FORMOSA
PHARMACEUTICALS, INC.
台新藥股份有限公司

CLINICAL STUDY PROTOCOL

A MULTICENTER, RANDOMIZED, DOUBLE-MASKED, TWO-PART, PLACEBO-CONTROLLED PHASE 2A STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND PRELIMINARY EFFICACY OF APP13007 FOR THE TREATMENT OF INFLAMMATION AND PAIN AFTER CATARACT SURGERY

PROTOCOL NUMBER: CPN-201

NCT04089735

Protocol Version:	1.1 (Amendment 1)
Version Date:	15 November 2019
Study Sponsor:	Formosa Pharmaceuticals, Inc. 5F-10, No.237, Sec. 2, Fuxing South Road Da'an Dist., Taipei Taiwan 106, Republic of China
Sponsor US Representative:	[redacted]
Contract Research Organization for Study Management and Monitoring:	[redacted]
Study Medical Monitor:	[redacted]

CONFIDENTIAL INFORMATION

This document is the property of Formosa Pharmaceuticals, Inc. [redacted] This document and any and all information contained herein has to be considered and treated as strictly confidential. This document shall be used only for the purpose of the disclosure herein provided. No disclosure or publication shall be made without the prior written consent of [redacted]

APPROVAL SIGNATURE PAGE

Approved by [redacted]

[redacted]

November 15, 2019

Chief Scientific and Medical Officer

Date

[redacted]

November 15, 2019

Vice President, Biostatistics

Date

PRINCIPAL INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical Protocol No. CPN-201 version 1.1 (Amendment 1) dated 15 November, 2019 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:

<Enter Name and Title>
<Enter Clinic>
<Enter Address>
Phone: <Enter Phone Number>

Signature **Date**

STUDY CONTACTS

SPONSOR REPRESENTATIVE:

[redacted]

PRIMARY CONTACT OF SPONSOR REPRESENTATIVE:

[redacted]

MEDICAL AND SAFETY MONITOR CONTACT:

[redacted]

SAE REPORTING CONTACT

[redacted]

SECONDARY CONTACT OF SPONSOR REPRESENTATIVE (Contract Research Organization for Study Management and Monitoring):

[redacted]

CHANGES IN PROTOCOL AMENDMENT 1

SUMMARY OF AMENDMENT CHANGES WITH RATIONALE

This protocol is being amended following review of key data (ACC count, pain score, IOP, the number of subjects rescued and AEs) from Part A for approximately 41 subjects completing POD15. Preliminary analysis of the mean ACC count in Part A for the two treatment groups (APP13007 0.05% BID and APP13007 0.05% matching vehicle placebo) provides the rationale for reducing the treatment duration in Part B from 21 days to 14 days. The scheduled visits, assessments, endpoints and analyses have been adjusted throughout the protocol to accommodate this change in the duration of dosing.

Note that the summary of these preliminary data are provided to the Institutional review Board (IRB) with this protocol amendment, but the data are not included in this amendment to reduce the risk of potentially unmasking the investigators.

On October 21, 2019, the IRB approved an informed consent form for use in the Screening period in Part B. As a result, text in the protocol has been updated to clarify the start of screening and the start of randomization in Part B.

The text in the protocol has been updated to clarify the differences between 'Rescue' and 'Withdrawal' and the assessments to be performed.

This amendment applies to all clinical sites performing this study.

TABLE OF CHANGES IN AMENDMENT 1

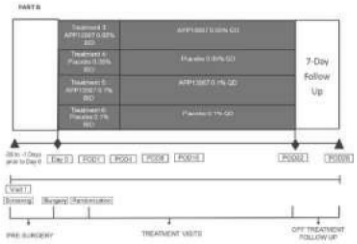
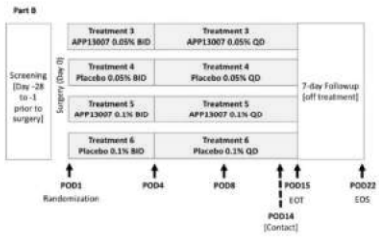
Protocol Section	Original Text	Amended Text
Table of contents	6.2.4. POD21 51 6.2.5. POD22 – End of Treatment (EOT) 52 6.2.6. POD28 – End of Study (EOS) 52	6.2.4. Day of Subject Contact: POD21 in Part A or POD14 in Part B 76 6.2.5. End of Treatment (EOT): POD22 in Part A or POD15 in Part B 77 6.2.6. End of Study (EOS): POD28 in Part A or POD22 in Part B 77
List of Tables	Table 2: Schedule of Events 19	Table 2A: Schedule of Events for Part A 42

	Table 5: Visits for Rescued Subjects 53	Table 2B: Schedule of Events for Part B 43 Table 5A: Visits for Rescued Subjects (Part A) 75 Table 5B: Visits for Rescued Subjects (Part B) 76
Protocol Synopsis (Objectives) *and* **Table 4 (Objectives)**	The primary safety objective of this study is to investigate the safety and tolerability of APP13007 versus corresponding matching vehicle placebo for the treatment of inflammation and pain through post-operative day (POD) 22 after cataract surgery.	The primary safety objective of this study is to investigate the safety and tolerability of APP13007 versus corresponding matching vehicle placebo for the treatment of inflammation and pain through post-operative day (POD) 22 in Part A and POD15 in Part B after cataract surgery.
Protocol Synopsis (Endpoints) *and* **Table 4 (Endpoints)**	• Anterior chamber cell (ACC) count at PODs 4, 8, and 22/EOT. • Pain grade on PODs 4, 8, and 22/EOT • Anterior chamber flare (ACF) grade on PODs 4, 8, 15 and 22/EOT • Use of rescue medication prior to each visit • Proportion of subjects with ACC count = 0 at PODs 4, 8, 15 and 22/EOT without receiving rescue medication; • Proportion of subjects who are pain-free at PODs 4, 8, 15 and 22/EOT without receiving rescue medication; • Proportion of subjects with flare grade = 0 at PODs 4, 8, 15	• Anterior chamber cell (ACC) count at PODs 4, 8, and 22/EOT (Part A) and PODs 4 and 8 (Part B). • Pain grade on PODs 4, 8, and 22/EOT (Part A) and PODs 4 and 8 (Part B) • Anterior chamber flare (ACF) grade on PODs 4, 8, 15 and 22/EOT (Part A) and PODs 4, 8 and 15/EOT (Part B) • Use of rescue medication prior to each visit • Proportion of subjects with ACC count = 0 at PODs 4, 8, 15 and 22/EOT (Part A) or at PODs 4, 8 and 15/EOT (Part B) without receiving rescue medication; • Proportion of subjects who are pain-free at PODs 4, 8, 15 and

	and 22/EOT without receiving rescue medication • Visual acuity (ETDRS Best corrected Visual Acuity by pinhole method)	22/EOT (Part A) and PODs 4, 8 and 15/EOT (Part B) without receiving rescue medication; • Proportion of subjects with flare grade = 0 at PODs 4, 8, 15 and 22/EOT (Part A) and PODs 4, 8 and 15/EOT (Part B) without receiving rescue medication • Visual acuity (ETDRS Best corrected Visual Acuity by pinhole method)
Protocol Synopsis (Study Design; Part A)	Following completion of Part A, then Part B (0.05% and 0.1% BID regimen for 3 days followed by QD regimen for 18 days) will be opened.	Following completion of Part A dosing, Part B (0.05% and 0.1% BID regimen for 3 days followed by QD regimen for 11 days) will be opened for randomization.
Protocol Synopsis (Study Design; Part A) *and* **Section 3.3 (Progression from Part A to Part B)**	Once all subjects in Part A have completed POD15 evaluation, all available key data will be summarized and reviewed by the Data Review Group.	Once approximately 40 subjects in Part A have completed POD15 evaluation, all available key data will be summarized and reviewed by the Data Review Group.
Protocol Synopsis (Study Design; Part B) *and* **Section 3.1 (Part B)** *and* **Section 5.1.2 (Study Treatments)**	• Treatment 3: 1 drop 0.05% APP13007 BID (morning and evening) for 3 days (PODs 1, 2 and 3) followed by 1 drop 0.05% APP13007 QD (morning) for 18 days (PODs 4 through 21) to the operated eye • Treatment 4: 1 drop 0.05% matching vehicle placebo (0.05% APP13007 vehicle) BID (morning and evening) for 3 days (PODs 1, 2 and 3) followed by 1 drop matching	• Treatment 3: 1 drop 0.05% APP13007 BID (morning and evening) for 3 days (PODs 1, 2 and 3) followed by 1 drop 0.05% APP13007 QD (morning) for 11 days (PODs 4 through 14) to the operated eye • Treatment 4: 1 drop 0.05% matching vehicle placebo (0.05% APP13007 vehicle) BID (morning and evening) for 3 days (PODs 1, 2 and 3) followed by 1 drop matching vehicle placebo QD

	vehicle placebo QD (morning) for 18 days (PODs 4 through 21) to the operated eye • Treatment 5: 1 drop 0.1% APP13007 BID (morning and evening) for 3 days (PODs 1, 2 and 3) followed by 1 drop 0.1% APP13007 QD (morning) for 18 days (PODs 4 through 21) to the operated eye • Treatment 6: 1 drop 0.1% matching vehicle placebo (0.1% APP13007 vehicle) BID (morning and evening) for 3 days (PODs 1, 2 and 3) followed by 1 drop matching vehicle placebo QD (morning) for 18 days (PODs 4 through 21) to the operated eye	(morning) for 11 days (PODs 4 through 14) to the operated eye • Treatment 5: 1 drop 0.1% APP13007 BID (morning and evening) for 3 days (PODs 1, 2 and 3) followed by 1 drop 0.1% APP13007 QD (morning) for 11 days (PODs 4 through 14) to the operated eye • Treatment 6: 1 drop 0.1% matching vehicle placebo (0.1% APP13007 vehicle) BID (morning and evening) for 3 days (PODs 1, 2 and 3) followed by 1 drop matching vehicle placebo QD (morning) for 11 days (PODs 4 through 14) to the operated eye
Protocol Synopsis (Study Design; Part B) *and* **Section 3.4 (Alternative options to Planned Dosing Regimens in part B)**	• Part B is opened for Screening, but only tests 0.05% APP13007 and matching vehicle placebo administered BID for 3 days and then QD for 18 days (2 treatments enrolling approximately 42 subjects). • Part B is opened for Screening but tests only 0.1% APP13007 and matching vehicle placebo administered BID for 3 days and then QD for 18 days (2 treatments enrolling approximately 42 subjects) • Part B is opened for Screening but tests 0.05% APP13007 and matching vehicle placebo administered BID for 21 days	• Part B is opened for Screening, but only tests 0.05% APP13007 and matching vehicle placebo administered BID for 3 days and then QD for 11 days (2 treatments enrolling approximately 42 subjects). • Part B is opened for Screening but tests only 0.1% APP13007 and matching vehicle placebo administered BID for 3 days and then QD for 11 days (2 treatments enrolling approximately 42 subjects) • Part B is opened for Screening but tests 0.05% APP13007 and matching vehicle placebo administered BID for 14 days (2

	(equivalent to a repeat of Part A, 2 treatments enrolling approximately 42 subjects)	treatments enrolling approximately 42 subjects)
Protocol Synopsis (Exclusion Criteria) *and* **Section 4.3 (Exclusion Criteria)**		Criteria numbers changed for consistency between Synopsis and Section 4.3.
Protocol Synopsis (Exclusion Criteria) *and* **Section 4.3 (Exclusion Criteria)**	8. Use of systemic or topical anti-inflammatory agents, analgesics/pain relievers (including opioids, narcotics, NSAIDS, aspirin, acetaminophen and other pain medications) or immunomodulating agents systemically or in either eye from the 'washout' period until the End-of-Study (EOS) visit. Note: Medications for anesthesia and pain control are allowed on the day of surgery only (See Section 5.4.2).	8. Use of systemic or topical anti-inflammatory agents, analgesics/pain relievers (including opioids, narcotics, NSAIDS, aspirin, acetaminophen and other pain medications) or immunomodulating agents systemically or in either eye (including Lifitegrast (Xiidra)) from the 'washout' period until the End-of-Study (EOS) visit. Note: Medications for anesthesia and pain control are allowed on the day of surgery only (See Section 5.4.2).
Protocol Synopsis (Table 1) *and* **Section 5.4.3 (Prohibited Medications and Minimum Washout Periods)**	Systemic acetaminophen, NSAIDS, acetylsalicylic acid (aspirin), or other systemic anti-inflammatory agents	Systemic acetaminophen, NSAIDS, acetylsalicylic acid (aspirin), or other systemic anti-inflammatory agents (including Lifitegrast (Xiidra))
Protocol Synopsis (Table 1) *and*	Note: Besifloxacin Ophthalmic suspension is not permitted.	Note: Antibiotics with anti-inflammatory activity and Besifloxacin Ophthalmic suspension are not permitted

Section 5.4.3 (Prohibited Medications and Minimum Washout Periods)		
Protocol Synopsis (Statistical methods; Analysis Populations) *and* **Section 10.2 (Analysis Populations)**	• Per-Protocol (PP) population: All randomized subjects who complete the study drug dosing through the POD15 visit and do not have any major protocol deviations.	• Per-Protocol (PP) population: All randomized subjects who complete the study drug dosing through POD14 and do not have any major protocol deviations.
Figure 1 (Study Schematics)	 Part B Schematic	 Part B Schematic – New Figure
Table 2	Table 2: Schedule of Events	Table 2A: Schedule of Events for Part A Table 2B: Schedule of Events for Part B (New table)
Section 1.4.3	Overall, the risk:benefit analysis supports the evaluation of 0.05% and 0.1% strengths of APP13007 and matching vehicle placebos administered BID or QD for 21 days after cataract surgery.	Overall, the risk:benefit analysis supports the evaluation of 0.05% and 0.1% strengths of APP13007 and matching vehicle placebos administered BID or QD for up to 21 days after cataract surgery.
Table 3	The lens in the non-operated eye will be evaluated at	The lens in the non-operated eye will be evaluated at Screening, EOS and Early Termination visits.

	Screening, POD28/EOS and Early Termination visits.	
Section 3.1 (Part A)	Following completion of the POD22 visit (i.e., End-of-Treatment (EOT) visit) for all subjects at all sites in Part A, Part B (0.05% and 0.1% along with respective matching vehicle placebo, BID regimen for 3 days followed by QD regimen for 18 days) will be opened.	Following completion of the POD22 visit (i.e., End-of-Treatment (EOT) visit) for all subjects at all sites in Part A, Part B (0.05% and 0.1% along with respective matching vehicle placebo, BID regimen for 3 days followed by QD regimen for 11 days) will be opened for randomization.
Section 3.1 (Part B)	Sites will be notified of a change in treatments in a communication when announcing the opening of Part B (Section 3.3).	Sites will be notified of a change in treatments in a communication when announcing the opening of randomization for Part B (Section 3.3).
Section 3.2 (Study Overview)	This study will include up to 8 clinic visits (including the surgery day) over a range of 29 to 57 days of total study duration.	This study will include up to 8 clinic visits (including the surgery day) over a range of 29 to 57 days in Part A, or 7 clinic visits (including the surgery day) over a range of 24 to 51 days in Part B.
Section 3.2 (Study Overview)	Dosing with study drug will continue for 21 days.	In Part A of the study, dosing with study drug will continue for 21 days.
Section 3.2 (Study Overview)	A summary of study events is provided in Table 2 (Schedule of Events) and a study schematic for Part A and Part B is provided in Figure 1 (Study Schematics).	In Part B of the study, dosing with study drug will continue for 14 days. Subjects will be reminded to bring diary card to each scheduled clinic visit. On POD14, subjects will be contacted by site staff to remind them to administer the last dose on POD14 and discontinue dosing on POD15 and to return to the clinic with their study drug

		bottle and diary card for End-of-Treatment (EOT) evaluations on POD15 (+1 day). Following study procedures on POD22, subjects will be released from the study (EOS). A summary of study events is provided in Table 2A and Table 2B (Schedule of Events for Part A and Part B, respectively) and a study schematic for Part A and Part B is provided in Figure 1 (Study Schematics).
Section 3.3 (Progression from Part A to Part B)	1. Part B will be opened for Screening only when all subjects have completed POD15 in Part A and the Sponsor has approved the progression to Part B.	1. Part B will be opened for Screening only when approximately 40 subjects have completed POD15 in Part A.
Section 5.1.2. Study Drug Dosing and Administration	If the subject loses the bottle of study drug or it is compromised after the POD15 visit, the subject will not receive a replacement bottle.	If the subject loses the bottle of study drug or it is compromised after the POD15 visit in Part A, the subject will not receive a replacement bottle.
Section 6.2.1 (Screening)	After obtaining written informed consent and HIPAA authorization, site staff will perform the assessments as shown in the Schedule of Events (Table 2).	After obtaining written informed consent and HIPAA authorization, site staff will perform the assessments as shown in the Schedule of Events (Table 2A or Table 2B).
Section 6.2.2. (Postoperative Day 1 (POD1) – Day of Randomization)	while in Part B, study drugs will be administered BID for the first 3 days and then QD thereafter for the duration of the treatment period in the study,	while in Part B, study drugs will be administered BID for the first 3 days and then QD thereafter for the duration of the treatment period in the study, i.e., for 11 days (POD4 to POD14).

	i.e., for 18 days (POD4 to POD21).	
Section 6.2.3. (PODs 1 through 15)	All assessments will be performed as shown in the Schedule of Events (Table 2). Note that blood samples for safety laboratory assessments and cortisol level will only be collected in Part A. Also note that ocular assessments will be performed only in the operated, study eye at PODs 1, 4, 8, and 15 visits. Note: Key data from visits up to and including the POD15 visit (ACC, pain score, IOP, number of subjects rescued and AEs) may be used to make decision of opening Part B for screening.	All assessments will be performed as shown in the Schedule of Events (Table 2A or Table 2B). Note that blood samples for safety laboratory assessments and cortisol level will only be collected in Part A. Also note that ocular assessments will be performed only in the operated, study eye at PODs 1, 4, 8, 15 and 22 visits in Part A and PODs 1, 4, 8 and 15 in Part B. Note: Key data from visits up to and including the POD15 visit (ACC, pain score, IOP, number of subjects rescued and AEs) may be used to make decision of opening of Part B for randomization.
Section 6.2.4. (Day of Subject Contact: POD21 (Day of subject contact in Part A or); POD14 (Day of subject contact in Part B))	POD21 is the last day of dosing for all treatments. Site personnel will contact the subject to remind him/her not to take study drug on POD22 and to bring the bottle of study drug and diary back to the clinical site at the POD22 visit. Any AEs reported to the site during the POD21 contact must be recorded in the source documents. Further assessment of any reported AEs may require an Unscheduled Visit on POD21 if medically significant or they may be	POD21 is the last day of dosing for the two treatments in Part A. POD14 is the last day of dosing for all treatments in Part B. Site personnel will contact the subject to remind him/her not to take study drug on POD22 (Part A) or POD15 (Part B) and to bring the bottle of study drug and diary back to the clinical site at the POD22 visit (Part A) or POD15 visit (Part B). Any AEs reported to the site during the POD21 (Part A) or POD14 (Part B) contact must be recorded in the source documents.

	assessed, as appropriate, during the POD22 visit.	Further assessment of any reported AEs may require an Unscheduled Visit on POD21 (Part A) or POD14 (Part B) if medically significant or they may be assessed, as appropriate, during the POD22 visit (Part A) or POD15 visit (Part B).
Section 6.2.5 (End of Treatment (EOT): POD22 in Part A or POD15 in Part B)	POD22 is the End-of-Treatment (EOT) visit. All ocular assessments must be performed on the operated, study eye only. Blood will be drawn for safety labs and cortisol level.	POD22 is the End-of-Treatment (EOT) visit in Part A. POD15 is the EOT visit in Part B. All ocular assessments must be performed on the operated, study eye only. Blood will be drawn for safety labs and cortisol level in Part A only.
Section 6.2.6 (End of Study (EOS): POD28 in Part A or POD22 in Part B)	The final EOS safety follow-up visit will occur on POD28 (± 1 day) or approximately 7 days (± 1 day) following the EOT visit. Blood will be drawn for safety labs.	The final EOS safety follow-up visit will occur on POD28 (± 1 day) or approximately 7 days (± 1 day) following the EOT visit in Part A or on POD22 (± 1 day) or approximately 7 days (± 1 day) following the EOT visit in Part B. Blood will be drawn for safety labs in Part A only.
6.2.7. Subject Early Termination	Subjects who are terminated from the study early should have POD22/EOT assessments (and indirect ophthalmoscopy) performed at the time of termination, or as soon thereafter as possible. In the case of early termination, the ocular assessments are to be performed on both eyes.	Subjects who are terminated from the study early, but the rescue criteria in Section 9.4.1 are not met, should have POD28/EOS (Part A) or POD22/EOS (Part B) assessments performed at the time of termination, or as soon thereafter as possible. At early termination the ocular assessments are to be performed on both eyes.

Section 6.2.8. (Unscheduled Visits)	If the subject is discontinuing study participation at the unscheduled visit, the eCRFs for POD22/EOT should be completed rather than the eCRFs for an Unscheduled Visit.	Text deleted to avoid confusion
Section 6.3 (Study Visit Schedule for Rescued Subjects)	Subjects who meet the criteria for rescue presented in Section 9.4 should discontinue study drug and receive rescue medication. Subjects who are rescued should continue in the study as indicated in Table 5 below. Note that the assessments in the check box under each visit in the Schedule of Events (Table 2) with a (R) next to "X" indicates that the assessments should be performed on rescued subjects at the indicated visits. Table 5 provides an overview of the study visits and assessments required for rescued subjects depending on when the rescue occurs during the study. It is important to note that subjects rescued on or before POD16 will be considered as having completed the study before POD28 as indicated by 'na' in Table 5.	Subjects who meet the criteria for rescue presented in Section 9.4 should discontinue study drug and receive rescue medication. Subjects who are rescued should continue in the study as indicated in Table 5A or Table 5B below. Note that the assessments in the check box under each visit in the Schedule of Events (Table 2A or Table 2B) with a (R) next to "X" indicates that the assessments should be performed on rescued subjects at the indicated visits. Table 5A or Table 5B provides an overview of the study visits and assessments required for rescued subjects depending on when the rescue occurs during the study. It is important to note that (i) subjects rescued on or before POD16 in Part A will be considered as having completed the study before POD28 as indicated by 'na' in Table 5A, and (ii) subjects rescued on or before POD9 in Part B will be considered as having completed the study before POD22 as indicated by 'na' in Table 5B.

Table 5	Table 5 Visits for Rescued Subjects	Table 5A Visits for Rescued Subjects (Part A) Table 5B Visits for Rescued Subjects (Part B) (New table)
Section 6.4. (Subject Withdrawal or Early Termination)	None; New text added to Amendment	1. A subject is rescued or withdrawn from the study because the investigator considers that the subject requires alternative medication (see Section 9.4.1 for clarification of 'rescued' and 'withdrawn').
Section 6.4. (Subject Withdrawal or Early Termination)	In the event that termination of a randomized subject is necessary, the Investigator should make every attempt to have the subject complete POD22/EOT assessments as soon as possible (Note: the ocular assessments need to be performed on both eyes) (Section 6.2.7, Table 2). The reason for premature termination of a subject should be recorded in the source document and entered in the eCRF.	In the event that termination of a randomized subject is necessary ('withdrawn' subject), the Investigator should make every attempt to have the subject complete POD28/EOS assessments (Part A) or POD22/EOS assessments (Part B) as soon as possible (Note: the ocular assessments need to be performed on both eyes) (Section 6.2.7, Table 2A or Table 2B). For the management of 'rescued' subjects see Section 9.4.1. The reason for premature termination of a subject should be recorded in the source document and entered in the eCRF.
Section 6.5.1. (Early Discontinuation of the Study or Change in the Conduct of Part B)	The sites, IRB and FDA will be notified of the change in the planned treatments for Part B in a written communication when announcing the opening of Part B for screening.	The sites, IRB and FDA will be notified of the change in the planned treatments for Part B in a written communication when announcing the opening of Part B for randomization.

Section 7.3 (Safety Assessments)	Note that these assessments are applied to both eyes (at Screening, POD28/EOS or early termination) or just the Study (or Operated) eye as indicated in Table 2 (Schedule of Events).	Note that these assessments are applied to both eyes (at Screening, POD28/EOS (Part A) or POD22/EOS (Part B) or early termination) or just the Study (or Operated) eye as indicated in Table 2A or Table 2B (Schedule of Events).
Section 7.3.4 (IOP Measurement)	IOP assessments will be performed at all study visits except the surgery visit as indicated in the Schedule of Events (Table 2).	IOP assessments will be performed at all study visits except the surgery visit as indicated in the Schedule of Events (Table 2A or Table 2B).
Section 7.3.5. (Dilated Ophthalmoscopy)	A dilated fundus examination will be performed according to the Investigator's standard technique and will occur as indicated in the Schedule of Events (Table 2).	A dilated fundus examination will be performed according to the Investigator's standard technique and will occur as indicated in the Schedule of Events (Table 2A or Table 2B).
Section 7.3.5. (Dilated Ophthalmoscopy)	If a subject has a cataract in the non-operated eye at the Screening visit, the Investigator should make an assessment whether there has been a change in the size or composition of the cataract at the EOS/POD28 visit or at early termination. This information will be recorded in the source document and eCRF.	If a subject has a cataract in the non-operated eye at the Screening visit, the Investigator should make an assessment whether there has been a change in the size or composition of the cataract at the EOS/POD28 visit (Part A) or EOS/POD22 visit (Part B) or at early termination. This information will be recorded in the source document and eCRF.
Section 8.1 (Definition of Adverse Events)	New text	• Adverse events occurring in rescued subjects should be reported in the eCF.

Section 9.1 (Stopping Criteria)	• Individual subject: Subjects with an IOP > 30 mmHg after randomization who do not respond to IOP lowering therapy should discontinue study drug and should be treated at the Investigator's discretion. These subjects will continue in the study with scheduled assessments to be performed at each visit until EOS/POD28.	• Individual subject: Subjects with an IOP > 30 mmHg after randomization who do not respond to IOP lowering therapy should discontinue study drug and should be treated at the Investigator's discretion. These subjects will continue in the study with scheduled assessments to be performed at each visit until EOS/POD28 (Part A) or EOS/POD22 (Part B).
Section 9.1 (Stopping Criteria)	Specifically, if it is observed that visual acuity worsens by 2 lines at POD28 in the treated study eye as compared to 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.	Specifically, if it is observed that visual acuity worsens by 2 lines at EOS in the treated study eye as compared to 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.
Section 9.4 Header	Rescue Management	Rescue and Increased IOP Management
Section 9.4.1. (Criteria for Starting Rescue Medication)	Subjects who, on examination of the anterior chamber, have one or more of the following situations may be discontinued from study drug dosing and placed on rescue mediation:	Subjects who, on examination of the anterior chamber, have one or more of the following criteria will be considered 'Rescued' subjects and should be discontinued from study drug dosing and placed on rescue mediation:
Section 9.4.1. (Criteria for Starting Rescue	Investigators will use clinical judgment to determine the appropriate rescue medication	Investigators will use clinical judgment to determine the appropriate rescue medication to

Medication; Management)	to use and when to withdraw study drug and procedures. While initiation of rescue medication is at the discretion of the Investigator, if one criterion above in Section 9.4.1 is met, the subject should be placed on rescue medication. Subjects not otherwise responding to study drug may be placed on rescue medication at the discretion of the Investigator even if none of the above criteria are met. The choice of rescue medication is at the Investigator's discretion and will be used as directed by the Investigator. Any subject placed on rescue medication will discontinue the study drug and continue in the study for study assessments as described in Section 6.3. A subject who is treated with an ocular corticosteroid product after POD22 will be considered to be a 'rescued' subject. Rescued subjects will be considered treatment failures, but the need for rescue medication will not be considered as an AE. Rescued subjects experiencing an AE at the time of rescue will be followed through by the Investigator to stabilization or resolution of the AE or the end of the study (whichever comes	use and when to withdraw study drug and perform procedures. While initiation of rescue medication is at the discretion of the Investigator, if one criterion above in Section 9.4.1 is met, the subject should be placed on rescue medication. Subjects not otherwise responding to study drug may be placed on alternative medication at the discretion of the Investigator even if none of the above criteria are met. In the situation where an investigator considers that alternative medication is required, but the above 'Rescue' criteria are not met, the subject is considered to be 'withdrawn' from the study and EOS assessments are to be performed. The choice of alternative medication is at the Investigator's discretion and will be used as directed by the Investigator. Any subject who is rescued based on the criteria in Section 6.3 and who is placed on rescue medication will discontinue the study drug and continue in the study for study assessments as described in Section 6.3. A subject who is treated with an ocular corticosteroid or other anti-inflammatory product after POD22 (Part A) or POD15 (Part B) will be considered to be a 'Withdrawn' subject.

	last). Rescued subjects should be followed to resolution of signs and symptoms of an AE or until the Investigator has deemed the subject is stable. *Note:* *If a subject is rescued, this event will be captured in the eCRF. Medications used for rescue will be recorded in the Concomitant Medications section of the eCRF. In addition, all the assessments in the check box with an (R) next to "X" in the Schedule of Events (Table 2) shall be performed on subjects who are rescued.*	Rescued subjects will be considered treatment failures, but the need for rescue medication will not be considered as an AE. Rescued or Withdrawn subjects experiencing an AE at the time of rescue/withdrawal will be followed through by the Investigator to stabilization or resolution of the AE or the end of the study (whichever comes last). Rescued/Withdrawn subjects should be followed to resolution of signs and symptoms of an AE or until the Investigator has deemed the subject is stable. *Note:* *Clarification of the distinction between 'Rescued' and 'Withdrawn':* *i) Process for 'Rescued' subjects:* *• The subject notifies the clinical site and is able to return for an unscheduled visit or scheduled visit before starting rescue medication.* *• The subject has a visit and the investigator documents that the subject meets one of the rescue criteria. The subject should be rescued. The study drug is stopped and the subject should be started on the investigator's preferred rescue medication.* *o EOT assessments are completed at the time of this evaluation and the subject returns for the EOS*

		assessments as shown in Table 5A or Table 5B. *• The subject's status is 'Rescued' and the reason for rescue must be one of the rescue criteria. This information is entered into the source and eCRF.* *ii) Process for 'Withdrawn' subjects:* *• The subject notifies the clinical site and is able to return for an unscheduled visit or scheduled visit. At the visit, the investigator's opinion is that the subject needs to be withdrawn because of inadequate control of inflammation and pain, but one or more of the rescue criteria are not met. The subject is withdrawn from the study, and at the investigator's discretion, the study drug is discontinued and alternative medication is started to treat the subject.* *• At this site visit, the EOS evaluation is completed.* *• The subject attends the clinical site for a scheduled visit and the investigator considers that the subject is inadequately treated by the study drug, but one or more of the rescue criteria are not met. The subject is withdrawn from the study because of inadequate control of inflammation and pain, and at the investigator's*

		discretion, the study drug is discontinued and alternative medication is used to treat the subject. *• The subject contacts the clinical site without attendance, and the investigator considers that the subject is inadequately treated by the study drug for inflammation and pain. Then the subject should return at the next available opportunity for assessment to determine whether or not the rescue criteria are met. If not, the subject is withdrawn and the EOS assessments are completed.* *• The subject's status is 'Withdrawn' from the study. The reason for subject withdrawal is recorded as "requiring alternate medication for inflammation and pain following cataract surgery" and any AEs should be recorded in the eCRF.* *If a subject is rescued, this event will be captured in the eCRF. Medications used for rescue will be recorded in the Concomitant Medications section of the eCRF. In addition, all the assessments in the check box with an (R) next to "X" in the Schedule of Events (Table 2A or Table 2B) shall be performed on subjects who are rescued.*

Section 10.3.2. (Analysis of Efficacy)	Secondary efficacy analyses will include for each dosing regimen, active and placebo separately: 1) the summary statistics of: • ACC on PODs 4, 8, 22/EOT; • Change from baseline (POD1/pre-dose) of ACC on PODs 4, 8, 22/EOT; • ACC grade* at PODs 4, 8, 15, 22/EOT; • Change from baseline (POD1/pre-dose) of ACC grade at PODs 4, 8, 15, 22/EOT; • Anterior chamber flare grade at PODs 4, 8, 15, 22/EOT; • Change from baseline (POD1/pre-dose) of anterior chamber flare at PODs 4, 8, 15, 22/EOT; • Pain grade for each treatment at PODs 1, 4, 8, 15, 22/EOT. • Change from baseline (POD1/pre-dose) of pain grade at PODs 4, 8, 15, 22/EOT; • Visual acuity (ETDRS Best corrected Visual Acuity measurement – pinhole method) at PODs 4, 8, 15, 22/EOT • Change from baseline (POD1/pre-dose) of visual acuity at PODs 4, 8, 15, 22/EOT	Secondary efficacy analyses will include for each dosing regimen, active and placebo separately: 1) the summary statistics of: • ACC on PODs 4, 8, 22/EOT (Part A) or PODs 4, 8 (Part B); • Change from baseline (POD1/pre-dose) of ACC on PODs 4, 8, 22/EOT (Part A) or on PODs 4, 8 (Part B); • ACC grade* at PODs 4, 8, 15, 22/EOT (Part A) or PODs 4, 8 and 15/EOT (Part B); • Change from baseline (POD1/pre-dose) of ACC grade at PODs 4, 8, 15, 22/EOT (Part A) or PODs 4, 8 and 15/EOT (Part B); • Anterior chamber flare grade at PODs 4, 8, 15, 22/EOT (Part A) or PODs 4, 8 and 15/EOT (Part B); • Change from baseline (POD1/pre-dose) of anterior chamber flare at PODs 4, 8, 15, 22/EOT (Part A) or PODs 4, 8 and 15/EOT (Part B); • Pain grade for each treatment at PODs 4, 8, 22/EOT (Part A) or PODs 4, 8 (Part B); • Change from baseline (POD1/pre-dose) of pain grade at PODs 4, 8, 15, 22/EOT (Part A) or PODs 4, 8 and 15/EOT (Part B);

		• Visual acuity (ETDRS Best corrected Visual Acuity measurement – pinhole method) at PODs 4, 8, 15, 22/EOT (Part A) or PODs 4, 8 and 15/EOT (Part B); • Change from baseline (POD1/pre-dose) of visual acuity at PODs 4, 8, 15, 22/EOT (Part A) or PODs 4, 8 and 15/EOT (Part B)
Section 10.3.2. (Analysis of Efficacy)	2) the proportion of subjects • with ACC = 0 at PODs 4, 8, 15 and 22/EOT without receiving rescue medication; • who are pain-free at PODs 4, 8, 15 and 22/EOT without receiving rescue medication; • with AC flare grade = 0 at PODs 4, 8, 15 and 22/EOT without receiving rescue medication.	2) the proportion of subjects • with ACC = 0 at PODs 4, 8, 15 and 22/EOT (Part A) or PODs 4, 8 and 15/EOT (Part B) without receiving rescue medication; • who are pain-free at PODs 4, 8, 15 and 22/EOT (Part A) or PODs 4, 8 and 15/EOT (Part B) without receiving rescue medication; • with AC flare grade = 0 at PODs 4, 8, 15 and 22/EOT (Part A) or PODs 4, 8 and 15/EOT (Part B) without receiving rescue medication.
Protocol		Minor formatting and typographical corrections

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

µL	microliter
ACC	Anterior Chamber Cell
ACF	Anterior Chamber Flare
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
$AUC_{0-\infty}$	Area Under the Curve from Time Zero to Infinite Time
BAK	Benzalkonium Chloride
BID	Twice Daily
BPH	Benign Prostatic Hyperplasia
BUN	Blood Urea Nitrogen
Cmax	Maximum Plasma Concentration
CME	Cystoid Macular Edema
ConMed	Concomitant Medications
CP	Clobetasol Propionate
CRF	Case Report Form
CRO	Contract Research Organization
CSME	Clinically Significant Macular Edema
DHHS	Department of Health and Human Services
DOS	Day of Surgery
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EE	Efficacy Evaluable
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIPAA	Health Insurance Portability and Accountability Act
HPA	Hypothalamic-Pituitary-Adrenal
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICSR	Individual Case Study Report

IEC	Independent Ethics Committee
IOL	Intraocular Lens
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
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mg/kg	milligrams per kilogram
mm	millimeter
mmHg	millimeters of mercury
ng/mL	nanograms per milliliter
NSAID	Nonsteroidal Anti-inflammatory Drug
OTC	Over the Counter
PCIOL	Posterior Chamber Intraocular Lens
PCO	Posterior Capsule Opacification
PDR	Proliferative Diabetic Retinopathy
PHI	Protected Health Information
PI	Principal Investigator
POD	Post-Operative Day
PRN	As Needed
QD	Once Daily
QID	Four Times Daily
R	Randomization
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAR	Suspected Adverse Reaction
SOA	Schedule of Assessments
SOP	Standard Operating Procedure
SRM	Study Reference Manual
WBC	White Blood Cells

PROTOCOL SYNOPSIS

Sponsor: Formosa Pharmaceuticals, Inc.,	**US Representative:** [redacted]
Title of Study: A Multicenter, Randomized, Double-Masked, Two-Part, Placebo-Controlled Phase 2a Study to Evaluate the Safety, Tolerability and Preliminary Efficacy of APP13007 for the Treatment of Inflammation and Pain after Cataract Surgery	
Protocol Number: CPN-201	**Phase:** 2a
Active Ingredient: [redacted]	
Name of Study drug: APP13007 [redacted]	
Indication: Clobetasol propionate ophthalmic nanosuspension is indicated for the treatment of postoperative inflammation and pain following ocular surgery	
Description of Study drug: APP13007 0.05% nanosuspension and matching vehicle placebo will be supplied for subjects enrolled in Part A. APP13007 0.05% nanosuspension and matching vehicle placebo and APP13007 0.1% nanosuspension and matching vehicle placebo will be supplied for subjects enrolled in Part B.	
Study Center(s): Approximately 8 study centers in the US are planned	
Objectives and Endpoints **Objectives**	**Endpoints**

The primary safety objective of this study is to investigate the safety and tolerability of APP13007 versus corresponding matching vehicle placebo for the treatment of inflammation and pain through post-operative day (POD) 22 in Part A and POD15 in Part B after cataract surgery
.
	• Early Treatment Diabetic Retinopathy Study (ETDRS) best corrected visual acuity by pinhole method
	• Slit-lamp biomicroscopy
	• Change from baseline to each post-surgery visit in ocular signs:
	  ○ Corneal edema
	  ○ Ciliary flush
	  ○ Bulbar conjunctival injection
	• Dilated indirect ophthalmoscopy
	• Intraocular pressure (IOP)
	• Adverse event (AE) monitoring
	• Clinical chemistry and hematology parameters (Appendix A)
	• Blood cortisol concentration

The primary efficacy objective of this study is to investigate the preliminary efficacy of APP13007 versus matching vehicle placebo for the treatment of inflammation and pain through post-operative day (POD) 15 after cataract surgery.	• Anterior chamber cell (ACC) count at POD15. • Pain grade on POD15
The secondary efficacy objective of this study is to compare the effects on markers of inflammation and pain and visual acuity between active APP13007 and matching vehicle placebo for each dose strength and frequency	• Anterior chamber cell (ACC) count at PODs 4, 8, and 22/EOT (Part A) and PODs 4 and 8 (Part B). • Pain grade on PODs 4, 8, and 22/EOT (Part A) and PODs 4 and 8 (Part B) • Anterior chamber flare (ACF) grade on PODs 4, 8, 15 and 22/EOT (Part A) and PODs 4, 8 and 15/EOT (Part B)

	• Use of rescue medication prior to each visit • Proportion of subjects with ACC count = 0 at PODs 4, 8, 15 and 22/EOT (Part A) or at PODs 4, 8 and 15/EOT (Part B) without receiving rescue medication ; • Proportion of subjects who are pain-free at PODs 4, 8, 15 and 22/EOT (Part A) and PODs 4, 8 and 15/EOT (Part B) without receiving rescue medication; • Proportion of subjects with flare grade = 0 at PODs 4, 8, 15 and 22/EOT (Part A) and PODs 4, 8 and 15/EOT (Part B) without receiving rescue medication • Visual acuity (ETDRS Best corrected Visual Acuity by pinhole method)

Study Design:
This is a Phase 2a, 2-part study (designated Parts A and B) that will evaluate APP13007 dose strength and dosing frequency in a randomized double-masked fashion for comparison to the respective matching vehicle placebo. Part A (0.05% BID regimen) will be conducted first. Subjects are considered to be enrolled into the study once they are randomized and receive study drug on POD1.

Part A: Approximately 42 subjects who experience postoperative inflammation on the first day following routine, uncomplicated, cataract surgery and who meet all other eligibility criteria will be randomized to one of two study treatments in an approximate 1:1 ratio to receive either Treatment 1 or Treatment 2 in a double-masked fashion (with sufficient number of subjects enrolled to allow approximately 40 subjects to complete dosing and study procedures through POD15).

- **Treatment 1:** 1 drop 0.05% APP13007 twice daily (BID) (morning and evening) for 21 days to the study eye

- **Treatment 2:** 1 drop matching vehicle placebo BID (morning and evening) for 21 days to the operated eye

Following completion of Part A dosing, Part B (0.05% and 0.1% BID regimen for 3 days followed by QD regimen for 11 days) will be opened for randomization.

The decision to progress to Part B will be based on ongoing safety review and futility analysis by the Data Review Group (Study Medical Monitor, the Sponsor Medical Monitor, and the Sponsor statistician). Review of key data (ACC count, pain score, IOP, the number of subjects rescued and AEs) will occur on an ongoing basis in a masked fashion. Once approximately 40 subjects in Part A have completed POD15 evaluation, all available key data will be summarized and reviewed by the Data Review Group. If masked data do not provide a clear indication that it is reasonable to progress to Part B, limited unmasked data will be used to determine whether or not to progress to Part B. For the unmasked review, the frozen database of ACC count, pain score, IOP, subject rescue and AE data through POD15 will be reviewed by the Sponsor Medical Monitor and the Sponsor statistician only (Note: the Study Medical Monitor will remain masked until completion of the study and database lock, except as indicated in Section 5.3). A recommendation will be made to the Sponsor on whether to proceed to Part B. The Sponsor management is responsible for determining if the study should progress to Part B. If applicable, the Institutional Review Board (IRB) will be informed in a memo if the unmasking of frozen key data up to POD15 is required before a decision is made to progress to Part B.

Part B: Approximately 84 subjects who experience postoperative inflammation on the first day following routine, uncomplicated, cataract surgery and who meet all other eligibility criteria will be randomized to one of four study treatments in an approximate 1:1:1:1 ratio to receive Treatment 3, Treatment 4, Treatment 5 or Treatment 6 in a double-masked fashion (with sufficient number of subjects enrolled to allow approximately 80 subjects to complete dosing and study procedures, approximately 20 per treatment, through POD15):

- **Treatment 3:** 1 drop 0.05% APP13007 BID (morning and evening) for 3 days (PODs 1, 2 and 3) followed by 1 drop 0.05% APP13007 QD (morning) for 11 days (PODs 4 through 14) to the operated eye
- **Treatment 4:** 1 drop 0.05% matching vehicle placebo (0.05% APP13007 vehicle) BID (morning and evening) for 3 days (PODs 1, 2 and 3) followed by 1 drop matching vehicle placebo QD (morning) for 11 days (PODs 4 through 14) to the operated eye
- **Treatment 5:** 1 drop 0.1% APP13007 BID (morning and evening) for 3 days (PODs 1, 2 and 3) followed by 1 drop 0.1% APP13007 QD (morning) for 11 days (PODs 4 through 14) to the operated eye
- **Treatment 6:** 1 drop 0.1% matching vehicle placebo (0.1% APP13007 vehicle) BID (morning and evening) for 3 days (PODs 1, 2 and 3) followed by 1 drop matching vehicle placebo QD (morning) for 11 days (PODs 4 through 14) to the operated eye

Alternate to Planned Dosing Regimen in Part B: Based on the recommendation resulting from analysis of data from Part A, the Sponsor will determine whether one of the following options will be adopted regarding Part B:

- Part B is opened for Screening as planned with the planned four treatment arms (4 treatments enrolling approximately 84 subjects).
- Part B is opened for Screening, but only tests 0.05% APP13007 and matching vehicle placebo administered BID for 3 days and then QD for 11 days (2 treatments enrolling approximately 42 subjects).
- Part B is opened for Screening but tests only 0.1% APP13007 and matching vehicle placebo administered BID for 3 days and then QD for 11 days (2 treatments enrolling approximately 42 subjects)
- Part B is opened for Screening but tests 0.05% APP13007 and matching vehicle placebo administered BID for 14 days (2 treatments enrolling approximately 42 subjects)
- The study is stopped after completion of Part A

The sites, IRB and FDA will be informed of any changes to the planned conduct of Part B before the changes are implemented.

Randomization: Subjects for both Parts will be randomized in an approximate 1:1 ratio of active to corresponding matching vehicle placebo. Each site will randomize subjects using the Integrated Web Response System (IWRS) module of the EDC system.

Test Product, Dose and Mode of Administration: Study drug (APP13007 0.05% and 0.1% and respective matching vehicle placebos) will be supplied in an eye drop bottle labeled in accordance with FDA regulations for investigational drug. One bottle will be dispensed to each subject in the trial. Study drug will be administered either once (in the morning) or twice (morning and evening) daily as indicated per protocol by instilling one drop into the conjunctival sac of the study eye. If the subject misses his/her eye during instillation, then a second drop will be instilled.

Number of Participants (Planned): Approximately 42 subjects for Part A and approximately 84 subjects for Part B are planned to be enrolled into this trial. Sufficient number of subjects will be enrolled to ensure approximately 20 subjects complete the study up to POD15 for each treatment arm.

Inclusion Criteria:

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

***At the Screening Visit*:**

1. Provide signed and dated informed consent
2. Age ≥ 50 years at time of informed consent
3. If female, be of non-childbearing potential. 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) or an FSH greater than 40 IU/L. Note: FSH will not be required if subject reports amenorrhea for > 12 months. (Pregnant women or nursing mothers are excluded from the study.)
4. Expected to undergo unilateral uncomplicated cataract extraction via phacoemulsification and posterior chamber intraocular lens (PCIOL) implantation in one eye (designated the 'Study Eye')
5. In the Investigator's opinion, have Early Treatment Diabetic Retinopathy Study (ETDRS) estimated potential of 0.7 (20/100) or better in study eye (best corrected visual acuity by the pinhole method).
6. 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

***At Postoperative Day (POD) 1/Day of Randomization*:**

7. Have undergone unilateral cataract extraction via phacoemulsification and posterior chamber intraocular lens (PCIOL) 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 results
8. Have > 10 cells and ≤ 30 cells in the anterior chamber (Note: Cell count should be taken twice at each visit and both counts need to meet eligibility criteria.).
9. Have an IOP ≤ 30 mmHg.

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 (BAK) and soybean lecithin
2. Have an ACC > 0 or any evidence of intraocular inflammation (e.g., flare) in either eye as found during the slit lamp examination at the Screening visit
3. Have a score > 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 would likely affect wound healing and/or resolution of inflammation after cataract surgery
6. Have suspected or known malignancy or received antineoplastic therapy within the 12 months prior to the Screening visit. 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. Use of treatments for macular degeneration including Eylea® (aflibercept), Avastin® (bevacizumab), and Lucentis® (ranibizumab)

8. Use of systemic or topical anti-inflammatory agents, analgesics/pain relievers (including opioids, narcotics, NSAIDS, aspirin, acetaminophen and other pain medications) or immunomodulating agents systemically or in either eye (including Lifitegrast (Xiidra)) from the 'washout' period until the End-of-Study (EOS) visit. Note: Medications for anesthesia and pain control are allowed on the day of surgery only (See Section 5.4.2).
9. Use of any of the prohibited medications (see Table 1) within a time period prior to surgery that is less than the minimum 'washout' period noted in the table. [NOTE: These medications may not be used after randomization through the EOS visit.]

Table 1: List of Prohibited Medications

Medication	Minimum 'Washout' Period Prior to Day 0 (Day of Surgery)
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 medication dosing; (ii) different restrictions for ocular products are listed below.	2 days
Topical ocular corticosteroids	7 days
Topical ocular nonsteroidal anti-inflammatory drugs (NSAIDs)	7 days
Topical eyelash growth medications	7 days
Systemic acetaminophen, NSAIDS, acetylsalicylic acid (aspirin), or other systemic anti-inflammatory agents (including Lifitegrast (Xiidra)) *Note: (i) Use of acetylsalicylic acid (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.*	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
Inhaled and/or nasal corticosteroids	14 days
Systemic (oral, injectable) corticosteroids	28 days
Systemic analgesics/pain relievers (e.g., gabapentin, pregabalin, opioids) *Note: Use of an opioid analgesic during cataract surgery is allowed*	14 days
Medications for benign prostatic hypertrophy (BPH) (e.g., Tamsulosin, silodosin, alfuzosin, finasteride)	28 days
Other study drugs or investigational products	28 days
Topical or systemic cyclosporine	60 days
Intraocular treatment with corticosteroid - dexamethasone drug delivery system	90 days after implantation
Intraocular treatment with corticosteroid – any other intravitreal injection	90 days after injection
Alterations of the dose of anticholinergics and antidepressants (except 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

10. Have an intraocular pressure (IOP) < 5 mmHg or > 22 mmHg in either eye at the Screening visit.
11. Have a history of documented and repeated elevated IOP
12. History of herpes keratitis in the study eye
13. Have active corneal abrasions or ulcers in the study eye
14. Have active or a history of chronic or recurrent inflammatory eye disease (e.g., iritis, scleritis, uveitis, iridocyclitis, rubeosis iridis) in the study eye
15. 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 blepharitis in the study eye
16. Have corneal dystrophies or dysthyroid ophthalmopathy in the study eye
17. Have uncontrolled and clinically significant dry eye syndrome in the study eye (mild dry eye with the use of artificial tears is allowed)
18. Have proliferative diabetic retinopathy (PDR), significant compromised macular function; significant macular diseases; clinically significant macular edema (CSME); or a history of cystoid macular edema in the study eye
19. Have had corneal or retinal surgery (laser or incisional) in the study eye within 6 months of the Screening visit, or be planning to have laser or incisional surgery during the study period in the study eye (other than cataract surgery)
20. Have surgery planned or scheduled for the contralateral eye during the study
21. 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 or the normal healing process)
22. 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
23. 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 related to cataract surgery, lid scrubs for mild blepharitis, or artificial tears for the management of dry eye. Note: subjects requiring IOP lowering medications pre-surgery for ocular hypertension or glaucoma are excluded
24. Have the potential for ocular hemorrhage in the study eye that may interfere with evaluation of post-surgery inflammation
25. 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
26. Have a planned use of or use anterior capsule staining for capsulorhexis (i.e., trypan blue) during cataract surgery
27. Have previously been enrolled in this clinical study, or have planned to participate in another clinical trial during the duration of this study
28. Have participated in another clinical study or received any investigational product within the past 28 days prior to the Screening Visit
29. Have any other condition that the Investigator determines should exclude the subject from the trial.
30. 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:
A Statistical Analysis Plan describing the details of all efficacy, safety and exploratory analyses will be written and finalized prior to database lock. All analysis variables will be summarized descriptively by each APP13007 dosing and matching vehicle placebo for each regimen. Summary statistics for continuous measures will be defined as mean, standard deviation, 95% confidence interval, median, and range. Categorical measures will be summarized by the number and percent of subjects.

Inferential statistics for primary and secondary efficacy endpoints will include Student t-test (with normality assumption met) or Wilcoxon rank-sum test (with normality unmet) for continuous endpoints, and Chi-square test for categorical endpoints.

Analysis Populations:

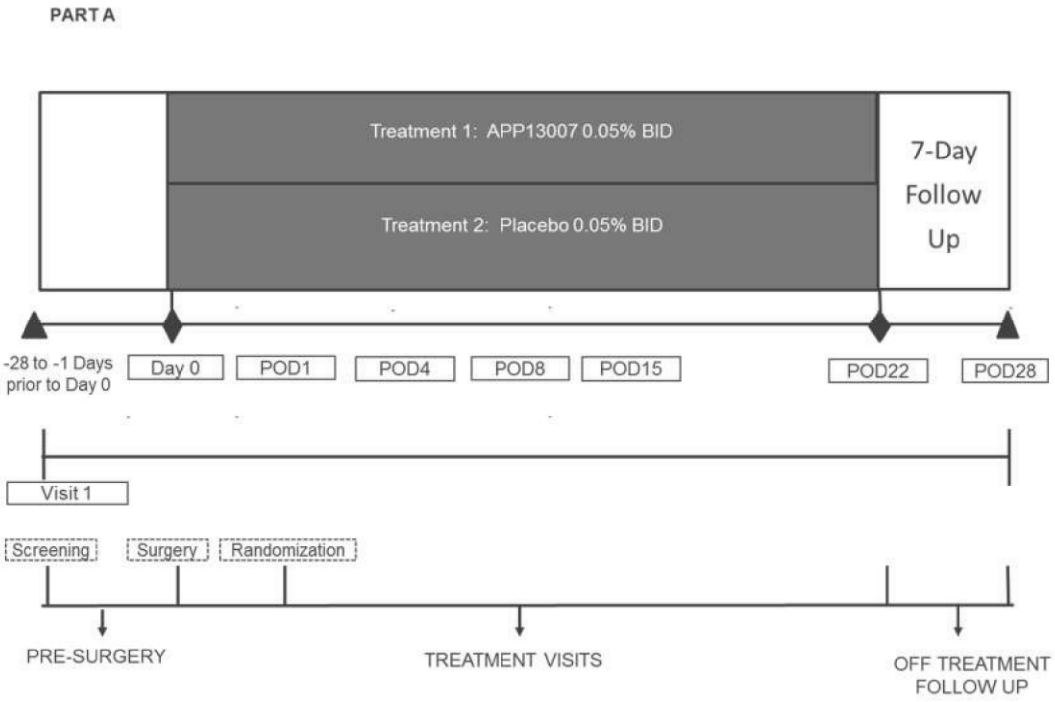
- Intent-to-Treat (ITT) population: All subjects who are randomized to study drug. If a subject is less than 75% compliant with dosing of study drug, the subject will be included in the 'ITT' analyses, but not in the 'Per-Protocol' analyses for efficacy endpoints.
- Safety Population: All subjects who receive at least one dose of study drug.
- Per-Protocol (PP) population: All randomized subjects who complete the study drug dosing through POD14 and do not have any major protocol deviations.

Sample Size: This is a Phase 2a trial to explore dosing regimens and no formal sample size calculations were used to determine the number of subjects enrolled into the trial. The sample size of approximately 21 subjects in each study treatment group was selected based on feasibility and integrated analysis of literature data. Assuming a dropout rate of 5%, approximately 21 subjects will be enrolled into each treatment arm so that approximately 20 subjects per treatment arm would be expected to complete study drug dosing through the POD15 visit.

Interim Analysis: No interim analyses are planned for this study.

STUDY DESIGN

Figure 1: Study Schematics



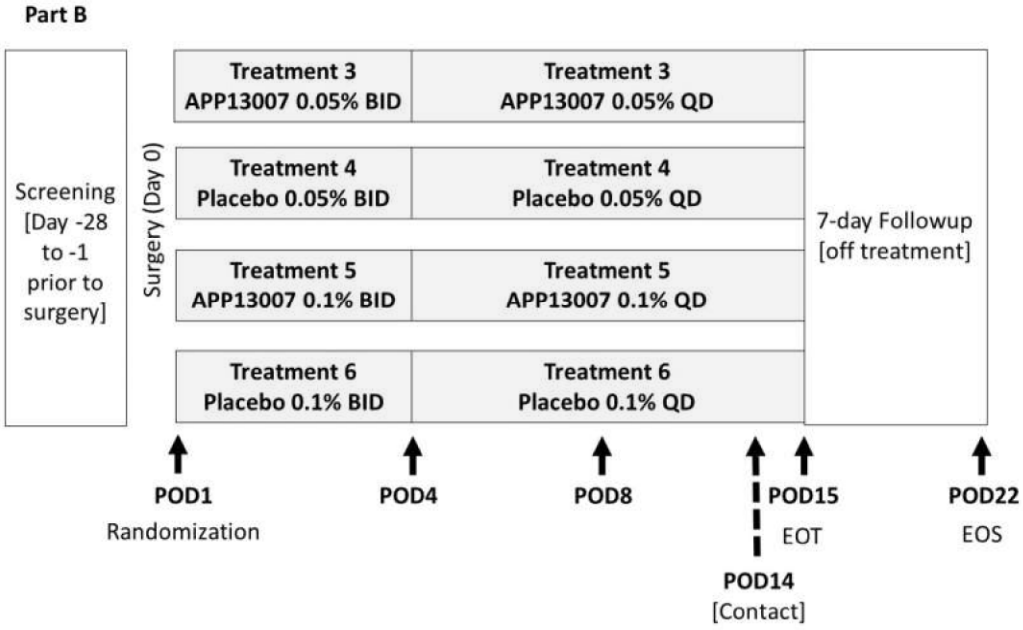


Table 2A: Schedule of Events for Part A

PROCEDURE/ASSESSMENTS[1]	Screening (D-28 to -1)	Surgery[2] Day 0	POD1[3]	POD4 (±1 Day)	POD8 (±1 Day)	POD15 (±1 Day)	POD21	EOT/POD22 (+1 Day)[4]	EOS/POD28 (±1 Day)[5]
ICF, Demography, Medical History, FSH[6] (menopausal status)	X								
Determine Eligibility, Review Inclusion/Exclusion Criteria	X		X						
Ocular Symptoms Assessment[7]	X		X	X (R)[16]	X (R)	X (R)		X (R)	X (R)
ETDRS Visual Acuity	X		X	X (R)	X (R)	X (R)		X (R)	X (R)
Slit Lamp Biomicroscopy[8]	X		X	X (R)	X (R)	X (R)		X (R)	X (R)
Indirect Ophthalmoscopy (dilated)	X								X (R)
IOP (Goldmann applanation tonometry)[9]	X		X	X (R)	X (R)	X (R)		X (R)	X (R)
Blood Draw for Safety Lab Parameters (Part A only)			X					X (R)	X (R)
Blood Draw for Cortisol (pre-Randomization&POD22) (Part A only)			X					X (R)	
Randomization			X						
Dispense Study Drug			X						
Study Drug Dosing for 21 days (POD1 to POD21)			X[10]	X	X	X	X		
Dispense Diary Card (with instructions for completion)			X	X	X	X			
Contact Subject[11]							X		
Collect Study Drug								X (R)	
Collect and Check Diary Cards for Accuracy and Compliance				X (R)	X (R)	X (R)		X (R)	
AEs[12] and Concomitant Medications[15]	X	X[13]	X	X (R)	X (R)	X (R)	X[14]	X (R)	X (R)

[1]Ophthalmic assessments will be performed in the study eye only except at the Screening and EOS/POD28 visits or at subject early termination when the ophthalmic assessments will be performed on both eyes.
[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 (Table 1).
[3]The POD1 visit must be scheduled between 18 to 34 hours following conclusion of surgery on Day 0. All assessments and blood draws done on POD1 are done prior to Randomization.
[4]POD22 is the End-of-Treatment (EOT) visit; subjects who discontinue study drug early (or early termination) should complete the POD22/EOT visit assessments (and indirect ophthalmoscopy) before or during their next scheduled visit.
[5]Subjects will have completed the study following the End-of-Study (EOS) visit on POD28.
[6]FSH should only be measured if needed to confirm postmenopausal status.
[7]Includes assessments of pain and irritation. See Section 8 for information on how to record AEs and how to determine attributability (relatedness) of AE to study procedures (including cataract surgery) or study drug.
[8]Ocular inflammation assessment of the ACC number (counted twice), flare grade, bulbar conjunctival injection, sclera - ciliary flush and corneal edema.
[9]IOP should (but not required) be assessed at each visit within ± 2 hr of the time IOP was assessed at the Screening Visit.
[10]The first dose of study drug should be instilled into the study eye at the clinic visit under supervision of clinic staff.
[11] The site must contact the subject via the subject's preferred reliable method to remind him/her not to instill study drug on POD22 and to bring the bottle of study drug and the diary back to the site at the POD22 visit.
[12]See Section 8 for information on how to record AEs and how to determine attributability (relatedness) of AE to study procedures (including cataract surgery) or study drug.
[13]AEs and ConMeds should only be recorded on Day 0 if they result in disqualification (i.e., screen failure) of the subject; otherwise, the AEs and ConMeds applicable to Day 0 should be recorded on POD1 when the subject returns at the POD1 visit.
[14]Any AEs reported to the site during the POD21 contact must be recorded in the source documents. Further assessment of any reported AEs may require an Unscheduled Visit on POD21 if medically significant or they may be assessed, as appropriate, during the POD22 visit.
[15]When concomitant medications are being used for rescue, the appropriate "Rescue" box should be filled in the eCRF.
[16]The designation (R) indicates that the procedure/assessment should be conducted for subjects who have been rescued and withdrawn from study treatment. (See Section 6.3). Subjects who have been rescued will not continue to instill study drug or receive diary cards.

Table 2B: Schedule of Events for Part B

PROCEDURE/ASSESSMENTS[1]	Screening (D-28 to -1)	Surgery[2] Day 0	POD1[3]	POD4 (±1 Day)	POD8 (±1 Day)	POD14	EOT/POD15 (+1 Day)[4]	EOS/POD22 (±1 Day)[5]
ICF, Demography, Medical History, FSH[6] (menopausal status)	X							
Determine Eligibility, Review Inclusion/Exclusion Criteria	X		X					
Ocular Symptoms Assessment[7]	X		X	X (R)[16]	X (R)		X (R)	X (R)
ETDRS Visual Acuity	X		X	X (R)	X (R)		X (R)	X (R)
Slit Lamp Biomicroscopy[8]	X		X	X (R)	X (R)		X (R)	X (R)
Indirect Ophthalmoscopy (dilated)	X							X (R)
IOP (Goldmann applanation tonometry)[9]	X		X	X (R)	X (R)		X (R)	X (R)
Randomization			X					
Dispense Study Drug			X					
Study Drug Dosing for 14 days (POD1 to POD14)			X[10]	X	X	X		
Dispense Diary Card (with instructions for completion)			X	X	X			
Contact Subject[11]						X		
Collect Study Drug							X (R)	
Collect and Check Diary Cards for Accuracy and Compliance				X (R)	X (R)		X (R)	
AEs[12] and Concomitant Medications[15]	X	X[13]	X	X (R)	X (R)	X[14]	X (R)	X (R)

[1]Ophthalmic assessments will be performed in the study eye only except at the Screening and EOS/POD22 visits or at subject early termination when the ophthalmic assessments will be performed on both eyes.
[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 (Table 1).
[3]The POD1 visit must be scheduled between 18 to 34 hours following conclusion of surgery on Day 0. All assessments done on POD1 are done prior to Randomization.
[4]POD15 is the End-of-Treatment (EOT) visit in Part B; subjects who discontinue study drug early (or early termination) should complete the POD15/EOT visit assessments (and indirect ophthalmoscopy) before or during their next scheduled visit.
[5]Subjects will have completed Part B the study following the End-of-Study (EOS) visit on POD22.
[6]FSH should only be measured if needed to confirm postmenopausal status.
[7]Includes assessments of pain and irritation. See Section 8 for information on how to record AEs and how to determine attributability (relatedness) of AE to study procedures (including cataract surgery) or study drug.
[8]Ocular inflammation assessment of the ACC number (counted twice), flare grade, bulbar conjunctival injection, sclera - ciliary flush and corneal edema.
[9]IOP should (but not required) be assessed at each visit within ± 2 hr of the time IOP was assessed at the Screening Visit.
[10]The first dose of study drug should be instilled into the study eye at the clinic visit under supervision of clinic staff.
[11] The site must contact the subject via the subject's preferred reliable method to remind him/her not to instill study drug on POD15 and to bring the bottle of study drug and the diary back to the site at the POD15 visit.
[12]See Section 8 for information on how to record AEs and how to determine attributability (relatedness) of AE to study procedures (including cataract surgery) or study drug.
[13]AEs and ConMeds should only be recorded on Day 0 if they result in disqualification (i.e., screen failure) of the subject; otherwise, the AEs and ConMeds applicable to Day 0 should be recorded on POD1 when the subject returns at the POD1 visit.
[14]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 the POD15 visit.
[15]When concomitant medications are being used for rescue, the appropriate "Rescue" box should be filled in the eCRF.
[16]The designation (R) indicates that the procedure/assessment should be conducted for subjects who have been rescued and withdrawn from study treatment. (See Section 6.3). Subjects who have been rescued will not continue to instill study drug or receive diary cards.

1. INTRODUCTION

1.1. Overview

APP13007 is an ophthalmic nanosuspension that is prepared by dispersing nanomilled clobetasol propionate (CP), a corticosteroid, with a mixture of excipients in a multi-dose preserved aqueous formulation. [redacted]

1.2. Background

1.2.1. Clobetasol Propionate

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® Product Insert 2018). It is reported to be the most potent corticosteroid in terms of binding affinity to the glucocorticoid receptor and resulting pharmacological effects (Olsen and Cornell 1986, Jacob and Steele 2006). CP has been used in dermal applications including ointments, creams and shampoos, where its efficacy and safety has been well-established (Clobex® Product Insert 2018; Temovate® Product Insert 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 (IOL) placement regularly leads to some degree of inflammation. The cellular damage on the surface of the cornea activates an inflammatory process that manifests initially as hyperemia, corneal edema, and increased anterior chamber cells and flare. More serious complications such as corneal edema, increases in intraocular pressure (IOP), cystoid macular edema (CME), and posterior capsule opacification (PCO) may result if the inflammatory process is not managed appropriately (J.L. 1978, Apple, Solomon et al. 1992). For this purpose, a 2-week 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, Colin et al. 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, Colin et al. 2017), and several marketed products are currently available that contain active ingredients such as dexamethasone, prednisolone, loteprednol etabonate and difluprednate.

CP, reportedly the most potent steroid and classified as a superpotent corticosteroid in the US, has been used extensively in dermatological applications (Olsen and Cornell 1986, Jacob and Steele 2006, Feldman and Yentzer 2009). Of note, 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]

[redacted]

[redacted]

1.3.2. **Pharmacokinetics**

[redacted]

The planned dosing regimen for this clinical study of APP13007 is one drop (not more than 50 µL) of 0.05% and 0.1% APP13007 given once or twice daily for 21 days. [redacted]

[redacted]

In summary, the systemic exposure to CP after ocular instillation of APP13007 is expected to be minimal and thus the associated systemic safety profile in humans is not expected to differ significantly from that previously demonstrated for dermal products containing CP.

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 data from repeat dose toxicology studies do not identify any unacceptable risk for human subjects. With respect to systemic effects, 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). [redacted]

1.4. Risk/Benefit Assessment

1.4.1. Potential Risks

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

As summarized in Section 1.3.3, there were no adverse ocular findings follow ocular instillation of APP13007, [redacted] the proposed dosing regimens for APP13007 in this study is expected to result in systemic exposure to CP not more than that seen with dermal CP products, and the associated systemic safety profile in humans is not expected to differ significantly from that previously demonstrated for dermal products containing CP.

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 and Cornell 1986, Hengge, Ruzicka et al. 2006, Feldman and Yentzer 2009). The majority of clinical trials of CP have been up to 2-4 weeks in duration in the two most prevalent steroid-responsive skin disorders, eczema and psoriasis (Feldman and Yentzer 2009).

This is the first clinical study investigating the safety, tolerability and preliminary efficacy of an [redacted] APP13007, which is being developed for the treatment of inflammation and pain after ocular surgery.

***Potential Non-Ocular Risks*:**

- Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression: Systemic absorption of topical corticosteroids can produce reversible HPA axis suppression and reduction of circulating cortisol concentration with the potential for glucocorticoid insufficiency after withdrawal from treatment. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids.

  Cushing's syndrome, hyperglycemia, and unmasking of latent diabetes mellitus can also result from systemic absorption of topical corticosteroids. 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. If irritation develops, APP13007 should be discontinued and appropriate therapy instituted. With prolonged use, local skin reactions

may include atrophy, striae, telangiectasias, burning, itching, irritation, dryness, acneiform eruptions, hypopigmentation, hypertrichosis, secondary infection and miliaria.

- Pregnancy and Nursing Mothers: [Note: females of child-bearing potential as well as pregnant and/or nursing mothers are excluded from participation in this study.] Corticosteroids have been shown to be 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.

  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.

[redacted] plasma CP concentrations in human subjects after ocular instillation of one drop of APP13007 are expected to be lower than that observed in human subjects after dermal application of CP-containing products.

Potential ocular risks are summarized below.

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] 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.

Potential Risks Associated with the APP13007 Formulation

[redacted]

1.4.1.1. 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 3.

1.4.1.2. 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.

[redacted]

1.4.2. **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™, and difluprednate (Durezol®). As summarized in the Product Inserts for Lotemax® and Durezol®, in clinical trials post ocular surgery, approximately 20-30% of subjects had clearing of anterior chamber cells and approximately 60-80% of subjects were pain free by Day 8 of treatment. Furthermore, approximately 40% of patients had clearing of anterior chamber cells and approximately 60% of patients were pain free after 15 days of treatment with Durezol®. In all clinical trials, corticosteroid therapies were dosed at a frequency of twice daily or more frequently. Thus, a more potent corticosteroid such as CP with a reduced dosing frequency may be advantageous over current therapies used to treat inflammation and pain following ocular surgery.

This is the first time that APP13007 will be administered to humans, therefore any potential direct benefit to subjects enrolled into this study is based on results of nonclinical pharmacology studies. However, given the potency of CP and known ocular use of corticosteroids, it is likely that subjects enrolled into this study and randomized to APP13007 may experience a reduction in inflammation and pain following cataract surgery.

It is known from 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 to some of the subjects enrolled into the study that are randomized to placebo.

1.4.3. **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 APP13007 may benefit from the treatment by reduction in inflammation and pain, while the risks associated with APP13007 treatment are

[redacted]

[redacted]

Subjects randomized to placebo are not expected to benefit from the study treatment, but a proportion of subjects receiving placebo may improve 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 procedures.

Overall, the risk:benefit analysis supports the evaluation of 0.05% and 0.1% strengths of APP13007 and matching vehicle placebos administered BID or QD for up to 21 days after cataract surgery.

Table 3: 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 of this protocol.	No dose modification is allowed in this study, but study drugs may be discontinued if there is substantial evidence indicating lack of efficacy of a dose regimen of APP13007.
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. While the risks of systemic exposure to CP following dermal/topical administration are well characterized, aqueous formulations of CP have not been dosed to the human eye before. Therefore, the Investigator should be alert to the possibility that unexpected safety events may occur. The list of expected safety events is including in Section 1.4.1 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 participation of subjects who may be at increased risk of steroid-induced IOP increase, eg. subjects with a history of raised IOP and subjects with IOP >30 mmHg at the POD1 pre-randomization assessment.	The toxicology studies with APP13007 indicate that there is a low risk of IOP increase during the 21 days of treatment. 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.

Potential Risk	Management	Comments
	Section 9 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 ≥ 24 mmHg AND an IOP increase ≥ 10 mmHg from pre-dose baseline is described in Section 9.4.2.	An IOP ≥ 24 mmHg AND an IOP increase ≥ 10 mmHg from pre-dose baseline 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, EOS and Early Termination visits.	Based on data from studies of dermal products of CP, use of APP13007 may result in posterior subcapsular cataract formation in the non-operated eye. While the risk is likely to be small, this cannot be quantified because the extent of CP systemic exposure in humans following ocular instillation of APP13007 is not known.
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.
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 potential low systemic CP exposure and data from studies of other steroids products approved for the treatment of inflammation and pain after ocular surgery.
Hypothalamic-Pituitary-Adrenal	Monitor for symptoms and signs of reduced adrenal function	Systemic absorption of topical corticosteroids can produce

Potential Risk	Management	Comments
Axis (HPA) Suppression	(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.	reversible HPA axis suppression with the potential for glucocorticoid insufficiency after withdrawal from treatment. 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. Recovery of adrenal function is generally prompt upon discontinuation of topical corticosteroids.
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. While the risk is likely to be small, this cannot be quantified because the extent of systemic exposure in humans following ocular instillation of APP13007 is not known.
Pregnancy Category C/Fetal effects	Women of child-bearing potential as well as pregnant and/or nursing mothers are excluded from the study	Corticosteroids are known teratogens in laboratory animals when administered systemically at relatively low dosage levels.
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 (Section 1.4.1)
Other Potential Risks		
[redacted]		

Potential Risk	Management	Comments
	seminal vesicles were seen at all dose levels.	
[redacted]		
[redacted]		
[redacted]		
Hypersensitivity Reactions	Subjects are excluded from the study if they have a history of hypersensitivity to CP, [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 are summarized in Section 1.4.1.

2. STUDY OBJECTIVES AND ENDPOINTS

The objectives and corresponding study endpoints are depicted in Table 4 below.

Table 4: Study Objectives and Endpoints

Objectives	Endpoints
The primary safety objective of this study is to investigate the safety and tolerability of APP13007 versus corresponding matching vehicle placebo for the treatment of inflammation and pain through POD22 in Part A and POD15 in Part B after cataract surgery.	• Early Treatment Diabetic Retinopathy Study (ETDRS) Best corrected Visual Acuity by pinhole method • Slit-lamp biomicroscopy • Change from baseline to each post-surgery visit in ocular signs: o Corneal edema o Ciliary flush o Bulbar conjunctival injection • Dilated indirect ophthalmoscopy • Intraocular pressure (IOP) • Adverse event (AE) monitoring • Clinical chemistry and hematology parameters (Appendix A) • Blood cortisol concentrations
The primary efficacy objective of this study is to investigate the preliminary efficacy of APP13007 versus matching vehicle placebo for the treatment of inflammation and pain through POD15 after cataract surgery.	• Anterior chamber cell (ACC) count at POD15 • Pain grade on POD15
The secondary efficacy objective of this study is to compare the effects on markers of inflammation and pain and visual acuity between active APP13007 and matching vehicle placebo for each dose strength and frequency.	• Anterior chamber cell (ACC) count at PODs 4, 8, and 22/EOT (Part A) and PODs 4 and 8 (Part B). • Pain grade on PODs 4, 8, and 22/EOT (Part A) and PODs 4 and 8 (Part B) • Anterior chamber flare (ACF) grade on PODs 4, 8, 15 and 22/EOT (Part A) and PODs 4, 8 and 15/EOT (Part B) • Use of rescue medication prior to each visit • Proportion of subjects with ACC count = 0 at PODs 4, 8, 15 and 22/EOT (Part A) and PODs 4, 8 and 15/EOT (Part B) without receiving rescue medication; • Proportion of subjects who are pain-free at PODs 4, 8, 15 and 22/EOT (Part A) and PODs 4, 8 and

	15/EOT (Part B) without receiving rescue medication; • Proportion of subjects with flare grade = 0 at PODs 4, 8, 15 and 22/EOT (Part A) and PODs 4, 8 and 15/EOT (Part B) without receiving rescue medication • Visual acuity (ETDRS Best corrected Visual Acuity by pinhole method)

3. STUDY DESIGN

3.1. Study Design Overview

This is a Phase 2a, 2-part study (designated Parts A and B) that will evaluate APP13007 dose strength and dosing frequency in a randomized double-masked fashion for comparison to the respective matching vehicle placebo. Part A (0.05% BID regimen) will be conducted first.

Part A:

Approximately 42 subjects who experience postoperative inflammation on the first day following routine, uncomplicated, cataract surgery and who meet all eligibility criteria will be randomized to one of two study treatments in an approximate 1:1 ratio to receive either Treatment 1 or Treatment 2 in a double-masked fashion (with sufficient number of subjects enrolled to allow approximately a total of 40 subjects, 20 per treatment, to complete dosing and study procedures through POD15).

- Treatment 1: 1 drop 0.05% APP13007 BID (morning and evening) for 21 days to the operated eye
- Treatment 2: 1 drop matching vehicle placebo BID (morning and evening) for 21 days to the operated eye

Following completion of the POD22 visit (i.e., End-of-Treatment (EOT) visit) for all subjects at all sites in Part A, Part B (0.05% and 0.1% along with respective matching vehicle placebo, BID regimen for 3 days followed by QD regimen for 11 days) will be opened for randomization.

See Section 3.3 for a detailed description of the process for progressing from Part A to Part B.

Part B:

Approximately 84 subjects who experience postoperative inflammation on the first day following routine, uncomplicated, cataract surgery and who meet all eligibility criteria will be randomized to one of four study treatments in an approximate 1:1:1:1 ratio to receive Treatment 3, Treatment 4, Treatment 5 or Treatment 6 in a double-masked fashion (with sufficient number of subjects enrolled to allow approximately a total of 80 subjects to complete dosing and study procedures, approximately 20 per treatment, through POD15):

- Treatment 3: 1 drop 0.05% APP13007 BID (morning and evening) for 3 days (PODs 1, 2 and 3) followed by 1 drop 0.05% APP13007 QD (morning) for 11 days (PODs 4 through 14) to the operated eye

- Treatment 4: 1 drop 0.05% matching vehicle placebo (0.05% APP13007 vehicle) BID (morning and evening) for 3 days (PODs 1, 2 and 3) followed by 1 drop

matching vehicle placebo QD (morning) for 11 days (PODs 4 through 14) to the operated eye

- Treatment 5: 1 drop 0.1% APP13007 BID (morning and evening) for 3 days (PODs 1, 2 and 3) followed by 1 drop 0.1% APP13007 QD (morning) for 11 days (PODs 4 through 14) to the operated eye

- Treatment 6: 1 drop 0.1% matching vehicle placebo (0.1% APP13007 vehicle) BID (morning and evening) for 3 days (PODs 1, 2 and 3) followed by 1 drop matching vehicle placebo QD (morning) for 11 days (PODs 4 through 14) to the operated eye

Alternatives to Planned Dosing Regimens in Part B: Based on the results from Part A, Part B may only enroll subjects into two of the treatment arms (either Treatments 3 and 4 or Treatments 5 and 6) or alternatively as shown in Section 3.3. Sites will be notified of a change in treatments in a communication when announcing the opening of randomization for Part B (Section 3.3). In addition, the IRB and FDA will be notified of any change in the planned treatments in Part B of the study.

3.2. Study Visit Overview

This study will include up to 8 clinic visits (including the surgery day) over a range of 29 to 57 days in Part A, or 7 clinic visits (including the surgery day) over a range of 24 to 51 days in Part B. Subjects will provide signed informed consent prior to the conduct of any study procedures or discontinuation of any medications related to this study. Screening will occur between 28 to 1 day(s) prior to surgery and subjects who meet preoperative screening inclusion/exclusion criteria will be entered into the study. 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 (Table 1). At Surgery/Day 0, subjects will undergo routine cataract surgery via phacoemulsification and posterior chamber intraocular lens (PCIOL) implantation according to the Investigator's normal procedures. Post-Operative Day 1/Randomization (POD1) will occur on the day following surgery. Subjects who continue to meet eligibility criteria will be randomized as described in Section 3.1. Following randomization (POD1), the first dose of study drug will be instilled into the study (operated) eye in the clinic under the supervision of Investigator or designee. Subjects will be instructed to return to the clinic to be evaluated at POD4 (± 1 day), POD8 (± 1 day) and POD15 (± 1 day in Part A and +1 day in Part B).

In Part A of the study, dosing with study drug will continue for 21 days. Subjects will be reminded to bring diary card to each scheduled clinic visit. On POD21, subjects will be contacted by site staff to remind them to administer the last dose on POD21 and discontinue dosing on POD22 and to return to the clinic with their study drug bottle and diary card for

End-of-Treatment (EOT) evaluations on POD22 (+ 1 day). Following study procedures on POD28, subjects will be released from the study (EOS).

In Part B of the study, dosing with study drug will continue for 14 days. Subjects will be reminded to bring diary card to each scheduled clinic visit. On POD14, subjects will be contacted by site staff to remind them to administer the last dose on POD14 and discontinue dosing on POD15 and to return to the clinic with their study drug bottle and diary card for End-of-Treatment (EOT) evaluations on POD15 (+1 day). Following study procedures on POD22, subjects will be released from the study (EOS).

A summary of study events is provided in Table 2A and Table 2B (Schedule of Events for Part A and Part B, respectively) and a study schematic for Part A and Part B is provided in Figure 1 (Study Schematics).

3.3. Progression from Part A to Part B

Part A (0.05% APP13007 or matching vehicle placebo BID regimen) will be conducted first.

The decision to progress to Part B will be based on ongoing safety review and futility analysis by the Data Review Group (Study Medical Monitor, the Sponsor Medical Monitor, and the Sponsor statistician). Review of key data (ACC count, pain score, IOP, the number of subjects rescued and AEs) will occur on an ongoing basis in a masked fashion. Once approximately 40 subjects in Part A have completed POD15 evaluation, all available key data will be reviewed by the Data Review Group. If masked data do not provide a clear indication that it is reasonable to progress to Part B, e.g., due to safety concerns or lack of efficacy, limited unmasked data will be used to determine whether or not to progress to Part B. For the unmasked data review, the frozen database of ACC count, pain score, IOP, subject rescue and AE data through POD15 will be reviewed by the Sponsor Medical Monitor and the Sponsor statistician only. If unmasking is required for decision-making, the integrity of the study assessments and objectives will be maintained by limiting access only to the unmasked data to these two individuals in the Data Review Group who are not involved in the study conduct. (*Note: Study Medical Monitor will remain masked until completion of the study and database lock, except as indicated in Section 5.3*). A recommendation will be made to the Sponsor on whether to proceed to Part B. The Sponsor management is responsible for determining if the study should progress to Part B as shown in Section 3.4.

If applicable, the Institutional Review Board (IRB) will be informed in a memo of the unmasking of frozen key data that are required before a decision is made to progress to Part B.

Notes:

1. *Part B will be opened for Screening only when approximately 40 subjects have completed POD15 in Part A.*

2. *In Part B, randomization to study drug will only occur after all subjects in Part A have completed EOT/POD22.*

3.4. Alternative options to Planned Dosing Regimens in Part B

Based on the recommendation resulting from analysis of data from Part A, the Sponsor will determine whether one of the following options will be adopted regarding Part B:

1. Part B is opened for Screening as planned with the planned four treatment arms (4 treatments enrolling approximately 84 subjects).

2. Part B is opened for Screening, but only tests 0.05% APP13007 and matching vehicle placebo administered BID for 3 days and then QD for 11 days (2 treatments enrolling approximately 42 subjects).

3. Part B is opened for Screening but tests only 0.1% APP13007 and matching vehicle placebo administered BID for 3 days and then QD for 11 days (2 treatments enrolling approximately 42 subjects).

4. Part B is opened for Screening but tests 0.05% APP13007 and matching vehicle placebo administered BID for 14 days (2 treatments enrolling approximately 42 subjects).

5. The study is stopped after completion of Part A.

The sites, IRB and FDA will be informed of any changes to the planned conduct of Part B before the changes are implemented.

3.5. Rationale for Study Design

3.5.1. Rationale for Number of Subjects to be Enrolled

This is an exploratory Phase 2a study; the number of subjects that are planned to be enrolled (n=21/treatment arm) is based on feasibility and integrated literature data analysis. Based on enrollment data from previous trials in this indication, the expected dropout rate is < 5%, and it is anticipated that approximately 20 subjects will complete dosing and study procedures through POD15, ie., the cutoff day of the primary efficacy endpoint.

3.5.2. Rationale for Use of ACC Absolute Count versus Grade

The use of the absolute ACC as the primary efficacy endpoint, rather than an ACC grading system, provides a wider dynamic range of this quantitative variable (e.g., from 0 to 30) as compared to grading (from 1 to 4) to assess the effect of dose strength and dose regimen of APP13007. Furthermore, the two measurements of ACC at each study visit will allow some estimation of the intra-subject variability of this quantitative endpoint.

It is anticipated that the FDA-specified endpoint of ACC grading will be used in pivotal trials, however, the absolute ACC count data collected in this Phase 2a exploratory trial will be invaluable in assessing the effectiveness of APP13007 via various strengths/dosing regimens in a small population and will be critical to informing the study design of pivotal trials of APP13007. In addition, the absolute ACC data can readily be converted to the grading system generally used by pivotal trials for this indication in the statistical analysis plan.

3.5.3. Rationale for Dose Strength and Dosing Regimen

[redacted]

These data indicate that the 0.05% and 0.1% formulations of APP13007 have the potential to reduce inflammation and pain after ocular surgery. [redacted]

[redacted]n Part A of the study, the lower 0.05% strength of APP13007 will be evaluated in a BID regimen to assess the impact on safety and efficacy endpoints. If there are no safety concerns that would impede further progression and the primary efficacy endpoint (ACC count) suggests that APP13007 is more effective than the matching vehicle placebo, then, 0.05% and 0.1% strengths of APP13007 will be evaluated using a QD regimen in Part B of the study as described in Section 3.4.

3.5.4. Rationale for Use of Two Placebo Formulations

This small exploratory study includes matching vehicle placebo rather than an active control to permit greater differentiation between treatments.

[redacted]

4. STUDY POPULATION

4.1. Number of Subjects

A maximum of approximately 126 subjects who have undergone routine, uncomplicated cataract surgery and have >10 and ≤ 30 anterior chamber cells in the study eye (operated eye) at POD1 will be enrolled such that approximately 120 subjects will complete the study (approximately 20 subjects per study treatment).

4.2. Inclusion Criteria

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

At the Screening Visit:

1. Provide signed and dated informed consent
2. Age ≥ 50 years at time of informed consent
3. If female, be of non-childbearing potential. 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) or an FSH greater than 40 IU/L. Note: FSH will not be required if subject reports amenorrhea for > 12 months. (Pregnant women or nursing mothers are excluded from the study.)
4. Expected to undergo unilateral uncomplicated cataract extraction via phacoemulsification and posterior chamber intraocular lens (PCIOL) implantation in one eye (designated the 'Study Eye')
5. In the Investigator's opinion, have Early Treatment Diabetic Retinopathy Study (ETDRS) estimated potential of 0.7 (20/100) or better in study eye (best corrected visual acuity by pinhole method).
6. 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

At Postoperative Day (POD) 1/ Day of Randomization:

7. Have undergone unilateral cataract extraction via phacoemulsification and posterior chamber intraocular lens (PCIOL) 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 results
8. Have > 10 and ≤ 30 cells in the anterior chamber. (Note: Cell count should be taken twice at each visit and both counts need to meet eligibility.)
9. Have an IOP ≤ 30 mmHg.

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
2. Have an ACC > 0 or any evidence of intraocular inflammation (e.g., flare) in either eye as found during the slit lamp examination at the Screening visit
3. Have a score > 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 would likely affect wound healing and/or resolution of inflammation after cataract surgery.
6. Have suspected or known malignancy or received antineoplastic therapy within the 12 months prior to the Screening visit. 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. Use of treatments for macular degeneration including Eylea® (aflibercept), Avastin® (bevacizumab), and Lucentis® (ranibizumab)
8. Use of systemic or topical anti-inflammatory agents, analgesics/pain relievers (including opioids, narcotics, NSAIDS, aspirin, acetaminophen and other pain medications) or immunomodulating agents systemically or in either eye (including Lifitegrast (Xiidra)) from the washout period until the End-of-Study (EOS) visit. Note: Medication for anesthesia and pain control at surgery are allowed on the day of surgery only. (See Section 5.4.2.)
9. Use of any of the prohibited medications (see Section 5.4.2) within a time period prior to surgery that is less than the minimum 'washout' period noted in the table. [NOTE: These medications may not be used after randomization through the EOS visit.]
10. Have an intraocular pressure (IOP) < 5 mmHg or > 22 mmHg in either eye at the Screening visit.
11. Have a history of documented repeated elevated IOP
12. History of herpes keratitis in the study eye
13. Have active corneal abrasions or ulcers in the study eye
14. Have active or a history of chronic or recurrent inflammatory eye disease (e.g., iritis, scleritis, uveitis, iridocyclitis, rubeosis iridis) in the study eye

15. 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 blepharitis in the study eye
16. Have corneal dystrophies or dysthyroid ophthalmopathy in the study eye
17. Have uncontrolled and clinically significant dry eye syndrome in the study eye (mild dry eye with the use of artificial tears are allowed)
18. Have proliferative diabetic retinopathy (PDR), significant compromised macular function; significant macular diseases; clinically significant macular edema (CSME); or a history of cystoid macular edema in the study eye
19. Have had corneal or retinal surgery (laser or incisional) in the study eye within 6 months of the Screening visit, or be planning to have laser or incisional surgery during the study period in the study eye (other than cataract surgery)
20. Have surgery planned or scheduled for the contralateral eye during the study
21. 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 or the normal healing process)
22. 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
23. 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 related to cataract surgery, lid scrubs for mild blepharitis, or artificial tears for the management of dry eye. Note: subjects requiring IOP lowering medications pre-surgery for ocular hypertension or glaucoma are excluded
24. Have the potential for ocular hemorrhage in the study eye that may interfere with evaluation of post-surgery inflammation
25. 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
26. Have a planned use of or use anterior capsule staining for capsulorhexis (i.e., trypan blue) during cataract surgery
27. Have previously been enrolled in this clinical study, or have planned to participate in another clinical trial during the duration of this study

28. Have participated in another clinical study or received any investigational product within the past 28 days prior to the Screening Visit
29. Have any other condition that the Investigator determines should exclude the subject from the trial
30. 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. STUDY DRUG AND TREATMENTS

5.1. Study Drug Administration

5.1.1. Study Drug Description

Dosage Form, Appearance, Packaging and Labeling

[redacted] The nanosuspension of APP13007 and matching vehicle placebo has the appearance of a translucent 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-201
- Bottle number
- Subject Number
- Study Eye: R or L
- Content: 0.05% **or** 0.1% 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

Bulk supplies of individual dropper bottles packaged with proper labels will be shipped to each study site from a central drug product packaging and distribution vendor. Sufficient quantity of each dose strength of APP13007 and matching vehicle placebo will be provided

to each site to accommodate the enrollment rate. 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

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 per 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 available or scheduled visit.

If a subject loses the single bottle of study drug or if it becomes compromised (e.g., 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 eCRFs.

If the subject loses the bottle of study drug or it is compromised after the POD15 visit in Part A, the subject will not receive a replacement bottle. Loss of study drug bottle should be noted in the eCRF. In this instance, failure to dose after loss or compromise of study drug will not be considered a protocol deviation.

Subject Diaries

A study diary will be given to each subject at the visits indicated on the Schedule of Events (Table 2A or Table 2B). 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. The subject will also use the diary to verify that study drug was administered a minimum of 5 minutes prior to administration of other eye medications in the study eye, and the subject will record the date and time of dosing of the study drug as well as other eye medications administered to the study eye. In the event that study drug is inadvertently instilled into the non-study eye, it will be documented on the diary including the date/time of its occurrence as well as the number of drop(s) instilled.

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.

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 it is confirmed 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. Subjects who are not greater than or equal to 75% compliant with dosing of study drug will not be included in the Per-Protocol Population.

Study Treatments

The treatments for Part A are as follows:

- Treatment 1: 1 drop 0.05% APP13007 twice daily (BID) (morning and evening) for 21 days to the operated eye
- Treatment 2: 1 drop matching vehicle placebo BID (morning and evening) for 21 days to the operated eye

The planned treatments for Part B are as follows:

- Treatment 3: 1 drop 0.05% APP13007 BID (morning and evening) for 3 days (PODs 1, 2 and 3) followed by 1 drop 0.05% APP13007 QD (morning) for 11 days (PODs 4 through 14) to the operated eye
- Treatment 4: 1 drop 0.05% matching vehicle placebo (0.05% APP13007 vehicle) BID (morning and evening) for 3 days (PODs 1, 2 and 3) followed by 1 drop matching vehicle placebo QD (morning) for 11 days (PODs 4 through 14) to the operated eye
- Treatment 5: 1 drop 0.1% APP13007 BID (morning and evening) for 3 days (PODs 1, 2 and 3) followed by 1 drop 0.1% APP13007 QD (morning) for 11 days (PODs 4 through 14) to the operated eye
- Treatment 6: 1 drop 0.1% matching vehicle placebo (0.1% APP13007 vehicle) BID (morning and evening) for 3 days (PODs 1, 2 and 3) followed by 1 drop matching vehicle placebo QD (morning) for 11 days (PODs 4 through 14) to the operated eye

Study Drug Dosing

Study drug (APP13007 and 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 study drug. One bottle will be dispensed to each subject throughout the study. Study drug will be self-administered either once or 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 attempt to instill a 3rd drop.

Study drug should be administered once or twice daily depending on the treatment assigned. 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.

The first dose of study drug should be applied 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 applied by the subject a minimum of 6 hours later. For all other days when study drug is instilled twice daily, the first dose should be applied in the morning and the second dose applied a minimum of 6 hours, but preferably 8 to 12 hours, later. For all study days when study drug is instilled QD in Part B, the dose should be applied in the morning. The number of drops per dose 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 study drug 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 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. 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, quantity, subject number, number of bottle, and each bottle ID number dispensed, lost or

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

As described in Section 3.3, if necessary, the Sponsor Medical Monitor and the Sponsor statistician may review frozen and unmasked data in the event that unmasking of key data (ACC count, pain score, IOP, the number of subjects rescued and AEs) is required to make a decision on whether to progress to Part B. If unmasking is required for decision-making, the integrity of the study assessments and objectives will be maintained by limiting access to the unmasked data to only the two individuals in the Data Review Group (Sponsor Medical Monitor and Sponsor Statistician) who are not involved in the study conduct. 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 uploaded into the EDC system. 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 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 due to an SAE, it will be made available to the Investigator, the Data Review Group and the Sponsor. Other personnel involved in the monitoring or conduct of this study will remain masked.

5.4. Concomitant Therapy and Rescue Medication

All 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 in the subject's source documents as well as in the ConMeds page of the eCRF. Information regarding the duration of treatment (including start and stop dates), dose, frequency, site of dosing (right eye, left eye, both eyes, non-ocular) and the reason why the concomitant medication is being taken will be recorded.

Note: The information on 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 not responding adequately to the study drug based on the Criteria for Rescue (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 the annotation indicating that the medication was used for rescue.

Rescued subjects will be considered as treatment failures, but the need for rescue therapy will not be considered an adverse event (AE). Rescued subjects should not be withdrawn from the study, but rather followed to resolution of signs and symptoms 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 through the EOS visit. 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. Medications for anesthesia and pain control are allowed on the day of surgery only.

5.4.3. **Prohibited Medications and Minimum Washout Periods**

Medication	**Minimum 'Washout' Period Prior to Day 0 (Day of Surgery)**
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 medication dosing; (ii) different restrictions for ocular products are listed below.	2 days
Topical ocular corticosteroids	7 days
Topical ocular nonsteroidal anti-inflammatory drugs (NSAIDs)	7 days
Topical eyelash growth medications	7 days
Systemic acetaminophen, NSAIDS, acetylsalicylic acid (aspirin), or other systemic anti-inflammatory agents (including Lifitegrast (Xiidra)) *Note: (i) Use of acetylsalicylic acid (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*	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
Inhaled and/or nasal corticosteroids	14 days
Systemic (oral, injectable) corticosteroids	28 days
Systemic analgesics/pain relievers (e.g., gabapentin, pregabalin, opioids) *Note: Use of an opioid analgesic during cataract surgery is allowed.*	14 days
Medications for benign prostatic hypertrophy (BPH) (e.g., Tamsulosin, silodosin, alfuzosin, finasteride)	28 days
Other study drugs or investigational products	28 days
Topical or systemic cyclosporine	60 days
Intraocular treatment with corticosteroid - dexamethasone drug delivery system	90 days after implantation
Intraocular treatment with corticosteroid – any other intravitreal injection	90 days after injection
Alterations of the dose of anticholinergics and antidepressants (except 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

6. STUDY CONDUCT

Refer to the Schedule of Events (Table 2A or Table 2B) for the list of study procedures/assessments to be conducted at each visit.

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. Screening and Day of Surgery

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 2A or Table 2B). All ocular assessments must be performed in both eyes at the Screening visit.

If surgery is not performed on the previously 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 was repeated/redone. Subjects who fail to qualify for the study on POD1 may not be rescreened.

Subjects who sign the informed consent form (ICF) and have study procedures/assessments, but do not meet eligibility criteria any time prior to randomization on POD1 will be considered as screen failures. Subjects will be considered as being enrolled into the study once they are randomized and receive study drug on POD1.

After screening exam and before surgery, the subject will undergo a pre-surgery medical assessment to determine that the subject is a suitable candidate for surgery, in addition, the routine medication list prescribed by the cataract surgeon should be reviewed to rule out prohibited medications (Table 1, Section 5.4.2).

Day of Surgery (Day 0)

Prior to surgery, the surgeon's routine medication list should be reviewed for the use of prohibited medications. Surgery should preferably be scheduled in the morning to accommodate BID dosing on POD1.

On Day 0, the surgeon will perform his/her routine cataract surgical procedure using phacoemulsification and implantation of a posterior chamber intraocular lens (PCIOL) 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).

Following surgery, the following procedures 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.

- Medications routinely administered prior to and following cataract surgery will be recorded in the source documents and as concomitant medications (ConMeds) in eCRF. These medications will be indicated for routine cataract surgery and should not be associated with treatment for AEs. If a medication is administered due to an AE, the medication (and AE) must be entered on the appropriate pages of the eCRF. NOTE: Acetaminophen may be administered as needed pre and post-operatively on the day of surgery.

- AEs and ConMeds should only be recorded on Day 0 if they result in disqualification (i.e., screen failure) of the subject; otherwise, the AEs and ConMeds applicable to Day 0 should be recorded on POD1 when the subject returns at the POD1 visit.

- Schedule the subject to return to the clinic on the following day POD1 in the morning (as much as possible).

6.2.2. Postoperative Day 1 (POD1) – Day of Randomization

Subjects will return to the clinic for the next 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 eligible subjects. The first dose of study drug is to be administered under supervision at the study site, and the second dose can be administered at home.

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 (SRM) 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. All assessments and blood draw for safety labs and blood cortisol level on POD1 must be done prior to Randomization. The site should administer the first dose of study drug to the subject in the clinic before dispensing the assigned study drug bottle along with written dosing instruction and diary to the subject.

Study drug dosing/administration including handling bottle replacement, diary/dosing compliance and the list of treatments are presented in Section 5.1.2. Subjects are reminded to bring diary to each clinic visit in order for site staff to review dosing compliance. Note that study drugs in Part A will be administered BID for 21 days (POD1 to POD21), while in Part B, study drugs will be administered BID for the first 3 days and then QD thereafter for the duration of the treatment period in the study, i.e., for 11 days (POD4 to POD14).

6.2.3. **PODs 1 through 15**

All assessments will be performed as shown in the Schedule of Events (Table 2A and Table 2B).

Note that blood samples for safety laboratory assessments and cortisol level will only be collected in Part A. Also note that ocular assessments will be performed only in the operated, study eye at PODs 1, 4, 8, 15 and 22 visits in Part A and PODs 1, 4, 8 and 15 in Part B.

Note: Key data from visits up to and including the POD15 visit (ACC, pain score, IOP, number of subjects rescued and AEs) may be used to make decision of opening of Part B for randomization. Therefore, to avoid delay in progressing to Part B, data from all visits up to the POD15 visit (and any other subsequent completed visits) should be entered into the eCRF as soon as possible as the monitor will plan to monitor each study site for preparation of freezing all data collected up to POD15, and including any available data collected after POD15. At a minimum, key data (ACC, pain score, IOP, number of subjects rescued and AEs) up to POD15 must be cleaned and frozen in anticipation of the potential for an unmasked review of these key data points by the Sponsor Medical Monitor and Sponsor statistician.

6.2.4. **Day of Subject Contact: POD21 in Part A orPOD14 in Part B**

POD21 is the last day of dosing for the two treatments in Part A. POD14 is the last day of dosing for all treatments in Part B. Site personnel will contact the subject to remind him/her not to take study drug on POD22 (Part A) or POD15 (Part B) and to bring the bottle of study drug and diary back to the clinical site at the POD22 visit (Part A) or POD15 visit (Part B).

Site personnel will contact the subject using the subject's preferred reliable method of communication, e.g., telephone call, cell phone text or email. Efforts by the site staff must be made to ensure that the subject receives and acknowledges the receipt of the message.

Any AEs reported to the site during the POD21 (Part A) or POD14 (Part B) contact must be recorded in the source documents. Further assessment of any reported AEs may require an Unscheduled Visit on POD21 (Part A) or POD14 (Part B) if medically significant or they may be assessed, as appropriate, during the POD22 visit (Part A) or POD15 visit (Part B).

6.2.5. **End of Treatment (EOT): POD22 in Part A or POD15 in Part B**

POD22 is the End-of-Treatment (EOT) visit in Part A. POD15 is the EOT visit in Part B. All ocular assessments must be performed on the operated, study eye only. Blood will be drawn for safety labs and cortisol level in Part A only.

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

6.2.6. **End of Study (EOS): POD28 in Part A or POD22 in Part B**

The final EOS safety follow-up visit will occur on POD28 (± 1 day) or approximately 7 days (± 1 day) following the EOT visit in Part A or on POD22 (± 1 day) or approximately 7 days (± 1 day) following the EOT visit in Part B. Blood will be drawn for safety labs in Part A only.

All ocular assessments must be performed on both eyes. If a subject had a cataract in the non-operated eye at the Screening visit, the Investigator should make an assessment whether there has been a change in the size or composition of the cataract and record this in the source document and eCRF.

Subjects with ongoing AEs or SAEs should be handled as discussed in Section 8.

6.2.7. **Subject Early Termination**

Subjects who are terminated from the study early, but the rescue criteria in Section 9.4.1 are not met, should have POD28/EOS (Part A) or POD22/EOS (Part B) assessments performed at the time of termination, or as soon thereafter as possible. At early termination the ocular assessments are to be performed on both eyes.

6.2.8. **Unscheduled Visits**

Any visits or procedures 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.

6.3. Study Visit Schedule for Rescued Subjects

Subjects who meet the criteria for rescue presented in Section 9.4 should discontinue study drug and receive rescue medication. Subjects who are rescued should continue in the study as indicated in Table 5A or Table 5B below. Note that the assessments in the check box under each visit in the Schedule of Events (Table 2A or Table 2B) with a (R) next to "X" indicates that the assessments should be performed on rescued subjects at the indicated visits. Table 5A or Table 5B provides an overview of the study visits and assessments required for rescued subjects depending on when the rescue occurs during the study. It is important to note that (i) subjects rescued on or before POD16 in Part A will be considered as having completed the study before POD28 as indicated by 'na' in Table 5A and (ii) subjects rescued on or before POD9 in Part B will be considered as having completed the study before POD22 as indicated by 'na' in Table 5B.

Table 5A: Visits for Rescued Subjects (Part A)

Time of Rescue	Protocol Defined Study Visits				
	POD4 (±1day)	**POD8 (±1day)**	**POD15 (±1day)**	**POD22 (+1day)**	**POD28 (±1day)**
PODs 2-5	Conduct EOT (POD22) assessments at time of rescue but no later than POD4/5	Complete POD8 assessments in Table 2A marked with an (R)	Complete EOS (POD28) assessments and terminate subject from the study	na	na
PODs 6-9	per protocol	Conduct EOT (POD22) assessments at time of rescue but no later than POD7/8/9	Complete EOS (POD28) assessments and terminate subject from the study	na	na
PODs 10-16	per protocol	per protocol	Conduct EOT (POD22) assessments at time of rescue but no later than POD14/15/16	Complete EOS (POD28) assessments and terminate subject from the study	na
PODs 17-22	per protocol	per protocol	per protocol	Complete EOT (POD22) assessments at time of rescue but no later than POD22/23	Complete EOS (POD28) assessments and termination subject from the study

na = not applicable

Table 5B: Visits for Rescued Subjects (Part B)

Time of Rescue	Protocol Defined Study Visits			
	POD4 (±1day)	POD8 (±1day)	POD15 (+1day)	POD22 (±1day)
PODs 2-5	Conduct EOT (POD15) assessments at time of rescue but no later than POD4/5	Complete POD8 assessments in Table 2B marked with an (R)	Complete EOS (POD22) assessments and terminate subject from the study	na
PODs 6-9	per protocol	Conduct EOT (POD15) assessments at time of rescue but no later than POD7/8/9	Complete EOS (POD22) assessments and terminate subject from the study	na
PODs 10-16	per protocol	per protocol	Conduct EOT (POD15) assessments at time of rescue but no later than POD15/16	Complete EOS (POD22) assessments and terminate subject from the study

na = not applicable

6.4. Subject Withdrawal or Early Termination

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 request is 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 also 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:

1. A subject is rescued or withdrawn from the study because the investigator considers that the subject requires alternative medication (see Section 9.4.1 for clarification of 'rescued' and 'withdrawn').

2. 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.

3. 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.

4. Any woman who becomes pregnant while participating in the study. Information on the pregnancy and outcome will be requested by the Investigator.

5. Subject's continued failure to comply with protocol requirements or study related procedures after being instructed on correctional procedures by the Investigator or site personnel.

6. Termination of the study by the Sponsor, FDA, or other regulatory authority.

In the event that termination of a randomized subject is necessary ('withdrawn' subject), the Investigator should make every attempt to have the subject complete POD28/EOS assessments (Part A) or POD22/EOS assessments (Part B) as soon as possible (*Note: the ocular assessments need to be performed on both eyes*) (Section 6.2.7, Table 2A or Table 2B). For the management of 'rescued' subjects see Section 9.4.1. The reason for premature termination of a subject should be recorded in the source document and entered in the eCRF.

Subjects who is withdrawn or terminated early from the study will not be replaced.

6.5. Study Discontinuation Criteria

6.5.1. Early Discontinuation of the Study or Change in the Conduct of Part B

The trial or parts of the trial 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.

Based on the results from Part A, Part B may only enroll subjects into the alternative treatment options shown in Section 3.4. The sites, IRB and FDA will be notified of the change in the planned treatments for Part B in a written communication when announcing the opening of Part B for randomization.

6.5.2. 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 protection of the safety and wellbeing of a subject.

7. STUDY ASSESSMENTS AND PROCEDURES

7.1. Demography and Medical History

Subjects' demographic information will be collected and recorded. A complete systemic and ocular medical history will be taken at screening. Interim history will be taken at the remaining visits.

7.2. Efficacy Assessments

Note that these assessments are applied to the Study (or Operated) Eye Only.

- Slit Lamp Biomicroscopy examination including assessment of anterior chamber inflammation, including anterior chamber cell count (number of cells), which will be counted twice for each subject at each visit; and grading of anterior chamber flare on a 0-4 Scale
- Subject-Rated Ocular Pain Assessment (0-5 Scale)
- Use of Rescue therapy
- ETDRS Assessment of Best Corrected Visual Acuity by Pinhole Method

7.2.1. Procedures for Efficacy End-Point Assessments:

Subject-Rated Ocular Pain Assessment

Ocular pain is defined as throbbing, or aching, and is graded by subjects on a 5-point scale. On the assessment days, the subjects will be required to subjectively rate their pain in the study eye at the time of the visit. Each subject will be asked to subjectively rate their pain based on the scale as follows:

0 = None: Absence of 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.

Anterior Chamber Cell Count and Grading of 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 twice 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.

1. Assessment of ACC will be performed by counting twice the number of cells seen in the field during the examination (see Section 7.3.3). There is no mandatory requirement of the minimum or maximum time interval between the two counts, but it is **recommended** that the two counts are performed within approximately 2 minutes of each other. Both counts will be recorded in the eCRF along with the time of each count. **Note: If >30 cells are observed, it will be recorded as >30 rather than obtaining the actual number of cells.**

2. Assessment of ACF will be assessed using the following Grading Scheme:

   Grading Scheme – Anterior Chamber Flare

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)

7.3. Safety Assessments

Note that these assessments are applied to both eyes (at Screening, POD28/EOS (Part A) or POD22/EOS (Part B) or early termination) or just the Study (or Operated) eye as indicated in Table 2A or Table 2B (Schedule of Events).

Safety parameters include:

- Assessments of AEs
- ETDRS Assessment of Best Corrected Visual Acuity by Pinhole Method
- Slit Lamp Biomicroscopy including assessment of the following signs of inflammation: corneal edema, ciliary flush, bulbar conjunctival injection
- IOP Measurement
- Dilated Ophthalmoscopy

7.3.1. Assessment of Adverse Events

All AEs spontaneously reported by the subject and 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 should not be addressed as AEs unless the complaint is outside the normal limits for cataract surgery or is associated with clinical sequelae (i.e., adverse slit lamp examination finding). Ocular complaints associated with and expected as a result of the surgery, that are not recorded as AEs in the eCRFs will be recorded as comments in the source documents.

See Section 8 for information on how to record AEs and how to capture relatedness to study procedures (including cataract surgery) or study drug.

7.3.2. 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 all study visits except the day of surgery. 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 at each visit consistently. 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 is 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 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.

7.3.3. Slit Lamp Biomicrocopy

The number of anterior chamber cells will be counted twice and anterior chamber flare assessed as described in Section 7.2.1.

In addition to the assessment of the anterior chamber cells and flare, the following parameters will be evaluated using the following scales during the slit lamp exam:

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

Lens Pathology (in the contralateral/non-surgical eye) will be evaluated as:

- Normal; no opacity in the lens
- Abnormal; existing opacity in the lens; aphakic or pseudophakic eyes or other abnormal findings.

7.3.4. 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 all study visits except the surgery visit as indicated in the Schedule of Events (Table 2A or Table 2B).

7.3.5. **Dilated Ophthalmoscopy**

A dilated fundus examination will be performed according to the Investigator's standard technique and will occur as indicated in the Schedule of Events (Table 2A or Table 2B). The Investigator should evaluate the vitreous, retina, macula, choroid, and optic nerve with cup/disc ratio and will note normal/abnormal findings.

The Investigator will determine whether or not abnormalities observed at the Screening visit would exclude a subject from study participation.

If a subject has a cataract in the non-operated eye at the Screening visit, the Investigator should make an assessment whether there has been a change in the size or composition of the cataract at the EOS/POD28 visit (Part A) or EOS/POD22 visit (Part B) or at early termination. This information will be recorded in the source document and eCRF.

8. 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.

Note:

- *Reporting of AEs that may or may not be related to the ocular surgical procedure depends on their severity:*
  - *i. An AE that the Investigator considers to be within what is normally expected for cataract surgery will be recorded in a table in the source documents and no further reporting is required.*
  - *ii. An AE that the Investigator considers to be outside what is normally expected for cataract surgery or is associated with clinical sequelae will be recorded in the full AE page in the source documents and also in the eCRF,*
- *Rescued subjects are considered to be treatment failures, and rescue itself is not considered an AE.*
- *Adverse events occurring in rescued subjects should be reported in the eCF.*
- *An anterior chamber cell count > 30 on POD1 that leads to disqualification of the subject prior to Randomization should be reported as an AE.*
- *An IOP > 30 mmHg after Randomization should be reported as an AE.*
- *An IOP ≥ 24 mmHg AND an IOP increase ≥ 10 mmHg from pre-dose baseline should be reported as an AE.*

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 after the study drug dosing is initiated. For the purpose of this study, a TEAE may be related to the ocular surgical procedure and/or to the initiation of the study drug.

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),
- inpatient 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 inpatient hospitalization, or the development of drug dependency or drug abuse.

A suspected unexpected serious adverse reaction (SUSAR) is defined as a 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 8 and the worst grade documented.

Table 6: 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 7 and Table 8.

Table 7: 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 8: 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 patient'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.

8.3.3. Expectedness

An AE or a suspected adverse event (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 Section 1.4.1 and 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 dose strength or dosing frequency of 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 discontinued 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

Overdose:

Dosing compliance will be assessed via a daily dosing diary completed by the subject and reviewed by the designated site personnel. If the subject reports over instillation of study drug, exceeding more than one drop (or equivalent) into the study eye per dose (further explained in Note below) or instillation of the study drug more than twice a day (when dosing BID) or more than once daily (when dosing QD) on two consecutive days or longer, this will be classified as an overdose event and a protocol deviation.

Note: As described in Section 5.1.2, 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. This will not be considered a protocol deviation or an overdose event. However, if the subject administers a third drop into the conjunctival sac, no matter if the second drop is missed, then this will be recorded as an overdose.

Under-dose:

Under-dosing will not be reported as a deviation until the subject has missed 2 consecutive doses (i.e. 2 consecutive missed doses in 1 day during BID dosing or 2 consecutive missed doses over 2 days during QD dosing).

8.6. Pregnancies

All female subjects enrolled into the study must be of non-childbearing potential. Therefore, no pregnancies should occur. 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 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, whether or not considered causally related to the investigational drug product, or to the study procedure(s). All SAEs will be recorded in the eCRF. SAEs will be recorded from the time of informed consent.

All Serious Adverse Events (SAE) must be reported, whether or not considered related to the study drug, on a separate SAE Report Form. All SAEs will also be recorded in the eCRF. The Sponsor will be responsible for reporting all SAEs to regulatory authorities and ethics committees (see NOTE below) in accordance with ICH Good Clinical Practice and local regulations. As soon as the Investigator is aware of a potential SAE he/she should contact [redacted] by fax or e-mail 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 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 Drug Safety Navigator.

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 site will report it to the IRB.

8.7.2. **Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)**

A suspected serious adverse reaction is any serious adverse event for which there is a reasonable possibility that the investigational product caused the adverse event. A serious adverse reaction 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.

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 15 calendar 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 Drug Safety Navigator.

NOTE: The Sponsor will notify the appropriate regulatory agency 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 ICSRs which qualify for expedited and periodic reporting, should be provided in compliance with U.S. Food and Drug Administration (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. SAFETY MANAGEMENT

9.1. Stopping Criteria

- Individual subject: Subjects with an IOP at POD1/pre-randomization > 30 mmHg will not be eligible for randomization and thus not enrolled in the study. After randomization to study drug, subjects with an IOP >30 mmHg may continue the study drug and be treated with IOP lowering medication at the discretion of the Investigator. (Note: use of a prostaglandin-based treatment to lower IOP is prohibited).

- Individual subject: Subjects with an IOP > 30 mmHg after randomization who do not respond to IOP lowering therapy should discontinue study drug and should be treated at the Investigator's discretion. These subjects will continue in the study with scheduled assessments to be performed at each visit until EOS/POD28 (Part A) or EOS/POD22 (Part B).

- Individual subject: In consultation with the Study Medical Monitor, the Investigator should consider whether to stop study drug and rescue a subject with an IOP ≥ 24 mmHg AND an IOP increase ≥ 10 mmHg from pre-dose baseline (both criteria must be met).

- Study Treatments: Part A of the study will be conducted as planned. Key data (ACC, pain score, IOP, number of subjects rescued and AEs) from Part A will be evaluated by the Data Review Group in a masked manner and if necessary by the Sponsor Medical Monitor and Sponsor statistician in a unmasked manner after freezing the key data to determine whether Part B is to be conducted as planned. See Section 3.3 and Section 3.4 for further information on the decision-making process to determine whether Part B is conducted as planned or which alternative treatment option is to be used. The study sites, IRB and FDA will be informed of any changes to the planned treatment arms in Part B of the protocol before the changes are implemented.

- Study: The study can be stopped at any time if deemed necessary by the Sponsor's Medical Monitor in consultation with the Study Medical Monitor due to safety concerns. Additionally, safety will be monitored on an ongoing basis by the Data Review Group via periodic masked review of AEs and other safety endpoints. Specifically, if it is observed that visual acuity worsens by 2 lines at EOS in the treated study eye as compared to 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 4 provide guidance for the Investigator on potential anticipated adverse events that may occur. Any potential 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. If a subject is less than 75% compliant with dosing of study drug, the subject will be included in the 'Intention-to-Treat' analyses, but not in the 'Per Protocol' analyses for efficacy endpoints.

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

9.3. Dosing Interruptions

Investigator is not allowed to modify the dosing regimen due to 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 not more than 1 day due to an AE.

9.4. Rescue and Increased IOP Management

9.4.1. Criteria for Starting Rescue Medication

Any subject not responding adequately to the study drug at any time after randomization on POD1 may be rescued and placed on an appropriate alternative therapy determined by the Investigator. Subjects who, on examination of the anterior chamber, have one or more of the following criteria will be considered 'Rescued' subjects and should be discontinued from study drug dosing and placed on rescue mediation:

1. After randomization, anterior chamber cells count >30 cells.
2. After randomization, an increase in anterior chamber cell count by > 15 cells from POD1/pre-dose baseline.
3. After randomization, ≥2 grade of increase in anterior chamber flare from POD1/pre-dose baseline.

Initiation of rescue medication is at the discretion of the Investigator, following discussion with the Study Medical Monitor, even if none of the above criteria are met. However, it is recommended that the Investigator uses the above criteria to determine when to consider a subject for rescue medication.

Management

Investigators will use clinical judgment to determine the appropriate rescue medication to use and when to withdraw study drug and perform procedures.

While initiation of rescue medication is at the discretion of the Investigator, if one criterion above in Section 9.4.1 is met, the subject should be placed on rescue medication. Subjects not otherwise responding to study drug may be placed on alternative medication at the discretion of the Investigator even if none of the above criteria are met. In the situation where an investigator considers that alternative medication is required, but the above 'Rescue' criteria are not met, the subject is considered to be 'withdrawn' from the study and EOS assessments are to be performed. The choice of alternative medication is at the Investigator's discretion and will be used as directed by the Investigator. Any subject who is rescued based on the criteria in Section 6.3 and who is placed on rescue medication will discontinue the study drug and continue in the study for study assessments as described in Section 6.3.

A subject who is treated with an ocular corticosteroid or other anti-inflammatory product after POD22 (Part A) or POD15 (Part B) will be considered to be a 'Withdrawn' subject.

Rescued subjects will be considered treatment failures, but the need for rescue medication will not be considered as an AE. Rescued or Withdrawn subjects experiencing an AE at the time of rescue/withdrawal will be followed through by the Investigator to stabilization or resolution of the AE or the end of the study (whichever comes last). Rescued/Withdrawn subjects should be followed to resolution of signs and symptoms of an AE or until the Investigator has deemed the subject is stable.

Note:

Clarification of the distinction between 'Rescued' and 'Withdrawn':

i) Process for 'Rescued' subjects:

- *The subject notifies the clinical site and is able to return for an unscheduled visit or scheduled visit before starting rescue medication.*
- *The subject has a visit and the investigator documents that the subject meets one of the rescue criteria. The subject should be rescued. The study drug is stopped and the subject should be started on the investigator's preferred rescue medication.*
    - *EOT assessments are completed at the time of this evaluation and the subject returns for the EOS assessments as shown in Table 5A or Table 5B.*

- *The subject's status is 'Rescued' and the reason for rescue must be one of the rescue criteria. This information is entered into the source and eCRF.*

ii) Process for 'Withdrawn' subjects:

- *The subject notifies the clinical site and is able to return for an unscheduled visit or scheduled visit. At the visit, the investigator's opinion is that the subject needs to be withdrawn because of inadequate control of inflammation and pain, but one or more of the rescue criteria are not met. The subject is withdrawn from the study, and at the investigator's discretion, the study drug is discontinued and alternative medication is started to treat the subject.*
    - *At this site visit, the EOS evaluation is completed.*
- *The subject attends the clinical site for a scheduled visit and the investigator considers that the subject is inadequately treated by the study drug, but one or more of the rescue criteria are not met. The subject is withdrawn from the study because of inadequate control of inflammation and pain, and at the investigator's discretion, the study drug is discontinued and alternative medication is used to treat the subject.*
- *The subject contacts the clinical site without attendance, and the investigator considers that the subject is inadequately treated by the study drug for inflammation and pain. Then the subject should return at the next available opportunity for assessment to determine whether or not the rescue criteria are met. If not, the subject is withdrawn and the EOS assessments are completed.*
- *The subject's status is 'Withdrawn' from the study. The reason for subject withdrawal is recorded as "requiring alternate medication for inflammation and pain following cataract surgery" and any AEs should be recorded in the eCRF.*

If a subject is rescued, this event will be captured in the eCRF. Medications used for rescue will be recorded in the Concomitant Medications section of the eCRF. In addition, all the assessments in the check box with an (R) next to "X" in the Schedule of Events (Table 2A or Table 2B) shall be performed on subjects who are rescued.

9.4.2. **Management of Increased IOP**

Criteria for Starting IOP-Lowering Medication

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

1. After randomization, an IOP > 30 mmHg
2. After randomization, an IOP ≥ 24 mmHg AND an increase of ≥ 10 mmHg from POD1/pre-dose baseline (both criteria must be met)

Initiation of IOP-lowering medication is at the discretion of the Investigator even if none 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.

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.

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. If 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, who will then discuss with the Sponsor Medical Monitor.

After randomization and start of study drug, an IOP of ≥ 24 mmHg AND an increase ≥ 10 mmHg from the 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 satisfactory reduction of IOP does not occur at the next visit, then the study drug may be discontinued after consultation with the Study Medical Monitor, who will then discuss with the Sponsor Medical Monitor.

Note:

Medications used for treating increased IOP will be recorded in the Concomitant Medications section of the eCRF.

10. STATISTICAL CONSIDERATIONS

10.1. Statistical Analytical Plan

A Statistical Analysis Plan (SAP) describing the details of all safety, efficacy and exploratory analyses will be written and 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. If a subject is less than 75% compliant with dosing of study drug, the subject will be included in the 'ITT' analyses, but not in the 'Per Protocol' analyses for efficacy endpoints.
- Safety Population: All subjects who receive at least one dose of study drug.
- Per-protocol (PP) Population: All randomized subjects who complete the study drug dosing through POD14 and do not have any major protocol deviations.

10.3. Statistical Methods

10.3.1. **General Approach**

All analysis variables will be summarized descriptively by each dosing regimen, active and matching vehicle placebo groups, respectively, within each study part. Summary statistics for continuous measures will be defined as mean, standard deviation, 95% confidence interval, median, and range. Categorical measures will be summarized by the number and percent of subjects.

Inferential statistics for primary and secondary efficacy endpoints will include Student t-test (with normality assumption met) or Wilcoxon rank-sum test (with normality unmet) for continuous endpoints, and Chi-square test for categorical endpoints.

10.3.2. **Analysis of Efficacy**

The primary analysis populations will be the 'Intent-to-Treat' Population. A subset of efficacy analyses will be examined for the Per-protocol Population as supportive analysis.

The primary efficacy analyses will include, for each dosing regimen, active and placebo separately, the summary statistics of:

1) ACC on POD15;
2) Pain grade on POD15;

3) Change from baseline (POD1/pre-dose) of ACC at POD15;
4) Change from baseline (POD1/pre-dose) of pain grade at POD15

Secondary efficacy analyses will include for each dosing regimen, active and placebo separately:

1) the summary statistics of:
    - ACC on PODs 4, 8, 22/EOT (Part A) or PODs 4, 8 (Part B);
    - Change from baseline (POD1/pre-dose) of ACC on PODs 4, 8, 22/EOT (Part A) or on PODs 4, 8 (Part B);
    - ACC grade* at PODs 4, 8, 15, 22/EOT (Part A) or PODs 4, 8 and 15/EOT (Part B);
    - Change from baseline (POD1/pre-dose) of ACC grade at PODs 4, 8, 15, 22/EOT (Part A) or PODs 4, 8 and 15/EOT (Part B);
    - Anterior chamber flare grade at PODs 4, 8, 15, 22/EOT (Part A) or PODs 4, 8 and 15/EOT (Part B);
    - Change from baseline (POD1/pre-dose) of anterior chamber flare at PODs 4, 8, 15, 22/EOT (Part A) or PODs 4, 8 and 15/EOT (Part B);
    - Pain grade for each treatment at PODs 4, 8, 22/EOT (Part A) or PODs 4, 8 (Part B);
    - Change from baseline (POD1/pre-dose) of pain grade at PODs 4, 8, 15, 22/EOT (Part A) or PODs 4, 8 and 15/EOT (Part B);
    - Visual acuity (ETDRS Best corrected Visual Acuity measurement – pinhole method) at PODs 4, 8, 15, 22/EOT (Part A) or PODs 4, 8 and 15/EOT (Part B);
    - Change from baseline (POD1/pre-dose) of visual acuity at PODs 4, 8, 15, 22/EOT (Part A) or PODs 4, 8 and 15/EOT (Part B)

    * Anterior Chamber Cell Grade Definition:

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

2) the proportion of subjects
    - with ACC = 0 at PODs 4, 8, 15 and 22/EOT (Part A) or PODs 4, 8 and 15/EOT (Part B) without receiving rescue medication;

- who are pain-free at PODs 4, 8, 15 and 22/EOT (Part A) or PODs 4, 8 and 15/EOT (Part B) without receiving rescue medication;
- with AC flare grade = 0 at PODs 4, 8, 15 and 22/EOT (Part A) or PODs 4, 8 and 15/EOT (Part B) without receiving rescue medication.

Details of statistical analyses will be included in the SAP.

10.3.3. **Analysis of Safety**

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

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

The analyses of IOP will include the summary statistics of IOP and its change from baseline (POD1/pre-dose) at each visit, the proportion of subjects with an IOP ≥ 24 mmHg AND an increase ≥ 10 mm Hg from pre-dose baseline, and the proportion of subjects with an IOP > 30 mmHg at any time following initiation of study drug.

The proportion of subjects with a visual acuity worsening from POD1/pre-dose visit of ≥ 2 lines will also be summarized.

Ocular symptoms, comfort grading assessment, ophthalmoscopy findings, and slit lamp biomicroscopy results will be categorically summarized.

Details of statistical analyses will be included in the SAP.

10.3.4. **Interim Analysis:**

No interim analyses are planned for this study.

10.4. Sample Size Estimation

This is a Phase 2a trial to explore dosing regimens, and no formal sample size calculations were used to determine the number of subjects to be enrolled into the trial. The sample size of 21 subjects in each study treatment group was selected based on feasibility and integrated analysis of literature data. Assuming a dropout rate of 5%, approximately 21 subjects will be

enrolled into each treatment arm so that approximately 20 subjects per treatment arm would be expected to complete study drug dosing through the POD15 visit.

10.5. Level of Significance

All reported p-values will be considered descriptive and hypothesis generating.

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

For the ACC endpoint, the last observation prior to the first rescue medication will be carried forward for data summary at the subsequent time points (visits) for the subjects who received rescue medication during the study. Other missing data will be imputed according to 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

Efficacy analysis will be performed for the ITT population. A subset of the efficacy analysis will be repeated using data from the 'Per Protocol' population.

AEs and other safety parameters will be analyzed for all randomized subjects receiving at least 1 dose of randomized study drug (Safety Population).

11. 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/Ethics Committees**

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 DHHS 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 visit the investigational study site 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 Monitor Representative. 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. 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. 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 and 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-Laboratories-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.

J.L., T. (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.

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. . Surgical Pharmacology of the Eye. Sears M and T. A. New York, NY, Raven Press**:** 83-133.

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.

Temovate® (2000). Temovate® (Clobetasol Propionate) Cream 0.05% [Package Insert]. Research-Triangle-Park-NC:-GlaxoWellsome-Inc.

van Velsen, S. G., M. P. De Roos, I. M. Haeck, R. W. Sparidans and 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 patients with severe atopic dermatitis." J Dermatolog Treat **23**(1): 16-20.

APPENDIX A: LABORATORY EVALUATION PARAMETERS

Part A ONLY: Clinical chemistry and hematology parameters. Venous blood samples will be drawn at POD1 (pre-dose of study drug), POD22 (or EOT visit) and at the EOS visit. If a subject withdraws from study early (early termination) or is rescued prior to POD22, then the venous blood samples will be drawn on the day that the subject discontinues the study drug (EOT), or as soon as possible after that.

Parameters to be tested are listed below:

Hematology

Platelet Count	*RBC Indices*:
RBC Count	MCV
Absolute WBC Count (absolute) and automated differential WBC count	MCH
Hemoglobin	MCHC

Clinical Chemistry

Glucose	Chloride	Sodium	ALT (alanine amino transferase)
Calcium	BUN (blood urea nitrogen)	Potassium	AST (aspartate amino transferase)
Albumin	Creatinine	CO_2	Bilirubin
Total protein	ALP (alkaline phosphatase)		
Cortisol - Blood drawn on POD 1/pre-Randomization and on POD22/EOT.			