Clinical Trial Protocol: 408-C-1307

Protocol Title:	A Multicenter, Randomized, Dose-Ranging, Double-Masked, Placebo-Controlled Phase 2 Study Evaluating the Safety and Efficacy of RTA 408 Ophthalmic Suspension for the Treatment of Ocular Inflammation and Pain following Ocular Surgery
Protocol Number:	408-C-1307
Study Phase:	2
Product Name:	RTA 408 Ophthalmic Suspension (0.5%, 1.0%)
IND Number:	[redacted]
Indication:	Inflammation and Pain Associated with Ocular Surgery
Investigators:	Multi-center clinical investigation
Sponsor:	Reata Pharmaceuticals 2801 Gateway Drive, Suite 150 Irving, TX 75063-2648
Contract Research Organization:	[redacted]
IRB/IEC:	[redacted]

	Date
Original Protocol:	21-Nov-2013
Amendment 1:	10-Feb-2014

SPONSOR PERSONNEL

Sponsor Representative:	[redacted]

CRO PERSONNEL

Project Lead:	[redacted]
Medical Monitor:	[redacted]
Department Vice President:	[redacted]

SYNOPSIS

Protocol Title:	A Multicenter, Randomized, Dose-Ranging, Double-Masked, Placebo-Controlled Phase 2 Study Evaluating the Safety and Efficacy of RTA 408 Ophthalmic Suspension for the Treatment of Ocular Inflammation and Pain following Ocular Surgery
Protocol Number:	408-C-1307
Study Drug:	1) RTA 408 Ophthalmic Suspension 0.5% 2) RTA 408 Ophthalmic Suspension 1.0% 3) Placebo for RTA 408 Ophthalmic Suspension
Study Phase:	Phase 2
Primary Objective:	To evaluate the clinical efficacy and safety of two concentrations of RTA 408 Ophthalmic Suspension against placebo in the treatment of patients with inflammation and pain following ocular surgery
Secondary Objective:	None
Overall Study Design	
Structure:	Multi-center, double-masked, randomized, placebo-controlled, dose-ranging, efficacy study
Duration:	Approximately 21 to 49 days (6 study visits)
Controls:	Placebo for RTA 408 Ophthalmic Suspension

Dosage/Dose Regimen:	Patients will be randomized in a 1:1:1 ratio to one of the following groups for BID dosing in the study eye in the morning and evening (approximately 12 hours apart) for 14 days: • RTA 408 Ophthalmic Suspension 0.5% • RTA 408 Ophthalmic Suspension 1.0% • Placebo for RTA 408 Ophthalmic Suspension
Summary of Visit Schedule:	Visit 1, Day ≥ -28: Screening, Baseline Evaluation Visit 2, Day 1 (24 ± 6 hours post-surgery): Study enrollment, Randomization, and 1st Study Drug Dose Visit 3, Day 4 (± 1): On Treatment Follow-up; Inflammation and Pain Assessments Visit 4, Day 8 (± 1): On Treatment Follow-up; Inflammation and Pain Assessments Visit 5, Day 15 (+ 1): Inflammation and Pain Assessments after End of Treatment Visit 6, Day 21 (± 1): Post-Treatment Follow-up; Exit Visit
Measures Taken to Reduce Bias:	Randomization will be used to avoid bias in the assignment of patients to treatment, to increase the likelihood that known and unknown patient attributes are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Masked treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

Study Population Characteristics	
Number of Patients:	Approximately 105 patients will be enrolled in this study to complete 93 patients: 31 per arm
Condition/Disease:	Inflammation and pain following ocular surgery
Inclusion Criteria:	Patients must: 1. Have provided written informed consent, approved by the appropriate institutional review board; 2. Be able to comply with study requirements and visit schedule; 3. Be greater than or equal to 18 years of age of either sex or any race; 4. Have undergone unilateral cataract extraction via phacoemulsification and posterior chamber intraocular lens (PCIOL) implantation in the study eye on the day prior to study enrollment/randomization; 5. Have a grade of ≥ 2 in anterior chamber cell score on day after surgery (Day 1) in the study eye; 6. Have a potential post-operative pin-hole visual acuity (VA) < 1.0 logarithm of the minimum angle of resolution (logMAR) in the operative eye and fellow eye as measured using an Early Treatment for Diabetic Retinopathy Study (ETDRS) chart; 7. (For females of childbearing potential) agree to have urine pregnancy testing performed at screening (must be negative) and at exit visit; must not be lactating; and must agree to use a medically acceptable form of birth control[1] throughout the study duration. Women of childbearing potential include all females who have experienced menarche and have not experienced menopause (as defined by

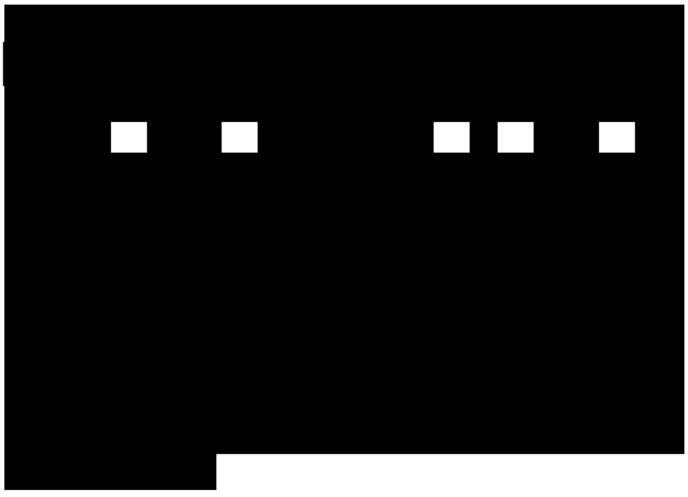
[1]Acceptable forms of birth control are spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of partner. For non-sexually active females, abstinence will be considered an acceptable form of birth control.

	amenorrhea for greater than 12 consecutive months) or have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy).
Exclusion Criteria:	Patients must <u>not</u>: 1. Have any intraocular inflammation present in the study eye during the screening slit lamp examination; 2. Have a score greater than "0" on the Ocular Pain Assessment at Screening in the study eye; 3. Have an immunosuppressive disease or an autoimmune disease that in the opinion of the Investigator could affect the quality of the ocular surface; 4. Have active or chronic/recurrent ocular or systemic disease that is uncontrolled and will likely affect wound healing; 5. Currently have suspected or known malignancy or is currently receiving antineoplastic therapy; 6. Be a female who is currently pregnant, planning a pregnancy, lactating, not using a medically acceptable form of birth control throughout the study duration, or has a positive urine pregnancy test at screening; 7. Use anti-inflammatory agents, analgesics/pain relievers (including opioids, narcotics and other pain medications) or immunomodulating agents, systemically, or in the study eye, and/or use medications for benign prostatic hyperplasia (BPH), from the washout period through the duration of the study. Washout periods for medications prior to surgery are as follows: a. Medications for BPH (tamsulosin, silodosin, alfuzosin, finasteride): 28 days b. Systemic corticosteroids: 14 days c. Systemic analgesics/pain relievers (e.g., gabapentin, pregabalin, NSAIDs and opioids): 14 days Note: Use of acetaminophen (up to 4,000 mg/day) and 'baby' aspirin (up to 81 mg/day) during the study are allowed. Use of an opioid during cataract surgery is allowed.

	d. Periocular injection of any corticosteroid solution: 28 days e. Corticosteroid depot in the study eye: 56 days after implantation f. Cyclosporine: 56 days g. Topical ocular corticosteroid: 7 days h. Topical ocular NSAID: 7 days 8. Have glaucoma or be taking medications to treat glaucoma in the study eye; 9. Have an intraocular pressure (IOP) $\leq$ 5 mmHg in either eye; 10. Currently have or have a history of Herpes Simplex Keratitis in the study eye; 11. Have active corneal abrasions or ulcers in the study eye; 12. Have active or a history of chronic or recurrent inflammatory eye disease (e.g. iritis, scleritis, uveitis, iridocyclitis, rubeosis iritis) in the study eye; 13. Have evidence of acute external ocular infections (bacterial, viral and/or fungal such as vaccinia, varicella, and other viral diseases of the cornea and conjunctiva); tuberculosis of the eye; corneal dystrophies; intraocular infections, dysthyroid ophthalmopathy, active chalazion, or uncontrolled blepharitis in the study eye; 14. Have uncontrolled and clinically significant dry eye syndrome in the study eye (artificial tears are allowed); 15. Have proliferative diabetic retinopathy (PDR), compromised macular function; significant macular diseases; clinically significant macular edema (CSME); or a history of cystoid macular edema in the study eye; 16. Have had corneal or retinal surgery (laser or incisional) within the past 6 months, or be planning to have laser or incisional surgery during the study period in the study eye (other than cataract surgery); 17. Have surgery planned or scheduled for the contralateral eye during the study; 18. Have previous ocular trauma with visible scarring or any deformities due to the trauma in the study eye; 19. Require the use of a contact lens or a collagen shield within 72 hours of investigational drug

	treatment or during the study period in the study eye; be unwilling to discontinue use of contact lenses during study period in the study eye; 20. Require use of non-diagnostic topical ophthalmic solutions (other than perioperative mydriatics, anesthetics and antiseptics, prophylactic antibiotics, lid scrubs for mild blepharitis, or artificial tears for the management of dry eye) in the study eye for the duration of the study; 21. Have known allergy or sensitivity to the investigational product or its components; 22. Have ocular hemorrhage in the study eye that interferes with evaluation of post-surgery inflammation; 23. Have undergone 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 and PCIOL implantation in the study eye; 24. Have previously enrolled in this clinical study, or are planning to participate in another clinical trial during the follow-up period, that could confound the treatment or outcomes of this investigation; 25. Be excluded if the Investigator determines that the patient should not be included for reasons not already specified (e.g., systemic or other ocular disease/abnormality), if the health of the patient or the validity of the study outcomes may be compromised by the patient's enrollment.
Study Formulation:	The drug product is a sterile aqueous suspension formulation 
Evaluation Criteria	

Efficacy Measures:	Hierarchical Primary Efficacy Measures 1. a. Absence of anterior chamber cells (i.e., score of '0') at Visit 5 (Day 15) for the 1.0% concentration of RTA 408 Ophthalmic Suspension compared to Placebo b. Absence of anterior chamber cells (i.e., score of '0') at Visit 5 (Day 15) for the 0.5% concentration of RTA 408 Ophthalmic Suspension compared to Placebo 2. a. Absence of pain (i.e., score of '0') at Visit 3 (Day 4) for the 1.0% concentration of RTA 408 Ophthalmic Suspension compared to Placebo b. Absence of pain (i.e., score of '0') at Visit 3 (Day 4) for the 0.5% concentration of RTA 408 Ophthalmic Suspension compared to Placebo Secondary Efficacy Measures 1. Absence of anterior chamber cells at Visits 3, 4 or 6 (Days 4, 8 or 21 respectively) 2. Absence of pain at Visits 4, 5 or 6 (Days 8, 15 or 21 respectively) 3. Absence of flare at Visits 3, 4, 5 or 6 (Days 4, 8, 15 or 21 respectively)
Safety Measures:	• Slit lamp biomicroscopy • Pin-hole visual acuity • IOP • Dilated indirect ophthalmoscopic examination • AE monitoring
Other:	None
General Statistical Methods and Types of Analyses:	**Efficacy Analysis:** Primary efficacy analyses will first test the difference in proportion of study eyes with a grade of '0' in anterior chamber cells between the 1.0% concentration of RTA 408 Ophthalmic Suspension and placebo and between the 0.5% concentration of

	RTA 408 Ophthalmic Suspension and placebo at Visit 5 (Day 15) using the Pearson chi-squared statistic. If the proportion of patients with a grade of '0' for anterior chamber cells is statistically significantly higher for the 1.0% concentration versus placebo at a 1-sided alpha = 0.10, then the hierarchical hypothesis testing will compare the proportion of patients with absence of ocular pain at Visit 3 (Day 4) between the 1.0% concentration of RTA 408 Ophthalmic Suspension and placebo using the Pearson chi-squared statistic at a 1-sided alpha=0.10. If the proportion of patients with a grade of '0' for anterior chamber cells is statistically significantly higher for the 0.5% concentration versus placebo at a 1-sided alpha=0.10, then the hierarchical hypothesis testing will compare the proportion of patients with absence of ocular pain at Visit 3 (Day 4) between the 0.5% concentration of RTA 408 Ophthalmic Suspension and placebo using the Pearson chi-squared statistic at a 1-sided alpha=0.10. Additionally, 95% confidence intervals will be constructed around the difference in proportions for each primary outcome using asymptotic normal approximations. Fisher's exact tests will be employed in cases of expected counts less than five. **Sample Size:** 

	General Considerations: The unit of analysis in this study will be the study eye for all efficacy and safety summaries. Additionally, non-ocular adverse events will be presented at the patient level. Non-study eye safety summaries will also be presented as appropriate. The primary analyses of all efficacy data will use last observation carried forward (LOCF) to impute missing data; data for visits after a patient is discontinued for lack of efficacy will be imputed as failures for success/failure endpoints and will be imputed using LOCF for other endpoints. To check robustness of results, sensitivity analyses of the primary efficacy data will include analyses of observed data only, imputing data from patient visits after discontinuation for lack of efficacy as failures. Other imputation methods may be applied as additional sensitivity analyses. Per protocol analyses will use observed data only, with the exception of patients who have missing data due to discontinuation for lack of efficacy; for these patients, missing data after discontinuation will be imputed as failures for success/failure endpoints and will be imputed using LOCF for other endpoints. Summaries for continuous variables will include the sample size (n), mean, standard deviation, median, minimum, and maximum. Summaries for discrete variables will include frequencies and percentages. Differences between treatment groups will be calculated as Test – Placebo and change from baseline will be calculated as follow-up visit – baseline. The baseline visit will be defined as the last non-missing measure prior to initiation of investigational treatment. All efficacy analyses will use a one-sided alpha=0.10 test unless otherwise stated. The secondary efficacy variables, study eyes with absence of anterior chamber cells (Visits 3, 4 or 6), study eyes with absence of pain (Visits 4, 5 or 6) and study eyes with absence of flare (Visits 3, 4, 5 or 6) will be summarized similarly to the primary efficacy summaries. Additionally, anterior chamber cells and flare as well as pain at each visit and change from

	baseline will be summarized using continuous and discrete summary statistics. The sum of anterior chamber cells and flare grade will be summarized similarly to anterior chamber cells and flare separately. **Safety Analysis:** The primary safety analysis will summarize ocular treatment emergent AEs (TEAEs) in the study eye for all treated patients using discrete summaries at the patient and event level by system organ class and preferred term for each treatment group. A TEAE will be defined as any AE that occurs after the treatment is initiated. An additional analysis will examine ocular AEs for the non-study eye. Non-ocular TEAEs will be summarized using discrete summaries at the patient and event level by system organ class and preferred term for each treatment group. Treatment related ocular and non-ocular TEAEs will be summarized similarly. Ocular and non-ocular TEAEs will also be summarized by severity. The IOP data will be summarized at each visit using both continuous summaries (including change from baseline) and discrete summaries (including the proportion of patients with change in IOP from baseline $\geq$ 10 mm Hg and the proportion of patients with an IOP $\geq$ 30 mm Hg that occurs at any time following initiation of study treatment) as well as shift tables. Slit lamp biomicroscopy and dilated indirect ophthalmoscopic examination measures will be summarized at each visit using discrete summary statistics. Visual Acuity data will be summarized at each visit, using discrete summaries including change from baseline in the number of lines and the proportion of patients with worsening from previous visit of $\geq$ 2 lines.
Summary of Known and Potential Risks and	This study is the first clinical study to evaluate the safety and efficacy of RTA 408 Ophthalmic Suspension.

Benefits to Human Patients	The ocular tolerability of RTA 408 was evaluated in multiple nonclinical studies in rats, guinea pigs, rabbits, and monkeys. No ocular or systemic toxicity was observed and systemic exposure was very low in all species tested. Conjunctival irritation was observed in the rabbit ocular GLP toxicity study with frequent dosing (4x/day); however, this was reversible, was not observed in a non-GLP study in rabbits, was not observed in the monkey ocular GLP toxicity study, and is readily monitorable in the clinic. *In vitro* and *in vivo* studies conducted to date demonstrate that RTA 408 is a potent activator of the Nrf2 pathway and an inhibitor of the NF-κB pathway, and should thus be an effective anti-inflammatory agent for ophthalmic indications of inflammation and pain.

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List of Abbreviations

AE	Adverse Event
AUC	Area under the curve
BID	Bis in die (twice daily)
BPH	Benign prostatic hyperplasia
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
CSME	Clinically significant macular edema
DHHS	Department of Health and Human Services
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HEC	Hydroxyethyl cellulose
HIPAA	Health Information Portability and Accountability Act
Hr	Hour
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
INF•	Interferon gamma
IOP	Intraocular Pressure
IRB	Institutional/Independent Review Board
ITT	Intent to Treat
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
mL	Milliliter
• g	Microgram
NCS	Not clinically significant
NDA	New Drug Application
NF-• •	Nuclear factor kappa-light-chain-enhancer of activated B-cells
ng	Nanogram
NO	Nitric oxide
NQ01	NADH quinine oxidoreductase 1
Nrf2	Nuclear factor erythroid-derived 2
NSAID	Non-steroidal anti-inflammatory agent
PCIOL	Posterior chamber intraocular lens
PDR	Proliferative diabetic retinopathy
PHI	Protected Health Information
PP	Per Protocol
PVP	Polyvinyl pyrrolidone
QD	Quaque die (Once daily)

SAE	Serious Adverse Event
SAP	Statistical analysis plan
SUN	Standardization of the Uveitis Nomenclature
VA	Visual acuity

1 INTRODUCTION

Following ophthalmic surgery, the current standard of care includes a topical ophthalmic corticosteroid or other anti-inflammatory agent to treat ocular inflammation and improve patient comfort. If left untreated, inflammation of the eye may result in further ocular complications including scarring, vision loss, or blindness. Although the exact dosing regimen is physician-dependent, patients are typically prescribed a topical corticosteroid for a period of 2-4 weeks following surgery, being tapered over the course of delivery as the inflammation subsides. Topical anti-inflammatory agents are usually administered multiple times per day, particularly in the early period following ophthalmic surgery. Continuing efforts in drug development aim to identify alternatives to ophthalmic corticosteroid use, due to their well-known local and systemic negative side effects.

Natural triterpenoids, such as oleanolic acid and ursolic acid, which are derived from plant extracts, have been used extensively in Asian medicine for their anti-inflammatory and anticancer properties (Reference 1. Liu, 1995). A series of semi-synthetic triterpenoids was prepared based on the structure of oleanolic acid, and tested to identify compounds optimized for their ability to inhibit the induction of nitric oxide (NO) in primary mouse macrophages treated with interferon-gamma (IFN•; Reference 2. Honda, 1998).

RTA 408 is a novel oleanane triterpenoid within this class of compounds. The results from *in vitro* and *in vivo* preclinical studies conducted to date demonstrate that RTA 408, as well as other semi-synthetic triterpenoids, are potent activators of the Nrf2 (nuclear factor erythroid-derived 2) pathway and inhibitors of the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B-cells) pathway, and thus induce an antioxidant and anti-inflammatory phenotype.

Reata has demonstrated in preclinical models that topical ocular administration of RTA 408 increases the expression of NQO1 (a prototypical Nrf2 target gene) in the corneal epithelium and the corneal endothelium of rabbits, with the greatest effect observed in the 1% dose group. Topical ocular administration of RTA 408 (2x/day), at concentrations as low as 0.01%, is efficacious *in vivo* as an anti-inflammatory agent in a rabbit model of paracentesis-induced ocular inflammation.

RTA 408 is readily absorbed and distributed into ocular tissues after topical ocular administration, with sustained concentrations observed for at least 24 hours after the last dose. This ocular pharmacokinetic profile is consistent with the efficacy observed with twice daily ocular dosing in rabbits.

Ocular GLP toxicity studies have been completed with RTA 408 Ophthalmic Suspension in rabbits and monkeys with repeated (4x/day) administration of RTA 408 (0.1%, 0.3%, and 1%) for 28 days. As expected, systemic exposure to RTA 408 was very low in rabbits and monkeys, with maximum concentrations (C_{max}) on Day 28 of approximately 3.0 and 2.6 ng/mL, respectively. Overall, the topical ocular administration of RTA 408 Ophthalmic Suspension, at concentrations of 0.1%, 0.3%, and 1% four times daily for 28 days in rabbits, but not monkeys, produced ocular irritation, but did not cause any ocular or systemic toxicity in rabbits or monkeys. Thus, the no-observed-adverse-effect-level (NOAEL) was determined to be at least 1% RTA 408 Ophthalmic Suspension

administered 4x/day for 28 days in rabbits and monkeys. The conjunctival irritation observed in the rabbit ocular GLP toxicity study was reversible, was not observed in a non-GLP study in rabbits, was not observed in the monkey ocular GLP toxicity study, and is readily monitorable in the clinic.

Although it is highly unlikely that meaningful systemic exposure will result following topical ocular administration in humans, the systemic toxicity potential of RTA 408 has been extensively investigated in rats and monkeys, with daily oral administration for up to 6 months in rats and 9 months in monkeys.

Based on an integrated assessment of the nonclinical data, it is concluded that RTA 408 has an acceptable safety profile for topical ophthalmic use as indicated in the proposed topical ocular study in patients following uncomplicated cataract surgery at concentrations of 0.5% and 1.0% with a BID dosage regimen.

2 STUDY OBJECTIVES

To evaluate the clinical efficacy and safety of RTA 408 Ophthalmic Suspension in two concentrations versus placebo in the treatment of patients with inflammation and pain following uncomplicated cataract surgery.

3 CLINICAL HYPOTHESES

It is hypothesized that RTA 408 Ophthalmic Suspension will be more effective than placebo in the alleviation of inflammation and pain following cataract surgery.

4 OVERALL STUDY DESIGN

This trial will be a multi-center, double-masked, randomized, dose-ranging, placebo-controlled study consisting of 6 visits over approximately 7 weeks (49 days). Randomization will be used to avoid bias in the assignment of patients to treatment, to increase the likelihood that known and unknown patient attributes (e.g., demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Masked treatment will be used to reduce potential of bias during data collection and evaluation of clinical endpoints.

At Visit 1 (Day -1 to Day -28), patients will be screened to ensure that they meet all initial inclusion criteria and none of the exclusion criteria. Medical and medication histories will be taken, the patients will subjectively grade ocular pain using the scales provided, and pin-hole visual acuity will be assessed. The Investigator will then perform a slit lamp biomicroscopic examination with intraocular pressure (IOP) measurement, and grading of anterior chamber inflammation. A dilated indirect ophthalmoscopic examination will also be performed. Female patients of childbearing potential will be given a urine pregnancy test.

At Visit 2 (Day 1, 24 ± 6 hours post-surgery), patients' medical and medication histories will be updated, patients will be queried for ocular pain, pin-hole visual acuity will be assessed, and the Investigator will perform a slit lamp biomicroscopic evaluation, IOP

measurement, and grading of anterior chamber inflammation. Qualifying patients will then be randomized to one of the following treatment groups (in a 1:1:1 ratio): RTA 408 Ophthalmic Suspension 0.5% (N=35), RTA 408 Ophthalmic Suspension 1.0% (N=35), or placebo for RTA 408 Ophthalmic Suspension (N=35). Study drug will be dispensed along with the Study Drug Compliance Diary. A trained unmasked technician will instruct patients on how to instill the study drug twice daily in the morning and evening (approximately 12 hours apart) for 14 days on the eye that underwent surgery. The first dose of study drug will be instilled in-office.

At Visits 3 (Day 4± 1), 4 (Day 8± 1), and 5 (Day 15+ 1), patients' medical and medication histories will be updated, patients will be queried for ocular pain, pin-hole visual acuity will be assessed, and the Investigator will perform a slit lamp biomicroscopic evaluation, IOP measurement, and grading of anterior chamber inflammation. AEs will be noted, and the Study Drug Compliance Diary will be reviewed. Day 14 will be the last day of study drug treatment at home. On Visit 5 (Day 15+ 1), the study drug and Study Drug Compliance Diary will be collected.

At Visit 6 (Day 21± 1), patients' medical and medication histories will be updated, patients will be queried for ocular pain, pin-hole visual acuity will be assessed, and the Investigator will perform a slit lamp biomicroscopic evaluation, IOP assessment, and grading of anterior chamber inflammation. A dilated indirect ophthalmoscopic examination will also be performed. AEs will be noted, and a urine pregnancy test will be given to females of childbearing potential. Patients will then exit the study.

5 STUDY POPULATION

5.1 Number of Patients

Approximately 105 patients will be enrolled in this multi-center study, 35 per arm, in order to complete 31 patients per arm.

5.2 Study Population Characteristics

Patients age 18 and older who are scheduled to undergo ocular surgery, and who meet all inclusion criteria and none of the exclusion criteria.

5.3 Inclusion Criteria

Each patient must meet the following criteria:

1. Have provided written informed consent, approved by the appropriate institutional review board;
2. Be able to comply with study requirements and visit schedule;
3. Be greater than or equal to 18 years of age of either sex or any race;
4. Have undergone unilateral cataract extraction via phacoemulsification and posterior chamber intraocular lens (PCIOL) implantation in the study eye on the day prior to study enrollment/randomization;
5. Have a grade of ≥ 2 in anterior chamber cell score on day after surgery (Day 1) in the study eye;

6. Have a potential post-operative pin-hole visual acuity (VA) < 1.0 logarithm of the minimum angle of resolution (logMAR) in the operative eye and fellow eye as measured using an Early Treatment for Diabetic Retinopathy Study (ETDRS) chart;
7. (For females of childbearing potential) agree to have urine pregnancy testing performed at screening (must be negative) and at exit visit; must not be lactating; and must agree to use a medically acceptable form of birth control[2] throughout the study duration. Women of childbearing potential include all females who have experienced menarche and have not experienced menopause (as defined by amenorrhea for greater than 12 consecutive months) or have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy).

5.4 Exclusion Criteria

Each patient may <u>not meet any of the following</u>:

1. Have any intraocular inflammation present in the study eye during the screening slit lamp examination;
2. Have a score greater than "0" on the Ocular Pain Assessment at Screening in the study eye;
3. Have an immunosuppressive disease or an autoimmune disease that in the opinion of the Investigator could affect the quality of the ocular surface;
4. Have active or chronic/recurrent ocular or systemic disease that is uncontrolled and will likely affect wound healing;
5. Currently have suspected or known malignancy or is currently receiving antineoplastic therapy;
6. Be a female who is currently pregnant, planning a pregnancy, lactating, not using a medically acceptable form of birth control throughout the study duration, or has a positive urine pregnancy test at screening;
7. Use anti-inflammatory agents, analgesics/pain relievers (including opioids, narcotics and other pain medications) or immunomodulating agents systemically, or in the study eye, and/or use medications for benign prostatic hyperplasia (BPH), from the washout period through the duration of the study. Washout periods for medications prior to surgery are as follows:
   a. Medications for BPH (tamsulosin, silodosin, alfuzosin, finasteride): 28 days
   b. Systemic corticosteroids: 14 days
   c. Systemic analgesics/pain relievers (e.g., gabapentin, pregabalin, NSAIDs and opioids): 14 days
      Note: Use of acetaminophen (up to 4,000 mg/day) and 'baby' aspirin (up to 81 mg/day) during the study are allowed. Use of an opioid during cataract surgery is allowed.
   d. Periocular injection of any corticosteroid solution: 28 days

[2]Acceptable forms of birth control are spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of partner. For non-sexually active females, abstinence will be considered an acceptable form of birth control.

e. Corticosteroid depot in the study eye: 56 days after implantation
f. Cyclosporine: 56 days
g. Topical ocular corticosteroid: 7 days
h. Topical ocular NSAID: 7 days

8. Have glaucoma or be taking medications to treat glaucoma in the study eye;
9. Have an intraocular pressure (IOP) $\leq$ 5 mmHg in either eye;
10. Currently have or have a history of Herpes Simplex Keratitis in the study eye;
11. Have active corneal abrasions or ulcers in the study eye;
12. Have active or a history of chronic or recurrent inflammatory eye disease (e.g. iritis, scleritis, uveitis, iridocyclitis, rubeosis iritis) in the study eye;
13. Have evidence of acute external ocular infections (bacterial, viral and/or fungal such as vaccinia, varicella, and other viral diseases of the cornea and conjunctiva); tuberculosis of the eye; corneal dystrophies; intraocular infections, dysthyroid ophthalmopathy, active chalazion, or uncontrolled blepharitis in the study eye;
14. Have uncontrolled and clinically significant dry eye syndrome in the study eye (artificial tears are allowed);
15. Have proliferative diabetic retinopathy (PDR), compromised macular function; significant macular diseases; clinically significant macular edema (CSME); or a history of cystoid macular edema in the study eye;
16. Have had corneal or retinal surgery (laser or incisional) within the past 6 months, or be planning to have laser or incisional surgery during the study period in the study eye (other than cataract surgery);
17. Have surgery planned or scheduled for the contralateral eye during the study;
18. Have previous ocular trauma with visible scarring or any deformities due to the trauma in the study eye;
19. Require the use of a contact lens or a collagen shield within 72 hours of investigational drug treatment or during the study period in the study eye; be unwilling to discontinue use of contact lenses during study period in the study eye;
20. Require use of non-diagnostic topical ophthalmic solutions (other than perioperative mydriatics, anesthetics and antiseptics, prophylactic antibiotics, lid scrubs for mild blepharitis, or artificial tears for the management of dry eye) in the study eye for the duration of the study;
21. Have known allergy or sensitivity to the investigational product or its components;
22. Have ocular hemorrhage in the study eye that interferes with evaluation of post-surgery inflammation;
23. Have undergone 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 and PCIOL implantation in the study eye;
24. Have previously enrolled in this clinical study, or are planning to participate in another clinical trial during the follow-up period, that could confound the treatment or outcomes of this investigation;
25. Be excluded if the Investigator determines that the patient should not be included for reasons not already specified (e.g., systemic or other ocular

disease/abnormality), if the health of the patient or the validity of the study outcomes may be compromised by the patient's enrollment.

5.5 Withdrawal Criteria

If at any time during the study the investigator determines that a patient's safety has been compromised, the patient may be withdrawn from the study.

Patients may withdraw consent from the study at any time.

Sponsor and/or investigator may discontinue any patient for non-compliance or any valid medical reason (see Section 8.6.2).

6 STUDY PARAMETERS

6.1 Efficacy Measures

The hierarchical primary efficacy variables are the following:

1. Absence of anterior chamber cells (i.e., score of '0') at Visit 5 (Day 15) for:
    a. The 1.0% concentration of RTA 408 Ophthalmic Suspension compared to Placebo
    b. The 0.5% concentration of RTA 408 Ophthalmic Suspension compared to Placebo.
2. Absence of pain (i.e., score of '0') at Visit 3 (Day 4) for:
    a. The 1.0% concentration of RTA 408 Ophthalmic Suspension compared to Placebo; to be tested if 1a. is statistically significant in favor of the active arm.
    b. The 0.5% concentration of RTA 408 Ophthalmic Suspension compared to Placebo; to be tested if 1b. is statistically significant in favor of the active arm.

6.1.1 Secondary Efficacy Variables

1. Absence of anterior chamber cells at Visits 3, 4, or 6 (Days 4±1, 8±1, or 21±1, respectively)
2. Absence of pain at Visits 4, 5 or 6 (Days 8±1, 15+1 or 21±1, respectively)
3. Absence of flare at Visits 3, 4, 5 or 6 (Days 4±1, 8±1, 15+1 or 21±1, respectively)

6.2 Safety Measures

- Slit lamp biomicroscopy
- Pin-hole visual acuity
- IOP
- Dilated indirect ophthalmoscopic examination
- AE monitoring

6.3 Other Measures

None.

7 STUDY MATERIALS

7.1 Study Treatments

7.1.1 Study Treatments/Formulations

The drug product is a sterile aqueous suspension [redacted] he concentrations to be tested are the following:

- RTA 408 Ophthalmic Suspension 0.5%
- RTA 408 Ophthalmic Suspension 1.0%
- Placebo for RTA 408 Ophthalmic Suspension

7.1.2 Instructions for Use and Administration

- Twenty-four ± 6 hours after surgery (Day 1), a trained technician will instruct patients on how to instill the study drug. The first dose will be instilled in-office at the patient's Day 1 visit.
- [redacted]
- Instructions to patients on study drug administration will include: [redacted] SHAKE WELL BEFORE USE. Instill one drop twice daily for 14 days in the morning and evening (approximately 12 hours apart) in the eye that underwent surgery. Study drugmust not be instilled within 30 minutes of instillation of any other ocular medications or artificial tears [redacted] Discontinue use of the study drug after instilling the second dose on Day 14. Keep out of reach of children.
- All bottles of active and placebo treatment will be identical in appearance and will be packaged in identical containers. The study drug kit and each bottle will have a label bearing information on each part. Study drug will be packaged and labeled based on the randomization list generated prior to the start of the study.

7.2 Other Study Supplies

Urine pregnancy tests [Clarity HCG tests] will be supplied.

8 STUDY METHODS AND PROCEDURES

8.1 Patient Entry Procedures

8.1.1 Overview

Patients as defined by the criteria in section 5.2, 5.3, and 5.4 will be considered for entry into this study. See Appendix 2 for a tabular summary of study visits and procedures required for each visit.

8.1.2 Informed Consent

Prior to a patient's participation in the trial (i.e., changes in a patient's medical treatment and/or study related procedures), the study will be discussed with each patient, and patients wishing to participate must give written informed consent using an informed consent form. The informed consent form must be the most recent version that has received approval/favorable review by a properly constituted Institutional Review Board.

8.1.3 Washout Intervals

Study staff will confirm that the patient has not used prior to Day 1 for the indicated washout interval, any of the following disallowed medications, systemically or in the study eye, grouped by washout period:

72 hours

- Contact lens or a collagen shield in the study eye

7 days

- Topical ocular corticosteroid
- Topical ocular NSAID

14 days

- Systemic corticosteroids
- Systemic analgesics/pain relievers (e.g., gabapentin, pregabalin, NSAIDs and opioids)
  Note: Use of acetaminophen (up to 4,000 mg/day) and 'baby' aspirin (up to 81 mg/day) during the study are allowed. Use of an opioid during cataract surgery is allowed.

28 days

- Periocular injection of any corticosteroid solution
- Systemic medications for BPH (tamsulosin, silodosin, alfuzosin, finasteride)

56 days

- Corticosteroid depot in the study eye (after implantation)

- Topical ocular cyclosporine

8.1.4 Procedures for Final Study Entry

Patients must satisfy all inclusion and none of the exclusion criteria in order to be entered into the study on Study Visit 2.

8.1.5 Methods for Assignment to Treatment Groups

All patients screened for the study who sign a consent form will be assigned a 3-digit screening number which will be entered in the Screening and Enrollment Log. The Patient ID number will be a 7-digit number consisting of the 4-digit site number combined with the 3-digit screening number.

Once a patient meets all qualification criteria, they will be randomly assigned to masked treatment using a 1:1:1 (0.5% RTA 408: 1.0% RTA 408: placebo) assignment ratio. Patients will be randomized on the first day post-surgery (Day 1) by assignment of the lowest 5-digit study drug kit number available at their investigative site. No study drug kit numbers will be skipped or omitted. A trained, unmasked technician will administer study drug from the bottle of the study drug kit assigned to the patient. Each study drug kit will be labeled with the 5-digit study drug kit number. The bottle of study drug will be dispensed to the patient for use on subsequent days.

8.2 Concurrent Therapies

The use of any concurrent medication, prescription or over-the-counter, used within the last 60 days before Visit 1 and for the duration of the study is to be recorded on the patient's source document and corresponding case report form (eCRF) along with the reason the medication was taken.

Concurrent enrollment in another investigational drug or device study is not permitted.

8.2.1 Prohibited Medications/Treatments

Prohibited medications/treatments for the duration of the study are:

- Topical ocular corticosteroid in the study eye
- Topical ocular NSAID in the study eye
- Systemic corticosteroids
- Periocular injection of any corticosteroid solution in the study eye
- Corticosteroid depot in the study eye (after implantation)
- Topical ocular cyclosporine in the study eye
- Anti-inflammatory or immunomodulating agents systemically, or in the study eye.

- Systemic medications for benign prostatic hyperplasia (BPH) (e.g., tamsulosin, silodosin, alfuzosin, finasteride).
- Systemic Analgesics/pain relievers, including opioids, narcotics and other pain medications systemically (e.g., gabapentin, pregabalin, NSAIDs and opioids).

  Note: Use of acetaminophen (up to 4,000 mg/day) and 'baby' aspirin (up to 81 mg/day) during the study are allowed. Use of an opioid during cataract surgery is allowed.
- Glaucoma medications or ocular hypertension medications in the study eye
- Contact lens or a collagen shield in the study eye
- Non-diagnostic topical ophthalmic solutions (other than perioperative mydriatics, anesthetics and antiseptics, prophylactic antibiotics, lid scrubs for mild blepharitis, or artificial tears for the management of dry eye) in the study eye
- Antineoplastic therapy
- 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 and PCIOL implantation in the study eye
- Plan to have laser or incisional surgery in the study eye (other than cataract surgery);
- Surgery planned or scheduled for the contralateral eye;

If a patient uses a disallowed medication, this use will be recorded as a protocol violation. Protocol violations must be reported to the IRB in accordance with their standard operating procedures.

8.2.2 Escape Medications

Use of escape medications should be avoided if possible. If in the investigator's assessment escape medication is required due to lack of efficacy, the study drug should be discontinued prior to administration of the first dose of escape medication. The patient should remain in the study, and continue to be followed per the protocol for all remaining visits and assessments to the end of the study. These patients who require escape medication should be considered as discontinued from study medication due to lack of efficacy, and the escape medication(s) used must be documented in the eCRF.

8.2.3 Special Diet or Activities

Not applicable.

8.3 Examination Procedures

8.3.1 Procedures to be Performed at Each Study Visit with Regard to Study Objectives

8.3.1.1 VISIT 1: Screening Visit (Day -1 to Day -28)

- *Informed Consent/HIPAA:* Prior to any changes in a patient's medical treatment and/or performing study visit procedures, the study will be discussed with each patient and patients wishing to participate must give written informed consent and sign a HIPAA form.
- *Review of Inclusion and Exclusion Criteria:* If patients meet all initial inclusion and none of the exclusion criteria, they may complete this visit.
- *Demographic data and medical/medication/ocular history:* Collect and record all demographic data, medical history, any medications (refer to Section 8.2) and any underlying condition(s). Current underlying conditions, including those that began within the last thirty days, which may have been resolved before screening must be recorded. Record any medications the patient is taking, as well as those the patient may have taken but discontinued within 60 days prior to screening (refer to Section 8.2).
- *Urine Pregnancy Test (for females of childbearing potential):* Women of childbearing potential must have a negative urine pregnancy test to continue in the study and must agree to use an adequate method of contraception for the duration of the study in order to be enrolled. Acceptable forms of birth control are spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of partner.
    - For non-sexually active females, abstinence will be considered an acceptable form of birth control.
- *Assessment of Ocular Pain:* Patients will assess ocular pain in the study eye (see Appendix 1).
- *Pin-Hole Visual Acuity Utilizing an ETDRS Chart:* Patients must have a potential post-operative pin-hole VA < 1.0 logMAR in the operative eye and in the fellow eye as measured using an ETDRS chart.
- *Slit Lamp Biomicroscopy:* A slit lamp exam will be performed in both eyes to exclude patients with disallowed ocular conditions (see Appendix 1).

- *Assessment of Ocular Inflammation:* The Investigator will assess anterior chamber cells and flare in the study eye using slit lamp biomicroscopy (see Appendix 1).
- *Assessment of Intraocular Pressure:* Tonometry will be used to assess intraocular pressure in both eyes. Patients who have ocular hypotension (IOP≤ 5mmHg) or are taking medications to treat ocular hypertension/glaucoma in the study eye will be excluded from the study.
- *Dilated Indirect Ophthalmoscopic Examination:* Dilated indirect ophthalmoscopic examination will be performed in both eyes for safety purposes (see Appendix 1).
- *Schedule for Visit 2*

8.3.1.2 VISIT 2: 24 ± 6 Hours Post Surgery (Day 1)

- *Update of Medical/Medication History*
- *Assessment of Ocular Pain*
- *Pin-Hole Visual Acuity Utilizing an ETDRS Chart*
- *Slit Lamp Biomicroscopy*
- *Assessment of Ocular Inflammation:* Only patients with ≥ 2 score in anterior chamber cell in the study eye will be included.
- *Assessment of Intraocular Pressure:* Patients will be excluded who have ≤ 5mmHg IOP on the day after surgery in either eye.
- *Review of Inclusion and Exclusion Criteria:* If patients meet all inclusion and none of the exclusion criteria, they will be enrolled in the study and randomized to receive drug.
- *Randomization:* Patients who meet all inclusion and none of the exclusion criteria and qualify to continue in the study will be randomized to masked treatment (refer to Section 8.1.5)
- *Study Drug Instillation:* A trained unmasked technician not involved in any other study assessments will instruct the patient to perform study drug instillation of one eye drop to the study eye. The first dose instilled during this visit will be considered the morning dose regardless of the time in which it is instilled. The second dose will be instilled in the evening and may be instilled less than approximately 12 hours apart.
- *Study Drug and Study Drug Compliance Diary Dispensation and Instructions*: A trained technician will instruct patients on how to instill the study drug (refer to Section 7.1.2) and complete the patient diary at home. The study drug and study drug compliance diary will be dispensed to patients for home use.

- *AE Query:* AEs (both elicited and observed) will be monitored throughout the study. All AEs (both elicited and observed) will be promptly reviewed by the Investigator for accuracy and completeness. All AEs will be documented on the appropriate eCRF.
- *Schedule for Visit 3*

8.3.1.3 VISIT 3: (Day 4±1)

- *Update of Medical/Medication History*
- *Review of Study Drug Compliance Diary*
- *Assessment of Ocular Pain*
- *Pin-Hole Visual Acuity Utilizing an ETDRS Chart*
- *Slit Lamp Biomicroscopy*
- *Assessment of Ocular Inflammation*
- *Assessment of Intraocular Pressure*
- *AE Query*
- *Schedule for Visit 4*

8.3.1.4 VISIT 4 (Day 8 ± 1)

- *Update of Medical/Medication History*
- *Review of Study Drug Compliance Diary*
- *Assessment of Ocular Pain*
- *Pin-Hole Visual Acuity Utilizing an ETDRS Chart*
- *Slit Lamp Biomicroscopy*
- *Assessment of Ocular Inflammation*
- *Assessment of Intraocular Pressure*
- *AE Query*
- *Schedule for Visit 5*

8.3.1.5 VISIT 5 (Day 15+ 1)

- *Update of Medical/Medication History*
- *Review of Study Drug Compliance Diary*
- *Collection of Study Drug and Study Drug Compliance Diary*
- *Assessment of Ocular Pain*
- *Pin-Hole Visual Acuity Utilizing an ETDRS Chart*

- *Slit Lamp Biomicroscopy*
- *Assessment of Ocular Inflammation*
- *Assessment of Intraocular Pressure*
- *AE Query*
- *Schedule for Visit 6*

8.3.1.6 VISIT 6/ EXIT VISIT (Day 21 ± 1 or Early Exit)

- *Update of Medical/Medication History*
- *Review of Study Drug Compliance Diary*[3]
- *Collection of Study Drug and Study Drug Compliance Diary*[5]
- *Assessment of Ocular Pain*
- *Pin-Hole Visual Acuity Utilizing an ETDRS Chart*
- *Slit Lamp Biomicroscopy*
- *Assessment of Ocular Inflammation*
- *Assessment of Intraocular Pressure*
- *Dilated Indirect Ophthalmoscopic Examination*
- *AE Query*
- *Urine Pregnancy Test for Women of Childbearing Potential*
- *Exit:* Patients will exit the study.

8.4 Schedule of Visits, Measurements and Dosing

8.4.1 Scheduled Visits

Refer to Appendix 2 for a schedule of visits and measurements.

8.4.2 Unscheduled Visits

These visits may be performed in order to ensure patient safety. All information gathered at unscheduled visits should be recorded on the Unscheduled Visit pages of the Source Document and corresponding eCRF.

If a randomized patient does not attend their scheduled visit, the eCRF pages for the missed visit will be skipped.

[3] These procedures are to be completed on Visit 6 only if not performed at Visit 5.

All efforts should be made to schedule patients for an Exit Visit to complete Exit Procedures. Information from Early Exit Visits should be recorded on the Visit 6/Exit Visit pages.

Evaluations that may be conducted at an Unscheduled Visit (as appropriate, depending on the reason for the visit) include:

- Update Medical/Medication History
- Review/Collect Study Drug Compliance Diary and Study Drug
- Assessment of ocular pain
- Pin-hole visual acuity
- Slit lamp biomicroscopy
- Assessment of Ocular Inflammation
- Intraocular pressure measurement
- Dilated indirect ophthalmoscopic examination
- Assessment of AEs
- Urine pregnancy test (for females of childbearing potential)

8.5 Compliance with Dosing

Site staff will review concomitant medication use at each visit.

Patients will be provided with a study drug compliance diary to document BID dosing for 14 days. Patient compliance with dosing will be assessed by in-office review of study drug compliance diary. Patients who miss more than 25% of their study drug doses (*more than* 7 total doses) will be considered non-compliant with dosing and a protocol deviation should be recorded.

8.6 Patient Disposition

8.6.1 Completed Patients

A completed patient is one who has not been discontinued from the study and continues study assessments through Visit 6 (Day 21).

8.6.2 Discontinued Patients

Patients may be discontinued from the study prior to their completion of the study due to any of the following reasons:

- AEs
- Protocol violations
- Lack of efficacy
- Administrative reasons (e.g., inability to continue, lost to follow up)

- Sponsor termination of study
- Voluntary withdrawal
- Pregnancy:

  If a female has a positive pregnancy test during the study, the patient should stop study treatment, and the Investigator will notify the sponsor immediately. The Investigator shall request copies of all related medical reports during the pregnancy and shall document the outcome of the pregnancy from the patient and/or patient's physician. The Investigator will retain these reports together with the patient's source documents and will provide a copy of all documentation to the sponsor.
- Other

Note: In addition, any patient may be discontinued for any sound medical reason.

Notification of a patient's discontinuation of study drug administration and the reason for discontinuation will be made to CRO and study Sponsor and will be clearly documented on the eCRF. Patients who receive escape medication are to discontinue study drug administration and are to remain in the study and be followed per the protocol to the end of the study. Patients who discontinue study drug administration for other reasons are encouraged to remain in the study and continue with study assessments through the end of the study.

Notification of a patient's discontinuation of study participation and the reason for discontinuation will be made to CRO and study Sponsor and will be clearly documented on the eCRF.

8.7 Study Termination

The study may be stopped at any time by the Investigator or the Sponsor with appropriate notification.

8.8 Study **Duration**

An individual patient's participation in the study is expected to last approximately 7 weeks from screening to exit.

8.9 Monitoring and Quality Assurance

During the course of the study a CRO monitor, or designee, will make routine site visits to review protocol compliance, assess study drug/device accountability, and ensure the study is being conducted according to the pertinent regulatory requirements. The review of the patients' medical records will be performed in a manner that adequately maintains patient confidentiality. Further details of the study monitoring will be outlined in a monitoring plan.

Regulatory authorities of domestic and foreign agencies, the Sponsor, and/or its designees may carry out on-site inspections and/or audits which may include source

data checks. Therefore direct access to the original source data will be required for inspections and/or audits. All inspections and audits will be carried out giving consideration to data protection as well as patient confidentiality to the extent that local, state, and federal laws apply.

9 ADVERSE EVENTS (AEs)

9.1 Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not the event is considered drug-related. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease occurring after the first dose of study drug, without any judgment about causality. Any pre-existing medical condition that worsens after first administration of the study drug will also be considered a new AE. The AE reporting period ends upon study exit. Study drug includes the investigational drug under evaluation and placebo given during any stage of the study.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, relationship to study drug, action(s) taken, seriousness, and outcome of any sign or symptom observed by the physician or reported by the patient upon indirect questioning.

9.1.1 Severity

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported to him/her by the patient. The assessment of severity is made irrespective of relationship to study drug or seriousness of the event and should be evaluated according to the following scale:

- *Mild*: Event is noticeable to the patient, but is easily tolerated and does not interfere with the patient's daily activities.
- *Moderate*: Event is bothersome, possibly requiring additional therapy, and may interfere with the patient's daily activities.
- *Severe*: Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the patient's daily activities.

9.1.2 Relationship to Study Drug

The relationship of each AE to the study drug should be determined by the Investigator using these explanations:

- *Suspected*: A reasonable possibility exists that the study drug caused the AE.
- *Not Suspected*: A reasonable possibility does not exist that the study drug caused the AE.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the study drug caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the study drug and the AE. Types of evidence that would suggest a causal relationship between the study drug and the AE include: the event follows a reasonable temporal sequence from the time of study drug administration, and/or, follows a known response pattern to the study drug, but could have been produced by other factors; a reasonable temporal sequence of the event with study drug administration exists and, based upon the known pharmacologic action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with study drug administration seems likely; a single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome); one or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture); an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

9.2 Serious Adverse Events (SAEs)

An AE is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following regulatory outcome definitions:

1. Death;
2. A life-threatening AE;
   - Note: An AE is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization or prolongation of existing hospitalization;
   - Note: The term "inpatient hospitalization" refers to any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include: emergency room visits; outpatient/same-day/ambulatory procedures; observation/short stay units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/Phase 1 units.
   - Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or

required for the reason for the initial admission as determined by the Investigator or treating physician.

4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
    - Note: An SAE specifically related to visual threat would be interpreted as any potential impairment or damage to the patient's eyes (e.g., hemorrhage, retinal detachment, central corneal ulcer or damage to the optic nerve).
5. A congenital anomaly/birth defect;
6. Important medical event.
    - Note: Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.3 Procedures for Reporting AEs

All AEs and their outcomes must be reported to the study Sponsor or designee, and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities and recorded on the appropriate eCRF. AEs should be reported from the first instillation of study drug until the final study visit.

9.3.1 Reporting a Suspected Unexpected Adverse Reaction

All AEs that are 'suspected' and 'unexpected' are to be reported to CRO, the study Sponsor and the IRB/IEC as required by the IRB/IEC, federal, state, or local regulations and governing health authorities.

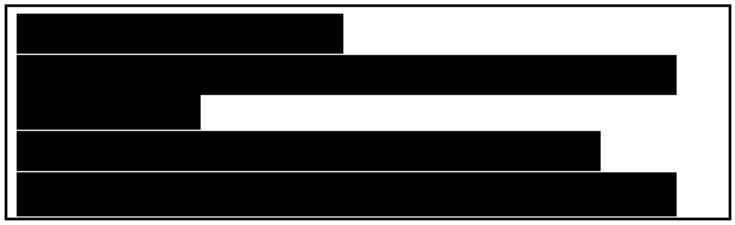
9.3.2 Reporting an SAE

To ensure patient safety, all SAEs, regardless of relationship to the study drug, must be immediately reported (i.e. no later than 24 hours after the site's awareness of the event). All information relevant to the serious AE must be recorded on the appropriate CRFs. The Investigator is obligated to pursue and obtain information requested by CRO and the Sponsor in addition to that information reported on the eCRF. All patients experiencing an SAE must be followed up and the outcome reported.

In the event of an SAE, the Investigator must notify the Sponsor or designee immediately (i.e. no later than 24 hours after the site's awareness of the event); obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient; provide CRO and the study Sponsor with a complete case history, which includes a statement as to whether the

event was or was not suspected to be related to the use of the study drug; and inform the IRB of the AE within their guidelines for reporting SAEs.

Contact information for reporting Serious AEs:



9.4 Procedures for Emergency Unmasking of Study Drug

With each shipment of study drug, sites will also receive one emergency unmasking envelope for every study drug kit received. The envelopes and kits will both be labeled with the same 5-digit study drug kit number. The envelopes are sealed and contain the unmasked treatment information for the corresponding study drug kit.

Envelopes should be stored in a secured location and should only be opened (i.e., breaking the randomization code for that patient) in the event of a medical emergency, or when knowing the treatment assignment is absolutely necessary for the medical management of the study patient. When possible (i.e., in non-emergent situations), the study sponsor or representative should be notified prior to unmasking study drug. In emergency situations, the investigator must notify the sponsor within 24 hours after determining that it is necessary to unmask the treatment assignment. If the investigator determines that emergency unmasking is necessary, the investigator should identify and retrieve the emergency unmasking envelope for the given patient. The emergency unmasking envelope should be opened by the designated site personnel. The investigator must also indicate in source documents and in the eCRF that the mask was broken and provide the date, time, and reason for breaking the mask. Any AE or SAE associated with breaking the mask must be recorded and reported as specified in this protocol.

Patients should have their study drug discontinued immediately if treatment assignment is unmasked.

9.5 Type and Duration of the Follow-up of Patients after AEs

The Investigator will follow unresolved AEs to resolution until the patient is lost to follow-up or until the AE is otherwise explained. Resolution means the patient has returned to baseline state of health or the Investigator does not expect any further improvement or worsening of the AE. If the patient is lost to follow-up, the Investigator should make 3 reasonable attempts to contact the patient via telephone, post, or certified mail. All follow-up will be documented in the patient's source document. Non-serious AEs identified on the last scheduled contact must be recorded on the AE eCRF with the status noted.

If the Investigator becomes aware of any new information regarding an SAE (i.e., resolution, change in condition, or new treatment), a new SAE/Unanticipated Report Form must be completed and faxed to the Sponsor or designee within 24 hours of the site's awareness of the event. The original SAE form is not to be altered. The report should describe whether the event has resolved or continues and how the event was treated.

10 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

10.1 Study Populations

10.1.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population consists of all patients who are randomized. All data will be included and no patients will be excluded because of protocol violations. The ITT population will be analyzed as randomized and will be used for the efficacy analyses.

10.1.2 Safety Population

The Safety population includes all randomized patients who received at least one dose of investigational treatment. The Safety population will be analyzed as treated and will be used for the safety analyses. No data will be excluded for any reason.

10.1.3 Per Protocol Population

The Per Protocol (PP) population is a subset of the ITT population and includes patients who remain in the study through Visit 5 (Day 15) with no major protocol violations that would affect the assessment of the primary efficacy endpoints of the study. Patients without major protocol violations thought to affect the primary efficacy outcome who discontinue the study due to lack of efficacy will be analyzed in the PP analysis with missing data after discontinuation imputed as failures for success/failure endpoints and will be imputed using last observation carried forward (LOCF) for other endpoints. Otherwise, this population will be analyzed as treated using observed data only for confirmatory analyses.

10.2 Unit of Analysis

The unit of analysis in this study will be the study eye for all efficacy and safety summaries. Additionally, non-ocular AEs will be presented at the patient level. Non-study eye safety summaries will also be presented as appropriate.

10.3 General Imputation Methods

The primary analyses of all efficacy data will use LOCF to impute missing data; data for visits after a patient is discontinued for lack of efficacy will be imputed as

failures for success/failure endpoints and will be imputed using LOCF for other endpoints. To check robustness of results, sensitivity analyses of the primary efficacy data will include analyses of observed data only, imputing data from patient visits after discontinuation for lack of efficacy as failures. Other imputation methods may be applied as additional sensitivity analyses.

Per Protocol analyses will use observed data only, with the exception of patients who have missing data due to discontinuation for lack of efficacy; for these patients, missing data after discontinuation will be imputed as failures.

10.4 Efficacy Variables

The primary efficacy variables are:

3. Absence of anterior chamber cells (i.e., score of '0') at Visit 5 (Day 15) for:
    a. The 1.0% concentration of RTA 408 Ophthalmic Suspension compared to placebo
    b. The 0.5% concentration of RTA 408 Ophthalmic Suspension compared to placebo.
4. Absence of pain (i.e., score of '0') at Visit 3 (Day 4) for:
    c. The 1.0% concentration of RTA 408 Ophthalmic Suspension compared to placebo; to be tested if 1a. is statistically significant in favor of the active arm.
    d. The 0.5% concentration of RTA 408 Ophthalmic Suspension compared to placebo; to be tested if 1b. is statistically significant in favor of the active arm.

Secondary efficacy variables include:

1. Absence of anterior chamber cells at Visits 3, 4, or 6 (Days 4, 8 or 21 respectively)
2. Absence of pain at Visits 4, 5 or 6 (Days 8, 15 or 21 respectively)
3. Absence of flare at Visits 3, 4, 5 or 6 (Days 4, 8, 15 or 21 respectively)

10.5 Safety Variables

The safety variables are:

- Slit Lamp Examination
- Pin-hole Visual Acuity
- Intraocular Pressure
- Dilated indirect ophthalmoscopic examination
- AEs

10.6 Statistical Hypotheses

H_{011}: The difference, between study eyes treated with the 1.0% concentration of RTA 408 Ophthalmic Suspension and study eyes treated with placebo, in

the proportion of study eyes with absence of anterior chamber cells (score of 0) at Visit 5 (Day 15) = 0.

H_{A11}: The difference, between study eyes treated with the 1.0% concentration of RTA 408 Ophthalmic Suspension and study eyes treated with placebo in the proportion of study eyes with absence of anterior chamber cells (score of 0) at Visit 5 (Day 15) ≠ 0, with superiority claimed if the difference is greater than 0 (RTA 408 Ophthalmic Suspension – Placebo).

H_{012}: The difference, between study eyes treated with the 0.5% concentration of RTA 408 Ophthalmic Suspension and study eyes treated with Placebo, in the proportion of study eyes with absence of anterior chamber cells (score of 0) at Visit 5 (Day 15) = 0.

H_{A12}: The difference, between study eyes treated with the 0.5% concentration of RTA 408 Ophthalmic Suspension and study eyes treated with placebo in the proportion of study eyes with absence of anterior chamber cells (score of 0) at Visit 5 (Day 15) ≠ 0, with superiority claimed if the difference is greater than 0 (RTA 408 Ophthalmic Suspension – Placebo).

and

H_{021}: The difference, between study eyes treated with the 1.0% concentration of RTA 408 Ophthalmic Suspension and study eyes treated with placebo in the proportion of study eyes with absence of pain (score of 0) at Visit 3 (Day 4) = 0.

H_{A21}: The difference, between study eyes treated with the 1.0% concentration of RTA 408 Ophthalmic Suspension and study eyes treated with placebo in the proportion of study eyes with absence of pain (score of 0) at Visit 3 (Day 4) ≠ 0, with superiority claimed if the difference is greater than 0 (RTA 408 Ophthalmic Suspension – Placebo).

H_{022}: The difference, between study eyes treated with the 0.5% concentration of RTA 408 Ophthalmic Suspension and study eyes treated with placebo in the proportion of study eyes with absence of pain (score of 0) at Visit 3 (Day 4) = 0.

H_{A22}: The difference, between study eyes treated with the 0.5% concentration of RTA 408 Ophthalmic Suspension and study eyes treated with placebo in the proportion of study eyes with absence of pain (score of 0) at Visit 3 (Day 4) ≠ 0, with superiority claimed if the difference is greater than 0 (RTA 408 Ophthalmic Suspension – Placebo).

The primary analyses will first test the difference in the proportion of patients with absence of anterior chamber cells in the study eye between the 1.0% concentration of RTA 408 Ophthalmic Suspension and placebo and between the 0.5% concentration of RTA 408 Ophthalmic Suspension and placebo at Visit 5 (Day 15) using the Pearson chi-squared statistic.

If the proportion of patients with a grade of ‘0’ for anterior chamber cells is statistically significantly higher for the 1.0% concentration versus placebo at a 1-

sided alpha=0.10, then the hierarchical hypothesis testing will compare the proportion of patients with absence of ocular pain at Visit 3 (Day 4) between the 1.0% concentration of RTA 408 Ophthalmic Suspension and placebo using the Pearson chi-squared statistic at a 1-sided alpha=0.10.

If the proportion of patients with a grade of '0' for anterior chamber cells is statistically significantly higher for the 0.5% concentration versus placebo at a 1-sided alpha=0.10, then the hierarchical hypothesis will compare the proportion of patients with absence of ocular pain at Visit 3 (Day 4) between the 0.5% concentration of RTA 408 Ophthalmic Suspension and placebo using the Pearson chi-squared statistic at a one-sided alpha=0.10.
Additionally, 95% confidence intervals will be constructed around the difference in proportions for each primary outcome using asymptotic normal approximations. Fisher's exact tests will be employed in cases of expected counts less than five.

If the test of the difference in the proportion of study eyes with absence of anterior chamber cells is statistically significant in favor of the 1.0% or 0.5% concentration of RTA 408 Ophthalmic Suspension versus placebo, then the study will be considered a success and the concentration(s) of RTA 408 Ophthalmic Suspension showing statistical significance will be declared to be superior to placebo in the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15).

10.7 Sample Size

10.8 Methods of Analyses

Summaries for continuous variables will include the sample size (n), mean, standard deviation, median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means, standard deviations, and medians will be presented to one additional decimal place than reported in the raw values. Summaries for discrete variables will include frequencies and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%). Differences between treatment groups will be calculated as Test – Placebo and change from baseline will be calculated as follow-up visit – baseline. The baseline visit will be defined as the last non-missing measure prior to initiation of investigational treatment.

All efficacy analyses will use a one-sided alpha=0.10 test unless otherwise stated. All summaries will be presented by treatment group and where appropriate by visit.

10.9 Demographics and Baseline Medical History

Patient demographics: gender, race, ethnicity, and age will be presented using discrete summary statistics. Age will also be presented using continuous summary statistics.

Non-ocular and ocular (study eye and fellow eye) medical history will be summarized by treatment group using discrete summaries.

10.10 Primary Efficacy Analyses

The primary efficacy variables, study eyes with absence of anterior chamber cells at Visit 5 (Day 15) and study eyes with absence of pain at Visit 3 (Day 4), will be summarized using discrete summary statistics, including 90% asymptotic normal confidence intervals for each treatment group. The primary efficacy analyses will first test the difference in proportion of study eyes with a grade of '0' in anterior chamber cells between the 1.0% concentration of RTA 408 Ophthalmic Suspension and placebo and between the 0.5% concentration of RTA 408 Ophthalmic Suspension and placebo at Visit 5 (Day 15) using the Pearson chi-squared statistic.
If the proportion of patients with a grade of '0' for anterior chamber cells is statistically significantly higher for the 1.0% concentration versus placebo at a 1-sided alpha=0.10, then the hierarchical hypothesis testing will compare the proportion of patients with absence of ocular pain at Visit 3 (Day 4) between the 1.0% concentration of RTA 408 Ophthalmic Suspension and placebo using the Pearson chi-squared statistic at a 1-sided alpha=0.10.

If the proportion of patients with a grade of '0' for anterior chamber cells is statistically significantly higher for the 0.5% concentration versus placebo at a 1-sided alpha=0.10, then the hierarchical hypothesis will compare the proportion of patients with absence of ocular pain at Visit 3 (Day 4) between the 0.5% concentration of RTA 408 Ophthalmic Suspension and placebo using the Pearson chi-squared statistic at a one-sided alpha=0.10.
Additionally, 95% confidence intervals will be constructed around the difference in proportions for each primary outcome using asymptotic normal approximations. Fisher's exact tests will be employed in cases of expected counts less than five.

If the test of the difference in the proportion of study eyes with absence of anterior chamber cells is statistically significant in favor of the 1.0% or 0.5% concentration of RTA 408 Ophthalmic Suspension versus placebo, then the study will be considered a success and the concentration(s) of RTA 408 Ophthalmic Suspension showing statistical significance will be declared to be superior to placebo in the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15).

Additionally, a Cochran-Armitage test will be used to test for trend separately in the proportion of study eyes with absence of anterior chamber cells and the proportion of study eyes with absence of pain with increasing active concentration, using all three treatment groups.

10.11 Secondary Efficacy Analyses

The secondary efficacy variables will be summarized at Days 4, 8, and 21 for absence of anterior chamber cells and at Days 8, 15 and 21 for absence of ocular pain, similarly to the primary efficacy summaries. Additionally, anterior chamber cell grade and ocular pain score at each visit and change from baseline will be summarized using continuous and discrete summary statistics.

Absence of anterior chamber flare and anterior chamber flare grade and the sum of anterior chamber cell and flare grade, including absence of both anterior chamber cell and flare will be summarized similarly to anterior chamber cells and pain at each visit.

10.12 Safety Analyses

The primary safety analysis will summarize ocular treatment-emergent AEs (TEAEs) in the study eye for all treated patients using discrete summaries at the patient- and event-level by system organ class and preferred term for each treatment group. A TEAE will be defined as occurring on or after the day that treatment is initiated. An additional analysis will investigate ocular AEs for the non-study eye. Non-ocular TEAEs will be summarized using discrete summaries at the patient- and event-level by system organ class and preferred term for each treatment group. Treatment-related ocular and non-ocular TEAEs will be summarized similarly. Ocular and non-ocular TEAEs will also be summarized by severity.

The IOP data will be summarized at each visit using both continuous summaries (including change from baseline) and discrete summaries (including the proportion of patients with change in IOP from baseline $\geq$ 10 mm Hg and the proportion of patients with an IOP $\geq$ 30 mm Hg that occurs at any time following instillation of study treatment) as well as shift tables.

Slit lamp biomicroscopy and dilated indirect ophthalmoscopic examination measures will be summarized at each visit using discrete summary statistics.

Visual acuity data will be summarized at each visit, using discrete summaries, including change from baseline in the number of lines and the proportion of patients with change from previous visit of $\geq$ 2 lines.

10.13 Subgroup Analysis

No subgroup analyses are planned.

10.14 Interim Analysis

No interim analyses are planned.

11 COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES

This study will be conducted in compliance with the protocol, Good Clinical Practices (GCPs), including the International Conference on Harmonization (ICH) Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of study drugs in the countries involved will be adhered to.

11.1 Protection of Human Subjects

11.1.1 Patient Informed Consent

Informed consent must take place before any study specific procedures are initiated. Signed and dated written informed consent must be obtained from each patient and/or from the patient's parent or legal guardian prior to enrollment into the study. If the patient is under the legal age of consent, the consent form must be signed by a legal guardian or as required by state and/or local laws and regulations.

All informed consent forms must be approved for use by the Sponsor and receive approval/favorable opinion from an IRB/IEC prior to their use. If the consent form requires revision (e.g., due to a protocol amendment or significant new safety information), it is the Investigator's responsibility to ensure that the amended informed consent is reviewed and approved by Sponsor prior to submission to the governing IRB/IEC and that it is read, signed and dated by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

If informed consent is taken under special circumstances (oral informed consent), then the procedures to be followed must be determined by CRO and study Sponsor and provided in writing by CRO and study Sponsor prior to the consent process.

11.1.2 Institutional Review Board (IRB) Approval

This study is to be conducted in accordance with Institutional Review Board regulations (U.S. 21 CFR Part 56.103). The Investigator must obtain appropriate IRB approval before initiating the study and re-approval at least annually.

Only an IRB/ERC approved version of the informed consent form will be used.

11.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

11.3 Patient Confidentiality

All personal study patient data collected and processed for the purposes of this study should be maintained by the Investigator and his/her staff with adequate precautions as to ensure that the confidentiality of the data in accordance with local, state, and federal laws and regulations.

Monitors, auditors and other authorized representatives of CRO, the Sponsor, the IRB/IEC approving this study, the FDA, the DHHS, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the study patient's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the patient's identity will not be disclosed in these documents.

11.4 Documentation

Source documents may include a patient's medical records, hospital charts, clinic charts, the Investigator's study patient files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and ECGs. The Investigator's copy of the CRFs serves as the Investigator's record of a patient's study-related data.

11.4.1 Retention of Documentation

All study related correspondence, patient records, consent forms, record of the distribution and use of all study drug and copies of CRFs should be maintained on file for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian.

11.5 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Study Drug

11.5.1 Labeling/Packaging

Each study drug kit will be labeled with a 5-digit study drug kit number and will contain one bottle of study drug. All bottles of active and placebo treatment will be identical in appearance and will be packaged in identical containers. The study drug kit and each bottle will have a label bearing information meeting applicable regulatory requirements. Study drug bottles will come with directions for use and other appropriate information on each part. Study drug will be packaged and labeled based on the randomization list generated prior to the start of the study.

11.5.2 Storage of Study Drug

The study drug product must be stored upright at 2° to 8°C (36° to 46° F), in a refrigerator, protected from freezing, protected from strong light, and stored in a secure area accessible only to the Investigator and his/her designees. The study drug product will be administered only to patients entered into the clinical study, in accordance with the conditions specified in this protocol.

11.5.3 Accountability of Study Drug

The study drug is to only be prescribed by the Principal Investigator or his/her named sub-Investigator(s), and is to only be used in accordance with this protocol. The study drug must only be distributed to patients properly qualified under this protocol to receive study drug.

The Investigator must keep an accurate accounting of the study drug received from the supplier. This includes the amount of study drug dispensed to patients, amount of study drug returned to the Investigator by the patients, and the amount returned or disposed upon the completion of the study. A detailed inventory must be completed for the study drug.

11.5.4 Return or Disposal of Study Drug

All study drug will be returned to the Sponsor or their designee or destroyed at the study site. The return or disposal of study drug will be specified in writing.

11.6 Recording of Data on Source Documents and eCRFs

The Investigator is responsible for ensuring that study data is completely and accurately recorded on each patient's eCRF, source document, and all study-related material. All study data should also be attributable, legible, contemporaneous, and original. Recorded datum should only be corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (e.g., by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data entry should make clear who made the

correction and when, by adding to the correction his/her initials as well as the date of the correction.

11.7 Handling of Biological Specimens

Not applicable.

11.8 Publications

Authorship and manuscript composition will reflect cooperation among all parties involved in the study. Authorship will be established before writing the manuscript. The Sponsor will have the final decision regarding the manuscript and publication.

12 REFERENCES

1. Liu J. Pharmacology of oleanolic acid and ursolic acid. J Ethnopharmacol 1995;49:57-68.
2. Honda T, Rounds BV, Gribble GW, Suh N, Wang Y, Sporn MB. Design and synthesis of 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid, a novel and highly active inhibitor of nitric oxide production in mouse macrophages. Bioorg Med Chem Lett 1998;8:2711-2714.
3. Jabs, D.A., R.B. Nussenblatt, J. T. Rosenbaum. Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 2005, 140(3):509-516.
4. National Institutes of Health (NIH). Numeric Pain Rating Scale (NPRS). Warren Grant Magnuson Clinical Center. Pain Intensity Instruments. July 2003.

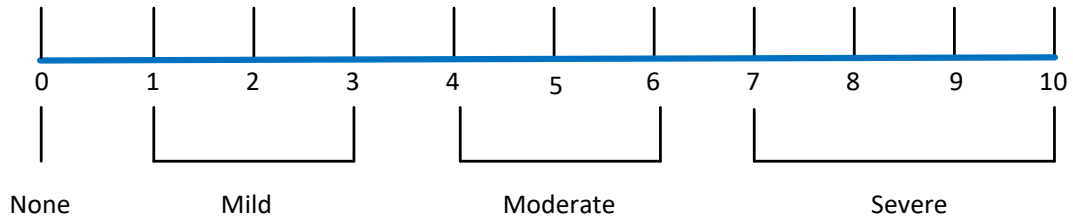
APPENDIX 1: EXAMINATION PROCEDURES

OCULAR PAIN GRADING SCALE (STUDY EYE)

Ocular Pain will be assessed by the patient at screening and at each follow-up visit, utilizing a Numerical Pain Rating Scale[1] graded from 0 to 10. Patients will assess the level of pain they are experiencing in the study eye at the time of the assessment. Patients may only select whole numbers on the scale.

The examiner will ask the patient the following question related to Figure 1:*On a scale of 0 to 10, in which 0 is no pain and 10 is the worst possible or unbearable pain, please mark on the scale the whole number that best describes the pain or discomfort you are feeling in the operated eye at this time. The middle of the scale (around 5) can be used to describe "moderate pain".*

Figure 1 Ocular Pain Grading Scale



At the screening assessment visit, the patient will be asked about the eye scheduled for surgery.

The examiner will record the number selected by the patient on the appropriate eCRF.

[1] Reference 4. National Institutes of Health (NIH). Numeric Pain Rating Scale (NPRS). . Warren Grant Magnuson Clinical Center. Pain Intensity Instruments. July 2003.

APPENDIX 1 (CONTINUED)

PIN-HOLE VISUAL ACUITY PROCEDURES (EACH EYE)

Pin-hole, LogMAR visual acuity must be assessed using an ETDRS chart. The procedure used will be consistent with the recommendations provided for using the ETDRS eye chart. Pin-hole visual acuity should be evaluated at the beginning of each visit in the study (i.e., prior to slit lamp examination). Pin-hole visual acuity testing should be done with a pin-hole occluder.

Equipment

The visual acuity chart to be used is the ETDRS chart. If smaller reproduction (18" by 18", e.g., from Prevent Blindness) wall charts are used, the patient viewing distance should be exactly 10 feet (or as specified by the manufacturer). In ALL cases, for purposes of standardizing the testing conditions during the study, all sites must use only the 'R' charts, and the right eye should be tested first. For reflectance (wall) charts, the chart should be placed frontally and well-illuminated.

Measurement Technique

The chart should be at a comfortable viewing angle. A pin-hole occluder should be applied to the right eye which should be tested first. The patient should attempt to read each letter, line-by-line, left to right, beginning with line 1 at the top of the chart. The patient should be told that the chart has letters only, no numbers. If the patient reads a number, he or she should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number.

The patient should be asked to read slowly, so as to achieve the best identification of each letter. He/she is not to proceed to the next letter until he/she has given a definite response.

If the patient changes a response (e.g., “that was a ‘C’ not an ‘O’”) before he has read aloud the next letter, then the change must be accepted. If the patient changes a response having read the next letter, then the change is not accepted. The examiner should never point to the chart or to specific letters on the chart during the test.

A maximum effort should be made to identify each letter on the chart. When the patient says he or she cannot read a letter, he or she should be encouraged to guess. If the patient identifies a letter as one of two letters, he or she should be asked to choose one letter and, if necessary, to guess. When it becomes evident that no further meaningful readings can be made, despite encouragement to read or guess, the examiner should stop the test for that eye. However, all letters on the last line should be attempted as letter difficulties vary and the last may be the only one read correctly. The number of letters missed or read incorrectly should be noted.

APPENDIX 1 (CONTINUED)

PIN-HOLE VISUAL ACUITY PROCEDURES (cont.)

LogMAR Visual Acuity Calculations

The last line in which a letter is read correctly will be taken as the base logMAR reading. To this value will be added the number "N x 0.02" where 'N' represents the total number of letters missed up to and included in the last line read. This total sum represents the logMAR visual acuity for that eye.

For example: Patient correctly reads 4 of 5 letters on the 0.2 line, and 2 of 5 letters on the 0.1 line.

Base LogMAR	= 0.1
N (total number of letters incorrect on line 0.2 as well as 0.1)	= 4
N x T (T=0.02)	= 0.08
Base logMAR + (N x T)	= 0.1 + 0.08
logMAR VA	**= 0.18**

Repeat the procedure for the left eye.

In order to provide standardized and well-controlled assessments of visual acuity during the study, all visual acuity assessments at a single site must be consistently done using the same lighting conditions and pin-hole during the entire study. If the same conditions and use of pin-hole cannot be used, the reason for the change in condition and pin hole should be documented.

APPENDIX 1 (CONTINUED)

SLIT LAMP BIOMICROSCOPY (EACH EYE):

Slit lamp biomicroscopy will be performed during the study. Observations will be graded as Normal or Abnormal. All abnormal findings, other than the endpoints being assessed by the study scales (anterior chamber cells and flare), will be documented on each patient's source document and corresponding electronic case report form (eCRF). All abnormal findings will be categorized as clinically significant (findings that may interfere with study parameters or otherwise confound the data as determined by the investigator) and not clinically significant.

The following will be examined at each visit:

- Eyelid
- Conjunctiva
- Cornea
- Iris
- Lens
- Anterior chamber

External examination and biomicroscopy will be performed using a slit lamp. Magnification will be consistent with standard clinical practice. The patient will be seated.

APPENDIX 1 (CONTINUED)

DURING SLIT-LAMP BIOMICROSCOPY: ANTERIOR CHAMBER CELLS AND FLARE (STUDY EYE)

The slit beam observations should be assessed in a dark room using a slit beam of 1.0 mm height and 1.0 mm width with maximum luminance, with 16x magnification, 1x1mm oblique high intensity beam fluorescein dye is to be instilled into the ocular cul-de-sac, or alternatively, fluorescein strips may be used to facilitate this examination.

Anterior Chamber Cells and Flare

The anterior chamber cell count will be recorded as the actual number of cells observed if fewer than 10 cells are seen (only white blood cells should be counted; red blood cells and pigment cells should not be counted). Flare will be graded using the SUN* Working Group grading scheme.

Anterior Chamber Cells	
Grade	**Number of Cells in Field**
0	0 cells
1	1 to 10 cells
2	11 to 20 cells
3	21 to 50 cells
4	> 50 cells

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*

*Reference 3. Standardization of the Uveitis Nomenclature (SUN): Jabs et al. 2005.

INTRAOCULAR PRESSURE (IOP) PROCEDURES (EACH EYE)

Applanation tonometry, Goldmann tonometer required. Do NOT use non-contact tonometry.

APPENDIX 1 (CONTINUED)

DILATED INDIRECT OPHTHALMOSCOPIC EXAMINATION (EACH EYE)

Dilated indirect ophthalmoscopic examination will be performed as indicated in the study flowchart in Appendix 2 after the patient ICF/authorization, medical history/demographics, urine pregnancy test (if applicable), pin-hole visual acuity, slit lamp biomicroscopy, and tonometry. The examination will not be performed until the patient's eyes are deemed sufficiently dilated in the opinion of the investigator. The investigator will note any findings present and whether or not the findings are clinically significant or not clinically significant. Findings which are clinically significant will be described.

The following will be examined:

- Vitreous
- Retina
- Macula
- Choroid
- Optic Nerve

APPENDIX 2: SCHEDULE OF VISITS AND MEASUREMENTS

Study Parameter	Visit 1 (≥ -28 Days Prior to Surgery)	Visit 2 (Day 1, 24 ± 6 hrs Post-Surgery)	Visit 3 (Day 4[2])	Visit 4 (Day 8[2])	Visit 5 (Day 15[3])	Visit 6 (Day 21[2], Exit or Early Exit Visit)
Informed Consent/ HIPAA	X					
Demographic Data	X					
Medical and Medication History	X					
Urine Pregnancy Test (for females of childbearing potential)	X					X
Review of Inclusion and Exclusion Criteria	X	X				
Medical and Medication History Update		X	X	X	X	X
Ocular Pain Assessment	X	X	X	X	X	X
Pin-hole Visual Acuity	X	X	X	X	X	X
Slit Lamp Biomicroscopy	X	X	X	X	X	X
Ocular Inflammation Assessment of Anterior Chamber Cell and Flare (at Slit-lamp Biomicroscopy)	X	X	X	X	X	X
Intraocular Pressure Assessment	X	X	X	X	X	X
Randomization of Study Patients		X				
Dilated Indirect Ophthalmoscopic Examination	X					X
Study Drug Instillation[1]		X				
Study Drug and Compliance Diary Instructions and Dispensation		X				
AE Query		X	X	X	X	X
Review of Study Drug Compliance Diary			X	X	X	X
Collection of Study Drug and Compliance Diary					X	X[4]
Exit from Study						X

[1] First study drug dose will be instilled in-office at Visit 2. Patients will instill study drug twice daily at-home in the morning and evening (approximately 12 hrs apart) between study visits, from Day 1 through Day 14.
[2] ± 1 Day
[3] + 1 Day
[4] In case of early termination or if patient did not return study drug prior to Visit 5.

APPENDIX 3: PROTOCOL AMENDMENTS

1. RATIONALE FOR AMENDMENT 1

The purpose of the protocol amendment is to make administrative updates throughout. Exclusion criteria #7 and #23 had additional exclusionary items specified, additional study drug dosing instructions were added to Section 7.1.2, additional details regarding escape medications were specified in Section 8.2.2, and Section 9.1.3 was deleted given Sponsor Pharmacovigilance will assess for adverse event expectedness.

2. SUMMARY OF CHANGES

In the table below the protocol text was amended by the following conventions:

- Deletions to original text are indicated by ~~strike through~~ letters
- Additions to amended text are indicated by **bold** letters
- Replacement of wording in the amended text are indicated by ***bold and italicized*** letters

Section	Reason for Amendment	Protocol Currently Reads	Amended Text
Title Page	Administrative update	[blank]	**Amendment 1: 10-Feb-2014**
Header	Administrative update	RTA 408 Sterile Ophthalmic Suspension	RTA 408 ~~Sterile~~ Ophthalmic Suspension
Header	Administrative update	Original Protocol: 21-Nov-2013	***Amendment 1*: *10-Feb-2014***
Synopsis pg 5 – Inclusion Criteria #4	Administrative update	Have undergone unilateral cataract extraction via phacoemulsification on the day prior to study enrollment/randomization;	Have undergone unilateral cataract extraction via phacoemulsification **and posterior chamber intraocular lens (PCIOL) implantation in the study eye** on the day prior to study enrollment/randomization;
Synopsis pg 5 – Inclusion Criteria #5	Administrative update	Have a grade of ≥2 in anterior chamber cell score on day after surgery (Day 1);	Have a grade of ≥2 in anterior chamber cell score on day after surgery (Day 1) **in the study eye**;
Synopsis pg 5 – Inclusion Criteria #6	Administrative update	Have a potential post-operative pin-hole visual acuity (VA) of greater than 1.0 logarithm of the minimum angle of resolution (logMAR) in the operative eye and fellow eye as measured using an Early Treatment for Diabetic Retinopathy Study (ETDRS) chart;	Have a potential post-operative pin-hole visual acuity (VA) ~~of greater than~~< 1.0 logarithm of the minimum angle of resolution (logMAR) in the operative eye and fellow eye as measured using an Early Treatment for Diabetic Retinopathy Study (ETDRS) chart;
Synopsis pg 5 – Inclusion Criteria #7	Administrative update	(For females of childbearing potential) agree to have urine pregnancy testing performed at screening (must be negative) and at exit visit[1]; must not be lactating; and must agree to use a medically acceptable form of birth control[2] throughout the study duration. _____	(For females of childbearing potential) agree to have urine pregnancy testing performed at screening (must be negative) and at exit visit[1]; must not be lactating; and must agree to use a medically acceptable form of birth control[1] throughout the study duration. _____

		[1] The subject must choose an acceptable method of birth control as specified in inclusion criterion 7 in order to continue in the study. [2] Acceptable forms of birth control are spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of partner. For non-sexually active females, abstinence will be considered an acceptable form of birth control.	~~[1] The subject must choose an acceptable method of birth control as specified in inclusion criterion 7 in order to continue in the study.~~ *1* Acceptable forms of birth control are spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of partner. For non-sexually active females, abstinence will be considered an acceptable form of birth control.
Synopsis pg 6 – Exclusion Criteria #7	Additional exclusion criteria added	Use the following anti-inflammatory or immunomodulating agents systemically, or in the study eye, for the duration of the study. Washout periods for medications prior to surgery are as follows: a. Systemic corticosteroids: 14 days b. Periocular injection of any corticosteroid solution: 28 days c. Corticosteroid depot in the study eye: 56 days after implantation d. Cyclosporine: 56 days e. Topical ocular corticosteroid: 7 days f. Topical ocular NSAID: 7 days	Use anti-inflammatory **agents, analgesics/pain relievers (including opioids, narcotics and other pain medications)** or immunomodulating agents systemically, or in the study eye, **and/or use medications for benign prostatic hyperplasia (BPH), from the washout period through** ~~for~~ the duration of the study. Washout periods for medications prior to surgery are as follows: ***a.*** **Medications for BPH (tamsulosin, silodosin, alfuzosin, finasteride): 28 days** ***b.*** Systemic corticosteroids: 14 days ***c.*** **Systemic analgesics/pain relievers (e.g., gabapentin, pregabalin, NSAIDs and opioids): 14 days** **Note: Use of acetaminophen (up to 4,000 mg/day) and 'baby' aspirin (up to 81 mg/day) during the study are allowed. Use of an opioid during cataract surgery is allowed.** ***d.*** Periocular injection of any corticosteroid solution: 28 days

			e. Corticosteroid depot in the study eye: 56 days after implantation ***f.*** Cyclosporine: 56 days ***g.*** Topical ocular corticosteroid: 7 days ***h.*** Topical ocular NSAID: 7 days
Synopsis pg 7 – Exclusion Criteria #9	Administrative update	Have an IOP ≤ 5 mmHg in either eye;	Have an **intraocular pressure (**IOP**)** ≤ 5 mmHg in either eye;
Synopsis pg 7 – Exclusion Criteria #16	Administrative update	Have had corneal or retinal surgery (laser or incisional) within the past 6 months, or be planning to have laser or incisional surgery during the study period in the study eye;	Have had corneal or retinal surgery (laser or incisional) within the past 6 months, or be planning to have laser or incisional surgery during the study period in the study eye **(other than cataract surgery)**;
Synopsis pg 7 – Exclusion Criteria #17	Administrative update	Have a scheduled surgery in the contralateral eye during the study;	Have ~~a~~ **surgery planned or** scheduled ~~surgery in~~ **for** the contralateral eye during the study;
Synopsis Pg 8 – Exclusion Criteria #23	Additional exclusion criteria added	Have undergone a vitrectomy procedure in addition to the cataract extraction procedure in the study eye;	Have undergone **any other ophthalmic surgical procedure (e.g., vitrectomy, relaxing incisions, iridectomy, conjunctival excisions, use of iris hooks or other iris dilators, etc.)** ~~a vitrectomy procedure~~ in addition to the cataract extraction procedure **and PCIOL implantation** in the study eye;
Synopsis Pg 8 – Exclusion Criteria #24	Administrative update	Have previously enrolled in this clinical study, or will be participating during the follow-up period in another clinical trial that could confound the treatment or outcomes of this investigation;	Have previously enrolled in this clinical study, or ~~will be~~**are planning to** participat***e*** **in another clinical trial** during the follow-up period**,** ~~in another clinical trial~~ that could confound the treatment or outcomes of this investigation;
Synopsis Pg 10 – General Statistical	Administrative update	If in addition to a statistically significant test of the difference in the proportion of study eyes with	~~If in addition to a statistically significant test of the difference in the proportion of study eyes with~~

Methods and Types of Analyses: Efficacy Analysis (5th Paragraph)		absence of anterior chamber cells at Visit 5 (Day 15) in favor of RTA 408 Ophthalmic Suspension, the test of the difference in the proportion of study eyes with absence of ocular pain at Visit 3 (Day 4) is statistically significant in favor of RTA 408 Ophthalmic Suspension, then RTA 408 Ophthalmic Suspension will be declared to be superior to placebo in both the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15) and the proportion of study eyes with absence of ocular pain at Visit 3 (Day 4).	~~absence of anterior chamber cells at Visit 5 (Day 15) in favor of RTA 408 Ophthalmic Suspension, the test of the difference in the proportion of study eyes with absence of ocular pain at Visit 3 (Day 4) is statistically significant in favor of RTA 408 Ophthalmic Suspension, then RTA 408 Ophthalmic Suspension will be declared to be superior to placebo in both the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15) and the proportion of study eyes with absence of ocular pain at Visit 3 (Day 4).~~
Synopsis Pg 11 – General Statistical Methods and Types of Analyses: General Considerations (5th and 6th Paragraphs)	Administrative update	The secondary efficacy variables, study eyes with absence of anterior chamber cells (Visits 3, 4 or 6), study eyes with absence of pain (Visits 4, 5 or 6) and study eyes with absence of flare (Visits 3, 4, 5 or 6) will be summarized and analyzed similarly to the primary efficacy summaries and analyses. Additionally, anterior chamber cells and flare as well as pain at each visit and change from baseline will be summarized using continuous and discrete summary statistics. The sum of anterior chamber cells and flare grade will be summarized and analyzed similarly to anterior chamber cells and flare separately.	The secondary efficacy variables, study eyes with absence of anterior chamber cells (Visits 3, 4 or 6), study eyes with absence of pain (Visits 4, 5 or 6) and study eyes with absence of flare (Visits 3, 4, 5 or 6) will be summarized ~~and analyzed~~ similarly to the primary efficacy summaries ~~and analyses~~. Additionally, anterior chamber cells and flare as well as pain at each visit and change from baseline will be summarized using continuous and discrete summary statistics. The sum of anterior chamber cells and flare grade will be summarized ~~and analyzed~~ similarly to anterior chamber cells and flare separately.
List of Abbreviations	Administrative update	… BID Bis in die (twice daily) CFR Code of Federal Regulations …	… BID Bis in die (twice daily) **BPH Benign prostatic hyperplasia** CFR Code of Federal Regulations

		NSAID Non-steroidal anti-inflammatory agent PDR Proliferative diabetic retinopathy …	… NSAID Non-steroidal anti-inflammatory agent **PCIOL Posterior chamber intraocular lens** PDR Proliferative diabetic retinopathy ...
Section 4 Paragraph 2	Administrative update	. . .The Investigator will then perform a slit lamp biomicroscopic examination with IOP measurement, and grading of anterior chamber inflammation. A dilated indirect ophthalmoscopic examination will also be performed. Female patients of childbearing potential will be given a urine pregnancy test.	...The Investigator will then perform a slit lamp biomicroscopic examination with **intraocular pressure (**IOP**)** measurement, and grading of anterior chamber inflammation. A dilated indirect ophthalmoscopic examination will also be performed. Female patients of childbearing potential will be given a urine pregnancy test.
Section 4 Paragraph 3	Administrative update	…Qualifying patients (with ≥2 score in anterior chamber cell, IOP ≤22 mm Hg) will then be randomized to one of the following treatment groups (in a 1:1:1 ratio): RTA 408 Ophthalmic Suspension 0.5% (N=35), RTA 408 Ophthalmic Suspension 1.0% (N=35), or placebo for RTA 408 Ophthalmic Suspension (N=35).	…Qualifying patients ~~(with ≥2 score in anterior chamber cell, IOP ≤22 mm Hg)~~ will then be randomized to one of the following treatment groups (in a 1:1:1 ratio): RTA 408 Ophthalmic Suspension 0.5% (N=35), RTA 408 Ophthalmic Suspension 1.0% (N=35), or placebo for RTA 408 Ophthalmic Suspension (N=35).
Section 5.3 Inclusion Criteria #4	Administrative update	Have undergone unilateral cataract extraction via phacoemulsification on the day prior to study enrollment/randomization;	Have undergone unilateral cataract extraction via phacoemulsification **and posterior chamber intraocular lens (PCIOL) implantation in the study eye** on the day prior to study enrollment/randomization;
Section 5.3 Inclusion Criteria #5	Administrative update	Have a grade of ≥2 in anterior chamber cell score on day after surgery (Day 1);	Have a grade of ≥2 in anterior chamber cell score on day after surgery (Day 1) **in the study eye**;
Section 5.3	Administrative	Have a potential post-operative pin-hole visual	Have a potential post-operative pin-hole visual

Inclusion Criteria #6	update	acuity (VA) of greater than 1.0 logarithm of the minimum angle of resolution (logMAR) in the operative eye and fellow eye as measured using an Early Treatment for Diabetic Retinopathy Study (ETDRS) chart;	acuity (VA) ~~of greater than~~< 1.0 logarithm of the minimum angle of resolution (logMAR) in the operative eye and fellow eye as measured using an Early Treatment for Diabetic Retinopathy Study (ETDRS) chart;
Section 5.3 Inclusion Criteria #7	Administrative update	(For females of childbearing potential) agree to have urine pregnancy testing performed at screening (must be negative) and at exit visit[1]; must not be lactating; and must agree to use a medically acceptable form of birth control[2] throughout the study duration. _____ [1] The subject must choose an acceptable method of birth control as specified in inclusion criterion 7 in order to continue in the study. [2] Acceptable forms of birth control are spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of partner. For non-sexually active females, abstinence will be considered an acceptable form of birth control.	(For females of childbearing potential) agree to have urine pregnancy testing performed at screening (must be negative) and at exit visit[1]; must not be lactating; and must agree to use a medically acceptable form of birth control[1] throughout the study duration. _____ [1] ~~The subject must choose an acceptable method of birth control as specified in inclusion criterion 7 in order to continue in the study.~~ [1] Acceptable forms of birth control are spermicide with barrier, oral contraceptive, injectable or implantable method of contraception, transdermal contraceptive, intrauterine device, or surgical sterilization of partner. For non-sexually active females, abstinence will be considered an acceptable form of birth control.
Section 5.4 Exclusion Criteria #7	Additional exclusion criteria added	Use the following anti-inflammatory or immunomodulating agents systemically, or in the study eye, for the duration of the study. Washout periods for medications prior to surgery are as follows: a. Systemic corticosteroids: 14 days b. Periocular injection of any corticosteroid solution: 28 days	Use anti-inflammatory **agents, analgesics/pain relievers (including opioids, narcotics and other pain medications)** or immunomodulating agents systemically, or in the study eye, **and/or use medications for benign prostatic hyperplasia (BPH), from the washout period through** ~~for~~ the duration of the study. Washout periods for medications prior to surgery are as

		c. Corticosteroid depot in the study eye: 56 days after implantation d. Cyclosporine: 56 days e. Topical ocular corticosteroid: 7 days f. Topical ocular NSAID: 7 days	follows: ***a.*** **Medications for BPH (tamsulosin, silodosin, alfuzosin, finasteride): 28 days** ***b.*** Systemic corticosteroids: 14 days ***c.*** **Systemic analgesics/pain relievers (e.g., gabapentin, pregabalin, NSAIDs and opioids): 14 days** **Note: Use of acetaminophen (up to 4,000 mg/day) and 'baby' aspirin (up to 81 mg/day) during the study are allowed. Use of an opioid during cataract surgery is allowed.** ***d.*** Periocular injection of any corticosteroid solution: 28 days ***e.*** Corticosteroid depot in the study eye: 56 days after implantation ***f.*** Cyclosporine: 56 days ***g.*** Topical ocular corticosteroid: 7 days ***h.*** Topical ocular NSAID: 7 days
Section 5.4 Exclusion Criteria #9	Administrative update	Have an IOP $\leq$ 5 mmHg in either eye;	Have an **intraocular pressure (**IOP**)** $\leq$ 5 mmHg in either eye;
Section 5.4 Exclusion Criteria #16	Administrative update	Have had corneal or retinal surgery (laser or incisional) within the past 6 months, or be planning to have laser or incisional surgery during the study period in the study eye;	Have had corneal or retinal surgery (laser or incisional) within the past 6 months, or be planning to have laser or incisional surgery during the study period in the study eye **(other than cataract surgery)**;
Section 5.4 Exclusion Criteria #17	Administrative update	Have a scheduled surgery in the contralateral eye during the study;	Have ~~a~~ **surgery planned or** scheduled ~~surgery in~~ **for** the contralateral eye during the study;

Section 5.4 Exclusion Criteria #23	Additional exclusion criteria added	Have undergone a vitrectomy procedure in addition to the cataract extraction procedure in the study eye;	Have undergone **any other ophthalmic surgical procedure (e.g., vitrectomy, relaxing incisions, iridectomy, conjunctival excisions, use of iris hooks or other iris dilators, etc.)** ~~a vitrectomy procedure~~ in addition to the cataract extraction procedure **and PCIOL implantation** in the study eye;
Section 5.4 Exclusion Criteria #24	Administrative update	Have previously enrolled in this clinical study, or will be participating during the follow-up period in another clinical trial that could confound the treatment or outcomes of this investigation;	Have previously enrolled in this clinical study, or ~~will be~~**are planning to participate in another clinical trial** ~~participating~~ during the follow-up period**,** ~~in another clinical trial~~ that could confound the treatment or outcomes of this investigation;
Section 6.1.2	Administrative update	This clinical study is designed to evaluate the efficacy and safety of two concentrations of RTA 408 Ophthalmic Suspension compared to placebo in the treatment of inflammation and pain following ocular surgery. To demonstrate clinical efficacy, RTA 408 Ophthalmic Suspension must be effective in eliminating anterior chamber cells (i.e. score of '0') at Visit 5 (Day 15) post-ocular surgery. If, in addition to absence of anterior chamber cells, RTA 408 Ophthalmic Suspension is also effective in elimination of ocular pain (i.e. score of '0') at Visit 3 (Day 4) post-ocular surgery, then absence of pain will also be claimed.	~~This clinical study is designed to evaluate the efficacy and safety of two concentrations of RTA 408 Ophthalmic Suspension compared to placebo in the treatment of inflammation and pain following ocular surgery. To demonstrate clinical efficacy, RTA 408 Ophthalmic Suspension must be effective in eliminating anterior chamber cells (i.e. score of '0') at Visit 5 (Day 15) post ocular surgery. If, in addition to absence of anterior chamber cells, RTA 408 Ophthalmic Suspension is also effective in elimination of ocular pain (i.e. score of '0') at Visit 3 (Day 4) post ocular surgery, then absence of pain will also be claimed.~~
Section 7.1.2 3rd Bullet Point	Additional dosing instructions specified	Instructions to patients on study drug administration will include: Remove from refrigerator. SHAKE WELL BEFORE USE. Instill one drop twice daily for 14 days in the	Instructions to patients on study drug administration will include: Remove from refrigerator. SHAKE WELL BEFORE USE. Instill one drop twice daily for 14 days in

		morning and evening (approximately 12 hours apart) in the eye that underwent surgery. Return drug to refrigerator for storage after each use. Discontinue use of the study drug after completing second dose on Day 14. Keep out of reach of children.	the morning and evening (approximately 12 hours apart) in the eye that underwent surgery. **Study drug must be not be instilled within 30 minutes of after instillation of any other ocular medications or artificial tears.** Return **the study** drug to refrigerator for storage after each use. Discontinue use of the study drug after **instilling** ~~completing~~ **the** second dose on Day 14. Keep out of reach of children.
Section 8.1.3	Administrative update	Study staff will confirm that the patient has not used prior to Day 1 for the indicated washout interval and for the duration of the study, any of the following disallowed medications, systemically or in the study eye, grouped by washout period: … <u>14 days</u> • Systemic corticosteroids <u>28 days</u> • Periocular injection of any corticosteroid solution	Study staff will confirm that the patient has not used prior to Day 1 for the indicated washout interval ~~and for the duration of the study~~, any of the following disallowed medications, systemically or in the study eye, grouped by washout period: … <u>14 days</u> • Systemic corticosteroids • **Systemic analgesics/pain relievers (e.g., gabapentin, pregabalin, NSAIDs and opioids)** **Note: Use of acetaminophen (up to 4,000 mg/day) and 'baby' aspirin (up to 81 mg/day) during the study are allowed. Use of an opioid during cataract surgery is allowed.** <u>28 days</u> • Periocular injection of any corticosteroid solution

			• **Medications for BPH (tamsulosin, silodosin, alfuzosin, finasteride)**
Section 8.2.1	Administrative update	• Glaucoma medications or ocular hypertension medications in the study eye • Ocular hypertension medications in the study eye … • Vitrectomy procedure in addition to the cataract extraction procedure in the study eye • If a patient uses a disallowed medication, this will be recorded as a protocol violation.	• **Systemic medications for benign prostatic hyperplasia (BPH) (e.g., tamsulosin, silodosin, alfuzosin, finasteride).** • **Systemic Analgesics/pain relievers, including opioids, narcotics and other pain medications systemically (e.g., gabapentin, pregabalin, NSAIDs and opioids).** • **Note: Use of acetaminophen (up to 4,000 mg/day) and 'baby' aspirin (up to 81 mg/day) during the study are allowed. Use of an opioid during cataract surgery is allowed.** • Glaucoma medications **or ocular hypertension medications** in the study eye • ~~Ocular hypertension medications in the study eye~~ … • **Any other ophthalmic surgical procedure (e.g., vitrectomy, relaxing incisions, iridectomy, conjunctival excisions, use of iris hooks or other iris dilators, etc.)** ~~Vitrectomy procedure~~ in addition to the cataract extraction procedure **and PCIOL implantation** in the study eye • **Plan to have laser or incisional surgery in the study eye (other than cataract surgery);**

			• **Surgery planned or scheduled for the contralateral eye;** If a patient uses a disallowed medication, this **use** will be recorded as a protocol violation.
Section 8.2.2	Additional details specified for escape medications	Use of escape medications should be avoided if possible. If escape medication is given, the study drug should be discontinued and the patient should remain in the study and followed per the protocol to the end of the study.	Use of escape medications should be avoided if possible. If **in the investigator's assessment** escape medication is **required** ~~given~~ **due to lack of efficacy**, the study drug should be discontinued **prior to** administration of **the first dose of escape medication.** ~~and~~ ***T***he patient should remain in the study**,** and **continue to be** followed per the protocol **for all remaining visits and assessments** to the end of the study. **These patients who require escape medication should be considered as discontinued from study medication due to lack of efficacy, and the escape medication(s) used must be documented in the eCRF.**
Section 8.3.1.1 Sub-bullet Pin-Hole Visual Acuity Utilizing an ETDRS Chart	Administrative update	Patients must have a potential post-operative pin-hole VA of greater than 1.0 logMAR in the operative eye and in the fellow eye as measured using an ETDRS chart.	Patients must have a potential post-operative pin-hole VA ~~of greater than~~< 1.0 logMAR in the operative eye and in the fellow eye as measured using an ETDRS chart.
Section 8.4.2	Administrative update	These visits may be performed in order to ensure patient safety. All information gathered at unscheduled visits should be recorded on the Unscheduled Visit/Early Exit Visit pages of the Source Document and corresponding eCRF. If a randomized patient does not attend their scheduled visit, the eCRF pages for the missed visit	These visits may be performed in order to ensure patient safety. All information gathered at unscheduled visits should be recorded on the Unscheduled Visit~~/Early Exit Visit~~ pages of the Source Document and corresponding eCRF. If a randomized patient does not attend their scheduled visit, the eCRF pages for the missed

		will be skipped. All efforts should be made to schedule patients for an Exit Visit to complete Exit Procedures.	visit will be skipped. All efforts should be made to schedule patients for an Exit Visit to complete Exit Procedures. **Information from Early Exit Visits should be recorded on the Visit 6/Exit Visit pages.**
Section 8.5	Administrative update	Patients will be provided with a study drug compliance diary to document BID dosing for 14 days. Patient compliance with dosing will be assessed by in-office review of study drug compliance diary. Patients who miss more than 25% of their study drug doses (*more than* 7 doses) will be considered non-compliant with dosing and a protocol deviation should be recorded.	Patients will be provided with a study drug compliance diary to document BID dosing for 14 days. Patient compliance with dosing will be assessed by in-office review of study drug compliance diary. Patients who miss more than 25% of their study drug doses (*more than* 7 **total** doses) will be considered non-compliant with dosing and a protocol deviation should be recorded.
Section 8.6.1 Completed Patients	Administrative update	A completed patient is one who has not been discontinued from the study.	A completed patient is one who has not been discontinued from the study **and continues study assessments through Visit 6 (Day 21)**.
Section 8.6.2 Discontinued Patients	Administrative update	Patients may be discontinued prior to their completion of the study due to any of the following reasons: … Notification of a patient's discontinuation and the reason for discontinuation will be made to CRO and study Sponsor and will be clearly documented on the eCRF.	Patients may be discontinued **from the study** prior to their completion of the study due to any of the following reasons: … **Notification of a patient's discontinuation of study drug administration and the reason for discontinuation will be made to CRO and study Sponsor and will be clearly documented on the eCRF. Patients who receive escape medication are to discontinue study drug administration and are to remain in the study and be followed per the protocol to the end of**

			the study. Patients who discontinue study drug administration for other reasons are encouraged to remain in the study and continue with study assessments through the end of the study. Notification of a patient's discontinuation **of study participation** and the reason for discontinuation will be made to CRO and study Sponsor and will be clearly documented on the eCRF.
Section 9.1.3	Sponsor Pharmacovigilance will assess for expectedness	The expectedness of an AE should be determined based upon existing safety information about the study drug using these explanations: • *Unexpected*: an AE that is not listed in the IB or is not listed at the specificity or severity that has been observed. • *Expected*: an AE that is listed in the IB at the specificity and severity that has been observed. • *Not applicable*: An AE unrelated to the study drug. AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with thethe particular drug under investigation are to be considered unexpected.	~~The expectedness of an AE should be determined based upon existing safety information about the study drug using these explanations:~~ ~~• *Unexpected*: an AE that is not listed in the IB or is not listed at the specificity or severity that has been observed.~~ ~~• *Expected*: an AE that is listed in the IB at the specificity and severity that has been observed.~~ ~~• *Not applicable*: An AE unrelated to the study drug.~~ ~~AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with thethe particular drug under investigation are to be considered unexpected.~~
Section 9.5 Paragraph 2	Administrative update	If the Investigator becomes aware of any new information regarding an SAE (i.e., resolution,	If the Investigator becomes aware of any new information regarding an SAE (i.e., resolution,

		change in condition, or new treatment), a new SAE/Unanticipated Report Form must be completed and faxed to CRO within 24 hours of the site's awareness of the event.	change in condition, or new treatment), a new SAE/Unanticipated Report Form must be completed and faxed to **the Sponsor or designee** ~~CRO~~ within 24 hours of the site's awareness of the event.
Section 10.6	Administrative update	If in addition to a statistically significant test of the difference in the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15) in favor of the 1.0% concentration of RTA 408 Ophthalmic Suspension, the test of the difference in the proportion of study eyes with absence of ocular pain at Visit 3 (Day 4) is statistically significant in favor of the 1.0% RTA 408 Ophthalmic Suspension, then the 1.0% concentration of RTA 408 Ophthalmic Suspension will be declared to be superior to placebo in both the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15) and the proportion of study eyes with absence of ocular pain at Visit 3 (Day 4). OR If in addition to a statistically significant test of the difference in the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15) in favor of the 0.5% concentration of RTA 408 Ophthalmic Suspension, the test of the difference in the proportion of study eyes with absence of ocular pain at Visit 3 (Day 4) is statistically significant in favor of the 0.5% RTA 408 Ophthalmic Suspension, then the 0.5% concentration of RTA 408 Ophthalmic Suspension will be declared to be superior to placebo in both	~~If in addition to a statistically significant test of the difference in the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15) in favor of the 1.0% concentration of RTA 408 Ophthalmic Suspension, the test of the difference in the proportion of study eyes with absence of ocular pain at Visit 3 (Day 4) is statistically significant in favor of the 1.0% RTA 408 Ophthalmic Suspension, then the 1.0% concentration of RTA 408 Ophthalmic Suspension will be declared to be superior to placebo in both the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15) and the proportion of study eyes with absence of ocular pain at Visit 3 (Day 4).~~ ~~OR~~ ~~If in addition to a statistically significant test of the difference in the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15) in favor of the 0.5% concentration of RTA 408 Ophthalmic Suspension, the test of the difference in the proportion of study eyes with absence of ocular pain at Visit 3 (Day 4) is statistically significant in favor of the 0.5% RTA 408 Ophthalmic Suspension, then the 0.5% concentration of RTA 408 Ophthalmic Suspension will be declared to be superior to~~

		the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15) and the proportion of study eyes with absence of ocular pain at Visit 3 (Day 4).	~~placebo in both the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15) and the proportion of study eyes with absence of ocular pain at Visit 3 (Day 4).~~
Section 10.10	Administrative update	If in addition to a statistically significant test of the difference in the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15) in favor of the 1.0% concentration of RTA 408 Ophthalmic Suspension, the test of the difference in the proportion of study eyes with absence of ocular pain at Visit 3 (Day 4) is statistically significant in favor of the 1.0% RTA 408 Ophthalmic Suspension, then the 1.0% concentration of RTA 408 Ophthalmic Suspension will be declared to be superior to placebo in both the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15) and the proportion of study eyes with absence of ocular pain at Visit 3 (Day 4). OR If in addition to a statistically significant test of the difference in the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15) in favor of the 0.5% concentration of RTA 408 Ophthalmic Suspension, the test of the difference in the proportion of study eyes with absence of ocular pain at Visit 3 (Day 4) is statistically significant in favor of the 0.5% RTA 408 Ophthalmic Suspension, then the 0.5% concentration of RTA 408 Ophthalmic Suspension will be declared to be superior to placebo in both the proportion of study eyes with absence of	~~If in addition to a statistically significant test of the difference in the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15) in favor of the 1.0% concentration of RTA 408 Ophthalmic Suspension, the test of the difference in the proportion of study eyes with absence of ocular pain at Visit 3 (Day 4) is statistically significant in favor of the 1.0% RTA 408 Ophthalmic Suspension, then the 1.0% concentration of RTA 408 Ophthalmic Suspension will be declared to be superior to placebo in both the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15) and the proportion of study eyes with absence of ocular pain at Visit 3 (Day 4).~~ ~~OR~~ ~~If in addition to a statistically significant test of the difference in the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15) in favor of the 0.5% concentration of RTA 408 Ophthalmic Suspension, the test of the difference in the proportion of study eyes with absence of ocular pain at Visit 3 (Day 4) is statistically significant in favor of the 0.5% RTA 408 Ophthalmic Suspension, then the 0.5% concentration of RTA 408 Ophthalmic Suspension will be declared to be superior to placebo in both the proportion of study eyes with~~

		anterior chamber cells at Visit 5 (Day 15) and the proportion of study eyes with absence of ocular pain at Visit 3 (Day 4). If in addition to a statistically significant test of the difference in the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15) in favor of the 1.0% concentration of RTA 408 Ophthalmic Suspension, the anterior chamber cells at Visit 5 (Day 15) is statistically significant in favor of the 0.5% concentration of RTA 408 Ophthalmic Suspension, then both concentrations of RTA 408 Ophthalmic Suspension will be declared to be superior to placebo in the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15). Finally, if a statistically significant test of the difference in the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15) in favor of the 0.5% concentration of RTA 408 Ophthalmic Suspension, the test of the difference in the proportion of study eyes with absence of ocular pain at Visit 3 (Day 4) is statistically significant in favor of the 0.5% RTA 408 Ophthalmic Suspension, then the 0.5% concentration of RTA 408 Ophthalmic Suspension will be declared to be superior to placebo in both the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15) and the proportion of study eyes with absence of ocular pain at Visit 3 (Day 4).	~~absence of anterior chamber cells at Visit 5 (Day 15) and the proportion of study eyes with absence of ocular pain at Visit 3 (Day 4).~~ ~~If in addition to a statistically significant test of the difference in the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15) in favor of the 1.0% concentration of RTA 408 Ophthalmic Suspension, the anterior chamber cells at Visit 5 (Day 15) is statistically significant in favor of the 0.5% concentration of RTA 408 Ophthalmic Suspension, then both concentrations of RTA 408 Ophthalmic Suspension will be declared to be superior to placebo in the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15).~~ ~~Finally, if a statistically significant test of the difference in the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15) in favor of the 0.5% concentration of RTA 408 Ophthalmic Suspension, the test of the difference in the proportion of study eyes with absence of ocular pain at Visit 3 (Day 4) is statistically significant in favor of the 0.5% RTA 408 Ophthalmic Suspension, then the 0.5% concentration of RTA 408 Ophthalmic Suspension will be declared to be superior to placebo in both the proportion of study eyes with absence of anterior chamber cells at Visit 5 (Day 15) and the proportion of study eyes with absence of ocular pain at Visit 3 (Day 4).~~
Section 10.11	Administrative update	The secondary efficacy variables will be summarized and analyzed at Days 4, 8, and 21 for	The secondary efficacy variables will be summarized ~~and analyzed~~ at Days 4, 8, and 21 for

		absence of anterior chamber cells and at Days 8, 15 and 21 for absence of ocular pain, similarly to the primary efficacy summaries and analyses. Additionally, anterior chamber cell grade and ocular pain score at each visit and change from baseline will be summarized using continuous and discrete summary statistics. Absence of anterior chamber flare and anterior chamber flare grade and the sum of anterior chamber cell and flare grade, including absence of both anterior chamber cell and flare will be summarized and analyzed similarly to anterior chamber cells and pain at each visit.	absence of anterior chamber cells and at Days 8, 15 and 21 for absence of ocular pain, similarly to the primary efficacy summaries ~~and analyses~~. Additionally, anterior chamber cell grade and ocular pain score at each visit and change from baseline will be summarized using continuous and discrete summary statistics. Absence of anterior chamber flare and anterior chamber flare grade and the sum of anterior chamber cell and flare grade, including absence of both anterior chamber cell and flare will be summarized ~~and analyzed~~ similarly to anterior chamber cells and pain at each visit.
Appendix 1 Ocular Pain Grading Scale (Study Eye)	Administrative update	Ocular Pain will be assessed by the patient at screening and at each follow-up visit, utilizing a Numerical Pain Rating Scale[1] graded from 0 to 10. Patients will assess the level of pain they are experiencing in the study eye at the time of the assessment. The examiner will ask the patient the following question: On a scale of 0 to 10, in which 0 is no pain and 10 is the worst possible or unbearable pain, please mark on the scale the number that best describes the pain or discomfort you are feeling in the operated* eye at this time. The middle of the scale (around 5) can be used to describe “moderate pain”. *At the screening assessment visit, the patient will be asked about the eye scheduled for surgery.	Ocular Pain will be assessed by the patient at screening and at each follow-up visit, utilizing a Numerical Pain Rating Scale[1] graded from 0 to 10. Patients will assess the level of pain they are experiencing in the study eye at the time of the assessment. **Patients may only select whole numbers on the scale.** The examiner will ask the patient the following question **related to Figure 1**: On a scale of 0 to 10, in which 0 is no pain and 10 is the worst possible or unbearable pain, please mark on the scale the **whole** number that best describes the pain or discomfort you are feeling in the operated~~*~~ eye at this time. The middle of the scale (around 5) can be used to describe “moderate pain”.

		1 Reference 4. Numeric Pain Rating Scale (NPRS). National Institutes of Health (NIH), Warren Grant Magnuson Clinical Center. Pain Intensity Instruments. July 2003.	**Figure 1 Ocular Pain Grading Scale** … ~~*~~At the screening assessment visit, the patient will be asked about the eye scheduled for surgery. 1 Reference 4. **National Institutes of Health (NIH).** Numeric Pain Rating Scale (NPRS). ~~National Institutes of Health (NIH),~~**.** Warren Grant Magnuson Clinical Center. Pain Intensity Instruments. July 2003.
Appendix 2 Footnote #4	Administrative update	In case of early termination or if patient did not return study drug at prior to Visit 5.	In case of early termination or if patient did not return study drug ~~at~~ prior to Visit 5.
Appendix 3	Rationale for Amendment 1 and the Table of Changes was inserted	Not applicable.	[Rationale for amendment 1 and the table of changes was inserted]
Appendix 4	Administrative update	Protocol Number: 408-C-1307	Protocol Number: 408-C-1307 **Amendment 1**
Appendix 4	Administrative update	Final Date: 21-Nov-2013	Final Date: ***10-Feb-2014***
Appendix 5	Administrative update	Protocol Number: 408-C-1307	Protocol Number: 408-C-1307 **Amendment 1**
Appendix 5	Administrative update	Final Date: 21-Nov-2013	Final Date: ***10-Feb-2014***

APPENDIX 4: SPONSOR APPROVALS

Protocol Title:	A Multicenter, Randomized, Dose-Ranging, Double-Masked, Placebo Controlled Phase 2 Study Evaluating the Safety and Efficacy of RTA 408 Ophthalmic Suspension for the Treatment of Ocular Inflammation and Pain following Ocular Surgery
Protocol Number:	408-C-1307 Amendment 1
Final Date:	10-Feb-2014

This clinical study protocol was subject to critical review and has been approved by the Sponsor.

[redacted]

APPENDIX 5: INVESTIGATOR'S SIGNATURE

Protocol Title: A Multicenter, Randomized, Dose-Ranging, Double-Masked, Placebo Controlled Phase 2 Study Evaluating the Safety and Efficacy of RTA 408 Ophthalmic Suspension for the Treatment of Ocular Inflammation and Pain following Ocular Surgery

Protocol Number: 408-C-1307 Amendment 1

Final Date: 10-Feb-2014

I agree to implement and conduct the study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations. I agree to maintain all information supplied by CRO and the Sponsor in confidence and, when this information is submitted to an Institutional Review Board (IRB), Ethical Review Committee (ERC) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety, including the above statement, and I agree to all aspects.

Signed:_____ Date:_____

<enter name and credentials>
<enter title>
<enter affiliation>
<enter address>
<enter phone number>