CLINICAL STUDY PROTOCOL

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.

PROTOCOL NUMBER: CPN-301

Protocol Version:	1.3 (Amendment 1)
Version Date:	18 May 2021
Study Sponsor:	Formosa Pharmaceuticals, Inc. 8F-6, No. 57, Fuxing North Road Songshan District, Taipei Taiwan 105, Republic of China
Sponsor US Representative:	[redacted]
Contract Research Organization for Study Management and Monitoring:	[redacted]
Study Medical Monitor:	[redacted]

APPROVAL SIGNATURE PAGE

Approved by [redacted]

[redacted] 18 May 2021
Chief Medical Officer Date

[redacted] 18 May 2021
Biostatistician Date

[redacted] May 18, 2021
Chief Development Officer Date

PRINCIPAL INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical Protocol No. CPN-301 (Version 1.3, Amendment 1) dated 18 May 2021 and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the Study in accordance with this protocol, current Good Clinical Practices and applicable FDA regulatory requirements:

Name of Principal Investigator:

Name:
Title:
Clinic:
Address:
Phone:

Signature Date

STUDY CONTACTS

SPONSOR REPRESENTATIVE

[redacted]

PRIMARY CONTACT OF SPONSOR REPRESENTATIVE
SPONSOR MEDICAL MONITOR

[redacted]

STUDY MEDICAL MONITOR CONTACT

[redacted]

SAE REPORTING CONTACT

[redacted]

SECONDARY CONTACT OF SPONSOR REPRESENTATIVE

[redacted]

CHANGES IN PROTOCOL AMENDMENT 1

This protocol is being amended to:

- Clarify the permitted and prohibited medications based on feedback from investigators and to permit vaccinations/immunizations
- Indicate that prohibited medications preferably should be withheld until after the POD22 assessments
- Correct minor formatting errors

This amendment applies to all clinical sites participating in this study.

TABLE OF CHANGES IN AMENDMENT 1

Protocol Section	Original Text	Amended Text (Bolded)
Synopsis and Section 4.3 (Exclusion Criterion 7) and Section 5.4.2	Subjects receiving therapy for macular degeneration (in either eye) with Eylea® (aflibercept), Avastin® (bevacizumab), Lucentis® (ranibizumab) or Visudyne® (verteporfin) are excluded	Subjects receiving therapy for macular degeneration (in either eye) with Eylea® (aflibercept), Avastin® (bevacizumab), Lucentis® (ranibizumab), **Beovu® (brolucizumab-dbll)** or Visudyne® (verteporfin) are excluded
Synopsis and Section 4.3 (Exclusion Criterion 7) and Section 5.4.2		**ii. PROKERA (preserved amniotic membrane) is excluded from 1 year prior to the Screening visit to the end of the study.**
Synopsis and Section 4.3 (Exclusion Criterion 7) and Section 5.4.2	from the beginning of the 'Washout' period in "List of Prohibited Medications" until after the POD15 assessments	from the beginning of the 'Washout' period in "List of Prohibited Medications" until after the POD15 assessments, **but preferably until after the POD22 assessments**
Synopsis and Section 4.3 (Exclusion Criterion 7) and Section 5.4.2	Anti-inflammatory agents, analgesics (including opioids, narcotics, nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, acetaminophen and other pain medications) or immune-modulating agents systemically or in either eye from the beginning of the 'Washout' period in the "List of Prohibited Medications"	Anti-inflammatory agents, analgesics (including opioids, narcotics, nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, acetaminophen and other pain medications) or immune-modulating agents systemically or in either eye from the beginning of the 'Washout' period in the "List of Prohibited Medications"

	until after the POD15 assessments. *Note: acetaminophen is permitted on the day of surgery.*	until after the POD15 assessments, **but preferably until after the POD22 assessments**. *Note:* ***(i) acetaminophen is permitted on the day of surgery; (ii) immunizations/vaccinations are permitted before and during the study.***
Synopsis and Section 4.3 (Exclusion Criterion 7) and Section 5.4.2	Systemic anti-inflammatory agents including acetaminophen, NSAIDS, acetylsalicylic acid (aspirin), and Lifitegrast. *Note: (i) Use of acetylsalicylic acid for cardiovascular prophylaxis (i.e., 81 mg dose QD) is allowed if dosage has been stable for at least 30 days prior to surgery and will remain stable for the duration of the study. (ii) Acetaminophen may be administered as needed pre- and post-operatively on the day of surgery.*	Systemic anti-inflammatory agents including acetaminophen, NSAIDS, acetylsalicylic acid (aspirin), and Lifitegrast. *Note: (i) Use of acetylsalicylic acid for cardiovascular prophylaxis (i.e., 81 mg dose QD) is allowed if dosage has been stable for at least 30 days prior to surgery and will remain stable for the duration of the study. (ii) Acetaminophen may be administered as needed pre- and post-operatively on the day of surgery,* ***(iii) Over-the-Counter preparations such as Fish Oils, Turmeric and Ginseng that may have mild anti-inflammatory effects are allowed.***
Synopsis and Section 4.3 (Exclusion Criterion 7) and Section 5.4.2	Systemic analgesics/pain relievers such as gabapentin, pregabalin, opioids	Systemic analgesics/pain relievers such as gabapentin, pregabalin, opioids ***Note: Marijuana/CBD-containing products have the same washout restrictions as "Systemic Analgesics" because they can affect pain perception***
Synopsis and Section 4.3 (Exclusion Criterion 7) and Section 5.4.2	Medications for benign prostatic hypertrophy (BPH) (e.g., finasteride). *Note: Investigators should consider excluding subjects who are taking or have taken α-1*	Medications for benign prostatic hypertrophy (BPH) (e.g., finasteride, **α-1 adrenergic receptor antagonists**) **are allowed based on the judgment of the**

	adrenergic receptor antagonists (eg. tamsulosin, silodosin, alfuzosin) because of the risk of intraoperative floppy iris syndrome. [28 Days]	**investigator**. *Note: Investigators should consider* ***the potential risk of intraoperative floppy iris syndrome in subjects*** *who are taking or have taken α-1 adrenergic receptor antagonists (eg. tamsulosin, silodosin, alfuzosin).* **[Stable dose for** 28 days**]**
Synopsis and Section 4.3 (Exclusion Criterion 7) and Section 5.4.2	Stable doses of anticholinergics and antidepressants are allowed. Alterations of the dose of anticholinergics and antidepressants (other than for prn use as a sleep aid) may be allowed following consultation with the Study Medical Monitor. Anticholinergic eye drops used to dilate the eye are allowed. Systemic anticholinergic drugs are allowed on the day of surgery. [90 days if altering the dose]	Additional new text **Note 1** **For anti-depressants used to treat depression: (i) Medication must not be washed-out for the purpose of enrollment in the study; (ii) Stable doses of anti-depressants are allowed; (iii) When the dose of an anti-depressant has been altered, the subject needs to be on the stable altered dose for at least 90 days prior to the day of surgery (Day 0).** **Note 2** **For anti-depressants used to treat pain: (i) The instructions provided for systemic analgesics/pain relievers apply, viz. at least a 14 day washout of the medication is required prior to the day of surgery (Day 0) continuing until the POD15 assessments have been completed.** **[See Note 1 and Note 2]**
Synopsis and Section 4.3 (Exclusion Criterion 14)	14. Have corneal dystrophies or dysthyroid ophthalmopathy in the study eye.	14. Have corneal dystrophies, **including corneal guttae and Fuchs' dystrophy**, or dysthyroid ophthalmopathy in the study eye.

Section 6.2.2 Day of Surgery	On Day 0, the surgeon will perform his/her routine cataract surgical procedure using phacoemulsification and implantation of a posterior chamber intraocular lens in the operated eye following the surgeon's usual pre-operative, operative, and post-operative procedures (with the exception of avoiding use of prohibited medications).	On Day 0, the surgeon will perform his/her routine cataract surgical procedure using phacoemulsification and implantation of a posterior chamber intraocular lens in the operated eye following the surgeon's usual pre-operative, operative, and post-operative procedures (with the exception of avoiding use of prohibited medications). **Aqueous release procedures are not permitted.**

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LIST OF ABBREVIATIONS

ACC	Anterior Chamber Cell
ACF	Anterior Chamber Flare
AE	Adverse Event
ANCOVA	Analysis of Covariance.
BID	Twice Daily
BPH	Benign Prostatic Hyperplasia
CME	Cystoid Macular Edema
ConMed	Concomitant Medications
CP	Clobetasol Propionate
CRF	Case Report Form
CRO	Contract Research Organization
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIPAA	Health Insurance Portability and Accountability Act
HPA	Hypothalamic-Pituitary-Adrenal
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IU/L	international units per liter
IWRS	Integrated Web Response System
kg	kilogram
LLOQ	Lower Limit of Quantification
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mg/kg	milligrams per kilogram
mm	millimeter
mmHg	millimeters of mercury
NSAID	Nonsteroidal Anti-inflammatory Drug
OTC	Over the Counter
PDR	Proliferative Diabetic Retinopathy
PHI	Protected Health Information
PI	Principal Investigator

PK	Pharmacokinetics
POD	Post-Operative Day
PP	Per-Protocol
PRN	As Needed
QD	Once Daily
QID	Four Times Daily
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SOA	Schedule of Assessments
SOP	Standard Operating Procedure
SRM	Study Reference Manual
SUSAR	Serious and Unexpected Suspected Adverse Reaction
TEAE	Treatment-Emergent Adverse Event

PROTOCOL SYNOPSIS

Protocol Synopsis	
Sponsor: Formosa Pharmaceuticals, Inc.	**US Representative:** [redacted]
Title of Study: 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	
Protocol Number: CPN-301	**Phase:** 3
Active Ingredient: [redacted]	
Name of Investigational Product: APP13007 [redacted]	
Description of Investigational Drug: APP13007	
Study Center(s): ~26 in the USA	
Study Duration: ~ 3-7 weeks from Screening to Final visit	
Study Objectives	**Study Endpoints**
Primary Efficacy Objective The primary efficacy objective is 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.	Primary Efficacy Endpoints • The proportion of subjects with Anterior Chamber Cell (ACC) Count = 0 [ACC Grade = 0] at post-operative day 8 (POD8), maintained through POD15 • The proportion of subjects with Ocular Pain Grade = 0 at POD4, maintained through POD15
Secondary Efficacy Objective The secondary efficacy objective of this study is to investigate the effect of APP13007 versus matching vehicle placebo on markers of inflammation, ocular pain and visual acuity after cataract surgery in the study eye.	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 Anterior chamber flare (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 best corrected visual acuity by pinhole method using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart at PODs 4, 8 and 15

<table>
<tr><th colspan="2">Protocol Synopsis</th></tr>
<tr><td>Safety Objective
The safety objective is to investigate the safety and tolerability of APP13007 versus matching vehicle placebo for the treatment of inflammation and pain after cataract surgery.</td><td>Safety Endpoints
• Adverse events (AEs)
• Best corrected visual acuity by pinhole method using an ETDRS chart from baseline to each post-surgery visit
• Slit-lamp biomicroscopy
○ Change-from-baseline in ocular signs to each post-surgery visit
• Dilated indirect ophthalmoscopy
○ Change-from-baseline in ocular signs to Visit 6 (POD22)
• Intraocular pressure (IOP) at each visit and change-from-baseline to Visit 6 (POD22) measured with a Goldmann applanation tonometer</td></tr>
<tr><td colspan="2">Study Design & Summary of Visit Schedule:
This Phase 3 study will evaluate APP13007 in comparison to the matching vehicle placebo in a randomized, parallel-group, double-masked fashion. The subjects will have undergone routine cataract surgery on Day 0 of the study and will be assessed the next day (POD1) after uncomplicated surgery for eligibility for randomization to study treatment.
Subjects who experience postoperative inflammation on POD1 and who meet all other eligibility criteria will be randomized to one of two study treatments (either Treatment 1 or Treatment 2) at a 1:1 ratio:
• Treatment 1: 1 drop APP13007 twice daily (BID) (morning and evening) for 14 days instilled to the operated study eye
• Treatment 2: 1 drop matching vehicle placebo BID (morning and evening) for 14 days instilled to the operated study eye

<u>Study Visits and Procedures</u>
Visit 1: Screening. Sign informed consent prior to the conduct of any study procedures or discontinuation of any medications related to this study. Screening will occur between 28 days to 1 day prior to cataract surgery. Review Inclusion and Exclusion criteria for eligibility.
Day 0/Day of Surgery: Subjects undergo routine cataract surgery via phacoemulsification and posterior chamber intraocular lens implantation according to the Investigator’s normal procedures.
Visit 2: POD1 will occur ~ 18-34 h after cataract surgery. Review Inclusion and Exclusion criteria. Baseline pre-Randomization assessments (ocular inflammation, pain and safety parameters). Randomization of eligible subjects. Instillation of first dose of study drug in the operated study eye in the clinic under the supervision of Investigator or designee.
Visit 3: POD4 (± 1 day). Ocular inflammation, pain and safety assessments.
Visit 4: POD8 (± 1 day). Ocular inflammation, pain and safety assessments.
[Note: Subjects will be contacted on POD14 to remind them to stop study drug after that day and to bring the study drug bottle and dosing diary to the clinic the next day.]
Visit 5: POD15 (+ 1 day). Ocular inflammation, pain and safety assessments. Urine pregnancy test.
Visit 6: POD22 (± 2 days). Ocular inflammation, pain and safety assessments. Final visit.
A detailed summary of study events is provided in Table 1 (Schedule of Events) and a study design schematic is provided in Figure 1 (Study Schematics).</td></tr>
</table>

Protocol Synopsis
Test Product, Dose and Mode of Administration: Study Drugs (APP13007 or matching vehicle placebo) will be supplied in an eye drop bottle. The formulations are preserved with benzalkonium chloride filled in a multi-dose opaque low density polyethylene (LDPE) 5 mL round dropper bottle with a LDPE tip and tightly closed with a pink high density polyethylene (HDPE) cap. The bottle will be labelled in accordance with FDA regulations for an investigational product. One bottle of study drug will be dispensed to each randomized subject in the trial. Study drug will be administered twice daily (morning and evening) by instilling one drop at each dosing time into the conjunctival sac of the study eye. If the subject misses his/her eye during instillation, then a second drop will be instilled and this will be documented in the dosing diary.
Randomization: Subjects who meet all eligibility criteria on POD1 will be randomized to one of the two study treatments at a 1:1 ratio (APP13007:placebo).
Number of Subjects: A sufficient number of subjects will be screened to allow approximately 370 subjects (185 on APP13007 and 185 on placebo) to be randomized**.**
Inclusion Criteria: To be eligible, a participant must meet the following criteria: *At the Screening Visit (Visit 1):* 1. Provide signed and dated informed consent 2. Age ≥ 18 years at time of informed consent 3. Males or females of non-childbearing potential. Females of non-childbearing potential is defined as women who have been permanently sterilized or are postmenopausal. Postmenopausal is defined as amenorrhea for a minimum of 12 months (without an alternative medical cause). Note: Pregnant women or nursing (breast-feeding) mothers are excluded from the study. 4. Women-of-childbearing-potential are eligible for enrollment if they have a negative urine pregnancy test on POD1 prior to Randomization and they agree 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 ring, percutaneous contraceptive patches, or intrauterine device from POD1 to Visit 6 (POD22). 5. Expected to undergo unilateral uncomplicated cataract extraction via phacoemulsification and posterior chamber intraocular lens implantation in one eye (designated the 'Study Eye') 6. Have a pin-hole corrected visual acuity without other correction of ≤ 1.3 logarithm of the minimum angle of resolution (logMAR) in the study eye to be operated and contralateral eye as measured using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart at Visit 1. Subjects who are unable to read the lines in an ETDRS chart because of the density of the cataract in the study eye may be enrolled if, in the opinion of the Investigator, there is no other significant ocular pathology that would account for the low visual acuity. 7. Willing and able to comply with study requirements and visit schedule; Able to either self-administer study medication or have someone available (e.g., spouse, caregiver, etc.) who can administer study medication according to the study schedule and instructions. *Additional Inclusion Criteria on Postoperative Day (POD) 1/Day of Randomization (Visit 2):* 8. Have 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.

Protocol Synopsis

9. No significant ocular pathology affecting visual acuity that is identified after posterior chamber intraocular lens implantation in the study eye.
10. Have ≥ 10 cells in the anterior chamber (excluding red blood and pigment cells)
11. Have an IOP ≤ 30 mmHg. Note: If the IOP is elevated post-surgery, the investigator may use non-prostaglandin based IOP-lowering medication(s) at their discretion on the day of surgery (Day 0) only. The IOP will be measured and recorded on POD1 to determine eligibility for Randomization.

Exclusion Criteria:

Participants will be excluded if they meet any of the following criteria:

1. Have 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
2. Have an ACC count > 0 or any evidence of intraocular inflammation (e.g., flare) in either eye at the Screening visit
3. Have a Grade > 0 on the Ocular Pain Assessment in either eye at the Screening visit
4. Have an immunosuppressive or autoimmune disease that in the opinion of the Investigator could affect intraocular inflammation or the normal healing process of the eye
5. Have active or chronic/recurrent ocular or systemic disease that is uncontrolled and could affect wound healing and/or resolution of inflammation after cataract surgery
6. Suspected or known malignancy or be currently receiving antineoplastic therapy. Note: subjects with basal cell carcinoma will not be excluded unless the Investigator believes that the condition has the potential to interfere with study procedures or analysis of results.
7. Are using certain medications, namely:
   i. Subjects receiving therapy for macular degeneration (in either eye) with Eylea® (aflibercept), Avastin® (bevacizumab), Lucentis® (ranibizumab), Beovu® (brolucizumab-dbll) or Visudyne® (verteporfin) are excluded.
   ii. PROKERA (preserved amniotic membrane) is excluded from 1 year prior to the Screening visit to the end of the study.
   iii. Anti-inflammatory agents, analgesics (including opioids, narcotics, nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, acetaminophen and other pain medications) or immune-modulating agents systemically or in either eye from the beginning of the 'Washout' period in the "List of Prohibited Medications" until after the POD15 assessments, but preferably until after the POD22 assessments. *Note: (i) acetaminophen is permitted on the day of surgery; (ii) immunizations/vaccinations are permitted before and during the study.*
   iv. Use of any of the prohibited medications in the "List of Prohibited Medications" within a time period prior to surgery that is less than the minimum 'washout' period noted in the table. *NOTE: (i) These medications may not be used from the beginning of the 'Washout' period in "List of Prohibited Medications" until after the POD15 assessments, but preferably until after the POD22 assessments; (ii) Medications for anesthesia related to cataract surgery, ocular pain control and non-prostaglandin-based therapy for the treatment of raised intraocular pressure (IOP) are allowed on the day of surgery only.*
   v. Non-approved drugs or investigational products other than the study drug in this study are prohibited from 28 days before surgery until after the subject has been released from the study.

Protocol Synopsis	
Medication	Minimum 'Washout' Period Prior to Day 0
All topical ophthalmic gels or ointments	2 days
Ocular mast cell stabilizers	2 days
Ocular antihistamines	2 days
Ocular and nasal decongestants	2 days
All eye drops (except antibiotic eye drops considered to be part of pre-cataract surgery standard-of-care). Note: Antibiotics with anti-inflammatory activity and Besifloxacin Ophthalmic suspension are not permitted. Note: (i) Artificial tears are allowed, but should not be used within 10 minutes of study procedures or medication dosing; (ii) specific restrictions for ocular products are listed below.	2 days
Topical ocular corticosteroids	14 days
Topical ocular NSAIDs	7 days
Topical prostaglandin eyelash growth medications	7 days
Systemic anti-inflammatory agents including acetaminophen, NSAIDS, acetylsalicylic acid (aspirin), and Lifitegrast. *Note: (i) Use of acetylsalicylic acid for cardiovascular prophylaxis (i.e., 81 mg dose QD) is allowed if dosage has been stable for at least 30 days prior to surgery and will remain stable for the duration of the study (ii) Acetaminophen may be administered as needed pre- and post-operatively on the day of surgery, (iii) Over-the-Counter preparations such as Fish Oils, Turmeric and Ginseng that may have mild anti-inflammatory effects are allowed.*	7 days
Topical dermatologic corticosteroids including OTC preparations (use of topical 0.1% hydrocortisone dermal preparations for less than 3 days over a small area of skin [~2 inches x ~2 inches] are allowed).	14 days
Systemic (oral, injectable), inhaled and/or nasal corticosteroids	21 days
Systemic analgesics/pain relievers such as gabapentin, pregabalin, opioids *Note: Marijuana/CBD-containing products have the same washout restrictions as "Systemic Analgesics" because they can affect pain perception*	14 days
Medications for benign prostatic hypertrophy (BPH) (e.g., finasteride, α-1 adrenergic receptor antagonists) are allowed based on the judgment of the investigator. *Note: Investigators should consider the potential risk of intraoperative floppy iris syndrome in subjects who are taking or have taken α-1 adrenergic receptor antagonists (eg. tamsulosin, silodosin, alfuzosin).*	Stable dose for 28 days
Topical or systemic cyclosporine	60 days
Periocular injection of corticosteroid	28 days
Intraocular treatment with corticosteroid - dexamethasone drug delivery system	90 days after implantation
Intraocular treatment with corticosteroid – fluocinolone acetonide drug delivery system	48 months after implantation

Protocol Synopsis	
Stable doses of anticholinergics and antidepressants are allowed. Alterations of the dose of anticholinergics and antidepressants (other than for prn use as a sleep aid) may be allowed following consultation with the Study Medical Monitor. Anticholinergic eye drops used to dilate the eye are allowed. Systemic anticholinergic drugs are allowed on the day of surgery. **Note 1** For anti-depressants used to treat depression: (i) Medication must not be washed-out for the purpose of enrollment in the study; (ii) Stable doses of anti-depressants are allowed; (iii) When the dose of an anti-depressant has been altered, the subject needs to be on the stable altered dose for at least 90 days prior to the day of surgery (Day 0). **Note 2** For anti-depressants used to treat pain: (i) The instructions provided for systemic analgesics/pain relievers apply, viz. at least a 14 day washout of the medication is required prior to the day of surgery (Day 0) continuing until the POD15 assessments have been completed.	See Note 1 and Note 2

8. Have an IOP < 5 mmHg or > 22 mmHg in either eye or a difference of > 5 mmHg between the eyes at the Screening visit.
9. Have a history of documented and repeated elevated IOP or glaucoma
10. History of herpes keratitis in the study eye
11. Have active corneal abrasions or ulcers in the study eye
12. Have active or a history of chronic or recurrent inflammatory eye disease (e.g., iritis, scleritis, uveitis, iridocyclitis, rubeosis iridis) in the study eye
13. Have 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
14. Have corneal dystrophies, including corneal guttae and Fuchs' dystrophy, or dysthyroid ophthalmopathy in the study eye
15. Have uncontrolled and clinically significant dry eye syndrome in the study eye (mild dry eye with the use of artificial tears is allowed)
16. Have proliferative diabetic retinopathy, significantly compromised macular function; significant macular disease; have clinically-significant macular edema or a history of cystoid macular edema in the study eye; have cup:disc ratio > 0.8
17. Have had corneal or retinal surgery (laser or incisional) in the study eye within 6 months of the Screening visit, or planning to have laser or incisional surgery during the study period in the study eye (other than cataract surgery)
18. Have ocular surgery planned, scheduled or performed on the contralateral eye within the 2 months prior to the surgery on the study eye
19. Have 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)

Protocol Synopsis
20. Require 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 21. Require use of non-diagnostic topical ophthalmic medications in either eye for the duration of the study with the exception of the following which are allowed: mydriatics, anesthetics, antiseptics, balanced salt solution, viscoelastics, osmotic agents (e.g., Muro 128), prophylactic antibiotics, non-prostaglandin 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. 22. In the opinion of the investigator, have the potential for ocular hemorrhage in the study eye that may interfere with evaluation of post-surgery inflammation 23. Have a planned use of or use of femtosecond laser or any other ophthalmic surgical procedure (e.g., 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 24. Have a planned use of or use anterior capsule staining for capsulorhexis (i.e., trypan blue) during cataract surgery 25. Have planned to participate in another clinical trial during the duration of this study 26. Have participated in another clinical study or received any investigational product within the past 28 days prior to the Screening Visit. Subjects who previously participated in Study CPN-201 are eligible if the planned cataract surgery is for the eye that was the 'non-study' eye in that study. 27. Have any other condition that the Investigator determines should exclude the subject from the trial. 28. Are an employee of the clinical site that is directly involved in the management, administration, or support of this study or are an immediate family member of the same.
Statistical Methods: All analysis variables will be summarized descriptively by treatment group. Summary statistics for continuous measures will include the number of subjects (n), mean, standard deviation, median, and range. Categorical measures will be summarized by the number and percent of subjects. *Analyses of Primary Efficacy Endpoints:* The primary efficacy analyses to compare APP13007 against placebo will be conducted on the Intent-To-Treat (ITT) population using the Pearson Chi-square statistic. Fixed sequence testing will be employed to maintain the 2-sided alpha = 0.05. The primary analyses will first test the difference in the proportion of subjects with ACC count = 0 (Grade = 0) at POD8 (Visit 4) maintained through POD15 (Visit 5) between treatment groups. If the test is statistically significant at the 2-sided alpha = 0.05 level in favor of APP13007, the difference in the proportion of subjects with Ocular Pain Grade = 0 at POD4 (Visit 3) maintained through POD15 (Visit 5) between treatment groups will be tested at the two-sided alpha = 0.05 level. *Analyses of Secondary Efficacy Endpoints:* Mean change-from-baseline in ACC Grade, Ocular Pain Grade, ACF Grade and visual acuity at PODs 4, 8 and 15 will be analyzed using an analysis of covariance (ANCOVA). The ANCOVA model will include treatment as a fixed effect and baseline as a covariate. The rest of secondary efficacy endpoints will be analyzed using the same method described for the primary efficacy endpoints. Rescued subjects will be considered to be treatment failures. *Safety Analysis:* The safety analysis will summarize ocular treatment emergent AEs (TEAEs) in the study eye and ocular AEs for the non-study eye. Ocular and non-ocular TEAEs will be summarized similarly. The other safety endpoints will be summarized as discussed in the Statistical Considerations section of the protocol.

STUDY DESIGN

Figure 1: Study Schematic

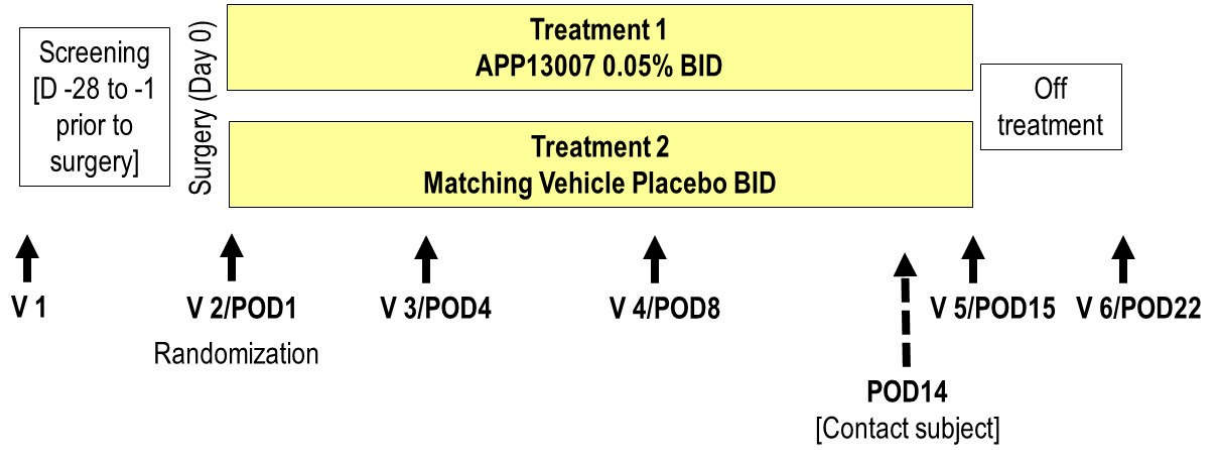

Table 1: Schedule of Events

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 women of child-bearing potential			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
lOP (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 will be performed in the study eye only at Visits 2-5; and performed on both eyes at Visit 1 (Screening) and at Visit 6 (POD22) or at subject Early Termination/Withdrawal.
[2] Surgery must occur between one to 28 days after Screening, preferably in the morning. If, due to unexpected events, surgery is postponed and would occur > 28 days past the Screening visit, contact the Study Medical Monitor to determine which, if any, of the screening procedures should be repeated. Subjects will be determined to be a suitable candidate for surgery during a pre-surgery medical assessment, where the routine medication list prescribed by the cataract surgeon should be reviewed to rule out prohibited medications (Section 5.4.2).
[3] Visit 2 (POD1) should be scheduled between 18 to 34 hours following conclusion of surgery on Day 0. All assessments done on POD1 are done prior to Randomization to ensure eligibility. Note: Women-of-childbearing-potential are eligible for enrollment if they have a negative urine pregnancy test on POD1 prior to Randomization and they agree to abstinence from sexual activity or use of highly effective method of contraception.
[4] Visit 5 (POD15) occurs on the day after the subject completes the study drug administration for 14 days. Women-of-childbearing-potential should have a urine pregnancy test.
[5] Visit 6 (POD22) is the last visit for subjects who complete the study. Subjects who are withdrawn early should have the Visit 6 assessments and a urine pregnancy test performed before they are released from the study.
[6] Includes assessments of ocular pain and irritation. See Section 8.0 of protocol for information on how to record AEs and how to determine attributability (relatedness) of AE to study procedures (including cataract surgery) or study drug.
[7] Ocular inflammation assessment using ACC count, anterior chamber flare grade, bulbar conjunctival injection, sclera - ciliary flush and corneal edema.
[8] IOP should (but not required) be assessed at each visit within ± 2 h of the IOP assessment time at Visit 1.
[9] The first dose of study drug should be instilled into the study eye at the clinic visit under supervision of clinic staff. The second dose on POD1 can be administered at home. Subjects who are rescued will not continue to instill study drug or receive further diary cards but will remain in the study to complete the procedures/assessments through Visit 6 (POD22).
[10] The site must contact 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 should be reported in the eCRF.
[12] AEs and Concomitant Medications should only be recorded on Day 0 if they result in disqualification (i.e., screen failure) of the subject; otherwise, the AEs and Concomitant Medications applicable to Day 0 should be recorded when the subject returns for Visit 2 (POD1).
[13] Any AEs reported to the site during the POD14 contact must be recorded in the source documents. Further assessment of any reported AEs may require an Unscheduled Visit on POD14 if medically significant or they may be assessed, as appropriate, during Visit 5 (POD15).

1.0 INTRODUCTION

1.1 Overview

APP13007 is an ophthalmic nanosuspension that is prepared by dispersing nanomilled [redacted], a corticosteroid, with a mixture of excipients in a multi-dose preserved aqueous [redacted]

1.2 Background

1.2.1 [redacted]

Corticosteroids regulate cellular signaling, immune function, inflammation and protein synthesis, and like other corticosteroids, CP has anti-inflammatory and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of CP is unclear, but it is thought to act by inducing lipocortins, proteins that inhibit phospholipase A2, an enzyme that releases arachidonic acid from membrane phospholipids. By inhibiting phospholipase A2, lipocortins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes.

CP is an analog of prednisolone with a very high degree of activity at the glucocorticoid receptor and only slight degree of mineralocorticoid activity (Clobex® 2018). It is reported to be the most potent corticosteroid in terms of binding affinity to the glucocorticoid receptor and resulting pharmacological effects (Olsen 1986), (Jacob 2006). CP has been used in dermal applications including ointments, creams and shampoos, where its efficacy and safety has been well-established (Clobex® 2018); (Temovate® 2000); (Olsen 1986); (Hengge 2006); (Feldman 2009).

1.2.2 Pain and Inflammation Following Cataract Surgery

Despite modern advances in surgical technique, trauma that occurs during cataract removal and intraocular lens 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 corneal edema, increases in intraocular pressure (IOP), cystoid macular edema (CME), and posterior capsule opacification may result if the inflammatory process is not managed appropriately (Tennant 1978) (Apple 1992). 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. When administered at the time of surgery and during the immediate postoperative period,

corticosteroids can reverse the clinical and non-clinical manifestations of inflammation (Leopold 1985) (Aptel 2017).

1.2.3 Rationale for Development of APP13007

Topical ocular administration of corticosteroids is a well-established therapy for the treatment of inflammation and pain after ocular surgery (Aptel 2017), and several marketed products are currently available that contain active ingredients such as dexamethasone, prednisolone, loteprednol etabonate and difluprednate.

CP has been used for over 30 years in the US, Europe and Japan to treat the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses such as psoriasis, eczema and atopic dermatitis. CP has not been previously developed for ophthalmic use, presumably due to its lack of aqueous solubility. Nevertheless, given its increased potency, an aqueous ophthalmic formulation of CP has the potential to produce rapid clearance of anterior chamber cells (ACC), return of visual acuity and relief of pain after ocular surgery, surpassing the effectiveness of corticosteroids currently on the market.

APP13007 is an ophthalmic nanosuspension that is prepared by dispersing nanomilled CP with a mixture of excipients. The proprietary nanomilling technology allows CP to be formulated as an aqueous suspension. This suspension of CP nanoparticles in APP13007 is designed to promote efficient penetration of CP into the eye upon ocular surface instillation, thus delivering therapeutically relevant concentrations of CP to the target tissues within the eye.

1.3 Nonclinical Studies

Multiple nonclinical pharmacology, pharmacokinetics, and toxicology studies have been conducted with various formulations of APP13007, and these are summarized in the APP13007 Investigator Brochure.

1.3.1 Primary Pharmacology

[redacted]

1.3.2 Pharmacokinetics

[redacted]

[redacted]

1.3.3 Toxicology

Data from non-GLP and 14-day and 28-day Good Laboratory Practice (GLP) toxicity studies of APP13007 are summarized in the APP13007 Investigator Brochure.

[redacted]The toxicology studies suggest that potential systemic effects in human subjects with ocular instillations of APP13007 are those typical of corticosteroids in general and that have been seen with approved dermal CP products, such as Temovate® and Clobex® (Temovate® 2000); (Clobex® 2018).

The data from repeat dose toxicology studies did not identify any unacceptable risk for human subjects.

1.4 Human Studies

Two clinical studies have been completed with APP13007, and details of the subject populations, study dosing, conduct and results are summarized in the APP13007 Investigator Brochure.

1.4.1 CPN-201: A Phase 2 Safety and Preliminary Efficacy Study Post Cataract Surgery

This was a multi-center, randomized, double-masked, placebo-controlled, parallel-group Phase 2 study conducted in two parts (Parts A and B) to evaluate two APP13007 dose strengths and two dosing frequencies in subjects who had undergone routine cataract surgery and lens implantation. On Post-Operative Day 1 (POD1), subjects who met eligibility criteria were enrolled in the study and randomized to one of the study treatments instilled in the operated study eye: Treatment 1 or 2 in Part A (1:1 ratio); Treatment 3, 4, 5, or 6 in Part B (1:1:1:1 ratio). A total of 45 subjects were randomized in Part A and 87 subjects randomized in Part B.

- Treatment 1: 1 drop 0.05% APP13007 BID for 21 days
- Treatment 2: 1 drop 0.05% matching vehicle placebo BID for 21 days
- Treatment 3: 1 drop 0.05% APP13007 BID for 3 days followed by 1 drop 0.05% APP13007 QD for 11 days
- Treatment 4: 1 drop 0.05% matching vehicle placebo BID for 3 days followed by 1 drop 0.05% matching vehicle placebo QD for 11 days
- Treatment 5: 1 drop 0.1% APP13007 BID for 3 days followed by 1 drop 0.1% APP13007 QD for 11 days
- Treatment 6: 1 drop 0.1% matching vehicle placebo BID for 3 days followed by 1 drop 0.1% matching vehicle placebo QD for 11 days

1.4.1.1 Safety Results

The 0.05% APP13007 and 0.1% APP13007 dosing regimens were well-tolerated with a safety profile similar to the matching placebo vehicles.

[redacted]

1.4.1.2 Efficacy Results

[redacted]

[redacted]

[redacted]

1.4.1.3 Conclusion

The safety and efficacy results from study CPN-201 support the further clinical evaluation of 0.05% APP13007 BID for the treatment of inflammation and pain following ocular surgery.

1.4.2 CPN-102: A Phase 1 Pharmacokinetic Study in Healthy Subjects

CPN-102 was an open-label, sequential dosing, Phase 1 pharmacokinetic (PK) study to evaluate the systemic exposure of CP following ocular instillation of 0.05% APP13007 in healthy subjects. [redacted]

1.4.2.1 Safety Results

The 0.05% APP13007 drops were well-tolerated. There were no AEs related to the study drug.

1.4.2.2 Pharmacokinetic Results

[redacted]

[redacted]

1.4.2.3 Conclusion

[redacted]

1.5 Risk/Benefit Assessment

1.5.1 Potential Risks

1.5.1.1 Potential Risks Anticipated Based on Results from the GLP Rabbit Toxicology Studies with APP13007

[redacted]

1.5.1.2 Potential Risks Anticipated Based on Results from the Human Studies with APP13007

As summarized in the APP13007 Investigator Brochure and in Section 1.4.1.2 and Section 1.4.2.2, 0.05% APP13007 BID for 21 days was well-tolerated. [redacted]

[redacted] the systemic tolerability profile after ocular instillation of 0.05% APP13007 BID for 14 days is expected to be considerably better than that for dermal CP products summarized below.

1.5.1.3 Potential Risks Associated with the Use of CP in the Treatment of Corticosteroid-Responsive Dermatoses

There is extensive experience with CP in the treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, where its safety and anti-inflammatory profile has been well defined (Olsen 1986); (Hengge 2006); (Feldman 2009). These risks are summarized in the APP13007 Investigator's Brochure.

Potential non-ocular risks include:

- Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids.
- Cushing's syndrome, hyperglycemia, and unmasking of latent diabetes mellitus. Use of more than one corticosteroid-containing product at the same time may increase the total systemic corticosteroid exposure.
- Skin: Allergic contact dermatitis may occur.
- Pregnancy and Nursing (Breast-feeding) Mothers:
  - Corticosteroids are teratogenic in laboratory animals when administered systemically at relatively low dosage levels (Pregnancy Category C). When administered subcutaneously, CP was a significant teratogen in both the rabbit and mouse. Females of child-bearing potential are eligible to participate in this study only if they have a negative urine pregnancy test on POD1 pre-randomization and they agree to use highly effective contraception from POD1 to POD22. Note: Pregnant and/or nursing (breast-feeding) mothers are excluded from participation in this study.
  - Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether ocular administration of APP13007 could result in sufficient systemic absorption of CP to produce detectable concentrations in human milk.

Potential ocular risks are summarized below.

1.5.1.4 Potential Class-Related Ocular Risks Associated with Corticosteroid Therapies for the Treatment of Ocular Inflammation and Pain after Ocular Surgery

The active ingredient in APP13007, [redacted] is a potent corticosteroid so it has the following anticipated ocular risks associated with the corticosteroid class:

- Intraocular pressure (IOP) increase – prolonged use may result in glaucoma with damage to the optic nerve, defects in visual acuity and field of vision.
- Cataracts – Prolonged use [redacted] may result in posterior subcapsular cataract formation in the non-operated eye.

- Delayed healing – Use [redacted] after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical corticosteroids.
- Risk of Infection
  - Bacterial infections – Prolonged use [redacted] may suppress the host immune response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, corticosteroids may mask infection or enhance existing infection.
  - Viral infections – Use of ocular corticosteroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).
  - Fungal Infections – Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local corticosteroid application. Fungus invasion must be considered in any persistent corneal ulceration while a subject is participating in this clinical trial.

In clinical studies evaluating the use of corticosteroids after ocular surgery, ocular adverse reactions that occurred in 5% to 15% of subjects included corneal edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis. Other ocular adverse reactions occurring in 1% to 5% of subjects included reduced visual acuity, punctate keratitis, eye inflammation, and iritis. Ocular adverse reactions occurring in less than 1% of subjects included application site discomfort or irritation, corneal pigmentation and striae, episcleritis, eye pruritus, eyelid irritation and crusting, foreign body sensation, increased lacrimation, macular edema, sclera hyperemia, and uveitis. Most of these reactions may have been the consequence of the surgical procedure.

1.5.1.5 Potential Risks Associated with the APP13007 Formulation

[redacted]

1.5.2 Risk Mitigation Plan

Given the potential risks noted above, a risk mitigation plan will be used to mitigate risks for subjects enrolled into the study. The Risk Mitigation Plan is shown in Table 2.

1.5.3 Contraindications

[redacted]

APP13007, as with other corticosteroids, is contraindicated in the presence of active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in subjects with mycobacterial infection of the eye and fungal diseases of ocular structures.

APP13007 must not be administered (i) to women of child-bearing potential without a negative urine pregnancy test on POD1 prior to randomization and agreement to use highly effective contraception or abstain from sexual activity from POD1 to POD22 or (ii) to pregnant or nursing (breast-feeding) woman.

1.5.4 Potential Benefits

Topical ocular administration of corticosteroids is a well-established therapy for the treatment of inflammation and pain after ocular surgery, with multiple marketed products currently available that utilize corticosteroids as the active ingredient such as dexamethasone (Maxidex®), prednisolone (PredForte®), loteprednol etabonate (Lotemax®, Inveltys®, Lotemax SM®), and difluprednate (Durezol®). In all clinical trials, corticosteroid therapies were dosed at a frequency of twice daily or more frequently.

As summarized in the APP13007 Investigator's Brochure, in Study CPN-201 a greater proportion of subjects treated with APP13007 0.05% BID had complete clearing of anterior chamber cells and complete resolution of ocular pain compared to placebo-treated subjects. Thus, it is likely that subjects randomized to active APP13007 will experience a clinically-meaningful reduction in inflammation and pain following cataract surgery.

It is known from large clinical trials of products for the treatment of inflammation and pain after ocular surgery that a proportion of subjects randomized to placebo improve in the days following surgery (Lotemax® Product Insert 2018; Durezol® Product Insert 2017). Thus, there may be a marginal benefit observed in some of the subjects enrolled into the study who are randomized to the matching vehicle placebo.

1.5.5 Assessment of Potential Risks and Benefits

This is a placebo-controlled study in which subjects will be randomized 1:1 to APP13007 or matching vehicle placebo. Subjects randomized to active APP13007 may benefit from the treatment by reduction in inflammation and pain, while the risks associated with active APP13007 treatment are likely to be low and manageable. This assessment is supported by the results of the nonclinical (See Section 1.3) and clinical studies (See Section 1.4) that are summarized in detail in the APP13007 Investigator's Brochure.

Subjects randomized to placebo are not expected to benefit from the study treatment, but a proportion of subjects receiving placebo may show improvement of inflammation in the days following surgery. Furthermore, the risks to subjects randomized to placebo in this study are mitigated as much as possible. Specifically, the protocol contains instructions for careful monitoring of safety and efficacy endpoints during the trial to identify subjects who show minimal improvement or worsening of the clinical conditions so that appropriate mitigation steps can be taken, including, but not limited to, withdrawal from study treatment and commencement of appropriate rescue medication.

Overall, the risk:benefit analysis supports the evaluation of 0.05% APP13007 and matching vehicle placebo administered BID for 14 days after cataract surgery.

Table 2: Risk Mitigation Plan

Potential Risk	Management	Comments
Risk Associated with Lack of Efficacy		
Minimal reduction or worsening of inflammation and pain endpoints or other factors suggesting lack of efficacy	Inflammation and pain endpoints will be monitored during the study. Guidance criteria and procedures for the rescue of subjects are provided in Section 9.4 of this protocol.	Minimal reduction or worsening of inflammation and pain endpoints or other factors suggesting lack of efficacy
Risk Associated with Unexpected Safety Events		
Unexpected safety events	Safety endpoints will be monitored during the trial. The Investigator will discuss unexpected safety events with the Study Medical Monitor who will then discuss unexpected safety events with the Sponsor to determine whether study drug should be stopped and rescue procedures commenced.	The toxicology studies with APP13007 indicate that there is a low risk of ocular toxicity. The risks of systemic exposure to CP following dermal application are well characterized. [redacted] Nevertheless, the Investigator should be alert to the possibility

Potential Risk	Management	Comments
		that unexpected safety events may occur. The list of expected safety events is including in Section 1.5.5 and in the APP13007 Investigator's Brochure.
Risks Associated with the Corticosteroid Class		
Intraocular pressure (IOP) increase	IOP will be monitored during the study. The protocol excludes subjects who may be at increased risk of steroid-induced IOP increase, e.g. subjects with a history of raised IOP/glaucoma and subjects with IOP >30 mmHg at the POD1 pre-randomization assessment. Section 9.5 includes stopping criteria for study drug due to IOP increase and criteria for initiation of IOP-lowering medication. After Randomization, the management of IOP > 30 mmHg or IOP ≥ 21 mmHg AND an IOP increase > 10 mmHg from pre-dose baseline is described in Section 9.5.2.	There was no clinically-meaningful APP13007-related elevation of IOP in the toxicology studies and in Study CPN-201. Prolonged use of CP may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. An IOP ≥ 30 mmHg after randomization should be reported as an AE.
Cataracts	The lens structure and posterior capsular opacification (POC) in the study eye will be monitored at each clinic visit throughout the study. The lens in the non-operated eye will be evaluated at Screening, Visit 6 (POD22) and Early Termination/Withdrawal visits.	[redacted]
Delayed Healing	Subjects with thinning of the cornea or sclera are excluded because of the greater risk of perforations with the use of topical steroids. Protocol includes stopping criteria for study drug if the Investigator, in consultation with the Study Medical Monitor, is concerned about delayed healing.	Use of APP13007 may delay healing after cataract surgery and increase the incidence of bleb formation. There were no reports of delayed healing after cataract surgery in Study CPN-201.

Potential Risk	Management	Comments
Risk of Infection	Subjects with on-going ocular bacterial, viral or fungal infections are excluded from the study. Ocular infections occurring during the study should be assessed and treated appropriately. The Investigator should discuss with the Study Medical Monitor whether to stop study drug if ocular infection occurs.	Use of APP13007 may suppress the host immune response and increase the hazard of ocular infections. This risk is likely to be low based on data from studies of other steroids products approved for the treatment of inflammation and pain after ocular surgery.
Hypothalamic-Pituitary-Adrenal Axis (HPA) Suppression	Monitor for symptoms and signs of reduced adrenal function (including fatigue, muscle weakness, loss of appetite and weight, abdominal pain, nausea and diarrhea, low blood pressure, depression and irritability, salt craving and hypoglycemia). The Investigator should discuss with the Study Medical Monitor who will then discuss with the Sponsor whether to stop study drug.	While systemic absorption of topical corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticoid insufficiency after withdrawal from treatment, this risk is likely to be very low [redacted] Nevertheless, Investigators should be aware that the symptoms and signs of reduced adrenal function can be nonspecific and they should remain alert to the possibility that this may occur.
Effects related to excessive corticosteroid pharmacology	Monitor for symptoms and signs of excess corticosteroid pharmacology such as Cushing's syndrome, hyperglycemia, and unmasking of latent diabetes mellitus. The Investigator should discuss with the Study Medical Monitor who will then discuss with the Sponsor whether to stop study drug.	These effects have been reported after dermal use of CP and result from systemic absorption of topical CP. The risk is likely to be very small [redacted]
Pregnancy Category C/Fetal effects	Women of child-bearing potential are excluded from the study if they have a positive urine pregnancy test on POD1 pre-randomization and/or do not agree to use highly effective contraception or abstain from sexual activity. Pregnant and/or nursing (breast-feeding) mothers are excluded from the study.	Corticosteroids are known teratogens in laboratory animals when administered systemically at relatively low dosage levels. [redacted]

Potential Risk	Management	Comments
Skin Irritation	If irritation develops appropriate therapy should be instituted. The Investigator should notify the Study Medical Monitor in advance if study drug is going to be stopped.	Allergic contact dermatitis may occur with CP. Other skin reactions have been described with topical dermal products (See APP13007 Investigator's Brochure).
Other Potential Risks		
[redacted]		
Hypersensitivity Reactions	Subjects are excluded from the study if they have a history of hypersensitivity to CP, corticosteroids, [redacted] If hypersensitivity reaction occurs, the Investigator should discuss with the Study Medical Monitor who will then discuss with the Sponsor Medical Monitor whether to stop study drug.	
Adverse reactions reported in clinical studies evaluating the use of corticosteroids after ocular surgery.	Most of these adverse reactions may have been the consequence of the surgical procedure and should be managed according to standard-of-care procedures.	Ocular adverse reactions reported in completed clinical studies of APP13007 are summarized in Section 1.5.1.

2.0 STUDY OBJECTIVES AND ENDPOINTS

The objectives and corresponding study endpoints are presented in Table 3 below:

Table 3: Study Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy Objective The primary efficacy objective is 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.	Primary Efficacy Endpoints • The proportion of subjects with Anterior Chamber Cell (ACC) Count = 0 [ACC Grade = 0] at post-operative day 8 (POD8), maintained through POD15 • The proportion of subjects with Ocular Pain Grade = 0 at POD4, maintained through POD15
Secondary Efficacy Objective The secondary efficacy objective of this study is to investigate the effect of APP13007 versus matching vehicle placebo on markers of inflammation, ocular pain and visual acuity after cataract surgery in the study eye.	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 Anterior chamber flare (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 best corrected visual acuity by pinhole method using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart at PODs 4, 8 and 15

Objectives	Endpoints

Safety Objective
The safety objective is to investigate the safety and tolerability of APP13007 versus matching vehicle placebo for the treatment of inflammation and pain after cataract surgery.
	Safety Endpoints
	• Adverse events (AEs)
	• Best corrected visual acuity by pinhole method using an ETDRS chart from baseline to each post-surgery visit
	• Slit-lamp biomicroscopy
	  o Change-from-baseline in ocular signs to each post-surgery visit
	• Dilated indirect ophthalmoscopy
	  o Change-from-baseline in ocular signs to Visit 6 (POD22)
	• Intraocular pressure (IOP) at each visit and change-from-baseline to Visit 6 (POD22) measured with a Goldmann applanation tonometer

3.0 STUDY DESIGN

3.1 Study Design Overview

This Phase 3 study will evaluate 0.05% APP13007 in comparison to the matching vehicle placebo in a randomized, parallel-group, double-masked fashion. Subjects will have routine cataract surgery on Day 0 of the study and will be assessed the next day (POD1) after uncomplicated surgery for eligibility for randomization to study treatment.

Subjects who experience postoperative inflammation on POD1 and who meet all other eligibility criteria will be randomized to one of two study treatments (either Treatment 1 or Treatment 2) at a 1:1 ratio:

- Treatment 1: 1 drop APP13007 twice daily (BID) (morning and evening) for 14 days instilled to the operated study eye
- Treatment 2: 1 drop matching vehicle placebo BID (morning and evening) for 14 days instilled to the operated study eye

Subjects will be discharged from the study after the assessments for Visit 6 (POD22) have been performed.

3.2 Study Visit Overview

This will include up to 7 clinic visits (including the surgery day) over a range of 24 to approximately 52 days.

Note: The study drug will be dosed BID for 14 days.

3.2.1 Study Visits and Procedures

Visit 1: Screening. Sign informed consent prior to the conduct of any study procedures or discontinuation of any medications related to this study. Screening will occur between 28 days to 1 day prior to cataract surgery. Review Inclusion and Exclusion criteria for eligibility.

Between Screening and the day of surgery (Day 0), the prospective subjects will be determined to be a suitable candidate for surgery during a pre-surgery medical assessment, where the routine medication list prescribed by the cataract surgeon should be reviewed to rule out prohibited medications (See Section 5.4.2).

Day 0/Day of Surgery: Subjects undergo routine cataract surgery via phacoemulsification and posterior chamber intraocular lens implantation according to the Investigator's normal procedures.

Visit 2: POD1 will occur ~ 18-34 h after cataract surgery. Review Inclusion and Exclusion criteria. Baseline pre-Randomization assessments (ocular inflammation, pain and safety assessments). Randomization of eligible subjects. Instillation of first dose of study treatment in the operated study eye in the clinic under the supervision of Investigator or designee.

Visit 3: POD4 (± 1 day). Ocular inflammation, pain and safety assessments.

Visit 4: POD8 (± 1 day). Ocular inflammation, pain and safety assessments.

[Note: Subjects will be contacted on POD14 to remind them to stop study drug **after** that day and to bring the study drug bottle and dosing diary to the clinic the next day.]

Visit 5: POD15 (+ 1 day). Ocular inflammation, pain and safety assessments. Urine pregnancy test.

Visit 6: POD22 (± 2 days). Ocular inflammation, pain and safety assessments. Final visit.

A detailed summary of study events is provided in Table 1 (Schedule of Events) and a study design schematic is provided in Figure 1 (Study Schematic).

3.2.2 Contingencies relating to the COVID-19 Pandemic

Appendix A describes the procedures that may be implemented because of the COVID-19 pandemic.

3.3 Rationale for Study Design

3.3.1 Rationale for Number of Subjects to be Randomized

This is a Phase 3 study. See Section 10.4 for rationale for the number of subjects to be enrolled in the study.

3.3.2 Rationale for the Primary Efficacy Endpoints

The two primary endpoints are clinically-meaningful to clinicians and the subjects undergoing ocular surgery and have been applied to support the approval of other corticosteroid ophthalmic drug products for the treatment of post-operative inflammation and pain following ocular surgery.

The efficacy data from Part A of Study CPN-201 summarized in the APP13007 Investigator's Brochure show that APP13007 0.05% BID, compared to matching vehicle placebo, produced a statistically and clinically-meaningful increase in the proportion of subjects who had an ACC Count = 0 at POD8 that was maintained through POD15.

A greater proportion of subjects dosed with APP13007 as compared to placebo had resolution of ocular pain (grade = 0) at POD4 that was maintained through POD15.

The US FDA has agreed with the primary endpoints in this study at an End-of-Phase 2 meeting.

3.3.3 Rationale for Dosing Regimen

The results from Study CPN-201 summarized in the APP13007 Investigator's Brochure show that 0.05% APP13007 BID as compared to its matching vehicle placebo produced a clinically-meaningful reduction of inflammation and pain after cataract surgery. In addition, all APP13007 dosing regimens were well-tolerated with a safety profile similar to the matching vehicle placebos.

These data support the selection of 1 drop of 0.05% APP13007 administered BID for 14 days as the dosage regimen for this Phase 3 clinical study.

The US FDA has agreed with the selection of the dosing regimen to be used in this study at an End-of-Phase 2 meeting.

4.0 STUDY POPULATION

4.1 Number of Subjects

Approximately 370 subjects who have undergone routine, uncomplicated cataract surgery and (i) meet the inclusion criteria, including having >10 anterior chamber cells in the study eye (operated eye) at POD1, and (ii) do not meet any of the exclusion criteria, will be randomized to study treatment.

4.2 Inclusion Criteria

To be eligible, a participant must meet the following criteria:

At the Screening Visit (Visit 1):

1. Provide signed and dated informed consent

2. Age ≥ 18 years at time of informed consent

3. Males or females of non-childbearing potential. Females of non-childbearing potential is defined as women who have been permanently sterilized or are postmenopausal. Postmenopausal is defined as amenorrhea for a minimum of 12 months (without an alternative medical cause). Note: Pregnant women or nursing (breast-feeding) mothers are excluded from the study.

4. Women-of-childbearing-potential to be eligible for enrollment if they have a negative urine pregnancy test on POD1 prior to Randomization and they agree 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 ring, percutaneous contraceptive patches, or intrauterine device from POD1 to Visit 6 (POD22).

5. Expected to undergo unilateral uncomplicated cataract extraction via phacoemulsification and posterior chamber intraocular lens implantation in one eye (designated the ‘Study Eye’).

6. Have a pin-hole corrected visual acuity without other correction of ≤ 1.3 logarithm of the minimum angle of resolution (logMAR) in the study eye to be operated and contralateral eye as measured using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart at Visit 1. Subjects who are unable to read the lines in an ETDRS chart because of the density of the cataract in the study eye may be enrolled if, in the opinion of the Investigator, there is no other significant ocular pathology that would account for the low visual acuity.

7. Willing and able to comply with study requirements and visit schedule; Able to either self-administer study medication or have someone available (e.g., spouse, caregiver, etc.) who can administer study medication according to the study schedule and instructions

4.2.1 Additional Inclusion Criteria on Postoperative Day (POD) 1/Day of Randomization (Visit 2)

8. Have 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

9. No significant ocular pathology affecting visual acuity that is identified after posterior chamber intraocular lens implantation in the study eye.

10. Have ≥ 10 cells in the anterior chamber (excluding red blood and pigment cells)

11. Have an IOP ≤ 30 mmHg. Note: If the IOP is elevated post-surgery, the investigator may use non-prostaglandin based IOP-lowering medication(s) at their discretion on the day of surgery (Day 0) only. The IOP will be measured and recorded on POD1 to determine eligibility for Randomization.

4.3 Exclusion Criteria

Participants will be excluded if they meet any of the following criteria:

1. Have 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.

2. Have an ACC count > 0 or any evidence of intraocular inflammation (e.g., flare) in either eye at the Screening visit.

3. Have a Grade > 0 on the Ocular Pain Assessment in either eye at the Screening visit.

4. Have an immunosuppressive or autoimmune disease that in the opinion of the Investigator could affect intraocular inflammation or the normal healing process of the eye.

5. Have active or chronic/recurrent ocular or systemic disease that is uncontrolled and could affect wound healing and/or resolution of inflammation after cataract surgery.

6. Suspected or known malignancy or be currently receiving antineoplastic therapy.
   Note: subjects with basal cell carcinoma will not be excluded unless the Investigator believes that the condition has the potential to interfere with study procedures or analysis of results.

7. Are using certain medications, namely:

   i. Subjects receiving treatment for macular degeneration (in either eye) with Eylea® (aflibercept), Avastin® (bevacizumab), Lucentis® (ranibizumab) Beovu® (brolucizumab-dbll) or Visudyne® (verteporfin) are excluded.

   ii. PROKERA (preserved amniotic membrane) is excluded from 1 year prior to the Screening visit to the end of the study.

   iii. Anti-inflammatory agents, analgesics (including opioids, narcotics, nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, acetaminophen and other pain medications) or immune-modulating agents systemically or in either eye from the beginning of the 'Washout' period in the List of Prohibited Medications (Section 5.4.2) until after the POD15 assessments, but preferably until after the POD22 assessments. *Note: (i) acetaminophen is permitted on the day of surgery; (ii) immunizations/vaccinations are permitted before and during the study.*

   iv. Use of any of the prohibited medications listed Section 5.4.2 within a time period prior to surgery that is less than the minimum 'washout' period noted in Table 4.
   [NOTE: (i) These medications may not be used from the beginning of the 'Washout' period in Table 4 until after the POD15 assessments, but preferably until after the POD22 assessments; NOTE: (ii) Medications for anesthesia related to cataract surgery, ocular pain control and non-prostaglandin-based therapy for the treatment of raised intraocular pressure (IOP) are allowed on the day of surgery only]

   v. Non-approved drugs or investigational products other than the study drug in this study are prohibited from 28 days before surgery until after the subject has been released from the study.

8. Have an IOP < 5 mmHg or > 22 mmHg in either eye or a difference of > 5 mmHg between the eyes at the Screening visit.
9. Have a history of documented and repeated elevated IOP or glaucoma.
10. History of herpes keratitis in the study eye.
11. Have active corneal abrasions or ulcers in the study eye.
12. Have active or a history of chronic or recurrent inflammatory eye disease (e.g., iritis, scleritis, uveitis, iridocyclitis, rubeosis iridis) in the study eye.
13. Have 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.
14. Have corneal dystrophies, including corneal guttae and Fuchs' dystrophy, or dysthyroid ophthalmopathy in the study eye.

15. Have uncontrolled and clinically significant dry eye syndrome in the study eye (mild dry eye with the use of artificial tears is allowed).
16. Have proliferative diabetic retinopathy, significantly compromised macular function; significant macular disease; have clinically-significant macular edema or a history of cystoid macular edema in the study eye; have cup:disc ratio > 0.8.
17. Have had corneal or retinal surgery (laser or incisional) in the study eye within 6 months of the Screening visit, or planning to have laser or incisional surgery during the study period in the study eye (other than cataract surgery).
18. Have ocular surgery planned, scheduled or performed on the contralateral eye within the 2 months prior to the surgery on the study eye.
19. Have 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).
20. Require 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.
21. Require use of non-diagnostic topical ophthalmic medications in either eye for the duration of the study with the exception of the following which are allowed: mydriatics, anesthetics, antiseptics, balanced salt solution, viscoelastics, osmotic agents (e.g., Muro 128), prophylactic antibiotics, non-prostaglandin 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.
22. In the opinion of the investigator, have the potential for ocular hemorrhage in the study eye that may interfere with evaluation of post-surgery inflammation.
23. Have a planned use of or use of femtosecond laser or any other ophthalmic surgical procedure (e.g., 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.
24. Have a planned use of or use anterior capsule staining for capsulorhexis (i.e., trypan blue) during cataract surgery.
25. Have planned to participate in another clinical trial during the duration of this study.
26. Have participated in another clinical study or received any investigational product within the past 28 days prior to the Screening Visit. Subjects who previously participated in Study CPN-201 are eligible if the planned cataract surgery is for the eye that was the ‘non-study’ eye in that study.
27. Have any other condition that the Investigator determines should exclude the subject from the trial.
28. Are an employee of the clinical site that is directly involved in the management, administration, or support of this study or are an immediate family member of the same.

5.0 STUDY DRUG AND TREATMENTS

5.1 Study Drug Administration

5.1.1 Study Drug Description

Dosage Form, Appearance, Packaging and Labelling

[redacted] The nanosuspension of APP13007 and matching vehicle placebo have the appearance of an opalescent liquid.

[redacted]

Each subject will be supplied with a single dropper bottle throughout the study period (see Section 5.1.2 below). Individual dropper bottles will be labelled according to FDA requirements. The labels will include the following information:

- Protocol number: CPN-301
- Bottle number
- Subject Number
- Study Eye: R or L
- Content: APP13007 [redacted] or Placebo [redacted]
- For Topical Ophthalmic Use in Clinical Trials Only. Keep Out of the Reach of Children.
- CAUTION: New drug – Limited by Federal (or United States) Law to Investigational Use

Acquisition

Individual dropper bottles packaged with proper labels will be shipped to each study site from a central drug product labeling, packaging and distribution vendor. Sufficient quantity of APP13007 and matching vehicle placebo will be provided to each site to accommodate the initial randomization rate, with the option to resupply high-enrolling sites. Once a subject is

randomized via the IWRS, the subject will be dispensed a dropper bottle with the specific bottle number assigned to the subject number based on the randomization schedule.

Storage and Stability

[redacted]

5.1.2 Study Drug Dosing and Administration

5.1.2.1 Dispensing and Replacing Study Drug

Study drug will be dispensed by personnel assigned to do so at the study site as indicated on the Site Delegation Log. One bottle will be dispensed to each subject for the duration of the study treatment period. If the subject discontinues study drug, the study drug bottle should be collected at the next clinic visit.

If a subject loses the single bottle of study drug or if it becomes compromised (e.g., damaged or dropped into the toilet) prior to the POD15 visit, the bottle of study drug should be replaced as soon as possible. The site should use the IWRS system to identify a replacement bottle. Subjects are instructed to notify the study site as soon as the study drug bottle is lost or compromised, so that the site can arrange for the replacement bottle to be provided as soon as possible. Any missed doses due to loss of study drug bottle will be documented in the diary and eCRF.

Failure to dose from the replacement bottle (issued prior to POD 15) will be considered a protocol deviation.

5.1.2.2 Subject Diaries

A study diary will be given to each subject at the visits indicated on the Schedule of Events (Table 1). The subject will record the date and time of each dose of study drug as well as the total number of drops applied (including missed drops) and the number of drop(s) instilled correctly into the conjunctival sac of the study eye at each dosing time. The diary will remind the subject to instill the study drug a minimum of 5 minutes prior to administration of other eye medications in the study eye.

At each study visit noted in the Schedule of Events, site personnel will collect the diary and dispense a new diary to the subject. Site personnel will review the diary to ensure compliance with drug dosing and diary recording procedures. Diary data will be entered into the eCRF. If there is an issue with dosing or recording compliance, site personnel will instruct the subject again on correct procedures at each visit. If the subject is unable to comply with required dosing procedures, the subject may be discontinued from the study. However, site personnel must contact the Study Medical Monitor prior to discontinuing a subject for compliance-related issues.

5.1.2.3 Study Drug Compliance

Site personnel will record the dosing record taken from the diary into the eCRF. This will include the number of drop(s) applied in the study eye, date/time of application and verification that no other drugs were administered within 5 minutes of study drug application in the study eye. If patient states that other drugs were administered in the study eye within 5 minutes of instillation of study drug, this will be recorded in the eCRF as a protocol deviation. Instillation of the study drug in the non-study eye will be recorded as a protocol deviation.

5.1.2.4 Study Treatments

The treatments are as follows:

- Treatment 1: 1 drop APP13007 twice daily (BID) (morning and evening) for 14 days instilled to the operated study eye
- Treatment 2: 1 drop matching vehicle placebo BID (morning and evening) for 14 days instilled to the operated study eye

5.1.2.5 Study Drug Dosing

Study drug (APP13007 or matching vehicle placebo) will be supplied in an eye drop bottle with a drop tip, and the bottle is labeled in accordance with FDA regulations for investigational drug. One bottle will be dispensed to each subject throughout the study. Study drug will be self-administered twice daily as indicated per protocol by instilling one drop into the conjunctival sac near the medial corner of the operated (study) eye.

If the subject misses the conjunctival cul-de-sac when dosing the first drop of study drug, the subject should use a tissue to wipe away the study drug around the eye, and then instill a second drop into the conjunctival cul-de-sac so that at least one drop of study drug is administered into the study eye. If the second drop also misses the conjunctival sac, then the subject should record the missed dose in the diary, but should not instill a third drop.

Study drug should be administered twice daily. If other concomitant eye drops/drugs are to be instilled into the study eye, the study drug should be instilled first followed by a minimum of a 5 minute lag time before any other ocular medications are applied to the study eye.

After randomization, the first dose of study drug should be administered in the clinic on POD1 so that the site personnel can ensure the subject is able to apply study drug correctly. The second drop of the study drug on POD1 should be administered by the subject a minimum of 6 hours later. For all other days the first dose should be instilled in the morning and the second dose instilled a minimum of 6 hours, but preferably 8 to 12 hours, later. The number of drops instilled and the date/time of instillation of each dose must be recorded by the subject in the subject's

diary. Subjects will be instructed on POD1 of recording the necessary information on the diary on each dosing day.

5.2 Study Drug Return and Accountability

Study monitors [redacted] will conduct accountability of APP13007 and matching vehicle placebo. Accountability will be ascertained by performing reconciliation between the number of bottles of study drug, along with bottle ID numbers, sent to the site and the number of bottles dispensed (used), unused or un-dispensed (along with bottle ID numbers) at the time of reconciliation. In addition, the number of bottles of study drug (along with bottle ID numbers) dispensed and returned will also be accounted for.

Clinical trial materials will be shipped to the investigational sites under sealed conditions with a temperature tracking device. Study drugs shipment records will be verified by comparing the shipment inventory sheet to the actual quantity of study drug (number of bottles and bottle ID numbers) received at the site. Accurate records of receipt and disposition of the study drug (e.g., dates, number of bottles and each bottle ID number received, dispensed, lost or compromised, and returned) and subject number associated with the bottle ID number must be maintained by the Investigator or his/her designee. [redacted]

At the end of the study, all study materials, including any used (and returned) and unused study drugs bottles, even if empty, will be returned to the drug packaging and distribution vendor in accordance with Sponsor or designee's standard operations procedures (SOPs), following approval by the Sponsor. All returns of study drugs will be documented. The study monitor or designee will verify drug accountability. All drug accounting procedures must be completed before the study is considered complete.

5.3 Masking and Unmasking

The Sponsor, the management and project team at the CRO responsible for trial management, monitoring and data collection and management, the study monitors, the Study Medical Monitor, the study subjects, the Investigators and the study site staff responsible for managing and administering the study, communicating with the study subjects, and/or performing assessments of study endpoints will be masked to study treatment assignment of each subject throughout the entire study.

The Study Medical Monitor will remain masked throughout the study unless unmasked information becomes necessary as part of the management of a medical emergency or SAE for a particular subject, as described below.

A randomization schedule will be computer-generated by a qualified biostatistician independent of the study conduct and management and will be uploaded into the EDC system by a designated person not involved in the study conduct, data collection or management. The EDC/IWRS system will be used for randomization and unmasking of treatment assignment when necessary.

In case of a medical emergency or occurrence of an SAE, the Investigator will treat each subject as needed and should contact the Study Medical Monitor, if required, to discuss whether it is appropriate to unmask the subject to reveal the subject's treatment assignment. If deemed necessary, the Investigator will log into the EDC system to obtain unmasking information. The Investigator must use their individual login information to gain access to the unmasking information. The Investigator will also notify the IRB and the CRO managing and monitoring this study when treatment assignment for a particular subject is unmasked. The Study Medical Monitor will notify the Sponsor Medical Monitor when treatment assignment for a particular subject is unmasked due to a medical emergency or SAE. It is important to note that the study treatment assignment will be revealed only on a subject-by-subject basis and the treatment assignment of the other subjects in the study, as described above, will remain masked until the final database is locked. Once the treatment assignment for a specific subject is unmasked, it will be made available to the Investigator and the Sponsor. Other personnel involved in the monitoring or conduct of this study will remain masked.

5.4 Prior/Concomitant Therapy and Rescue Medication

All prior/concomitant medications (prescription and OTC) a subject is receiving at the Screening visit and 90 days prior to the Screening visit and taken throughout the course of the study will be recorded as follows:

- Information regarding the duration of a prior/concomitant medication (including start and stop dates), dose, frequency, site of dosing (right eye, left eye, both eyes, non-ocular) and the reason why the prior/concomitant medication is being taken will be recorded in the source documents and in the Prior/Concomitant Medications (ConMeds) page of the eCRF.
- Medications used for the surgical procedure will be recorded in the source documents and in the ConMeds page of the eCRF.
- The ocular medications (mydriatics and topical analgesics) used to perform the dilated ophthalmoscopy and Goldmann applanation tonometry assessments will be recorded in the source documents only.

Note: The information on prior/concomitant medications will be used to determine whether a subject is taking or has taken prohibited medications as outlined in Section 5.4.2.

5.4.1 Rescue Medication

Any subjects who have evidence of persistent or worsening inflammation as described in Section 9.4 may be rescued and placed on appropriate alternate therapy. The choice of rescue medication is at the Investigator's discretion. Rescue medication should be entered into the eCRF with annotation indicating that the medication was used for rescue.

Rescued subjects will be considered as treatment failures, and the need for rescue therapy will not be considered an adverse event (AE). Rescued subjects will stop study drug and should not be withdrawn from the study, and will be assessed at each subsequent visit, if possible, through completion of the Visit 6 (POD22) assessments or until the Investigator has deemed the subject is stable and can be released from the study as detailed in Section 6.3.

5.4.2 Prohibited Medications

The subject must provide signed informed consent before any prior medication is changed or discontinued because of participation in this study. The following medications may not be used after randomization as indicated below. If used prior to surgery (Day 0), the medications must have been used in a timeframe that equals or exceeds the minimum 'washout' period noted below.

The following medications are prohibited:

i. Eylea® (aflibercept), Avastin® (bevacizumab), Lucentis® (ranibizumab), Beovu® (brolucizumab-dbll) or Visudyne® (verteporfin) (in either eye).

ii. PROKERA (preserved amniotic membrane) is excluded from 1 year prior to the Screening visit to the end of the study.

iii. Anti-inflammatory agents, analgesics (including opioids, narcotics, nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, acetaminophen and other pain medications) or immune-modulating agents systemically or in either eye from the beginning of the 'Washout' period in Table 4 until after the POD15 assessments, but preferably until after the POD22 assessments. *Note: (i) acetaminophen is permitted on the day of surgery; (ii) immunizations/vaccinations are permitted before and during the study.*

iv. Use of any of the prohibited medications listed Table 4 below within a time period prior to surgery that is less than the minimum 'washout' period noted in the table.
NOTE: (i) These medications may not be used from the beginning of the 'Washout' period in Table 4 until after the POD15 assessments, but preferably until after the POD22 assessments; NOTE: (ii) Medications for anesthesia related to cataract surgery, ocular pain control and non-prostaglandin-based management of raised intraocular pressure (IOP) are allowed on the day of surgery only.

v. Non-approved drugs or investigational products other than the study drug in this study are prohibited from 28 days before surgery until after the subject has been released from the study.

Table 4: Prohibited Medications and Minimum Washout Periods

Medication	Minimum 'Washout' Period Prior to Day 0
All topical ophthalmic gels or ointments	2 days
Ocular mast cell stabilizers	2 days
Ocular antihistamines	2 days
Ocular and nasal decongestants	2 days
All eye drops (except antibiotic eye drops considered to be part of pre-cataract surgery standard-of-care). Note: Antibiotics with anti-inflammatory activity and Besifloxacin Ophthalmic suspension are not permitted. Note: (i) Artificial tears are allowed, but should not be used within 10 minutes of study procedures or medication dosing; (ii) specific restrictions for ocular products are listed below.	2 days
Topical ocular corticosteroids	14 days
Topical ocular NSAIDs	7 days
Topical prostaglandin eyelash growth medications	7 days
Systemic anti-inflammatory agents including acetaminophen, NSAIDS, acetylsalicylic acid (aspirin), and Lifitegrast. *Note: (i) Use of acetylsalicylic acid for cardiovascular prophylaxis (i.e., 81 mg dose QD) is allowed if dosage has been stable for at least 30 days prior to surgery and will remain stable for the duration of the study (ii) Acetaminophen may be administered as needed pre- and post-operatively on the day of surgery, (iii) Over-the-Counter preparations such as Fish Oils, Turmeric and Ginseng that may have mild anti-inflammatory effects are allowed.*	7 days
Topical dermatologic corticosteroids including OTC preparations (use of topical 0.1% hydrocortisone dermal preparations for less than 3 days over a small area of skin [~2 inches x ~2 inches] are allowed).	14 days
Systemic (oral, injectable), inhaled and/or nasal corticosteroids	21 days
Systemic analgesics/pain relievers such as gabapentin, pregabalin, opioids *Note: Marijuana/CBD-containing products have the same washout restrictions as "Systemic Analgesics" because they can affect pain perception*	14 days
Medications for benign prostatic hypertrophy (BPH) (e.g., finasteride, α-1 adrenergic receptor antagonists) are allowed based on the judgment of the investigator. *Note: Investigators should consider the potential risk of intraoperative floppy iris syndrome in subjects who are taking or have taken α-1 adrenergic receptor antagonists (eg. tamsulosin, silodosin, alfuzosin).*	Stable dose for 28 days
Topical or systemic cyclosporine	60 days
Periocular injection of corticosteroid	28 days

Medication	Minimum 'Washout' Period Prior to Day 0
Intraocular treatment with corticosteroid - dexamethasone drug delivery system	90 days after implantation
Intraocular treatment with corticosteroid – fluocinolone acetonide drug delivery system	48 months after implantation
Stable doses of anticholinergics and antidepressants are allowed. Alterations of the dose of anticholinergics and antidepressants (other than for prn use as a sleep aid) may be allowed following consultation with the Study Medical Monitor. Anticholinergic eye drops used to dilate the eye are allowed. Systemic anticholinergic drugs are allowed on the day of surgery. **Note 1** For anti-depressants used to treat depression: (i) Medication must not be washed-out for the purpose of enrollment in the study; (ii) Stable doses of anti-depressants are allowed; (iii) When the dose of an anti-depressant has been altered, the subject needs to be on the stable altered dose for at least 90 days prior to the day of surgery (Day 0). **Note 2** For anti-depressants used to treat pain: (i) The instructions provided for systemic analgesics/pain relievers apply, viz. at least a 14 day washout of the medication is required prior to the day of surgery (Day 0) continuing until the POD15 assessments have been completed.	See Note 1 and Note 2

6.0 STUDY CONDUCT

Refer to the Schedule of Events (Table 1) for the list of study procedures/assessments to be conducted at each visit.

Data should be entered into the eCRF as soon as possible, preferably within 72 hours of collection from each subject.

6.1 Study Subject Number

Subject Number – assigned upon Screening examination.

Randomization Number – assigned by IWRS upon randomization of a subject on POD1.

Bottle Number – associated with the Randomization Number, assigned by IWRS.

If a subject requires a replacement study drug bottle, then a replacement Bottle Number will be identified through IWRS.

6.2 Description of Study Visits

6.2.1 Visit 1 - Screening

The Screening visit should occur no more than 28 days and no less than one (1) day prior to surgery. After obtaining written informed consent and HIPAA authorization, site staff will perform the assessments as shown in the Schedule of Events (Table 1). All ocular assessments must be performed on both eyes at the Screening visit.

If surgery is not performed on the planned scheduled day such that screening procedures would fall outside of the 28 day screening window, site staff must contact the Study Medical Monitor to determine which, if any, of the screening procedures must be repeated.

Subjects may be rescreened, if, in the opinion of the Investigator, the subject would qualify for the study if a procedure/assessment is repeated/redone (in this case, the subject keeps the same subject number). *Note: If subject who has failed screening is rescreened at a later time, the subject will be assigned a new subject number.*

Subjects who sign the informed consent form (ICF) and have undergone study procedures/assessments, but do not meet eligibility criteria any time prior to randomization on POD1 will be considered as screen failures. Limited information on screen failures will be transcribed to the eCRF.

After the screening assessments and before surgery, the subject may have a pre-surgery medical assessment to determine whether the subject is a suitable candidate for surgery. At this time, the

routine medication list prescribed by the cataract surgeon should be reviewed to rule out prohibited medications (Table 4, Section 5.4.2).

6.2.2 Day of Surgery (Day 0)

Prior to surgery, the surgeon's routine medication list should be reviewed to exclude prohibited medications (Table 4, Section 5.4.2). Surgery should preferably be scheduled in the morning to accommodate BID dosing on POD1. However, if surgery has to be scheduled in the afternoon, subjects should still instill two doses of study drug on POD1 at least 6 hours apart.

On Day 0, the surgeon will perform his/her routine cataract surgical procedure using phacoemulsification and implantation of a posterior chamber intraocular lens in the operated eye following the surgeon's usual pre-operative, operative, and post-operative procedures (with the exception of avoiding use of prohibited medications). Aqueous release procedures are not permitted.

Following surgery, the following should be performed:

- Give the subject instructions regarding routine post-surgical care and instructions regarding the use of concomitant medications and restricted medications during the study.
- Record surgery parameters (surgery time, phaecoemulsion energy and an assessment of surgery difficulty) in the source documents and eCRF.
- Record the medications routinely administered for cataract surgery in the source documents. These medications will be reported as being used for routine cataract surgery.
- If a medication is administered due to an AE, the medication must be entered in the source documents, indicating that the medication was used to treat an AE.
- If a non-prostaglandin medication is used to lower IOP, the medication must be entered in the source documents and in the ConMeds page of the eCRF.
- AEs and ConMeds associated with an AE should only be recorded in the source document on Day 0 if they result in screen failure of the subject. If a subject is not a screen failure on Day 0, the AEs and ConMeds applicable to Day 0 should be recorded in the source documents when the subject returns for Visit 2 on POD1.
- Only for subjects who are randomized, enter the medications routinely used for cataract surgery and concomitant medications in the ConMeds page of the eCRF and AEs in the AE page of the eCRF.
- Schedule the subject to return to the clinic on the following day, ie., POD1, in the morning (if possible).

6.2.3 Visit 2 - POD1 (Day of Randomization)

Subjects will return to the clinic for the study visit on POD1 between 18 to 34 hours following conclusion of surgery on Day 0. This visit should be scheduled in the morning, as much as

possible, to allow for administration of two doses of study drug during the day on POD1 for randomized subjects. However, if surgery is to be performed in the afternoon, subjects should still instill two doses of study drug on POD1 at least 6 hours apart.

All assessments will be performed as shown in the Schedule of Events (Table 1). Ocular assessments will be performed only on the operated, study eye.

The site will review eligibility criteria (Section 4.2 and Section 4.3) to determine if the subject qualifies for randomization. If the subject meets all criteria, the subject will be randomized by site personnel using the EDC/IWRS system. The site should follow the instructions provided in the Study Reference Manual)/eCRF Completion Guidelines to enter appropriate subject data into the eCRF and randomize the subject. A study drug bottle number will be assigned to the subject based on the predetermined randomization by the EDC/IWRS system. The designated site personnel should supervise the administration of the first dose of study drug by the subject in the clinic before dispensing the assigned study drug bottle along with written dosing instructions and diary to the subject. The second dose will be administered at home.

A subject who fails to qualify for the study on POD1 will not be rescreened.

Note that the use of IOP-lowering medications or aqueous release procedures are not allowed on POD1.

Study drug dosing/administration procedures including handling bottle replacement, diary/dosing compliance and the list of treatments are presented in Section 5.1.2. Subjects are reminded to bring the diary to each clinic visit in order for site staff to review dosing compliance.

6.2.4 Visit 3 (POD4 ± 1) and Visit 4 (POD8 ± 1)

All assessments will be performed as shown in the Schedule of Events (Table 1).

Ocular assessments will be performed only on the operated, study eye at Visit 3 (POD4) and Visit 4 (POD8).

6.2.5 Day of Subject Contact on POD14

POD14 is the last day of dosing. Site personnel will contact the subject on POD14 (no specific window) to remind the subject not to take study drug on POD15 and onward and to bring the bottle of study drug and diary back to the clinical site at Visit 5 (POD15). Site personnel will contact the subject using the subject's preferred reliable method of communication, e.g., telephone call, cell phone text or email. The site staff must make an effort to ensure that the subject receives and acknowledges the receipt of the message. Method of contact and whether or not the subject was reached is to be documented in the source document.

Any AEs reported to the site during the POD14 contact must be recorded in the source documents and eCRF. Further assessment of any reported AEs may require an Unscheduled Visit on POD14 if medically significant or they may be assessed, as appropriate, at Visit 5 (POD15).

6.2.6 Visit 5 (POD15 + 1)

All assessments will be performed as shown in the Schedule of Events (Table 1).

Ocular assessments will be performed only on the operated, study eye.

Study drug bottle and final diaries will be collected at this visit.

6.2.7 Visit 6 (POD22 ± 2)

This is the final visit for the subjects.

All assessments will be performed as shown in the Schedule of Events (Table 1).

Ocular assessments will be performed on both eyes.

Subjects with ongoing AEs or SAEs should be handled as discussed in Section 8.0.

6.2.8 Early Termination/Withdrawal

Subjects who are terminated/withdrawn from the study early will have the Visit 6 (POD22) assessments and a urine pregnancy test performed at the time of early termination, or as soon thereafter as possible. At an Early Termination/Withdrawal visit the ocular assessments are to be performed on both eyes.

Appendix A describes the Early Termination/Withdrawal procedures that may be implemented because of the COVID-19 pandemic.

6.2.9 Unscheduled Visits

Any visits performed beyond those specified within the protocol must be documented in the Unscheduled Visit pages of the eCRF. Unscheduled visits may include, but are not limited to, reporting and/or follow-up of AEs/SAEs, changes in concomitant medications, follow-up of subjects receiving rescue or IOP-lowering medications or ophthalmic assessments as deemed appropriate by the Investigator.

6.2.10 Study Visit Schedule for Rescued Subjects

Subjects who are rescued as discussed in Section 9.4 will discontinue study drug and receive rescue medication.

The Investigator should make every effort to keep subjects who are rescued in the study until they complete the Visit 6 (POD22) assessments (Table 1).

6.3 Subject Early Termination (Withdrawal)

Any subject who wishes to voluntarily discontinue study drug or withdraw from participation in the study for any reason is entitled to do so without obligation. If a subject requests to discontinue the study drug, the subject will be withdrawn from the study as an Early Termination (see Section 6.2.7).

The Investigator may discontinue any subject from study drug or from study participation, if deemed necessary at any time during the study for any reason including, but not limited to:

- The investigator considers that the subject requires alternative medication that is incompatible with further continuation of the study drug or participation in the study.
- Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol.
- Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation in the study is not in the best interest of the subject or that continued participation could affect study objectives.
- Any woman who reports becoming pregnant while participating in the study. Information on the pregnancy and outcome will be requested by the Investigator.
- Subject's continued failure to comply with protocol requirements or study-related procedures after being instructed on the correct requirements or procedures by the Investigator or site personnel.
- Termination of the study by the Sponsor, FDA, or other regulatory authority.

In the event that early termination/withdrawal of a randomized subject is necessary ('withdrawn' subject), the Investigator should make every attempt to complete the Visit 6 assessments and perform a urine pregnancy test as soon as possible (Table 1). Note: the Visit 6 ocular assessments need to be performed on both eyes.

The reason for early termination/withdrawal of a subject should be recorded in the source documents and entered in the eCRF.

Subjects who are terminated early from the study will not be replaced.

6.4 Study Discontinuation Criteria

6.4.1 Early Discontinuation of the Study

The study or parts of the study may be discontinued by the Sponsor or at the recommendation of the Investigator after consultation with the Sponsor. This may be based on a significant number of AEs of a similar nature that warrant such action.

6.4.2 Discontinuation of a Study Site

The Sponsor may discontinue the study at a site for reasons that include GCP violations, protocol deviations, lack of enrollment or for the protection of the safety and wellbeing of a subject.

7.0 STUDY ASSESSMENTS AND PROCEDURES

7.1 Demography and Medical History

Subjects' demographic information will be collected and recorded in the eCRF. A complete systemic and ocular medical and surgical history will be taken at screening, and abbreviated assessment will be taken at the subsequent visits.

7.2 Efficacy Assessments

7.2.1 List of Efficacy Assessments

The ocular efficacy assessments apply to the Study (Operated) Eye Only.

- Slit Lamp Biomicroscopy assessment of (i) ACC count and (ii) ACF grade using a 5 point scale (0-4).
- Subject-Rated Ocular Pain Assessment (0-4 Scale)
- Number of subjects who are rescued
- Best corrected visual acuity by pinhole method using an ETDRS chart

7.2.2 Procedures for Assessment of Efficacy Endpoints

7.2.2.1 Anterior Chamber Cell Count and Anterior Chamber Flare

The biomicroscopy examination will be performed with the slit lamp using a slit-beam. The Investigator should use their usual examination technique. Anterior chamber cells should be counted using the high light intensity level and the high magnification (Haag-Streit 16 X or comparable), with the slit beam set at an oblique angle, and the height and width of the beam set to 1.0 X 1.0 mm.

ACF will be graded as shown below:

Grade	Description
0	None
1	Faint
2	Moderate (iris and lens details clear)
3	Marked (iris and lens details hazy)
4	Intense (fibrin or plastic aqueous)

7.2.2.2 Subject-Rated Ocular Pain Assessment

Ocular pain is defined as throbbing, or aching, and will be graded by the subject on a 5-point scale. At the visits shown in Table 1, subjects will be required to subjectively rate their pain in the study eye before any other ocular assessments are performed.

Ocular Pain will be graded a shown below:

Grade	Description
0	None: No pain.
1	Minimal: Presence of minimal throbbing or aching pain (expected following cataract surgery).
2	Mild: Presence of mild throbbing or aching pain, easily tolerated.
3	Moderate: Presence of moderate throbbing or aching pain leading to the desire to use an analgesic.
4	Severe: Presence of severe throbbing or aching pain that is not tolerable

7.2.2.3 Best Corrected Visual Acuity

The assessment of best corrected visual acuity in the study (operated) eye will be performed as described in Section 7.3.1.2.

7.3 Safety Assessments

The safety assessments are applied to both eyes at Visit 1 (Screening) and Visit 6 (POD22) or Early Termination/Withdrawal or to the Study (operated) eye only at Visit 2 through Visit 5. (Table 1 Schedule of Events). The safety assessments in Table 1 are not performed on the day of surgery.

7.3.1 List of Safety Assessments

- AEs
- ETDRS Assessment of Best Corrected Visual Acuity by Pinhole Method
- Slit Lamp Biomicroscopy assessment of the following signs of inflammation: corneal edema, ciliary flush, bulbar conjunctival injection. The assessments in the non-study eye will include an assessment of the lens
- IOP Measurement using Goldmann applanation tonometry
- Dilated Ophthalmoscopy assessment of the vitreous, retina, macula, choroid, and optic nerve with cup/disc ratio, and an assessment of the presence and severity of a cataract if present in the non-study eye

7.3.1.1 Assessment of Adverse Events

All AEs spontaneously reported by the subject or in response to an AE query from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded in the source document and on the appropriate pages of the eCRF. Any clinically relevant deterioration in a clinical finding is considered an AE and must be recorded. When possible, signs and symptoms indicating a common underlying pathology should be noted as one (1) comprehensive event. Any pre-existing medical condition that worsens after administration of study drug will also be considered as an AE.

Ocular complaints associated with and expected as a result of the surgery, that are not recorded as AEs in the eCRFs will be recorded in the source documents. An ocular complaint will be recorded in the eCRF as AE when the complaint is outside the normal limits for cataract surgery or is associated with clinical sequelae (i.e., adverse slit lamp examination finding).

See Section 8.0 for information on how to record AEs and how to attribute relatedness of an AE to study procedures, cataract surgery or study drug.

7.3.1.2 ETDRS Best Corrected Visual Acuity Measurement by Pinhole Method

Best corrected visual acuity measurement will be performed using the ETDRS eye chart at a preferred (but not required) distance of 4 meters. The testing should be conducted under standardized lighting conditions using the pinhole method for the study visits indicated in Table 1. Other testing distances may be used as long as it is consistent with the recommendations provided for the ETDRS chart being used and will be used consistently at each visit.

The subject starts at the top of the chart and reads down until the subject reaches a row where the subject is unable to correctly read any letters on that line.

The ETDRS Acuity Log Score was calculated as follows:

1. Determine the last row where the subject can correctly identify at least one (1) letter in that row. This is the Base Logarithm of the Minimum Angle of Resolution (logMAR) line.

2. Determine the log score for the Base logMAR line.

3. Add 0.02 (T=0.02) log units for every letter that is incorrectly identified up to and including the Base logMAR line.

The results will be recorded in the source documentation and the eCRF.

7.3.1.3 Slit Lamp Biomicroscopy

In addition to the assessment of ACC and ACF (Section 7.2.2.1), the following safety parameters will be evaluated at Visits 1 through 6 as indicated in Table 1 using the following scales during the slit lamp examination:

Bulbar Conjunctival Injection

Grade	Description
0	Absent
1	Mild
2	Moderate
3	Severe

Sclera - Ciliary Flush

Grade	Description
0	Absent
1	Mild
2	Moderate
3	Severe

Corneal Edema

Grade	Description
0	Absent
1	Mild
2	Moderate
3	Severe

The lens in the non-study eye will be classified as phakic, pseudo-phakic or non-phakic.

7.3.2 IOP Measurement

IOP measurements will be performed utilizing Goldmann applanation tonometry according to the Investigator's standard procedure. All pressures will be recorded in mmHg. IOP assessments will be performed at Visits 1 (Screening) through Visit 6 (POD22) or Early Termination/Withdrawal as indicated in Table 1.

7.3.3 Dilated Ophthalmoscopy

A dilated fundus examination will be performed according to the Investigator's standard technique at the Visits indicated in Table 1. The Investigator should evaluate the vitreous, retina, macula, choroid, and optic nerve with cup/disc ratio and will note normal/abnormal findings. If a cataract is present in the non-study eye, the Investigator will make an assessment of its location and severity as described below.

The Investigator will determine whether or not abnormalities observed at Visit 1 (Screening) would exclude a subject from study participation.

If a subject had an abnormality in the study eye or non-study eye at Visit 1 (Screening), the Investigator should make an assessment whether there has been a change at Visit 6 (POD22) or at Early Termination/Withdrawal and record this in the source document and eCRF. It is recommended that the Investigator refer to the documentation at Visit 1 (Screening) when making the assessment of a change in status.

Grading a Cataract in the Non-Study Eye

For subjects with a natural lens in the non-study eye, when present, a cataract will be assessed (a) by location - Nuclear, Cortical, and Posterior Subcapsular, and (b) by severity (minimal, mild, moderate or severe). Appendix B provides a guidance that may be used to grade the severity of a nuclear, cortical or posterior subcapsular cataract in the non-study eye.

If a subject had a cataract in the non-study eye at Visit 1 (Screening), the Investigator should make an assessment whether there has been a change in the size or composition of the cataract at Visit 6 (POD22) or at Early Termination/Withdrawal and record this in the source document and eCRF. It is recommended that (i) the cataract grading is performed by the same Investigator at Screening and Visit 6 (POD22) or at Early Termination/Withdrawal, and (ii) the Investigator refers to the documentation of the non-study eye at Visit 1 (Screening) when making the assessment of change in the lens status.

8.0 ADVERSE EVENTS

8.1 Definition of Adverse Events (AEs)

Adverse event means any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment (21CFR312.32 (a); ICF E6 Section 1). An AE can therefore be any unfavorable sign and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

In addition to the considerations in Sections 8.2 to 8.4, AEs will be reported in the source document from the time of signature of the informed consent form as indicated in Section 8.1.1 and Section 8.1.2.

8.1.1 Subjects who are Randomized

- An AE related to cataract surgery will be recorded in the Surgical AE log table in the source documents and in the eCRF.
- AEs occurring prior to study drug administration will be recorded in the source documents only.
- AEs occurring from the start of study drug administration will be reported in the source documents and eCRF.
- Rescued subjects are considered to be treatment failures, and being rescued itself is not considered to be an AE.
- Adverse events occurring in rescued subjects will be reported in the source documents and eCRF.
- An IOP > 30 mmHg after Randomization will be reported as an AE in the source documents and eCRF.
- An IOP ≥ 21 mmHg AND an IOP increase > 10 mmHg from pre-dose baseline will be reported as an AE in the source documents and eCRF.
- Serious Adverse Events will be collected from the time of signature of the informed consent form and reported in the source documents and eCRF.

The term “severe” is used to describe the intensity of an AE; the event itself could be of relatively minor clinical significance (e.g., ‘severe’ headache). This is not the same as “serious”. Seriousness of AEs is based on the outcome of an AE and usually associated with events that pose a threat to a subject’s life or functioning.

A Treatment Emergent Adverse Event (TEAE) will be defined as any AE that occurs from the start of study drug administration through Visit 6 (POD22).

8.1.2 Subjects who are Not Eligible for Randomization (Screen Failures)

- AEs will be reported in the source documents only
- Serious Adverse Events will be collected from the time of signature of the informed consent form and reported in the source documents and eCRF

8.2 Definition of Serious Adverse Events (SAEs)

An AE is considered "serious" if the event results in any of the following outcomes:

- death,
- a life-threatening adverse event (i.e. the subject is, in the view of the investigator, at immediate risk of death from the AE as it occurs),
- subject hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.

Important medical events that may not result in death, but may be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse.

A serious and unexpected suspected adverse reaction (SUSAR) is defined as a serious adverse reaction or suspected serious adverse reaction that is not listed in the APP13007 Investigator's Brochure or is not listed at the specificity or severity that has been observed, or that is mentioned in the APP13007 Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the study drug, but is not specifically mentioned as occurring with the particular drug under investigation (See Section 8.7.2).

8.3 Classification of an Adverse Event

8.3.1 Severity of Event

Assessment of severity of an AE will be rated according to the definitions below in Table 5 and the worst grade documented.

Table 5: Definitions of AE Severity

Mild	Events require minimal or no treatment and do not interfere with the participant's daily activities.
Moderate	Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
Severe	Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.2 Relationship to Ocular Surgical Procedure or Study Drug

Determination of the relationship (if any) between the AE and the study drug will be made using the guidelines presented in Table 6 and Table 7.

Table 6: Guidelines for Determining the Relationship (if any) between an Adverse Event and the Ocular Surgical Procedure

Related	This causal relationship is assigned if the AE starts at a reasonable time during or after the surgical intervention and could reasonably be explained by the known characteristics of the surgical intervention.
Not Related	This causal relationship is assigned when the time association or the subject's clinical state is such that the surgical intervention was not likely to have had an association with the observed AE.

Table 7: Guidelines for Determining the Relationship (if any) between an Adverse Event and the Study Drug

Definite	This causal relationship is assigned if the AE starts a reasonable time after the administration of study drug, stops/improves when the study drug is stopped, and could reasonably be explained by known characteristics of the study drug.
Probable	This causal relationship is assigned when the AE starts a reasonable time after the administration of study drug, stops/improves when the study drug is stopped, and could not be reasonably explained by known characteristics of the subject's clinical state.
Possible	This causal relationship is assigned when the AE starts a reasonable time after the administration of study drug, but could be produced by the subject's clinical state or other modes of therapy administered to the subject.
Not Related	This causal relationship is assigned when the time association or the subject's clinical state is such that the study drug was not likely to have had an association with the observed AE.

The attributability (relatedness) of an AE to the surgical procedure or to the study drug will be reported in the source documents and in the eCRF as described in Section 8.1.1 and Section 8.1.2.

8.3.3 Expectedness

An AE or a suspected adverse reaction (SAR) is considered "unexpected" if it is not listed in the APP13007 Investigator's Brochure or is not listed at the specificity or severity that has been observed. Expected events for APP13007 administration include those events described in the APP13007 Investigator's Brochure.

8.3.4 Action Taken with Study drug

The action to be taken in response to an AE will be to either discontinue or continue study drug.

Subjects will be permitted to restart study drug if there is a temporary interruption of study drug dosing not more than 1 day due to an AE.

Decrease in the dosing frequency or dosing duration of the study drug is not allowed in this study.

8.3.5 Adverse Event Outcome

If an AE occurs, the Investigator will institute support and/or treatment as deemed appropriate.

The outcome of the adverse event will be categorized as follows:

- Resolved
- Resolved with sequelae
- Ongoing
- Death
- Unknown

The Investigator should make every attempt to follow SAEs to resolution.

8.4 Adverse Event Follow-Up

If a non-serious AE is unresolved at the time of the subject's final study visit, the subject will still be released from the study, but an effort will be made to follow up until the AE is resolved or stabilized, the subject is lost to follow-up, or there is some other resolution of the event. The Investigator should make every attempt to follow all SAEs to resolution.

8.5 Overdose/Under-dose for Assessment of Compliance

8.5.1 Overdose

Dosing compliance will be assessed via a daily dosing diary completed by the subject and reviewed by the designated site personnel.

The following will be classified as an overdose event and a protocol deviation (further explained in Note below):

- Subject instills > 2 doses of study drug (each dose = 1 drop) into the study eye on 2 consecutive days.

Note: (i) As described in Section 5.1.2, if the subject misses the conjunctival cul-de-sac when dosing the study drug, the subject should use a tissue to wipe away the study drug around the eye and then instill a second drop into the conjunctival cul-de-sac. This will not be considered a protocol deviation. However, if the subject administers a third drop or more into the conjunctival sac, no matter if the previous drops were missed, this will be considered to be a protocol

deviation; (ii) the importance of the protocol deviation (major/minor) will be determined by the amount dosing over that specified in the protocol.

8.5.2 Under-dose

Under-dosing will not be reported as a protocol deviation until the subject has missed both of the doses on 2 or more consecutive days.

The importance of the protocol deviation (major/minor) will be determine by the amount of dosing under that specified in the protocol.

8.6 Pregnancies

All female subjects enrolled into the study must be of non-childbearing potential or have a negative urine pregnancy test on POD1 prior to randomization (and agree to abstain from sexual activity or use an effective method of contraception). Therefore, no pregnancies should occur. A urine pregnancy test will also be performed at Visit 5 (POD15) or Early Termination/Withdrawal visit prior to POD15. If there is an unexpected pregnancy, it will be handled on a case-by-case basis by discussing with the Study Medical Monitor and then the Sponsor Medical Monitor.

Additionally, the Investigator should report the information to the Sponsor in a Pregnancy-specific CRF as per the procedures to be followed for an SAE. Although a pregnancy itself is not an SAE, it has potentially serious consequences in subjects exposed to investigational drugs that can result in an SAE.

The pregnancy and follow-up of the pregnancy must be reported on the appropriate pregnancy CRF and Pregnancy Reporting Form. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated fertility date, pregnancy result and neonatal data etc., should be included in this information.

The investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE and will report the outcome to the Sponsor. Follow-up visits must continue until the end of the pregnancy, even if that lasts beyond the end of the study.

When the outcome of the pregnancy falls under the criteria for SAEs (spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly [including anomaly in a miscarried fetus]), the investigator should respond in accordance with the report procedure for SAEs. Additional information regarding the outcomes of a pregnancy which are categorized as an SAE is mentioned below:

- "Spontaneous abortion" includes abortion and missed abortion.
- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug.

- If an infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as "possible" by the investigator.
- In the case of a delivery of a living newborn, the "normality" of the infant is evaluated at birth.
- "Normality" of a miscarried fetus is evaluated by visual examination unless test results which indicate a congenital anomaly are obtained prior to miscarriage.

8.7 Serious Adverse Event Reporting

8.7.1 Reporting Requirements

It is the responsibility of the Investigators or their designees to report any event of this nature to the Sponsor or a designee within 24 hours of the event being brought to the Investigators' or their staffs' attention. It is also the responsibility of the Investigator to report all SAEs reported at their site to the IRB, as required. The Investigator should make every attempt to follow all SAEs to resolution.

All SAEs have to be reported on a separate SAE Report Form, whether or not considered causally related to the study drug, or to the study procedure(s). All SAEs will be recorded in the eCRF. SAEs will be recorded from the time the informed consent form is signed.

The Sponsor will be responsible for reporting all SAEs to regulatory authorities and the Investigator is responsible for reporting all SAEs to the IRB (see NOTE below) in accordance with IRB guidelines and FDA regulations. As soon as the Investigator is aware of a potential SAE he/she should contact [redacted] and in any case no later than 24 hours after the knowledge of such a case. At the time of initial reporting the Investigator must provide as a minimum requirement, subject number, birth date, description of the SAE and a preliminary assessment of causality.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform the Study Medical Monitor, the Sponsor, and the CRO for Study Management and Monitoring of any follow-up information on a previously reported SAE immediately but no later than within 24 hours of when the Investigator becomes aware of it. The Study Medical Monitor or Sponsor Medical Monitor will advise the Investigator/study site personnel how to proceed. The Investigator will immediately follow-up events deemed by the Sponsor to be Serious and Unexpected Suspected Adverse Reactions (SUSARs) or possible SUSAR events needing immediate follow-up in order to meet the 15 calendar day reporting requirements.

The SAE reporting procedures are detailed in the study-specific Safety Management Plan. This plan is an agreement between the Sponsor, the CRO for Study Management and Monitoring and [redacted].

NOTE: If an unexpected SAE occurs at any one site that is determined to be related, probably related or possibly related to study drug, all study sites will be notified by the Sponsor via the CRO for Study Management and Monitoring and each Investigator will report it to the IRB.

8.7.2 Reporting of Serious and Unexpected Suspected Adverse Reactions (SUSARS)

A serious suspected adverse reaction is any serious adverse event for which there is a reasonable possibility that the study drug caused the adverse event. A serious adverse reaction is considered "unexpected" (serious and unexpected suspected adverse reaction; SUSAR) if it is not listed in the APP13007 Investigator's Brochure or is not listed at the specificity or severity that has been observed.

SUSARs with an outcome of death or are life threatening must be reported to the relevant Regulatory Authorities within 7 calendar days, all other SUSARs must be submitted within 15calendar days. The SUSAR reporting procedures are detailed in the study Safety Management Plan. This plan is an agreement between the Sponsor, the CRO for Study Management and Monitoring and Synergy Research Pharmacovigilance.

NOTE: The Sponsor will notify the U.S. Food and Drug Administration (FDA) and all participating site Investigators of any SUSARs (via the CRO for Study Management and Monitoring) on an expedited basis and in accordance with applicable regulations. In addition the sponsor is responsible for informing all Investigators in all ongoing studies involving the study drug about all SUSARs.

Medical and administrative data related to Individual Case Safety Reports which qualify for expedited and periodic reporting, should be provided in compliance with U.S. FDA Code of Federal Regulations (CFR) 21, 312.32.

It is the responsibility of the Investigator to promptly notify the IRB and other appropriate institutional regulatory bodies of all unexpected serious adverse reactions involving risk to human subjects as per their applicable requirements.

9.0 SAFETY MANAGEMENT

9.1 Stopping Criteria

9.1.1 Individual Subject

9.1.1.1 Lack of Efficacy (See Section 9.4)

The Investigator should consider whether to stop the study drug because of lack of efficacy and rescue the subject with alternative therapy (see Section 9.4).

Rescued subjects shall continue in the study and be assessed at each subsequent scheduled visit until Visit 6 (POD22). The study drug will be stopped as indicated in Section 9.4.2.

9.1.1.2 Elevated Intraocular Pressure (See Section 9.5)

The Investigator should consider whether to stop the study drug because of an elevation of IOP. The study drug may or may not be continued as indicated in Section 9.5.2.

9.1.1.3 Deleterious Effects of the Study Drug

The investigator may stop the study drug and withdraw the subject if in their opinion the study drug is having a deleterious effect on the subject's health or wellbeing. The investigator should make an effort to follow up the subject until the deleterious effect is resolved.

9.1.1.4 Lack of Compliance

The investigator may stop the study drug and withdraw the subject if in their opinion the subject is not complying with study procedures, including, but not limited to, dosing of the study drug.

9.1.2 Study Termination

- The study can be stopped at any time if deemed necessary by the Sponsor Medical Monitor, in consultation with the Study Medical Monitor, due to safety concerns. Safety will be monitored on an ongoing basis via periodic masked review of AEs and other safety endpoints.
    - If it is observed that visual acuity worsens by 2 lines (Base LogMAR change of 0.2 using ETDRS chart) at Visit 6 (POD22) in the treated study eye as compared to Visit 2 (POD1), in 6 consecutive subjects, no further doses of study drug will be administered to any subjects in the study until a comprehensive evaluation can be performed, and, if possible, a cause is identified.
- Safety assessments will be performed throughout the course of the study. The APP13007 Investigator's Brochure, Section 1.4.1 and the Risk Mitigation plan in Table 2 provide guidance for the Investigator on potential anticipated AEs that may occur. Any potential

important safety issues that arise will be reviewed by the Study Medical Monitor, in consultation with the Sponsor Medical Monitor, to identify the appropriate course of action.

- If the Sponsor elects to terminate the study for any reason, the Investigator will be responsible for notification of the IRB and will withhold further dosing of study drug.

9.2 Dose Modification

No dose modification is permitted.

All instances of missed doses must be recorded.

Note: Study drug bottle will be replaced if a bottle is lost or otherwise compromised before Visit 5 (POD15) (see Section 5.1.2).

9.3 Dosing Interruptions

Investigator is not allowed to modify the dosing regimen due to an AE or any other circumstance, but the Investigator has the option of stopping study drug after consultation with the Study Medical Monitor, if feasible.

Subjects will be permitted to restart study drug if there is a temporary dosing interruption of study drug of not more than 1 day due to an AE.

9.4 Rescue Management

9.4.1 Criteria for Starting Rescue Medication

Any subject not responding to the study drug because of lack of efficacy at any time after randomization at Visit 2 (POD1) may be rescued and placed on an appropriate alternative therapy determined by the Investigator.

In general, at any visit, a subject with worsening inflammation or showing no improvement in degree of inflammation compared with the previous visit is eligible for rescue therapy at the discretion of the Investigator. However, the following guidance is provided to Investigators for consistency in the way subjects are rescued:

1. Subjects who, on examination of the anterior chamber, have one or more of the following quantitative criteria should be rescued and discontinued from study drug dosing and placed on rescue mediation:

    - An increase of ACC count by > 15 cells from the Visit 2 (POD1) pre-dose baseline.

    - A ≥ 2 grade increase in ACF grade from the Visit 2 (POD1) pre-dose baseline.

2. Subjects who have the following qualitative criteria may be rescued. If the subject is rescued, the study drug should be discontinued and rescue mediation started:

    - Subjects who have pain and/or photophobia that does not improve, even when there is an improvement in ACC count and/or ACF grade, may be rescued at the discretion of the investigator.
    - Subjects who have pain and/or photophobia that worsens may be rescued at the discretion of the investigator.

Initiation of rescue medication is at the discretion of the Investigator. However, it is recommended that the Investigator uses the above guidance to determine when to rescue a subject. If the quantitative ACC count or ACF grade criteria are not met, the Investigator should discuss the qualitative reason(s) for rescue with the Study Medical Monitor for consistency across the study.

9.4.2 Management

Investigators will use clinical judgment to determine when to rescue a subject using the guidance provided in Section 9.4.1 and the appropriate rescue medication to use. All rescued subjects will stop study drug at the time of rescue and will continue in the study through completion of the Visit 6 (POD22) assessments (Table 1).

If a subject needs to be rescued at Visit 5 (POD15), the Visit 5 (POD15) assessments (Table 1) should be completed before the subject is administered rescue medication.

Rescued subjects will be considered treatment failures, and the need for rescue medication will not be considered as an AE.

An AE occurring at the time of rescue will be recorded in the eCRF and will be followed by the Investigator to stabilization or resolution of the AE or the end of the study (whichever comes last).

If a subject is rescued, this event will be recorded in the eCRF (not as an AE). Medications used for rescue will be recorded in the ConMeds section of the eCRF, indicating that they were used for rescue.

9.5 Management of Increased IOP

9.5.1 Criteria for Starting IOP-Lowering Medication

Investigators should use the following criteria to determine whether to start IOP-lowering medication:

- After randomization, an IOP > 30 mmHg in the study eye

- After randomization, an IOP ≥ 21 mmHg **AND** an increase of > 10 mmHg from the Visit 2 (POD1) pre-dose baseline in the study eye (both of these criteria must be met)

Initiation of IOP-lowering medication is at the discretion of the Investigator even if neither of the above criteria are met, however, it is recommended that the Investigator uses these criteria to determine when to consider a subject for IOP-lowering medication.

9.5.2 Management

Investigator will use clinical judgment to determine the appropriate IOP-lowering medication to use and when to withdraw study drug and procedures, in consultation with the Study Medical Monitor.

It is important to note that prostaglandin-based IOP lowering medications are prohibited in this study.

- After randomization and start of study drug, if a subject has an IOP > 30 mmHg the Investigator may commence non-prostaglandin-based IOP-lowering medication while continuing the study drug, with appropriate follow-up at the next planned visit or at an unscheduled visit. The subject may require assessment at an unscheduled visit at the investigator's discretion.
  - If the IOP is < 30 mmHg at the next visit, the subject may continue on study drug.
  - If at the next visit, the IOP remains > 30 mmHg while on IOP-lowering medication, then the study drug may be discontinued and alternative IOP-lowering medication may be started, after consultation with the Study Medical Monitor. The subject should continue in the study and complete the assessments indicated in Table 1 through Visit 6 (POD22). The Study Medical Monitor should discuss the persistent elevation of IOP with the Sponsor Medical Monitor.
- After randomization and start of study drug, an IOP of ≥ 21 mmHg AND an increase > 10 mmHg from the Visit 2 (POD1)/pre-dose baseline (both criteria must be met) is considered clinically significant and the Investigator should consider starting non-prostaglandin-based IOP-lowering medication while continuing the study drug, with appropriate follow-up at the next planned visit or at an unscheduled visit.
  - If the IOP reduction is satisfactory at the next visit, the subject may continue on study drug.
  - If the IOP reduction of IOP is not satisfactory at the next visit, then the study drug may be discontinued and alternative IOP-lowering medication may be started, after consultation with the Study Medical Monitor. The subject should continue in the study and complete the assessments indicated in Table 1 through Visit 6 (POD22). The Study Medical Monitor should discuss the persistent elevation of IOP with the Sponsor Medical Monitor.

Medications used for treating increased IOP will be recorded in the Concomitant Medications section of the eCRF, noting that they were used to reduce IOP.

10.0 STATISTICAL CONSIDERATIONS

10.1 Statistical Analytical Plan

The Statistical Analysis Plan (SAP) will describe the details of all efficacy and safety analyses and will be finalized prior to database lock.

10.2 Analysis Populations

The analysis populations are defined as follows:

- Intent-to-Treat (ITT) Population: All subjects who are randomized to study drug. Following the ITT principle, subjects will be analyzed according to the treatment they are assigned to at randomization.
- Per-protocol (PP) Population: All subjects in the ITT population who (i) received at last 1 dose of study drug, (ii) do not have major protocol deviations that would impact the evaluation of efficacy and (iii) have at least 80% overall dosing compliance.
- Safety Population: All randomized subjects who receive at least one dose of study drug.

10.3 Statistical Methods

10.3.1 General Approach

All analysis variables will be summarized descriptively by treatment group. Summary statistics for continuous measures will include mean, standard deviation, median, and range. Categorical measures will be summarized by the number and percent of subjects.

10.3.2 Analysis of Efficacy

All efficacy analyses and summaries will be based on assessments in the study eye for each subject.

Subjects who are rescued at any time prior to Visit 5 (POD15) will be considered as treatment failures for the primary efficacy endpoints and the relevant secondary efficacy endpoints. For subjects who discontinue from the study prior to Visit 5 (POD15), the last observation carried forward (LOCF) approach will be used to impute missing data.

For continuous secondary efficacy endpoints, the LOCF approach will also be used to impute the data at visits after subjects are rescued.

The ACC count will be graded as shown below:

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

10.3.2.1 Analyses of Primary Efficacy Endpoints:

The primary efficacy analyses to compare APP13007 against placebo will be conducted on the ITT population using the Pearson Chi-square statistic. Fixed sequence testing will be employed to maintain the 2-sided alpha = 0.05. The primary analyses will first test the difference between treatments in the proportion of subjects with ACC count = 0 (Grade = 0) at POD8 (Visit 4) maintained through POD15 (Visit 5). If the test is statistically significant at the 2-sided alpha = 0.05 level in favor of APP13007, the difference between treatments in the proportion of subjects with Ocular Pain grade = 0 at POD4 (Visit 3) maintained through POD15 (Visit 5) will be tested at the two-sided alpha = 0.05 level.

To confirm the robustness of primary analysis results, sensitivity analyses, including using observed data from all subjects, will be performed. The detailed sensitivity analyses will be described in the SAP.

10.3.2.2 Analyses of Secondary Efficacy Endpoints:

Mean change-from-baseline in ACC Grade, ocular Pain Grade, ACF Grade and visual acuity at PODs 4, 8 and 15 will be analyzed using an analysis of covariance (ANCOVA). The ANCOVA model will include treatment as a fixed effect and baseline as a covariate. The rest of secondary efficacy endpoints will be analyzed using the same method described for the primary efficacy endpoints.

10.3.3 Analysis of Safety

Analysis of safety data will be performed for all subjects in the Safety Population.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and classified by system organ class and preferred terms. Adverse events will be summarized by total number of TEAEs, number of subjects reporting TEAEs, ocular TEAEs (affecting the study eye and/or the non-study eye and/or both eyes, when appropriate), non-ocular TEAEs, SAEs, serious and unexpected suspected adverse reaction (SUSARs), discontinuing study drug due to an AE, by relationship to study drug and/or ocular surgical procedure, and by severity.

The IOP data for both eyes will be summarized at screening, Visit 6 (POD22)/Early Termination (Withdrawal) visit and change from screening. The observed IOP data and change-from-baseline (POD1) for the study eye will be summarized at each post-surgery visit.

The data for slit lamp biomicroscopy examination endpoints will be summarized at each visit. The summary of change-from-baseline at each post-surgery visit will be presented for the study eye.

Dilated indirect ophthalmoscopic examination findings for the study and non-study eye will be summarized at screening and Visit 6 (POD22)/Early Termination (Withdrawal).

Visual Acuity data will be summarized at each visit. The summary of change-from-baseline at each post-surgery visit will be presented for the study eye.

10.3.4 Interim Analysis

No interim analyses are planned for this study.

10.4 Sample Size Estimation

The assumption for the sample size determination was estimated using the Package Inserts of Durezol®, Lotemax® and Inveltys® and results from the APP13007 Phase 2 study (CPN-201). The sample size for ACC count primary efficacy endpoint is based on the assumption of 26% of subjects in APP13007 group with ACC Count = 0 at POD8 and maintained through POD15 and 12% of subjects in matching vehicle placebo group. The two-group chi-square test, with a two-sided significance level of 5% and 92% power, requires 175 subjects per treatment group to detect the difference between APP13007 and placebo.

The same sample size using the assumption of 57% of subjects with Ocular Pain Grade = 0 at POD4 and maintained through POD15 in APP13007 group and 38% of subjects in placebo group will provide 95% power to detect the treatment difference.

With an estimated 5% dropout rate, this study will randomize approximately 185 subjects per treatment group for a total of approximately 370 subjects.

10.5 Level of Significance

Unless otherwise specified, all statistical tests will be two-sided and the statistical significance will be tested at the 5% level.

The primary efficacy endpoints will be evaluated using the fixed sequence testing described in Section 10.3.2.1.

10.6 Procedure for Accounting for Missing, Unused, or Spurious Data

If more than 5% of data points are missing at POD15 in any treatment group, a tipping point analysis will be performed to assess the sensitivity of the primary efficacy results to the distribution of the allocation of treatment success and failure to the missing data points. Other missing data imputations will be detailed in the SAP.

10.7 Procedure for Reporting Deviations from the Statistical Plan

Any deviations from the SAP will be described and a justification given in the final clinical study report.

10.8 Subjects to be Included in the Analysis

All efficacy analyses will be performed using the ITT population. In addition, the analysis of the primary efficacy endpoints will be performed using the PP population as a supportive analysis. AEs and other safety endpoints will be analyzed using the Safety Population.

11.0 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 Regulatory, Ethical and Legal Obligations

11.1.1 Declaration of Helsinki

The Principal Investigator will ensure that this study is conducted in accordance with the most recent revision of the Declaration of Helsinki.

11.1.2 Good Clinical Practice

The Study will be conducted according to the study protocol and to Standard Operating Procedures (SOPs) that meet the guidelines provided by the International Conference on Harmonisation (ICH) for Good Clinical Practice in clinical studies and applicable regulatory requirements.

11.1.3 Institutional Review Boards

This protocol and the informed consent form must be approved by an appropriately constituted and qualified IRB and the approvals made available to the Sponsor or designee prior to the start of enrollment into the study. Materials used to recruit subjects or supplied to subjects for the study will be approved by the appropriate IRB and the approvals made available to the Sponsor or designee prior to their use. In addition, the APP13007 Investigator's Brochure will be submitted to the IRB. Written IRB approval must adequately identify the protocol and informed consent form. Copies of all approved materials, all correspondence with the IRB, and written approval from the IRB must be made available to the Sponsor (or designated Study Monitor).

Any modification of study procedures or amendments to the protocol must be approved by the IRB and submitted to FDA prior to implementation. In the event that a modification or amendment is considered by the Investigator to be immediately necessary to ensure subject safety, the Investigator will promptly notify his or her IRB, the Study Medical Monitor, and the CRO for Study Management and Monitoring who will then notify the Sponsor.

Investigators will report all SAEs reported at their site to their IRB, as appropriate.

11.1.4 Informed Consent Process

Written informed consent will be obtained from each participant prior to any study-related procedures being performed (prior to or on the Screening visit). A copy of the signed and dated informed consent document will be given to each subject. The original signed and dated informed consent document must be maintained in the study files at the investigative site and be available for the CRO for Study Management and Monitoring and the Sponsor or designee(s) to review.

Each informed consent will contain Investigator contact information with a telephone number the subject or the subject's authorized representative can call 24 hours a day and 7 days a week if they have medical concerns.

11.1.5 Subject Confidentiality and Disclosure

Study personnel will have access to a subject's protected health information (PHI). This information may be obtained by the Sponsor, which includes any persons or companies that are working with, working for, or owned by the Sponsor. PHI may be given to the U.S. FDA Department of Health and Human Services agencies, other governmental agencies in the U.S., governmental agencies in other countries, and governmental agencies to which certain diseases (reportable diseases) must be reported.

11.2 Monitoring and Auditing Study Documentation

The Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data and documents (such as tests performed as a requirement for participation in the study and other medical records) to the Study Monitor or the Sponsor or its designee.

11.2.1 Clinical Monitoring

Before an investigational site can enter a subject into the study, a representative of the Sponsor or its designee such as the CRO for Study Management and Monitoring [redacted] and its Study Monitor will perform pre-study site evaluation at each of the investigational study sites in person or remotely to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities about protocol adherence, and the responsibilities of the Sponsor or its designated Study Monitor and representatives. This will be documented in a Clinical Study Agreement between the Sponsor (Formosa Pharmaceuticals, Inc.) and the Investigator.
- Confirm qualified staff are trained on the protocol, study processes and systems.
- Confirm all supplies and study product are onsite and stored accordingly.
- Collect any outstanding essential documents.

During the study, a monitor from the Sponsor or its designated CRO for Study Management and Monitoring [redacted] and its Study Monitor or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.

- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that study treatment accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject's medical records at the investigational site, and other records relevant to the study. This will require direct access to all original records for each subject (e.g. clinic charts or electronic records).
- Record and report any protocol deviations not previously sent to the Sponsor and the IRB.
- Confirm the site has adequate supplies and study drugs.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm that any and all SAEs have been forwarded to the Sponsor via the CRO for Study Management and Monitoring and those SAEs that met criteria for reporting have been forwarded to the IRB.

The Study Monitor and other representatives at the CRO for Study Management and Monitoring will be available between visits if the Investigator(s) or other staff needs information or advice.

11.2.2 Auditing of Sites and Study Documentation

Quality control and quality assurance may be performed before, during, and after the study by the Sponsor or Sponsor's designee, such as the CRO for Study Management and Monitoring and its Study Monitors. Regulatory authorities in certain countries reserve the right to audit study sites following submission of data in regulatory applications. The Investigator may be given due notice of any intended audit by a regulatory body. By signing this protocol and the FDA Form 1572, the Investigator acknowledges that these inspection procedures may take place and agrees to provide access to the required subject records and other study documentation. Furthermore, the Investigator agrees to inform the Sponsor via the CRO for Study Management and Monitoring immediately of any known or suspected inspection by authorities. If the Investigator does not comply with the protocol, GCP, or regulations, the Sponsor reserves the right to disqualify the Investigator and/or site from the current or future protocols.

11.3 Data Handling and Record Keeping

All procedures for the handling and analysis of data will be conducted using GCP and will meet ICH guidelines and US FDA regulations for the handling and analysis of data for clinical trials.

11.3.1 Data Collection and Management Responsibilities

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database. Query reports pertaining to data omissions and discrepancies will be forwarded to the Investigator and Study Monitor(s) from the CRO for Study Management and Monitoring for resolution. The study database will be updated

in accordance with the resolved query reports. All changes to the study database will be documented.

11.3.2 Study Records Retention

The study center will retain all records related to the study in accordance with local and ICH GCP guidelines.

11.4 Protocol Deviations

Monitoring will be conducted to verify compliance. Instances of minor, major and critical deviations that occur at investigative sites will be documented and communicated to the Sponsor and documented at the investigative site and recorded in the eCRF. Any noted protocol deviations meeting the IRB reporting requirements will reported to the IRB.

11.5 Publication and Data Sharing Policy

The Institutions and Investigators participating in this trial shall have no right to publish or present the results of this study without the prior written consent of the Sponsor.

12.0 REFERENCES

Apple, D. J., K. D. Solomon, M. R. Tetz, E. I. Assia, E. Y. Holland, U. F. Legler, J. C. Tsai, V. E. Castaneda, J. P. Hoggatt, A. M. Kostick. 1992. "Posterior capsule opacification." *Surv Ophthalmol* 37(2): 73-116.

Aptel, F., C. Colin, S. Kaderli, C. Deloche, A. M. Bron, M. W. Stewart, C. Chiquet and O. group. 2017. "Management of postoperative inflammation after cataract and complex ocular surgeries: a systematic review and Delphi survey." *Br J Ophthalmol* 101(11): 1-10.

Baudouin, C., A. Labbe, H. Liang, A. Pauly and F. Brignole-Baudouin. 2010. "Preservatives in eyedrops: the good, the bad and the ugly." *Prog Retin Eye Res* 29(4): 312-334.

Clobex®. 2018. *Clobex® (Clobetasol Propionate) Spray 0.05% [Package Insert].* Fort Worth-TX: Galderma-Laboratores L.P.

Feldman, S. R. and B. A. Yentzer. 2009. "Topical clobetasol propionate in the treatment of psoriasis: a review of newer formulations." *Am J Clin Dermatol* 10(6): 397-406.

Hengge, U. R., T. Ruzicka, R. A. Schwartz and M. J. Cork. 2006. "Adverse effects of topical glucocorticosteroids ." *J Am Acad Dermatol* 54(1): 1-15; quiz 16-18.

Jacob, S. E. and T. Steele. 2006. "Corticosteroid classes: a quick reference guide including patch test substances and cross-reactivity." *J Am Acad Dermatol* 54(4): 723-727.

Kaur, I. P., S. Lal, C. Rana, S. Kakkar and H. Singh. 2009. "Ocular preservatives: associated risks and newer options." *Cutan Ocul Toxicol* 28(3): 93-103.

Leopold, I. 1985. "Nonsteroidal and steroidal anti-inflammatory agents." In *Surgical Pharmacology of the Eye*, by Sears M and T. A., 83-133. New York, NY: Raven Press.

Olsen, E. A. and R. C. Cornell. 1986. "Topical clobetasol-17-propionate: review of its clinical efficacy and safety." *J Am Acad Dermatol* 15(2 Pt 1): 246-255.

Sparidans, R.W., van Velsen S.G., de Roos M.P., Schellens J.H., Bruijnzeel-Koomen C.A., Beijnen J.H. 2010 "Liquid chromatography-tandem mass spectrometric assay for clobetasol propionate in human serum from subjects with atopic dermatitis." *J Chromatogr B Analyt Technol Biomed Life Sci* 878(23):2150-4.

Temovate®. 2000. *Clobetasol Propionate Cream 0.05% [Package Insert].* Research Triangle Park, NC: GlaxoWellcome Inc.

Tennant, J.L. 1978. "Cystoid maculopathy: 125 prostaglandins in ophthalmology." *Current Concepts in Cataract Surgery: Selected proceedings of the fifth biennial cataract surgical congress, Section 3.* E. J.M St. Louis, MO: CV Mosby. 360-362.

van Velsen, S. G., M. P. De Roos, I. M. Haeck, R. W. Sparidans, C. A. Bruijnzeel-Koomen. 2012. "The potency of clobetasol propionate: serum levels of clobetasol propionate and adrenal function during therapy with 0.05% clobetasol propionate in subjects with severe atopic dermatitis." *J Dermatolog Treat* 23(1): 16-20.

APPENDIX A CONTINGENCY PLANS RELATED TO THE COVID-19 PANDEMIC

In March 2020 the FDA issued the Guidance: "Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic".

Based on the stated goal in this FDA Guidance, the following plans may be implemented:

1. When a clinical site plans to or has to close operations and visits cannot be scheduled per protocol:

- If possible, schedule an Early Termination/Withdrawal visit before the clinical site closes.
  - Ask subject to stop the study drug, if before Visit 5 (POD15).
  - Collected study drug and dosing diary.
  - Conduct the Visit 6 (POD22) assessments.
- A Protocol Deviation is documented as "Early Termination/Withdrawal visit performed because the study site closed for operations prior to completion of the study visits due to COVID-19 infection-control requirements".

2. When a subject cannot or does not want to return for an in-person visit:

- The clinical site coordinator contacts the subject by telephone (or alternative method of communication) and asks the subject to stop the study drug, if before Visit 5 (POD15), and collects AE and concomitant medication information.
  - The available information is entered in the Early Termination/Withdrawal section of the eCRF.
  - If before Visit 5 (POD15), the study coordinator requests the subject to send the study drug bottle and dosing diary to the study coordinator at the clinical site.
- The Investigator withdraws the subject from the study and considers alternative methods of assessing the subject.
- A Protocol Deviation is documented as "Subject withdrawn early (Early Termination) and the assessments for Visits X, Y and Z were not performed because the subject could not or did not want to return for an in-person visit due to COVID-19 infection-control requirements".

APPENDIX B GUIDANCE THAT MAY BE USED FOR GRADING THE SEVERITY OF A NUCLEAR, CORTICAL OR POSTERIOR SUBCAPSULAR CATARACT IN THE NON-STUDY EYE

Location	Minimal	Mild	Moderate	Severe
Nuclear	Minimal Changes in nuclear zone	In the nuclear zone, the anterior and posterior embryonal nuclei are distinctly more opalescent (more visible) than normally seen, but the central clear zone is still easily distinguishable in its entirety	The nuclear zone is more uniformly opaque and the central clear zone between the anterior and posterior nuclei is not clearly visible. The posterior part of the zone is often more opaque.	The nuclear zone is densely opaque with more or less uniform nuclear opacity extending to the edge of the nuclear zone; nuclear features are only partially visible, if at all.
Cortical	Cataract involves < ⅛ of the circumference	Cataract involves ⅛, but less than ¼, of the circumference.	Cataract involves ¼, but less than ½, of the circumference.	Cataract involves ≥ ½ of the circumference.
Posterior subcapsular	< 1 mm	≥ 1 mm, but < 2 mm	≥2 mm, but < 3 mm	≥ 3 mm