scheme, once the 2-sided p-value exceeded 0.05, the comparison of endpoints further down in the sequence was not claimed for statistical significance. 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.

6.2. CPN-302: A Multicenter, Randomized, Double-Masked, Placebo-Controlled, Parallel- Group Study to Evaluate the Efficacy and Safety of APP13007 for the Treatment of Inflammation and Pain after Cataract Surgery, Including a Corneal Endothelial Cell Sub-study

6.2.1. Study Design

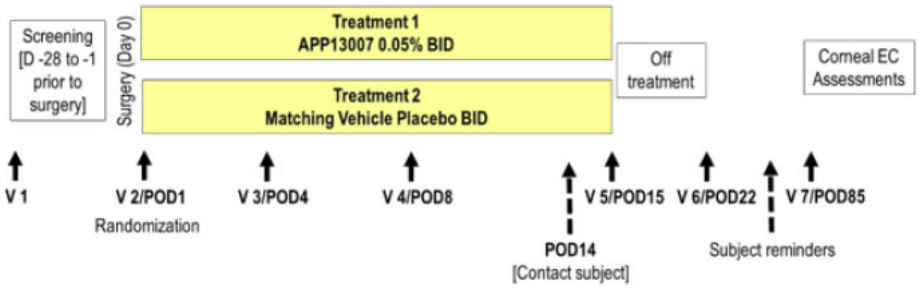
Overview and Objective

The primary efficacy objective was to investigate the efficacy of APP13007 versus matching vehicle placebo for the treatment of inflammation and pain through post-operative day (POD) 15 after cataract surgery in the study eye.

Trial Design

This was a Phase 3, multicenter, randomized, double-masked, placebo-controlled, parallel-group study in subjects experiencing ocular inflammation and pain following routine cataract surgery without complications. The study comprised the Main Study (all subjects) and the Corneal Endothelial Cell Sub-study (only those subjects from the Main Study meeting specific criteria for the Sub-study). Approximately 370 subjects were planned to be randomized (approximately 185 subjects per treatment group) in the Main Study across multiple sites in the US. The Sub-study was planned to comprise a subgroup of approximately 176 subjects at study sites qualified to perform the assessment of corneal endothelial cell parameters (endothelial cell density [cells/mm2], percent hexagonality and coefficient of variation).

Figure 2: Schematic Diagram of the Study Design for CPN-302



BID=twice daily; D=Day; EC=endothelial cell; POD=post-operative day; V=visit

At Visit 2 (Baseline; Randomization; POD1), subjects were eligible for randomization to APP13007 or matching vehicle placebo via the electronic data capturing (EDC)/Interactive Webbased Response (IWRS) system. Women of childbearing potential (WOCBP) had a urine pregnancy test at the POD1 visit prior to randomization. Randomized subjects received the first dose of the study drug at the study site and then returned for ocular assessments of the operated study eye on Visit 3 (POD4; ±1 day), Visit 4 (POD8; ±1 day), and Visit 5 (POD15; +1 day). Eligible subjects were randomized to one of the following 2 treatment groups in a 1:1 ratio:

- Treatment 1: 1 drop APP13007 BID for 14 days instilled to the operated study eye.
- Treatment 2: 1 drop matching vehicle placebo BID for 14 days instilled to the operated study eye.

Randomized subjects returned for the POD15 visit for ocular assessments on the study eye. The study drug bottle and dosing diary were collected from subjects during the POD15 visit. WOCBP had a urine pregnancy test at the POD15 visit. Subjects were instructed to return for the POD22 visit after the POD15 visit assessments had been completed. Subjects returned for a clinic visit on POD22 (Visit 6; POD22 ±2 days). Subjects not participating in the Sub-study were released from the study after completion of the assessments including those in both the study and non-study eyes. Subjects participating in the Sub-study underwent measurement of corneal endothelial cell parameters in the study eye. Subjects who were discontinued from the study early or who withdrew from the study were required to complete Visit 6 assessments and a urine pregnancy test [only for WOCBP] at the time of early termination/withdrawal, or as soon as possible thereafter. Visit 6 (POD22 ±2 days; or Early Termination/Withdrawal from the Main study) served as an End of Study visit for subjects not participating in the Sub-study.

Subjects in the Sub-study returned for the POD85 visit (Visit 7, ±4 days) for assessments, which included further measurement of corneal endothelial parameters in the study eye and recording of AEs and concomitant medications. Subjects who were discontinued or withdrew from the study after POD22 and before POD85 were required to complete POD85 assessments at the time of early termination/withdrawal, or as soon as possible thereafter. Visit 7 (POD85

±4 days; or Early Termination/Withdrawal from the Sub-study) served as an End of Study visit for subjects participating in the Sub-study.

Inclusion Criteria
Identical to CPN-301.

Exclusion Criteria
Identical to CPN-301 except for the following:

Additional Considerations for the Sub-study
For participation in the Sub-study, in addition to the Inclusion and Exclusion criteria listed above, the following two criteria applied:

- Subjects with Type 1 diabetes mellitus were excluded from the sub-study
- Subjects with a central corneal endothelial cell density <1800 cells/mm2 in either eye at
- the Screening visit were excluded from the sub-study, but participation in the main study was allowed

Treatments Administered/Investigational Product
Identical to CPN-301.

Rescue Medication
Any subjects who had evidence of persistent or worsening post-operative inflammation (evidence of lack of efficacy) were eligible to be rescued and placed on appropriate alternate therapy selected at the Investigator's discretion. The need for rescue was not considered an AE. Rescued subjects were considered treatment failures and stopped administration of the study drug. Rescued subjects placed on an alternate therapy were not withdrawn from the study and were asked to continue attending each subsequent visit after rescue medication was started, if possible, through completion of the Visit 6 (POD22) assessments (if participating in the Main Study only) or Visit 7 (POD85) assessments (if participating in the Sub-study) or until the Investigator determined the subject could be released from the study.

Study Flow Chart

Table 4 Schedule of Events

PROCEDURE/ASSESSMENTS [1]	Visit 1 Screening (Day -28 to -1)	Surgery[2] Day 0	Visit 2 POD1[3]	Visit 3 POD4 (±1 Day)	Visit 4 POD8 (±1 Day)	Contact POD14	Visit 5 POD15 (+1 Day)[4]	Visit 6 POD22 (±2 Days)[5]	Reminders (~POD50 & ~POD78)	Visit 7 POD85 (±4 Days)[6]
ICF, Demography, Medical History	X									
Determine Eligibility, Review Inclusion/Exclusion Criteria	X		X							
Urine pregnancy test only for women of child-bearing potential			X				X			
Ocular Symptoms Assessment [7]	X		X	X	X		X	X		
ETDRS Visual Acuity	X		X	X	X		X	X		
Slit-lamp Biomicroscopy [8]	X		X	X	X		X	X		
Indirect Ophthalmoscopy (dilated)	X							X		
IOP (Goldmann applanation tonometry) [9]	X		X	X	X		X	X		
Corneal Endothelial Cell Parameters [10]	X							X		X
Randomization			X							
Dispense Study Drug			X							
Study Drug Dosing BID for 14 days (POD1 to POD14) [11]			X	X	X	X				
Dispense Diary Card (with instructions for completion)			X	X	X					
Contact Subject [12]						X			X	
Collect Study Drug							X			
Collect and Check Diary Cards for Accuracy and Compliance				X	X		X			
AEs [7] and Concomitant Medications [13]	X	X [14]	X	X	X	X [15]	X	X		X [15]

Abbreviations: POD=post-operative day; ICF=Informed Consent; EDTRS= Early Treatment Diabetic Retinopathy Study; IOP=Intra-Ocular Pressure; BID=twice daily; AEs=Adverse Events

[1] Ophthalmic assessments were performed in the study eye only at Visits 2-5 and Visit 7, and on both eyes at Visit 1 (Screening) and at Visit 6 (POD22) or at subject Early Termination/Withdrawal. In the Sub-study, corneal endothelial cell parameters were measured in both eyes at Screening and in the study eye only at Visit 6 (POD22) and Visit 7 (POD85).

[2] Surgery occurred between 1 to 28 days after Visit 1 (Screening), preferably in the morning. If, due to unexpected events, surgery was postponed and would occur > 28 days past the Screening visit, the Study Medical Monitor was contacted to discuss which, if any, of the screening procedures should be repeated. Subjects were determined to be a suitable candidate for surgery during a pre-surgery medical assessment, where the routine medication list prescribed by the cataract surgeon was reviewed to rule out prohibited medications.

[3] Visit 2 (POD1) was scheduled between 18 to 34 hours following conclusion of surgery on Day 0. All assessments done on POD1 were done prior to Randomization to ensure eligibility. Note: Women-of-childbearing-potential were eligible for enrollment if they had a negative urine pregnancy test on POD1 prior to Randomization and they agreed to abstinence from sexual activity or use of highly effective method of contraception.

[4] Visit 5 (POD15) occurred on the day after the subject completed the study drug administration for 14 days. Women-of-childbearing-potential had a urine pregnancy test.

[5] Visit 6 (POD22) was the last visit for subjects participating in the Main Study only. Subjects who were withdrawn early had the Visit 6 assessments and a urine pregnancy test performed prior to their release from the study.

[6] Visit 7 (POD85) was the last visit for subjects participating in the Sub-study. Subjects in the Sub-study who withdrew early after POD22 had Visit 7 assessments performed prior to their release

[7] Included assessments of ocular pain and irritation.

[8] Ocular inflammation assessment using ACC count, anterior chamber flare grade, bulbar conjunctival injection, sclera – ciliary flush and corneal edema.

[9] IOP was assessed at each visit, when possible, within ± 2 hours of the IOP assessment time at Visit 1.

[10] Only performed in the subjects in the Sub-study at participating centers, testing: endothelial cell density (cells/mm^2), percent hexagonality and coefficient of variation. Performed in both eyes at the Screening visit and in the study eye at Visit 6 (POD22) and Visit 7 (POD85)

[11] The first dose of study drug was instilled into the study eye at the clinic visit under supervision of clinic staff. The second dose on POD1 could be administered at home. Subjects who were rescued did not continue to instill study drug or receive further diary cards but remained in the study to complete the procedures/assessments through Visit 6 (POD22) (Main Study) or Visit 7 (Cell Sub-study).

[12] The site contacted the subject via the subject's preferred method on POD14 to remind him/her not to instill study drug on POD15 and to bring the bottle of study drug and the dosing diary back to the site at the POD15 visit. In addition, the subjects in the Sub-study were sent U.S. mail/email/voicemail/text message reminders on ~POD50 and ~POD78 to return for Visit 7 (POD85).

[13] Concomitant medications used for rescue were reported in the eCRF.

[14] AEs and Concomitant Medications were only recorded on Day 0 if they resulted in disqualification (i.e., screen failure) of the subject; otherwise, the AEs and Concomitant Medications applicable to Day 0 were recorded when the subject returned for Visit 2 (POD1).

[15] Any AEs reported to the site during the POD14 contact or because of the POD50/POD78 reminders were recorded in the source documents. Further assessment of any reported AEs could require an Unscheduled Visit if medically significant or could be assessed, as appropriate, during Visit 5 (POD15) or Visit 7 (POD85), respectively.

Reviewer's Comment:

The PIND meeting (IND 128,133) on 1/21/16 states on p. 6 of the meeting minutes "It is recommended that the topical clinical program include enough patients to identify adverse events that occur at a rate of 1% or greater. To accomplish this, it is recommended that approximately 500 or more subjects using the test drug product complete treatment with a concentration of the test drug product at least as high as proposed for marketing with a frequency at least as frequent as proposed for marketing. Safety should be demonstrated in at least 300 patients who have completed 14 days of follow-up after the initiation of treatment using the proposed dosing regimen (including concentration)."

Study CPN-302 only studied safety after 7 days of initiation of treatment. At the POD85 only ECC cell counts were examined.

List of Investigators

Study CPN-302: List of Investigators

Study Center	Investigator	Number of Patients Enrolled
151	Jason Bacharach, MD 104 Lynch Creek Way Suite 12 Petaluma, CA 94954	6
152	Jonathan Eric Downing, MD 420 E. 3rd Street Suite 603 Los Angeles, CA 90013	13
153	Damien Goldberg, MD 23600 Telo Avenue Suite 100 Torrance, CA 90505	10
154	John D. Goosey, MD 2855 Gramercy Street Houston, TX 70025	16
155	David Vroman, MD 137 Gateway Drive Ladson, SC 29456	2
156	Robert Gross, MD 3815 E Bell Road Suite 2500 Phoenix, AZ 85032	10
157	Jeffrey Levenson, MD 751 Oak Street Suite 200 Jacksonville, FL 32204	48
158	Parag A. Majmudar, MD 1585 N. Barrington Road Suite 502 Hoffman Estates, IL 60169	2
159	Michael Nordlund, MD 1945 CEI Drive Cincinnati, OH 45242	13
160	Bernard R. Perez, MD 4506 Wishart Place Tampa, FL 33603	5
161	Stephen E. Smith, MD 4225 Evans Avenue Fort Myers, FL 33901	7
163	Stephen S. Khachikian, MD 2800 Third Street Rapid City, SD 57701	5
164	Norman Lui, MD 12665 Garden Grove Blvd. Suite 401 Garden Grove, CA 92843	31

Study Center	Investigator	Number of Patients Enrolled
165	Ranjan Malhotra, MD 12990 Manchester Road Suite 200 St. Louis, MO 63131	25
166	Harvey James Reiser, MD 703 Rutter Avenue Kingston, PA 18704	26
167	Ehsan Sadhri, MD 361 Hospital Road Suite 324 Newport Beach, CA 92663	29
169	Michael Stiles, MD 7200 W. 129th Street Overland Park, KS 66213	1
170	Michael Khanah Le Tran, MD 15355 Brookhurst Street Suite 104 Westminster, CA 92683	17
171	Brennan P. Greene, MD 1536 Story Avenue Louisville, KY 40206	16
172	Kent L. Wellish, MD 2110 E. Flamingo Road Suite 210 Las Vegas, NV 89119	30
173	Andreas Wolter, MD 23 Davis Avenue Poughkeepsie, NY 12603	8
175	Mahdi Basha, DO 33080 Utica Road Suite B Fraser, MI 48026	10
176	Jennifer Lee Kim, MD 1000 Corporate Center Drive Suites 100 and 120 Morrow, GA 30260	11
177	Joseph Meyer, MD 1880 Round Rock Avenue Suite 100 Round Rock, TX 78681	2
178	El-Roy Dixon, MD 806 North Jefferson Street Albany, GA 31701	1
179	David S. Chu, MD 540 Bergen Blvd. Palisades Park, NJ 07650	5
181	Pankajkumar Gopaldas Shah, MD 1506 E. Griffin parkway Mission, TX 78572	16

Study Center	Investigator	Number of Patients Enrolled
183	Thomas LoBue, MD 40700 California Oaks Road Suite 106 Murrieta, CA 92562	4
184	Michael Depenbusch, MD 1500W. Ray Road Chandler, AZ 85224	1

Study Endpoints

Primary Efficacy Endpoint
ACC count was assessed by the Investigator using a slit-lamp biomicroscope and then graded on a 5-point numeric rating scale from 0 (0 cell) to 4 (> 30 cells).

Grade	0	1	2	3	4
ACC Count	0 cell	1-5 cells	6-15 cells	16-30 cells	> 30 cells

The primary efficacy variables were assessed sequentially.

- The first primary efficacy variable was the proportion of subjects with ACC count = 0 (ACC grade = 0) at POD8 maintained through POD15
- The second primary efficacy variable was the proportion of subjects with Ocular Pain Grade = 0 at POD4 maintained through POD15

Secondary Efficacy Endpoints
Identical to CPN-302.

Statistical Analysis Plan/Analysis Populations
Identical to CPN-301.

Primary Efficacy Analysis
Identical to CPN-301.

6.3. CPN-301 and CPN-302 Study Results

Compliance with Good Clinical Practices

Financial Disclosure
See Section 13.2 for the financial disclosure template.

Patient Disposition

Study CPN-301: Subject Disposition

	APP13007	Vehicle
Number of randomized subjects	181	197
ITT population	181	197
Safety population	181	197
PP population	175	195
Study completed	180	197
Discontinued study early	1	0
Reason for subject withdrawal		
Consent withdrawn	0	0
AE	0	0
Investigator discretion	1	0
Lost to f/u	0	0
Other	0	0

Study CPN-302: Subject Disposition

	APP13007	Vehicle
Number of randomized subjects	185	185
ITT population	185	185
Safety population	184	185
PP population	180	178
Study completed	179	179
Discontinued study early	6	6
Reason for subject withdrawal		
Consent withdrawn	1	3
AE	0	1
Investigator discretion	1	0
Lost to f/u	2	1
Other	2	1
Randomized in the Sub-Study	75	76
Study completed	70	73
Discontinued study early	5	3
Reason for subject withdrawal Sub-study		
Consent withdrawn	1	1
AE	0	0
Investigator discretion	1	1
Lost to f/u	2	1
Other	1	1

Table of Demographic Characteristics

Study CPN-301: Demographics

	APP13007 N=181	Vehicle N=197
Age		
Mean	68.7 (8.9)	67.8 (8.6)
Min, max	30, 91	33, 87
<65	39	56
>=65	142	141
Male	75	78
Female	106	119
Ethnicity		
Hispanic or Latino	35	52
Not Hispanic or Latino	146	145
Race		
American Indian	1	1
Asian	11	16
African American	18	27
Native Hawaiian	0	0
White	150	151
Multiple	1	2
Iris Color		
Blue	49	42
Brown	101	123
Other	31	32

Study CPN-302: Demographics

	APP13007 N=185	Vehicle N=185
Age		
Mean	67.2 (9.7)	68.0 (8.4)
Min, max	30, 89	30, 87
<65	61	48
>=65	124	137
Male	87	88
Female	98	97
Ethnicity		

	APP13007 N=185	Vehicle N=185
Hispanic or Latino	38	35
Not Hispanic or Latino	147	150
Race		
American Indian	0	0
Asian	15	17
African American	20	22
Native Hawaiian	0	1
White	150	145
Multiple		
Iris Color		
Blue	41	50
Brown	115	112
Other	29	23

Efficacy Results – Primary Endpoint

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	
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%)	

	APP13007 N=181	Vehicle N=197	P-value
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%)	
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).

Data Quality and Integrity

No issues related to data quality or data integrity were identified in this review.

Secondary Efficacy and other relevant 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
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%.

Rescue Medication

More subjects in the placebo group (116 subjects [58.9%]) than the APP13007 group (16 subjects [8.8%]) required at least one rescue medication up to POD15 (this includes subjects who were rescued during the treatment period and after end of treatment). The most common rescue medications (including tapering regimens of the initial rescue medication) in both the APP13007 and placebo groups, respectively, were prednisolone acetate eye drops and prednisolone eye drops.

Dose/Dose Response

Only one dose was studied.

Durability of Response/Persistence of Effect

This product is only intended for short-term use for the post-operative period so there was no evaluation of durability.

Additional Analyses Conducted

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

	APP13007 N=175	Vehicle N=195	P-value
Absence of Anterior Chamber Cells at Day 8-Yes (Responder)	46 (26.3%)	10 (5.1%)	<0.001
Absence of Anterior Chamber Cells at Day 8-No (Non-responder)	129 (73.7%)	185 (94.9%)	

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

	APP13007 N=175	Vehicle N=195	P-value
Absence of Pain at Day 8-Yes (Responder)	119 (68.0%)	46 (23.6%)	<0.01
Absence of Pain at Day 8-No (Non-responder)	56 (32.0%)	149 (76.4%)	

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

	APP13007 N=180	Vehicle N=178	P-value
Absence of Anterior Chamber Cells at Day 8-Yes (Responder)	49 (27.2%)	16 (9.0%)	<0.001

	APP13007 N=180	Vehicle N=178	P-value
Absence of Anterior Chamber Cells at Day 8-No (Non-responder)	131 (72.8%)	162 (91.0%)	

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

	APP13007 N=180	Vehicle N=178	P-value
Absence of Pain at Day 8-Yes (Responder)	137 (76.1%)	58 (32.6%)	<0.001
Absence of Pain at Day 8-No (non-responder)	43 (23.9%)	120 (67.4%)	

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The main support for efficacy comes from two trials (CPN-301 and CPN-302).

7.1.1. Primary Endpoints

The primary and secondary efficacy objectives of both studies were achieved. Treatment with APP13007 BID for 14 days after cataract surgery resulted in a statistically significantly greater proportion of subjects with complete clearance of ocular inflammation from POD8 and complete absence of ocular pain from POD4 maintained through POD15 compared with matching vehicle placebo.

7.1.2. Secondary and Other Endpoints

See Section 6.1.2.

7.1.3. Subpopulations

The primary efficacy analysis was also performed on the following subgroups of the ITT Population: age group (<65 or ≥65 years); [redacted] race (white, non-white); and iris color (blue, brown, and other) for both studies. No statistical comparisons were made between these subgroups. Greater efficacy was observed in the APP13007 group than the placebo group for both primary endpoints in all subgroups (by age, [redacted] race, and iris color) for both studies.

7.1.4. Dose and Dose-Response

Only one dose was studied.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

This product is only intended for short-term use for the post-operative period so there was no evaluation of durability.

7.2. Additional Efficacy Considerations

None.

7.3. Integrated Assessment of Effectiveness

The primary and secondary efficacy objectives of the study were achieved. Treatment with APP13007 BID for 14 days after cataract surgery resulted in a statistically significantly greater proportion of subjects with complete clearance of ocular inflammation from POD8 and complete absence of ocular pain from POD4 maintained through POD15 compared with placebo. Results of all sensitivity and additional analyses, together with all secondary efficacy endpoint analyses, support the efficacy of APP13007 BID for 14 days for the treatment of post-operative ocular inflammation and pain.

8. Review of Safety

8.1. Safety Review Approach

The main support for safety comes from two trials (CPN-301 and CPN-302). In addition, on 8/31/23 (SDN-7) the Sponsor submitted the 120 Day Safety update and stated: “we have not identified any new safety concerns or adverse events related to the use of APP13007. At the time of the NDA submission there were no ongoing clinical or non-clinical studies of APP13007, and no new studies have been initiated since then. As such the safety data submitted with the original NDA are the only safety data available for APP13007 to date.”

8.2. Review of the Safety Database

8.2.1. Overall Exposure

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)

	AP13007 N=181	Vehicle N=197
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

8.2.2. Relevant characteristics of the safety population

The safety population is representative of the population that the drug product is intended to treat.

8.2.3. Adequacy of the safety database

The safety database is adequate with respect to size, duration of exposure, duration of treatment, patient demographics, and disease characteristics.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

This submission was of sufficient quality to allow for a substantive review. No issues related to

data quality or data integrity were identified in this review.

8.3.2. Categorization of Adverse Events

All adverse events in CPN-301 and CPN-302 were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.1 (Sep 2020) and classified by system organ class (SOC) and preferred term (PT).

8.3.3. Routine Clinical Tests

See section 8.4.6.

8.4. Safety Results

8.4.1. Deaths

There were no deaths reported in either CPN-301 or CPN-302.

8.4.2. 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).

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

CPN-301: Two patients discontinued from the study due to an AE (both in the APP13007 group) for nausea and visual impairment.

CPN-302: Two patients discontinued from study due to an AE (both in the placebo group) for anterior chamber fibrin and hypopyon.

8.4.4. Significant Adverse Events

See section 8.4.2.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

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

	AP13007 N=181	Vehicle N=197
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
Cardiac disorders		
CHF	0	1
Injury		
Alcohol poisoning	0	1
Joint injury	0	1
Musculoskeletal disorders		
Neck pain	0	1

	AP13007 N=184	Vehicle N=185
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.*

8.4.6. Laboratory Findings

No clinical laboratory evaluations were performed in either study CPN-301 or CPN-302. A urine pregnancy test was performed on female subjects of childbearing potential at Visit 2 (POD1) prior to randomization and Visit 5 (POD15). There were no positive pregnancy tests reported.

8.4.7. Vital Signs

No vital sign evaluations or physical examinations were performed during either study CPN-301 or CPN-302.

8.4.8. Electrocardiograms (ECGs)

Not performed.

8.4.9. QT

Not performed.

8.4.10. Immunogenicity

Not performed.

8.5. Analysis of Submission-Specific Safety Issues

N/A.

8.5.1. IOP Elevation

CPN-301: The majority of subjects in both treatment groups had reductions in the IOP (change ≤0 mmHg) from baseline at POD4, POD8, POD15, and POD22 in the study eye. Two subjects, both in the APP13007 group, had IOP increases that met the protocol-specified AE criteria (one had an IOP of 37 mmHg on POD8 and the other had an IOP of 22 mmHg on POD4 that represented an 11 mmHg increase from baseline). Neither TEAEs required discontinuation of

the study drug. The IOP of 37 mmHg resolved upon using IOP-lowering medication; the other IOP TEAE did not require treatment.

CPN-302: The majority of subjects in both treatment groups had reductions in the IOP (change ≤0 mmHg) from baseline at POD4, POD8, POD15, and POD22 in the study eye. Only 1 subject in the APP13007 group (Subject (b) (6) had an IOP increase of >10 mmHg from baseline at POD22; no elevations of >10 mmHg were reported in any other subject or at any other visit. Note that Subject (b) (6) (on APP13007) had a Screening IOP of 22 mmHg, was treated with a dorzolamide/timolol eyedrop on the day of surgery prior to receiving study drug which caused the baseline IOP on POD1 to decrease to 11 mmHg; while the IOP at POD22 was 21 mmHg, 1 mmHg less than the Screening IOP value.

8.6. Safety Analyses by Demographic Subgroups

Not performed.

8.7. Specific Safety Studies/Clinical Trials

Study CPN-302 also examined corneal endothelial cell counts. Corneal endothelial cell specular microscope images of the study eye were obtained by the study centers at Screening and Visit 7 (POD85) approximately 3 months after the start of study drug dosing and two and a half months after last dose of study drug.

CPN-302: Endothelial Cell Counts

	APP13007	Vehicle
Baseline	N=75	N=76
Mean cells/mm^2 (SD)	2508 (306)	2517 (400)
Min, Max	1878, 3085	1806, 3360
POD85	N=66	N=70
Mean cells/mm^2 (SD)	2231 (504)	2179 (556)
Min, Max	773, 3028	882, 3341
Mean change from screening	-276 (408)	-354 (437)
Percent change from screening	11.1%	14.1%

Reviewer's Comment:
There were no clinically meaningful differences between the two treatment groups in the observed endothelial cell densities at Screening and at POD85 Visit, or in the changes of endothelial cell densities from Screening to POD85 Visit.

The PIND meeting (IND 128,133) on 1/21/16 states on p. 6 of the meeting minutes "it is recommended that at least 100 patients undergo endothelial cell assessments at a 3 month or later time point during the clinical development program." The study only studied 75 patients; however, this is acceptable.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

N/A.

8.8.2. Human Reproduction and Pregnancy

This product was not studied in pregnant women.

8.8.3. Pediatrics and Assessment of Effects on Growth

This product triggers PREA as a new indication. The Applicant requested a drug-specific waiver for all pediatric age groups for APP13007 and believes that the corticosteroid in APP13007 will not contribute any 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 a 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.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Clobetasol is a non-narcotic and does not have abuse potential.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

N/A.

8.9.2. Expectations on Safety in the Postmarket Setting

No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events.

8.9.3. Additional Safety Issues From Other Disciplines

N/A.

8.10. Integrated Assessment of Safety

The most common ocular adverse events for clobetasol reported in the study eye 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%. The benefits of using this drug product outweigh the risks for the above indication.

9. Advisory Committee Meeting and Other External Consultations

There were no issues identified in the review of the application that were thought to benefit from an Advisory Committee discussion.

10. Labeling Recommendations

See Appendix Section 13.3. This is DRAFT labeling, not final labeling. See the CDTL memo for final labeling.

11. Risk Evaluation and Mitigation Strategies (REMS)

No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events.

12. Postmarketing Requirements and Commitments

There are no recommended Post-marketing Requirements or Phase 4 Commitments.

13. Appendices

13.1. References

No additional literature references were identified that were utilized for this review.

13.2. 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)

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/s/

SONAL D WADHWA
02/29/2024 11:18:08 AM

RHEA A LLOYD
02/29/2024 11:58:05 AM