CLINICAL STUDY PROTOCOL - NPIF-2018-01

Nepafenac Punctal Plug Delivery System, 204 µg/L67

IND 136640

A CLINICAL STUDY EVALUATING THE SAFETY AND EFFICACY OF A PUNCTAL PLUG DELIVERY SYSTEM (Evolute®) OF NEPAFENAC (N-PPDS) COMPARED WITH A PLACEBO PUNCTAL PLUG DELIVERY SYSTEM (p-PPDS) IN CONTROLLING POST-OPERATIVE OCULAR PAIN AND INFLAMMATION IN SUBJECTS UNDERGOING ROUTINE UNILATERAL CATARACT SURGERY

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Protocol Version 5: April 25, 2018

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Protocol Version 7: August 27, 2018

Mati Therapeutics Inc.
4317 Dunning Lane
Austin TX 78746

PROTOCOL APPROVAL

Protocol Number: NPIF-2018-01

Title of Protocol: A Clinical Study Evaluating the Safety and Efficacy of a Punctal Plug Delivery System (Evolute®) of Nepafenac (N-PPDS) compared with a Placebo Punctal Plug Delivery System (p-PPDS) in Controlling Post-Operative Ocular Pain and inflammation in Subjects undergoing Routine Unilateral Cataract Surgery

Prepared by: _____ 27 Aug, 18
Daniel Schwob, Consultant — Date
D'Ellis Group Inc.

Study Director: _____ _____
Robert Williams, MD — Date
Clinical Consultant

Approved by: _____ _____
Deepank Utkhede — Date
Chief Scientific Officer,
Mati Therapeutics Inc.

Approved by: _____ _____
Robert Butchofsky — Date
President,
Mati Therapeutics Inc.

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Prepared by:

Daniel Schwob, Consultant
D'Ellis Group Inc.

Date

Study Director:

Robert Williams, MD
Clinical Consultant

8/27/18
Date

Approved by:

Deepank Utkhede
Chief Scientific Officer,
Mati Therapeutics Inc.

Date

Approved by:

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Approved by: _____ _____
Deepank Utkhede — Date
Chief Scientific Officer,
Mati Therapeutics Inc.

Approved by:  8/27/18
Robert Butchofsky — Date
President,
Mati Therapeutics Inc.

STATEMENT OF COMPLIANCE

Mati Therapeutics Inc. Protocol NPIF-2018-01

A CLINICAL STUDY EVALUATING THE SAFETY AND EFFICACY OF A PUNCTAL PLUG DELIVERY SYSTEM (Evolute®) OF NEPAFENAC (N-PPDS) COMPARED WITH A PLACEBO PUNCTAL PLUG DELIVERY SYSTEM (P-PPDS) IN CONTROLLING POST-OPERATIVE OCULAR PAIN AND INFLAMMATION IN SUBJECTS UNDERGOING ROUTINE UNILATERAL CATARACT SURGERY

Protocol Version Date: June 27 2018

Sponsor and Medical Monitor Approval:

Signature:_____Date: _____
Dr. Robert Williams, M.D., Medical Monitor

Investigator Agreement:

I have read this protocol. I agree to:

a. Implement and conduct this study in strict compliance with this agreement; the protocol; ICH guidelines for Good Clinical Practices and all other applicable regulatory requirements. No deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from an Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard(s) to the study participants.
b. Obtain written Informed Consent (IC), that is IRB/IEC approved, from each prospective study subject at screening and prior to any study specific examination/test.
c. Maintain reliable study medication dispensing/dosing log, receipt and return shipping records, and to store study supplies in a secure, locked facility accessible only to authorized study personnel
d. Maintain adequate and accurate source documents in accordance with Food and Drug Administration (FDA) regulations (e.g., CRFs, consent forms, AE/SAE forms, IRB/IEC documentation, study supply records). Keep source documentation for the maximum period of time permitted by the hospital, institution, or private practice. In addition, will notify the Sponsor immediately if any documents are to be destroyed, transferred to a different facility or owner
e. Maintain all information supplied by Mati Therapeutics Inc. in confidence and, when this information is submitted to an independent IRB/IEC or any other group, it will be submitted with a designation that the material is confidential.
f. Attempt to complete the study within the time designated
g. By signing this protocol, the Investigator grants permission to personnel from the Sponsor, its representatives, third parties and appropriate regulatory authorities for on-site monitoring and review of all appropriate study documentation, as well as on-site review of the procedures employed in data collection, where clinically appropriate.

Investigator Signature: _____Date:_____
"TYPE/Print Name of INVESTIGATOR"

Acknowledged By/Sponsor's Representative Signature:

_____Date:_____
"TYPE/Print Name of Representative"

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

ACCF	Anterior Chamber Cells and Flare
ADE	Adverse Device Effect
AE	Adverse Event
AI	Arcuate Incision
BCDVA	Best-Corrected Distance Visual Acuity
BCVA	Best-Corrected Visual Acuity
CE	Cataract Extraction
CFR	Code of Federal Regulations
CRF	Case Report Form
CRC	Clinical Research Coordinator
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICH E6	International Conference on Harmonisation Guidance for Industry, Good Clinical Practice: Consolidated Guidance
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IOL	Intraocular Lens
IRB	Investigational Review Board
LRI	Limbal Relaxing Incision
LSMEANS	Least-squares Means
NCR	No Carbon Required
N-PPDS	Nepafenac Punctal Plug Deliver System
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
p-PPDS	placebo Punctal Plug Delivery System (plug does not contain an active drug core)
PCO	Posterior Capsule Opacity
PI	Principal Investigator
PP	Punctal Plug
PPDS	Punctal Plug Delivery System
QC	Quality Control
SAE	Serious Adverse Event
SOIS	Summed Ocular Inflammation Score
Study Subject	An individual that has signed a HIPAA form and an IRB approved study consent form
SubjectIndividual	being considered for enrollment in to the study
UP	Unanticipated Problem

STUDY SYNOPSIS

Title: A clinical study evaluating the safety and efficacy of punctal plug delivery system (Evolute®) of Nepafenac (N-PPDS) compared with a Placebo Punctal Plug Delivery System (p-PPDS) in Controlling Post-Operative Ocular Pain and inflammation in Subjects undergoing Routine Unilateral Cataract Surgery

Sponsor: Mati Therapeutics Inc.

Clinical Phase: 2

Investigational Masked Product: N-PPDS (Nepafenac Punctal Plug Deliver System) is an L-shaped, silicone punctal plug with a drug eluting core that contains nepafenac (active)

Comparator Masked Product: p-PPDS (placebo Punctal Plug Delivery System) is an L-shaped, silicone punctal plug with a drug insert that contains no active ingredient (placebo).

Number of Sites: up to 3 sites in the USA.

Study Population: Approximately 75 qualified subjects (75 eyes) who have given written consent, have met all study inclusion/exclusion criteria and are scheduled to undergo unilateral cataract surgery with the implantation of an intraocular lens (IOL) will be enrolled in to the study.

***Study Objectives*:** To evaluate the safety and ocular efficacy of N-PPDS in controlling post-operative ocular pain and inflammation associated with cataract surgery.

Study Design: This is a Phase 2, multi-center, randomized, parallel-arm, double-masked, placebo-controlled study. One (1) to 2 days prior to their scheduled cataract surgery, each study subject will be randomized (2:1) in to one of two treatment groups:

Group A: A total of 50 study subjects (50 eyes) will have an N-PPDS inserted in the lower punctum of their scheduled surgical eye.

Group B: A total of 25 study subjects (25 eyes) will have a p-PPDS inserted in the lower punctum of their scheduled surgical eye.

All plugs will remain in the study subject's lower punctum for a period of 2 weeks following cataract surgery.

Subject Selection: The following are inclusion and exclusion criteria for a prospective study subject:

Study Inclusion Criteria:

1. A male or female subject in good general health, $\geq$ 22 years of age at the time of the screening visit
2. A patient must be able to read, comprehend and willing to give HIPAA & informed consent.
3. A woman of child-bearing potential must not be pregnant or lactating, must have a negative pregnancy test at screening and must be practicing an adequate method of birth control. Acceptable methods of birth control include intrauterine device (IUD); oral, dermal ("patch"), implant or injected contraceptives; tubal ligation; and barrier methods with spermicide.
4. A subject has the availability, willingness and sufficient cognitive awareness to comply with exam procedures and able to return for all scheduled study visits
5. A subject with a cataract for which routine phacoemulsification extraction and implantation of an intraocular lens has been planned
6. A subject has a preoperative corneal astigmatism of 3.0 D or less in their scheduled operative eye
7. A subject with clear ocular media other than cataract in their scheduled operative eye
8. A subject has the potential for a post-operative Snellen BCDVA of 20/30 or better in their scheduled surgical eye
9. A subject has a lower puncta that can be dilated to 1.0 mm in their scheduled surgical eye
10. A subject with a dry eye condition being treated with a marketed punctal plug, where the marketed plug will be replaced by a masked study plug.

Study Pre-Operative Exclusion Criteria:

1. A subject with a history of complications, adverse events, trauma or disease in the nasolacrimal area, whether or not it was due to punctal plug wear, including but not limited to dacryocystitis, inflammation or canaliculitis in either eye
2. A subject with structural lid abnormalities (e.g., ectropion, entropion) in their scheduled surgical eye
3. A subject with a puncta >0.9 mm prior to dilation in their scheduled surgical eye
4. A subject experiencing any ocular pain in either eye at the screening visit or on the day the plug is to be inserted
5. A subject with any moderate to severe lid, conjunctival or corneal findings in either eye at the screening visit
6. A subject with any signs of intraocular inflammation (cells/flare) in either eye at the screening visit
7. A subject with a known sensitivity to nepafenac or any inactive ingredient of the punctum plug, silicone, fluorescein, topical anesthetic, or any other products required for study procedures or cataract surgery
8. A subject with a history as a steroid responder
9. A subject with a known or suspected allergy or hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs), or to any component of the test article
10. A subject with only one eye with potentially good vision
11. A subject with a known pathology that may affect visual acuity (as determined by the Investigator); particularly retinal changes that affect vision (macular degeneration, cystoid macular edema, proliferative diabetic retinopathy, etc.) in their scheduled surgical eye
12. A subject that has a condition associated with the fluctuation of hormones that could lead to refractive changes
13. A subject with amblyopia or strabismus
14. A subject with capsule or zonular abnormalities with preoperative lens tilt and/or decentration (e.g., Marfan's syndrome), or may affect postoperative centration or tilt of the lens (e.g. pseudoexfoliation syndrome)
15. A subject has a history of ocular trauma in their scheduled surgical eye
16. A subject that has undergone prior intraocular surgery in the scheduled surgical eye within the last 6 months or laser surgery within three months prior to screening
17. A subject with pupil abnormalities (non-reactive, tonic pupils, abnormally shaped pupils, or pupils that do not dilate at least 3.5 mm under mesopic/scotopic conditions) in their scheduled surgical eye.
18. A subject with a corneal abnormality (e.g., stromal, epithelial or endothelial dystrophies) in their scheduled surgical eye
19. A subject with evidence of clinically significant keratoconus in their scheduled surgical eye
20. A subject with evidence of Epithelial Basement Membrane Dystrophy on slit-lamp exam
21. A subject that has been wearing PMMA lenses within 6 months, gas permeable lenses within one month, or extended-wear or daily soft contact lens within 7 days of their scheduled surgery
22. A subject with an inability to achieve keratometric stability for contact lens wearers
23. A subject with a history of chronic/recurrent inflammatory eye disease (e.g., scleritis, uveitis, herpes keratitis) in either eye
24. A subject with uncontrolled glaucoma
25. A subject that requires an LRI or AI procedure before, during or after cataract surgery
26. A subject that may or is expected to undergo surgical intervention prior to or during the study period other than cataract surgery
27. A subject that requires the use of systemic or ophthalmic NSAIDs or corticosteroid medications during the study period, with the exception of a subject who has been prescribed and has been taking a baby aspirin (≤81mg/daily), (Note: All other NSAIDs or corticosteroid medications must be discontinued at least 48 hours prior to the insertion of the punctal plug)
28. A subject that requires the use of systemic or ocular medications that may affect vision, ocular inflammation or pain
29. A subject with an acute or chronic disease, or illness, that would increase risk or confound study results (e.g., autoimmune disease, connective tissue disease, immunocompromised, suspected glaucoma, glaucomatous changes in the fundus or visual field, ocular inflammation, etc.)
30. A subject with an uncontrolled systemic disease: A potential subject in whom therapy for a systemic disease is not yet stabilized will not be considered for entry into the study

31. A subject with diabetes that is poorly controlled
32. A subject currently participating or has participated in another clinical trial within 30 days prior to enrollment.
33. A subject that requires a stent implant during cataract extraction, with the exception of the implantation of the iStent® by GLAUKOS®

Intra-Operative Exclusion Criteria (Surgical Complications):

1. Sulcus-sulcus or bag-sulcus fixation
2. Posterior capsular rupture or zonular dialysis
3. Disruption of anterior hyaloids face
4. Vitreous loss
5. Capsulorhexis tear
6. Floppy iris syndrome
7. Requirement for the use of trypan blue, capsular tension ring or other intraocular device other than the IOL
8. Inability to place IOL in capsular bag
9. Significant anterior chamber hyphema
10. Zonular rupture.

***Study Duration*:** The project study duration is approximately six months. The study is projected to start in the 1st quarter of 2018.

Study Variables: At the study pre-op and each scheduled post-op visits, the following procedures will be performed and recorded:

a. Uncorrected distance visual acuity testing (Visit 1, 5, 6 and 7 only)

b. Manifest Refraction (Visit 1, 6 and 7 only)

c. Slit Lamp Examination [Lid, conjunctiva, cornea, anterior chamber cells and flare (ACCF)]

NOTE: The Investigator that performs the slit-lamp evaluation at Visit 4 (Day 1 post-op) should perform the slit-lamp evaluation at ALL post-op visits

d. Record the use of permitted concomitant medication(s), alteration in use or addition of any open-label medication(s) during the study period.

e. Investigator evaluation of ocular pain

NOTE: The Investigator that interviews and record the subject's response to ocular pain at Visit 4 (Day 1 post-op) should interview the subject at ALL post-op visits (Visits 4, 5, 6 and 7).

f. Assessment of any reported Adverse Events

Additional procedures will be performed and recorded at Visit 1 (Screening/Baseline, Day -30 to -1), Visit 2 (Punctal Plug Insertion Visit, 1-2 days pre-op), Visit 3 (Surgical day, Day 0) and Visit 7 (Final study visit, Day 14 post-op)

a. Visit 1:
   - Grade Cataract Density (scale: 1 to 4)
   - Fundus examination
   - Evaluation of lower puncta

b. Visit 2:
   - Insertion of masked study punctal plug
   - Inspection of the punctal plug via the slit-lamp in addition, performed at each follow-up visit.

NOTE: All NSAIDs or corticosteroid medications, with the exception of a subject who has been prescribed and has been taking a baby aspirin (≤81mg/daily), must be discontinued at least 48 hours prior to the insertion of the punctal plug.

c. Visit 3:
   - Pupil measurements (prior to and immediately following surgery)
   - Monocular cataract extraction/IOL implantation
     - Indicate the incision Type, Location and Size (mm)
     - Nucleus removal time
     - Ease Cortex removal
     - Effective Phaco Power (Phaco Time and Power)
     - Type of IOL (e.g., monofocal, toric etc.) and lens power
     - Record any surgical complications
   - Subject reported AEs prior to or after surgery

d. Visit 7:
   - Fundus examination

Study Efficacy Variables:

Primary: Investigator evaluation of study subject post-op ocular pain at visits 4, 5, 6 and 7.

Secondary: Mean anterior chamber scores for cells and flare at visits 4, 5, 6 and 7

Study Safety Variables: Safety outcome measures include

a. Distance visual acuity
b. Slit Lamp Examination (Lid, conjunctiva, cornea)
c. Fundus Examination
d. Use of concomitant (rescue) medication(s)
e. Incidents of reported Adverse Events

Sample Size Determination: Since this is a pilot study, no formal sample size estimation was performed.

Schedule of Assessments, Events

EXAM PARAMETERS	v1	v2	v3	v4	v5	v6	v7
Inform Consent/HIPPA	❶						
Demographic data/Medical Hx	❶ A						
Concomitant Medication	❶	❷	❸	❹	❺	❻	❼
Urine Pregnancy Test (if applicable)	❶ B						
Subject Randomization to Treatment		❷					
Investigator Evaluation of Ocular Pain	❶ C	❷		❹ F	❺ F	❻ F	❼ F
Uncorrected Distance VA	❶ C				❺	❻	❼
Manifest Refraction	❶ C					❻	❼
Best-Corrected Distance VA	❶ C					❻	❼
Slit Lamp Examination	❶ C			❹ F	❺ F	❻ F	❼ F
Insertion of Masked Punctal Plug		❷					
Inspection of Masked Punctal Plug		❷ D	❸ E	❹ D	❺ D	❻ D	❼ D
Evaluation of lower puncta	❶						
Pupil Measurements			❸ G				
Type and Grade Cataract	❶						
Monocular Cataract Extraction/IOL Implantation			❸				
Fundus Examination	❶						❼
Removal of Masked Punctal Plug							❼ H
Adverse Event Recording		❷	❸	❹	❺	❻	❼

Keys to Abbreviations:

A = Prior 12 months
B = Pregnancy test (women of childbearing potential)
C = Evaluation of Both Eyes
D = Evaluation using slit-lamp
E = Visual inspection after surgery
F = Investigator that performs the slit-lamp and/or ocular pain evaluation at Visit 4 (Day 1 post-op) should perform ALL post-op visit evaluations
G = Measurement to occur prior to surgery and immediately after surgery
H = All masked punctal plugs must be removed at the subject last visit

Visit Schedule:

v1 = Day -30 to -1
v2 = 1 to 2 days prior to surgery
v3 = Surgery Day
v4 = 1 day post-op
v5 = 3 ± 1 days post-op
v6 = 7 ± 1 days post-op
v7 = 14 ± 2 days post-op

1 KEY ROLES

Investigators: Eric Donnenfeld, MD
ericdonnenfeld@gmail.com
Site 1: Ophthalmic Consultants of Long Island
711 Stewart Ave
Garden City, NY 11530
516 500-4200
Site 2: Island Eye Surgicenter – Carle Place
1500 Jericho Turnpike
Westbury, NY 11590
516 877-2400

Edward Holland, MD
eholland@holprovision.com
Cincinnati Eye Institute – Edgewood
580 South Loop Road, Suite 200
Edgewood, KY 41017
859 331-9000

Kerry Solomon, MD
kds@cepmd.com
Site 1: Carolina Eyecare Physicians, LLC.
1101 Clarity Rd., Suite 100
Mt. Pleasant, SC 29464
843 881-3937
Site 2: The Physician's Eye Surgery Center
2060 Charlie Hall Blvd, Suite 301
Charleston, SC 29414
843 203-5799

Medical Monitor: Robert Williams, MD
89 Wilks Way
Friday Harbor, WA 98250
360 378-7916
iopdoc1@gmail.com

Sponsor: Mati Therapeutics Inc. (Headquarters)
4317 Dunning Lane
Austin, TX 78746
512 329-6360

Sponsor Personnel
Clinical Trial Coordinator: Deepank (Deeps) Utkhede
Chief Scientific Officer

Mati Therapeutics Canada Inc. (R&D Branch)
201-4475 Wayburne Drive
Burnaby, BC V5G 4X4
778 991-3301
dutkhede@matitherapeutics.com

Study Monitor/Biostatistician:

Daniel Schwob
D'Ellis Group, Inc.
26741 Portola Pkwy, Ste 1E 717
Foothill Ranch, CA 92610
949 916-2800/949 735-1320
dschwob@dellisgroup.com

Regulatory Specialist:

Caroline Stokl, Ph.D.,
Consultant, Regulatory Affairs
201-4475 Wayburne Drive
Burnaby, BC V5G 4X4
604 983-9103
cstokl@matitherapeutics.com

Emergency Telephone Numbers:

24 hour Adverse Event FAX number	360 282-6871
Robert Williams, MD	Office: 360.378-7916 Cell: 360.298-5325
Deepank Utkhede	Cell: 778.991-3301
Daniel Schwob	Office: 949.916-2800 Cell: 949.735-1320

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

This study will be conducted in compliance with the protocol, International Conference on Harmonization (ICH), Good Clinical Practice (GCP) guidelines and applicable regulatory requirements.

2.1 Background Information

Punctal plugs are medical devices designed to block the drainage of tear fluid from the eye; several models are approved and commercially available. Punctal plugs are classified by the FDA as a Class II Pre-Amendment medical device. Furthermore, plugs are not identified as significant risk devices on the FDA Information Sheet titled "Significant Risk and Non-Significant Risk Medical Device Studies."

Mati Therapeutics Inc. is the first to use punctal plugs as an anchoring device for a drug delivery platform. A drug-eluting core is inserted into Mati's proprietary punctal plug (Evolute® PPDS), which allows medication to be continuously released into the tear film of the eye over a period of time. This platform has the potential to become a viable alternative to eye drop therapy and could address significant compliance issues that currently exist with patients who will not or cannot properly self-administer eye drop medications.

Cataract surgery is the most commonly performed surgery in the nation, with more than 3.5 million of these procedures done annually in the United States. Multiple studies have reported noncompliance and self-administration difficulties with topical medications among cataract surgery patients (Kholdebarin 2008; Winfield 1990). A 2014 study showed that 92.6% of patients incorrectly administered topical medications after cataract surgery (An 2014).

Although recent advances in cataract extraction (CE) surgery have decreased the physical trauma associated with ocular surgery, disruption of the blood–aqueous barrier during surgery can lead to the release of inflammatory mediators, increasing the risk of secondary ocular complications. Favorable post-operative outcome depends on the proper use of topical medications to shorten the inflammatory response induced by cataract surgery. Untreated, post-operative inflammation can increase the risk of mild iritis with increased cells and flare in the anterior chamber (AC) and can interfere with the patient's visual rehabilitation. In rare cases, inflammation can lead to complications such as cystoid macular edema, posterior capsule fibrosis, keratopathy, fibrin reaction, or chronic uveitis. Therefore, anti-inflammatory agents are routinely prescribed to resolve post-op signs and symptoms of cataract surgery more rapidly and to improve patient comfort.

The US Food and Drug Administration approved Nepafenac ophthalmic suspension 0.1% (NEVANAC ®) in 2005 and Nepafenac ophthalmic suspension 0.3% (ILVERO®) in 2005 from Alcon Laboratories, Fort Worth, Texas, USA. Both ophthalmic suspension concentrations received an indication for the treatment of pain and inflammation associated with cataract surgery.

NEVANAC® ophthalmic suspension was compared with its vehicle in two double-masked, randomized clinical trials in which patients were dosed three-times-daily beginning one day prior to cataract surgery, continued on the day of surgery and for the first two weeks of the postoperative period. Nepafenac 0.1% treated patients were less likely to have ocular pain and measurable signs of inflammation (cells and flare) in the early postoperative period through the end of treatment than those treated with its vehicle. For ocular pain, both studies had a significantly higher percentage of patients (approximately 80%) in the Nepafenac group reporting no ocular pain on the day following cataract surgery (Day 1) compared to those in the vehicle group (approximately 50%).

ILEVRO® ophthalmic suspension was compared with its vehicle in two double-masked, randomized clinical trials in which patients were dosed once a day beginning one day prior to cataract surgery, continued on the day of surgery and for the first two weeks of the postoperative period. Nepafenac 0.3% treated patients were less likely to have ocular pain and measurable signs of inflammation (aqueous cells and flare) in the early postoperative period through to the end of treatment than those treated with its vehicle. In the two studies, Nepafenac cleared inflammation at day 14 post operation in 65% and 61% of patients compared to 32% and 24% of patients on vehicle. Pain free rates in the Nepafenac group were 86% and 84% compared to 46% and 38% of patients on vehicle. The Day 14 results for reduction of both pain and inflammation were statistically significantly superior to the vehicle.

This study will enroll approximately 75 qualified subjects (75 eyes) who have given written consent, have met all study inclusion/exclusion criteria and are scheduled to undergo unilateral cataract surgery with the implantation of an intraocular lens (IOL) will be enrolled in to the study.

2.2 Rationale

Past clinical studies with topical dosing of 0.1% and 0.3% ophthalmic suspensions of Nepafenac (NEVANAC®/ILEVRO®) have demonstrated the safety and efficacy of Nepafenac in the treatment of pain and inflammation associated with ocular surgery. The objective for this study is to evaluate the use of a punctal plug drug delivery device that can deliver a sustained, safe and effective concentration of Nepafenac to a subject undergoing cataract surgery, for the treatment of post-operative ocular pain and inflammation.

Placebo has been selected as the control group. This will allow the results obtained from this study to be compared to treatment results from similarly design Phase 3 and 3B studies of Nepafenac.

2.3 Potential Risks and Benefits

2.3.1 Known Potential Risks

A study subject randomized to receive N-PPDS may have unforeseen risk and could exhibit moderate to severe post-op inflammation and/or ocular pain. However, the risk associated with using N-PPDS to deliver a sustain release of Nepafenac are anticipated to be similar, if not less than, those of commercially available topical 0.1% and 0.3% ophthalmic suspension

of Nepafenac and silicone punctal plug products. In ocular surgery clinical studies with Nevanac®, adverse reactions that occurred in 5-15% of study patients included capsular opacity, decreased visual acuity, foreign body sensation, increase intraocular pressure, and sticky sensation. Adverse reactions that occurred in 1-5% of study patients included conjunctival edema, corneal edema, dry eye, lid margin crusting, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, photophobia, tearing and vitreous detachment. Some of these reactions may have been the consequence of the surgical procedure. A summary of known potential risks to humans of topical 0.1% and 0.3% ophthalmic suspension of Nepafenac can be found in the NEVANAC® and ILEVRO® prescribing information (see Appendices 4 and 5).

A study subject randomized to receive a placebo Punctal Plug Delivery System (p-PPDS) could exhibit moderate to severe post-op inflammation and/or ocular pain. Other risks associated with using a p-PPDS are anticipated to be similar to commercially available punctal plugs use in humans. A study subject could experience ocular discomfort, epiphora, loss of plug, ocular inflammation, and subconjunctival hemorrhage. Less common, but serious, side effects are pyogenic granuloma, damage to the muscle at the opening of the punctum, canaliculitis, or migration of the plug into the canaliculus requiring irrigation or surgery.

2.3.2 Known Potential Benefits

The potential benefit associated with the use of N-PPDS to deliver a sustain release of nepafenac is the reduction of post-operative ocular inflammation and ocular pain. In addition, the use of N-PPDS eliminates the subject non-compliance issue with daily dosing of an anti-inflammatory drug.

A summary of known benefits to humans of topical 0.1% and 0.3% ophthalmic suspensions of nepafenac can be found in the NEVANAC® and ILEVRO® prescribing information (see Appendices 4 and 5).

3 OBJECTIVES AND PURPOSE

To evaluate the safety and efficacy of N-PPDS in the treatment of post-operative ocular pain and inflammation associated with cataract surgery.

4 STUDY DESIGN AND ENDPOINTS

4.1 Description of the Study Design

This is a Phase 2, multi-center, randomized, parallel-arm, double-masked, placebo-controlled study. One (1) to 2 days prior to their scheduled cataract surgery, each study subject will be randomized (2:1) in to one of two treatment groups:

Group A: A total of 50 study subjects (50 eyes) will have an N-PPDS inserted in the lower punctum of their scheduled surgical eye.

Group B: A total of 25 study subjects (25 eyes) will have a p-PPDS inserted in the lower punctum of their scheduled surgical eye.

All plugs will remain in the study subject's lower punctum for a period of 2 weeks following cataract surgery.

4.2 Study Endpoints

The study will be complete when 75 study subjects (75 eyes) have been evaluated at Visit 7 (Day 14 post-op) or have been terminated from the study.

4.2.1 Primary Efficacy Endpoint

The primary effectiveness endpoint will analyze the Investigator's evaluation of study subject's ocular pain following cataract surgery compared with placebo at 1, 3, 7 and 14 days post-op.

4.2.2 Secondary Efficacy Endpoints

The secondary effectiveness will analyze the complete (CR) and partial response (PR) to therapy regarding the Summed Ocular Inflammation Score (sum of the mean anterior chamber cells and flare) following cataract surgery compared with placebo at 3, 7 and 14 days post-op.

4.2.3 Safety Endpoints

Safety assessments will include the incidence and severity of reported AEs after randomization, distance visual acuity, slit-lamp biomicroscopy findings, fundus findings, and use of concomitant rescue medications.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Subject Inclusion Criteria

The following are inclusion criteria for a prospective study subject:

1. A male or female subject in good general health, ≥22 years of age at the time of the screening visit

2. A patient must be able to read, comprehend and willing to give HIPAA & informed consent.

3. A woman of child-bearing potential must not be pregnant or lactating, must have a negative pregnancy test at screening and must be practicing an adequate method of birth control. Acceptable methods of birth control include intrauterine device (IUD); oral, dermal ("patch"), implant or injected contraceptives; tubal ligation; and barrier methods with spermicide.

4. A subject has the availability, willingness and sufficient cognitive awareness to comply with exam procedures and able to return for all scheduled study visits

5. A subject with a cataract for which routine phacoemulsification extraction and implantation of an intraocular lens has been planned

6. A subject has a preoperative corneal astigmatism of 3.0 D or less in their scheduled operative eye

7. A subject with clear ocular media other than cataract in their scheduled operative eye

8. A subject has the potential for a post-operative Snellen BCDVA of 20/30 or better in their scheduled surgical eye

9. A subject has a lower puncta that can be dilated to 1.0 mm in their scheduled surgical eye.

10. A patient with a dry eye condition being treated with a marketed punctal plug, where the marketed punctal plug will be replaced by a masked study plug.

5.2 Subject Pre-Operative Exclusion Criteria

The following are pre-surgical exclusion criteria for a prospective study subject:

1. A subject with a history of complications, adverse events, trauma or disease in the nasolacrimal area, whether or not it was due to punctal plug wear, including but not limited to dacryocystitis, inflammation or canaliculitis in either eye

2. A subject with structural lid abnormalities (e.g., ectropion, entropion) in their schedule surgical eye

3. A subject with a puncta >0.9 mm prior to dilation in their scheduled surgical eye

4. A subject experiencing any ocular pain in either eye at the screening visit or on the day the plug is to be inserted

5. A subject with any moderate to severe lid, conjunctival or corneal findings in either eye at the screening visit

6. A subject with any signs of intraocular inflammation (cells/flare) in either eye at the screening visit

7. A subject with a known sensitivity to nepafenac or any inactive ingredient of the punctum plug, silicone, fluorescein, topical anesthetic, or any other products required for study procedures or cataract surgery

8. A subject with a history as a steroid responder

9. A subject with a known or suspected allergy or hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs), or to any component of the test article

10. A subject with only one eye with potentially good vision

11. A subject with a known pathology that may affect visual acuity (as determined by the Investigator); particularly retinal changes that affect vision (macular degeneration, cystoid macular edema, proliferative diabetic retinopathy, etc.) in their scheduled surgical eye

12. A subject that has a condition associated with the fluctuation of hormones that could lead to refractive changes

13. A subject with amblyopia or strabismus

14. A subject with capsule or zonular abnormalities with preoperative lens tilt and/or decentration (e.g., Marfan's syndrome), or may affect postoperative centration or tilt of the lens (e.g. pseudoexfoliation syndrome)

15. A subject has a history of ocular trauma in their scheduled surgical eye

16. A subject that has undergone prior intraocular surgery in the scheduled surgical eye within the last 6 months or laser surgery within three months prior to screening

17. A subject with pupil abnormalities (non-reactive, tonic pupils, abnormally shaped pupils, or pupils that do not dilate at least 3.5 mm under mesopic/scotopic conditions) in their scheduled surgical eye.

18. A subject with a corneal abnormality (e.g., stromal, epithelial or endothelial dystrophies) in their scheduled surgical eye

19. A subject with evidence of clinically significant keratoconus in their scheduled surgical eye

20. A subject with evidence of Epithelial Basement Membrane Dystrophy on slit-lamp exam

21. A subject that has been wearing PMMA lenses within 6 months, gas permeable lenses within one month, or extended-wear or daily soft contact lens within 7 days of their scheduled surgery

22. A subject with an inability to achieve keratometric stability for contact lens wearers

23. A subject with a history of chronic/recurrent inflammatory eye disease (e.g., scleritis, uveitis, herpes keratitis) in either eye

24. A subject with uncontrolled glaucoma

25. A subject that requires an LRI or AI procedure before, during or after cataract surgery

26. A subject that may or is expected to undergo surgical intervention prior to or during the study period other than cataract surgery

27. A subject that requires the use of systemic or ophthalmic NSAIDs or corticosteroid medications during the study period, with the exception of a subject who has been prescribed and has been taking a baby aspirin (≤81mg/daily), (Note: All other NSAIDs or corticosteroid medications must be discontinued at least 48 hours prior to the insertion of the punctal plug)

28. A subject that requires the use of systemic or ocular medications that may affect vision, ocular inflammation or pain

29. A subject with an acute or chronic disease, or illness, that would increase risk or confound study results (e.g., autoimmune disease, connective tissue disease, immunocompromised, suspected glaucoma, glaucomatous changes in the fundus or visual field, ocular inflammation, etc.)

30. A subject with an uncontrolled systemic disease: A potential subject in whom therapy for a systemic disease is not yet stabilized will not be considered for entry into the study

31. A subject with diabetes that is poorly controlled

32. A subject currently participating or has participated in another clinical trial within 30 days prior to enrollment.

33. A subject that requires a stent implant during cataract extraction, with the exception of the implantation of the iStent® by GLAUKOS®.

5.3 Intra-Operative Exclusion Criteria (Surgical Complications)

If any of the following surgical complication occurs during cataract surgery, the study subject will be discontinued from the study (see Section 5.5.2.2 regarding handling of discontinued study subjects), have their study punctal plug removed and excluded from further participation in the study:

1. Sulcus-sulcus or bag-sulcus fixation

2. Posterior capsular rupture or zonular dialysis

3. Disruption of anterior hyaloids face

4. Vitreous loss

5. Capsulorhexis tear

6. Floppy iris syndrome

7. Requirement for the use of trypan blue, capsular tension ring or other intraocular device other than the IOL

8. Inability to place IOL in capsular bag

9. Significant anterior chamber hyphema

10. Zonular rupture.

5.4 Strategies for Recruitment and Retention

To increase study subject enrollment and retention in the study, sites should dedicate an individual [Clinical Research Coordinator (CRC)] who is well informed regarding the study design, required inclusion/exclusion criteria and visit schedule, as the main contact who is readily available to answer all potential subject questions and/or concerns about participating in the clinical study. The CRC should be prepared to discuss with a potential study subject the differences in the amount of time, examination procedures and visit schedule they would experience if they agreed to participate in the study. In addition, should a subject agree to participate in the study, the CRC would be readily available and their main contact person while participating in the study.

To encourage recruitment and retention of a study subject, sites should offer a subject reimbursement for transportation cost and a stipend for their time and effort for participation, offer less waiting time in the doctor's office by scheduling more flexible and reliable appointment times. In addition, discuss the advantages of participating in the study by not having to remember or instilling one less drop prior to or after cataract surgery.

5.5 Study Subject Withdrawal or Termination Criteria

Each study subject will be informed that they are free to withdraw from the study at any time. The Investigator, the Investigator in consultation with the Medical Monitor, or the Medical Monitor may exercise his or her medical judgment to terminate a study subject's participation in the study if it is in the best interest of the study subject. A terminated study subject will be followed through Day 14 or until the condition has resolved or has become medically stable.

Medical Monitoring for this study will be conducted by:

Robert Williams, MD
Phone (Office): 360-378-7916
Phone (Cell): 360-298-5325
Email: iopdoc1@gmail.com

The name of the Medical Monitor and contact information will be provided to each study site.

Mati Therapeutics Inc. reserves the right to terminate the study at any time. Every effort will be made to collect all data required by the protocol during or following the study subject's early termination visit.

5.5.1 Reasons for Termination, Discontinuation or Disqualified

At a study subject last visit (scheduled or unscheduled), they will have their masked punctal plug removed and a study exit case report form (CRF) must be completed, whether or not the study subject completed the final study visit (Visit 7, day 14 post-op). The reason for any early exiting from the study will be indicated on the study exit form and all efforts will be made to complete and report the observations as thoroughly as possible. The primary reason for a study subject early exiting the study should be selected from the following standard categories (see Sections 5.5.1.1 – 5.5.1.3 below).

5.5.1.1 Reason for Termination

A study subject will be terminated from the study if in the Investigators medical judgment, it was in the best interest of the study subject that developed or reported: a) moderate to severe signs or symptoms of ocular inflammation or pain, b) reported a serious AEs, regardless of relation to the study drug/device or has died.

5.5.1.2 Reason for Discontinued

A study subject will be discontinued from the study if the Investigator is unable to insert a punctal plug in to the study subject's lower punctum, they have experienced a complication (intra-operative exclusion criteria) during surgery, the punctal plug has been extruded after the surgical visit (Visit3), study subject has used a prohibited concomitant therapy, is non-compliant, has missed scheduled study visits, has personal reasons, has relocated out of the area or has a desired to withdraw from further participation in the study in the absence of a medical need as determined by the Investigator. Other reason – the study subject was discontinued for a reason other than those listed above, the Investigator must specify the reason

5.5.1.3 Reason for Disqualification

A study subject will be disqualified from the study if there was a failure to obtain written informed consent or HIPAA Authorization, improper entry (did not meet all inclusion/exclusion criteria), had a positive pregnancy test (after Visit 1).

5.5.2 Handling of Study Subject Termination, Discontinued or Disqualified

5.5.2.1 Handling of Terminated Study Subject

A terminated study subject will return to the clinic for an end of study safety evaluation and the removal of the masked punctal. A terminated study subject will receive appropriate treatment at the discretion of the Investigator. Notification of termination will be clearly documented on the appropriate Case Report Form. A terminated study subject is considered to have completed the study and **will NOT be replaced**.

5.5.2.2 Handling of Discontinued Study Subject

A study subject may voluntarily discontinue (withdraw) from the study at any time they choose. Notification of discontinuation will be clearly documented on the appropriate Case Report Form. If a study subject elects to withdraw from the study during the study follow-up period, the Investigator will make every effort to have the study subject return to the clinic for an end of study safety evaluation and the removal of the masked punctal plug. A study subject who is discontinued from the study **will be replaced**.

5.5.2.3 Handling of Disqualified Study Subject

Notification of disqualification will be clearly documented on the appropriate Case Report Form. If a study subject was inserted with a masked punctal plug, the Investigator will make every effort to have the study subject return to the clinic for an end of study safety evaluation and the removal of the masked punctal plug. A study subject disqualified from the study **will be replaced**.

5.6 Premature Termination or Suspension of Study or Study Site

Mati Therapeutics Inc. reserves the right to terminate or suspended the study at any time. Every effort will be made to collect all data required by the protocol during or following the study subject's early termination visit.

If representatives of Mati Therapeutics Inc., the Principal Investigator, the Study Monitor (Clinical Research Associate [CRA]), the Medical Monitor, or the FDA officials discover conditions arising during the study that indicate that the study will be halted or that participation by the study center will be terminated, this action may be taken after appropriate consultation with representatives of Mati Therapeutics Inc., the Principal Investigator, the CRA, and the Medical Monitor. Conditions that may warrant termination of the study include, but are not limited to the following:

a. The discovery of an unexpected, serious, or unacceptable risk to a study subject enrolled in the study

b. A decision on the part of Mati Therapeutics Inc. to suspend or discontinue testing, evaluation, or development of the product

c. Failure of the Principal Investigator to enroll study subjects into the study at an acceptable rate

d. Failure of the Principal Investigator to comply with pertinent FDA regulations and ICH Guidelines

e. Submission of knowingly false information from the research facility to Mati Therapeutics Inc., or designee, the CRA, the Medical Monitor, or the FDA

f. Insufficient adherence to protocol requirements.

Study termination and follow-up will be performed in compliance with the conditions set forth in 21 CFR 312.50 and 21 CFR 312.56.

6 STUDY AGENT

6.1 Study Treatments

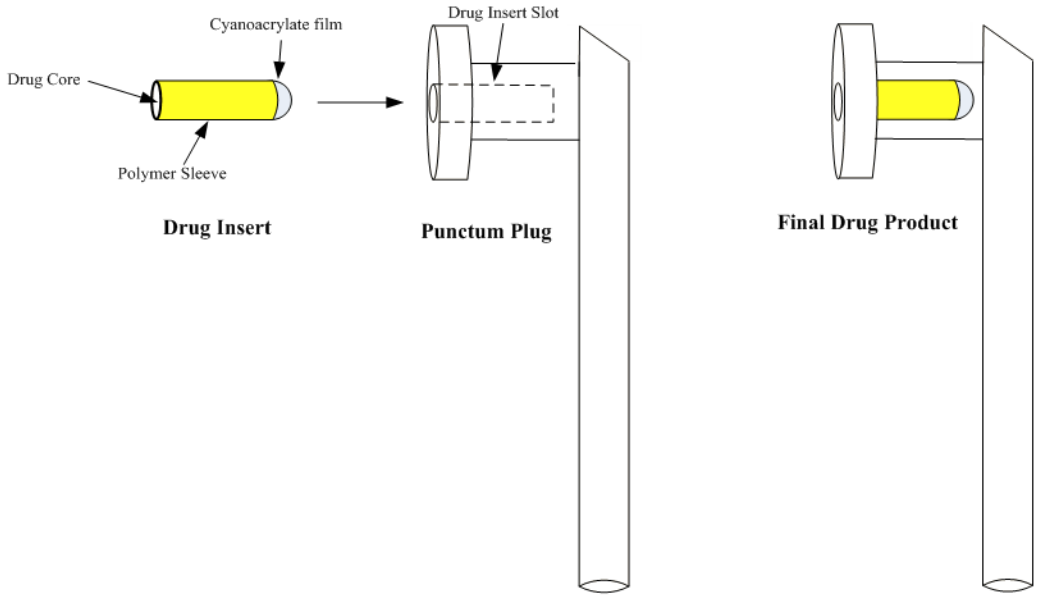
6.1.1 Route of Administration

Each qualified study subject as they are enrolled in to the study will be sequentially assigned a Subject ID number. Treatment assignments for this study have been randomized (see Section 10.6.1 for details on treatment randomization) to determine which one of the two masked punctal plug drug delivery systems a study subject will receive for the duration of the study.

6.1.2 Formulation, Appearance, Packaging and Labeling

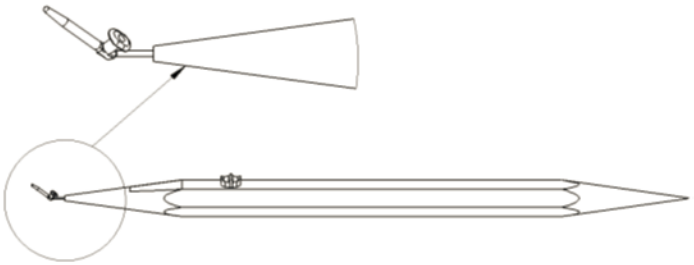
The N-PPDS and p-PPDS consist of a drug insert that is placed in to the bore of an L-shaped punctum plug (Figure 1). The plug component for both the N-PPDS and p-PPDS products consists of an inactive medical grade silicone and 2% green colorant. The drug insert of the N-PPDS contains 204 µg of nepafenac (active ingredient) dispersed within a solid sustained release matrix. The drug insert for the p-PPDS consist of the same excipients as the N-PPDS however contains no active (nepafenac) ingredient (see Appendix 6 for details).

Figure 1: Component of the N-PPDS and p-PPDS inserts



Both the N-PPDS and the p-PPDS are provided pre-loaded on an insertion tool (see Figure 2).

Figure 2: Pre-Loaded masked study product on an Insertion Tool



The pre-loaded masked punctum delivery systems will be supplied in a sealed sterilized tray, labeled with investigational drug statement in accordance with applicable regulations.

6.1.3 Product Storage and Stability

All used and unused study punctum delivery system products must be stored in a secure area with controlled access. All plugs must be refrigerated between 36 – 46°F (2 – 8°C). All study punctum delivery system products have a retest date of 6 months.

A daily temperature log will be maintained documenting appropriate investigational product and required concomitant medication storage conditions and will be made available for the study monitor to inspect.

6.1.4 Starting Dose

One (1) to 2 days prior to their scheduled cataract surgery, a subject will be randomized (2:1) in to one of two treatment groups. The assigned punctal plug will be inserted in their lower punctum of their scheduled surgical eye.

NOTE: All systemic, topical and ophthalmic NSAIDs or corticosteroid medications, with the exception of a subject who has been prescribed and has been taking a baby aspirin (≤81mg/daily), must be discontinued at least 48 hours prior to the insertion of the punctal plug.

6.1.5 Preparation for Insertion of Masked Punctal Plug

a. A study subject will be placed in a recline position

b. To anesthetize the area around the lower punctum, use a proparacaine or lidocaine soaked cotton-tipped swab, placing the swab directly on the lower punctum of the scheduled surgical eye for ~30 to 60 seconds (proparacaine or lidocaine can be irrigated into the canaliculus for better anesthesia if desired)

c. The dilator is engaged vertically in the punctum with a gentle twisting motion. The dilator is moved to a horizontal position passing it into the proximal canaliculus dilating the punctum

d. The punctum is dilated to **at least 1.0 mm**. Once the punctum is dilated to 1.0 mm, leave dilator in place for 15 to 30 seconds to allow the sphincter to fully relax

NOTE: For smaller puncta, hold and rotate the dilator in the punctum and canaliculus for a longer period of time (1 – 2 minutes or longer). Dilation may require very firm pressure. Add more anesthesia if needed.

6.1.6 Masked Punctal Plug Insertion

a. While dilating, prep the plug to insert it in the punctum

b. Remove dilator and immediately attempt to insert the plug before the sphincter starts to close

NOTE: The punctum may constrict before the plug can be inserted, additional dilation would then be required. If a plug is partially inserted (e.g., cap not flush with the lid) the plug should be removed and the punctum re-dilated or dilated to a larger diameter. Placement of the plug can then be re-attempted. Multiple attempts are sometimes necessary.

c. After insertion the punctal opening should be visually inspected using a slit-lamp to confirm the retention and correct placement of the plug, with the cap still visible. The position of the study plug may be adjusted with forceps, if necessary.

NOTE: Any questions or concerns regarding the insertion or removal of a punctal plug contact:

Robert Williams, MD
Phone (Office): 360-378-7916
Phone (Cell): 360-298-5325
Email: iopdoc1@gmail.com

6.1.7 Unable to Insert/Extruded/Lost Masked Punctal Plug

6.1.7.1 Unable to insert masked punctal plug

If the plug cannot be inserted after a few attempts with gentle dilation, the subject will not be eligible for the study. Lubricants are not to be used.

6.1.7.2 Punctal Plug extruded pre-operative

If a study subject extrudes their plug prior to surgery, a new plug will be inserted in the lower punctum of the subject's schedule surgical eye. The study subject will then be rescheduled for surgery in 1 to 2 days after re-insertion of the new plug. The punctal plug will remain in the study subject's lower punctum during cataract surgery and for a period of 2 weeks following surgery.

6.1.7.3 Punctal Plug extruded during surgery

If a study subject extrudes their plug during the surgical procedure, a new plug will be inserted in to the lower punctum of the subject's surgical eye upon completion of the surgery. The punctal plug will remain in the study subject's lower punctum for a period of 2 weeks following surgery.

6.1.7.4 Punctal Plug extruded after surgery

A study subject that has noticed a plug has been extruded or lost during the follow-up period after surgery should immediately contact the Investigator and/or his/her staff and return to the Investigator's office as soon as possible. The Investigator will discontinue the study subject from the study and place them on open-label post-op medication(s) deemed necessary for the patient's welfare by the Investigator.

For any study subject where the plug has been lost, the Investigator will retro-illuminate or palpate the canaliculi to confirm the plug has not migrated into the canal. Information regarding the loss of any plug must be recorded in the source documents, CRFs and Accountability Logs.

NOTE: If an extruded plug can be located by a study subject, the plug should be returned and collected by the Investigator and/or his/her staff. If the plug tears or has separated, report this as a technical complaint (Section 8.6). Retain the plug for accountability of investigational supplies.

6.1.8 Duration of Therapy

All plugs will be inserted in to the lower punctum of the subject's schedule surgical eye 1 to 2 days prior to surgery and will remain in the study subject's lower punctum during cataract surgery and for a period of 2 weeks following surgery.

6.1.9 Removal of a Masked Punctal Plug

The masked punctal plug can be removed from the study subject's punctum using sterile ophthalmic forceps and a gentle tugging motion. A drop of anesthetic may be administered if necessary.

a. Stabilize/constrain eyelid with fingers or with help from assistant

b. It is recommended that a 0.12 1x2 teeth Castroviejo Suture forceps or similar toothed forceps with platforms should be used for plug removal. NOTE – using a jewelers forceps is not advisable

c. Teeth should be placed on the far side of the plug with the blades straddling the neck

d. Care must be taken not to grasp the outermost edge of the cap on the punctal plug as this may cause the cap to tear and separate, making it difficult to remove the plug from the canaliculus and/or causing plug intrusion.

e. The teeth should not be used to grasp the plug but are used instead to prevent the blades of the forceps from sliding off the neck. Grasping the plug with the teeth may fracture it

f. The motion to remove should be towards the medial canthus (not up or temporally), which is necessary to disengage the heel of the plug.

If the cap becomes separated, try to remove the plug using toothed 0.12 forceps (0.12 Castroviejo forceps or similar) by grasping the neck of the plug through the punctum. If this is not possible, and it doesn't seem as if the plug will lodge in the canal, and only if you feel comfortable doing so, you may attempt to irrigate the canal until the plug flushes out of the nasolacrimal duct.

NOTE: Study plugs are larger than commercially available silicone plugs and may become lodged in the canal more easily. Clinical judgment should be exercised when proceeding. Referral to tertiary care is advised in cases where the plug cannot be retrieved by massaging/milking through the punctal opening or by irrigation.

NOTE: **Removal of a masked punctal plug immediately after insertion may result in the cap of the plug being torn off**; the Investigator should wait at least 24 hours after insertion before attempting to remove a masked punctal plug. However, if the plug tears or separates, report this as a technical complaint. Retain the plug for accountability of investigational supplies.

6.2 Study Plug Accountability Procedures

The Investigator is responsible for maintaining the study treatment (punctal plugs) accountability log, which will contain inventory records acknowledging the receipt and dispensing of all study plugs. The study center will keep a complete accounting of all used, unused, damaged, extruded and lost study plugs. All lost/extruded study plugs must be recorded into the accountability log and on the CRFs of the study subject who lost/extruded their masked study plug, noting the suspected date the study plug was lost/extruded.

All used and unused masked study plugs must be accounted for and kept in the designated secure area at the study center until the Sponsor provides instructions for the return of all study materials. Final accountability for investigational study plugs will be verified by the Sponsor and/or their representatives and considered complete when the study plugs are no longer actively used and all study plugs (used, unused, extruded, lost) have been accounted for and returned to the Sponsor.

7 STUDY PROCEDURES AND SCHEDULE

Data will be captured and compiled using procedures developed by representatives of Mati Therapeutics Inc. All requested study data must be recorded clearly on study NCR CRFs and other study forms, as required. An explanation must be provided for all missing data. Only the Investigator or his/her staff members who are identified on the Study Personnel Identification List may enter or correct data on a CRF. Incomplete or inconsistent data on the CRFs will result in data queries that will require resolution by the Investigator.

7.1 Protocol Amendments

Modification of the protocol is prohibited without prior written agreement in the form of a protocol amendment. All amendments will be created by the Sponsor and must be approved by the IRB prior to implementation except when required to mitigate immediate safety risks or when the changes involve only logistical or administrative revisions.

7.2 Study Procedures/Evaluations

7.2.1 Study specific procedures

Procedures that will be required during the course of the study include (see Section 7.4 for details):

a. Informed consent and HIPAA authorization: The Investigator and or qualified staff will review and answer any questions a potential study subject may have regarding the study, the consent or HIPAA authorization forms. Prior to the initiation of any study specific activities, the subject must sign both documents

b. Record subject's medical history for the previous 12 months and demographic data

c. Investigator evaluation of ocular pain: The Investigator will interview and record subject responses in regards to any ocular pain they may be experiencing

   NOTE: The Investigator that interviews and record subject responses to ocular pain at Visit 4 (Day 1 post-op) should interview the subject at ALL post-op visits (Day 3, 7, and 14).

d. Concomitant Medication use: All prescription systemic, ophthalmic and over-the-counter concomitant medications used during the study, including all pre-, intra- and post-operative medications, including intravenous solutions, dilating drops, irrigations, viscoelastics, antimicrobials/anti-infective, miotics, etc. related to the surgery, will be documented. The medication name, start and stop dates, indication, dose, route of administration and any dosing alterations must be documented on the Concomitant Medications CRF through completion of the last study visit.

e. Distance Visual Acuity testing: Visual acuity with and without correction, will be measured using a Snellen chart. The test distance and lighting conditions specified for the Investigator's chart must be used and kept constant throughout the study (see Appendix 3 for details).

f. Manifest Refraction: A poropter or an auto refractor will be used to determine the study subject's best visual acuity with correction

g. Slit-Lamp Examination: Slit-lamp examination will include assessment of the lid, conjunctiva, cornea and anterior chamber. Evaluation of the anterior chamber will be performed using a slit beam of 1 mm height and 1 mm width with maximum luminance

through the highest powered lens using the Investigator's standard slit lamp equipment and procedure. Grading of any slit lamp findings is defined in Appendix 2.

NOTE: The investigator that performs the slit-lamp evaluation at Visit 4 (Day 1 post-op) should perform the slit-lamp evaluation at ALL post-op visits (Day 3, 7, and 14).

h. Evaluation of lower punctum size

i. Insertion of the study punctal plug, see Section 6.1.6 of the protocol for details.

j. Removal of the study punctal plug, see Section 6.1.9 of the protocol for details.

k. Fundus examination: The back part of the eye (fundus), including the retina, optic disc, choroid and blood vessels, will be examined using an ophthalmoscope (see Appendix 3 for details)

l. Adverse Event Reporting, see Sections 8.3.1 and 8.3.2 of the protocol for details: To optimize consistency of AE reporting across centers, the study subject will be asked a standard question to elicit any AEs. At each study visit or telephone evaluation of the study subject, study personnel (non-observer) will ask the following question:

"**Have you had any problems since your last visit?**"

7.2.2 Standard of care Study Procedures

At Visit 1 (Screening/Baseline), in addition to study specific examinations, the Investigator will perform pre-operative examinations that are part of the Investigator's standard pre-operative evaluations for a potential subject being considered for cataract surgery.

At the operative visit (Visit 3) for each study subject, the Surgeon/Investigator will use their standard surgical procedure for the extraction of the cataract. The procedure for the implantation of an IOL will be based upon the package insert of the intraocular lens being implanted. The procedures use for the extraction of the cataract and implantation of an IOL should be consistent for all study related cases.

Pre-, intra- and post-operative open-label medications will be used as is customary for the Surgeon/Investigator and should be consistent for all cases. However the use of any pre-, intra- or post-operative NSAID or corticosteroid is prohibited.

At the conclusion of the study, a study subject may be scheduled for additional, non-study related, post-operative examinations based upon the Surgeon/Investigator's standard of care.

7.3 Laboratory Procedures/Evaluations

N/A.

7.4 Study Visit Schedule

7.4.1 Visit 1: (Screening/Baseline Visit, Day -30 to -1)

A potential study subject qualifications will be assessed according to the inclusion/exclusion criteria listed in the protocol (see Sections 5.1, 5.2 and 5.3). Prior to undergoing any study-specific procedures, both the study Informed Consent and Authorization for Use/Disclosure of Health Information forms (HIPAA authorization) must be signed by a potential subject who has agreed to participate in the study. During this visit, the following information will be collected/evaluated and recorded in the appropriate sections of the study case report forms for both eyes:

a. Obtain informed consent and HIPAA release

b. Record the subject's demographic data and prior 12 month medical history

c. Record the use of all systemic, topical and/or ophthalmic concomitant medications over the previous 30 days

d. Urine pregnancy test (if applicable)

e. Investigator evaluation of ocular pain

f. Monocular Distance Visual Acuity, Uncorrected and Best-Corrected

g. Manifest Refraction

h. Slit-lamp examination

i. Evaluation of lower punctum (scheduled study eye only)

j. Type and grade of cataract (scheduled study eye only)

k. Fundus examination (scheduled study eye only)

A subject who meets all of the study inclusion/exclusion criteria will be scheduled for surgery. Each qualified subject will be scheduled to return to the Investigators office 1 to 2 days before their scheduled surgery for the insertion of the study punctal plug.

7.4.2 Visit 2: (Masked Punctal Plug Insertion Visit, 1-2 days pre-op)

Each qualified study subject as they are enrolled in to the study will be sequentially assigned an ID number. Treatment assignments for this study have been randomized (see Section 10.6.1 for details on treatment randomization) to determine which one of the two treatments the study subject will receive during the study. In addition, the ID number and the study subject initials will be recorded on study case report forms, in lieu of recording their name, in order to maintain subject confidentiality.

At this visit the following will be performed and recorded:

a. Investigator evaluation of ocular pain

b. Insertion of the assigned masked punctal plug in to the lower punctum of the schedule surgical eye

c. Inspection of the masked punctal plug via the slit lamp to ensure the plug is properly positioned, with the cap still visible and secured in place.

   NOTE: The position of the masked punctal plug may be adjusted with forceps

d. Recording of any reported adverse event(s).

e. Concomitant medication

7.4.3 Visit 3: (Surgical Visit, Day 0)

Cataract surgery (e.g., corneal incision, anterior capsulotomy, fragmentation/removal of the lens/cataract) may be performed with the assistance of a femtosecond laser. It is recommended the surgeon use a standard phacoemulsification extraction surgical technique. The anterior capsulotomy should be a well centered continuous curvilinear capsulorhexis approximately 5.5 mm in diameter and the lens must be placed in the capsular bag. A viscoelastic should be used to protect the endothelium. At this visit the following surgical data will be recorded:

a. Surgical Eye Pupil measurements (prior to and immediately following surgery)

b. Monocular cataract extraction/IOL implantation recording the following information:

   - Indicate the incision Type (clear cornea, limbal, sclera), Location (nasal, temporal, superior, other) and Size (mm)
   - Nucleus removal time (< 1min, 1 - < 2 min, 2 - < 3 min, 3 - < 4 min, >4 min)
   - Ease of Cortex removal (Very Easy, Easy, Difficult, Very Difficult)
   - Effective Phaco Power (recording of phaco time and power)
   - Type of IOL (e.g., monofocal, toric, etc.) and lens power
   - Record any surgical complications

c. Visual Inspection of the masked punctal plug at the conclusion of surgery

d. Subject reported AEs prior to or after surgery

e. Concomitant medication

Should a surgical complication occur, implantation of the lens will be at the Investigator's discretion. If any of the surgical complications occur, as listed in Section 5.3, the study subject's punctal plug will be removed after surgery and the subject terminated from the study.

Pre-, intra- and post-operative open-label medications will be used as is customary for the Surgeon/Investigator, and should be consistent for all cases. All pre-, intra- and post-operative open-label medications must be recorded on the Concomitant Medication CRF. However the use of any pre-, intra- or post-operative NSAID or corticosteroid is prohibited, with the exception of a subject who has been prescribed and has been taking a baby aspirin (≤81mg/daily). An LRI or AI procedure required for any sphere/cylinder correction before, during or after cataract surgery is prohibited during the study period.

Each study subject will be scheduled to return within 1, 3, 7 and 14 days after their surgical procedure. The Surgeon/Investigator and/or his/her staff will review with each study subject the proper use or discontinuation of any post-op open-label medications prescribed by the Investigator.

7.4.4 Visit 4 through Visit 6: Follow-up visits

7.4.4.1 Visit 4: (Day 1 Post-Op)

At this visit the following will be performed on the surgical eye only:

a. Investigator evaluation of ocular pain

b. Inspection of the masked punctal plug via the slit lamp

c. Slit-Lamp examination.

d. Recording of any reported adverse event(s).

e. Concomitant medication

Each study subject will be scheduled to return in 2 days for a follow-up study examination (Visit 5, day 3 post-op). The Investigator and/or his/her staff will review with each study subject the proper use or discontinuation of any post-op open-label medications prescribed by the Investigator. Any changes, discontinuation or addition of an open-label medication(s) must be recorded on the Concomitant Medication CRF.

7.4.4.2 Visit 5: (Day 3 ± 1 Post-Op)

At this visit the following will be performed on the surgical eye only:

a. Investigator evaluation of ocular pain

NOTE: The Investigator that interviewed and record the subject's response to ocular pain at Visit 4 (Day 1 post-op) should interview the subject at this visit

b. Monocular Distance Visual Acuity (Uncorrected)

c. Inspection of the masked punctal plug via the slit lamp

d. Slit-Lamp examination

NOTE: The Investigator that performed slit-lamp evaluation at Visit 4 (Day 1 post-op) should perform the slit-lamp evaluation at this visit.

e. Recording of any reported adverse event(s).

f. Concomitant medication

Each study subject will be scheduled to return in 4 days for a follow-up study examination (Visit 6, day 7 post-op). The Investigator and/or his/her staff will review with each study subject the proper use or discontinuation of any post-op open-label medications prescribed by the Investigator. Any changes, discontinuation or addition of an open-label medication(s) must be recorded on the Concomitant Medication CRF.

7.4.4.3 Visit 6: (Day 7 ± 1 day Post-Op)

At this visit the following will be performed on the surgical eye only:

a. Investigator evaluation of ocular pain

NOTE: The Investigator that interviewed and record the subject's response to ocular pain at Visit 4 (Day 1 post-op) should interview the subject at this visit

b. Monocular Distance Visual Acuity (Uncorrected and Best-Corrected)

c. Manifest Refraction

d. Inspection of the masked punctal plug via the slit lamp

e. Slit-Lamp examination

NOTE: The Investigator that performed the slit-lamp evaluation at Visit 4 (Day 1 post-op) should perform the slit-lamp evaluation at this visit.

f. Recording of any reported adverse event(s).

g. Concomitant medication

Each study subject will be scheduled to return in 7 days for a follow-up study examination (Visit 7, day 14 post-op). The Investigator and/or his/her staff will review with each study subject the proper use or discontinuation of any post-op open-label medications prescribed by the Investigator. Any changes, discontinuation or addition of an open-label medication(s) must be recorded on the Concomitant Medication CRF.

7.4.5 Visit 7: (Final Study Visit, Day 14 ± 2 days Post-Op)

At the final scheduled study visit the following will be performed on the surgical eye only:

a. Investigator evaluation of ocular pain

   NOTE: The Investigator that interviewed and record the subject's response to ocular pain at Visit 4 (Day 1 post-op) should interview the subject at this visit

b. Monocular Distance Visual Acuity (Uncorrected and Best-Corrected)

c. Manifest Refraction

d. Inspection of the masked punctal plug via the slit lamp

e. Slit-Lamp examination

   NOTE: The Investigator that performed slit-lamp evaluation at Visit 4 (Day 1 post-op) should perform the slit-lamp evaluation at this visit.

f. Fundus examination

g. Removal of the masked punctal plug

h. Recording of any reported adverse event(s).

i. Concomitant medication

An exit form will be completed at this final study examination (Visit 7), or whenever the study subject completes or leaves the study for any reason. The Investigator and/or his/her staff will review with each study subject the proper use or discontinuation of any post-op open-label medications prescribed by the Investigator. Any changes, discontinuation or addition of an open-label medication(s) must be recorded on the Concomitant Medication CRF.

7.4.6 Early Exit Visit

Any study subject exiting the study early, the Investigator must remove the study subject's masked punctal plug. In addition, the Investigator should record the following:

a. Investigator evaluation of ocular pain

   NOTE: The Investigator that interviewed and record the subject's response to ocular pain at Visit 4 (Day 1 post-op) should interview the subject at this visit

b. Monocular Distance Visual Acuity (Uncorrected and Best-Corrected)

c. Manifest Refraction

d. Inspection of the masked punctal plug via the slit lamp

e. Slit-Lamp examination

NOTE: The Investigator that performed slit-lamp evaluation at Visit 4 (Day 1 post-op) should perform the slit-lamp evaluation at this visit.

f. Fundus examination

g. Removal of the masked punctal plug

h. Recording of any reported adverse event(s).

i. Concomitant medication

Any changes, discontinuation or addition of an open-label medication(s) must be recorded on the Concomitant Medication CRF.

7.4.7 Unscheduled Visit

The Investigator has the option of bringing a study subject back in for an unscheduled visit during the treatment period for safety reasons [e.g., study subject complaint of moderate to severe ocular symptom(s), an AE]. An unscheduled visit CRF should be completed. At minimum, the Investigator should record the following:

a. Investigator evaluation of ocular pain

NOTE: The Investigator that interviewed and record the subject's response to ocular pain at Visit 4 (Day 1 post-op) should interview the subject at this visit

b. Inspection of the masked punctal plug via the slit lamp, if applicable

c. Monocular Distance Visual Acuity (Uncorrected)

d. Slit-Lamp examination

NOTE: The Investigator that slit-lamp evaluation at Visit 4 (Day 1 post-op) should perform the slit-lamp evaluation at this visit.

e. Recording of any reported adverse event(s).

f. Concomitant medication

Any changes, discontinuation or addition of an open-label medication(s) must be recorded on the Concomitant Medication CRF.

Table 1: Schedule of Assessments, Events

EXAM PARAMETERS	v1	v2	v3	v4	v5	v6	v7
Inform Consent/HIPPA	❶						
Demographic data/Medical Hx /Medication Use	❶ A						
Concomitant Medication	❶	❷	❸	❹	❺	❻	❼
Urine Pregnancy Test (if applicable)	❶ B						
Subject Randomization to Treatment		❷					
Investigator Evaluation of Ocular Pain	❶ C	❷		❹ F	❺ F	❻ F	❼ F
Uncorrected Distance VA	❶ C				❺	❻	❼
Manifest Refraction	❶ C					❻	❼
Best-Corrected Distance VA	❶ C					❻	❼
Slit Lamp Examination	❶ C			❹ F	❺ F	❻ F	❼ F
Insertion of Masked Punctal Plug		❷					
Inspection of Masked Punctal Plug		❷ D	❸ E	❹ D	❺ D	❻ D	❼ D
Evaluation of lower puncta	❶						
Pupil Measurements			❸ G				
Type and Grade Cataract	❶						
Monocular Cataract Extraction/IOL Implantation			❸				
Fundus Examination	❶						❼
Removal of Masked Punctal Plug							❼ H
Adverse Event Recording		❷	❸	❹	❺	❻	❼

Keys to Abbreviations:

A = Prior 12 months
B = Pregnancy test (women of childbearing potential)
C = Evaluation of Both Eyes
D = Evaluation using slit-lamp
E = Visual inspection after surgery
F = Investigator that performs the slit-lamp and/or ocular pain evaluation at Visit 4 (Day 1 post-op) should perform ALL post-op visit evaluations
G = Measurement to occur prior to surgery and immediately after surgery
H = All masked punctal plugs must be removed at the subject last visit

Visit Schedule:

v1 = Day -30 to -1
v2 = 1 to 2 days prior to surgery
v3 = Surgery Day
v4 = 1 day post-op
v5 = 3 ± 1 days post-op
v6 = 7 ± 1 days post-op
v7 = 14 ± 2 days post-op

7.5 Emergency Anaphylactic or Overdose Procedures, Dose Modification

Dose modification of the study drug/device is not required in this study.

> **NOTE**: Use caution when administering nepafenac to a subject who has previously exhibited sensitivities to phenylacetic acid derivatives and salicylate hypersensitivity as the potential for cross-sensitivity exists. This study is not expected to cause AEs different in type or intensity from those previously reported in published clinical research literature regarding the use of topical nepafenac (NEVANAC® or ILEVRO®). Refer to the Investigator Brochure and Appendices 4 and 5 for additional information.

Should a subject experience a significant medical issue, the subject may be treated according to the Investigator's medical judgment. Any changes, discontinuation or addition of a post-op medication(s) must be recorded on the Concomitant Medication CRF.

7.6 Concomitant Medications

7.6.1 Pre-Study Concomitant Medication Use

Pre-study concomitant medications are defined as all prescription and over-the-counter medications taken within 30 days (whether continuing or not) prior to Visit 3 (Day 0). All prior medications must be documented on the Concomitant Medications CRF.

7.6.2 Concomitant Medication Use

Each study subject will be instructed not to use any other ocular drops, gels or ointments in his or her eyes that have not been prescribed by the Investigator. Systemic medications being used at Visit 1 that are permitted by the study protocol (see inclusion/exclusion criteria for details), are considered necessary for the study subject's welfare, and will not interfere with the study may be used.

All prescription systemic, ophthalmic and over-the-counter concomitant medications used concurrently (from Day -30 to Day 14), that are considered necessary for the study subject's welfare, and will not interfere with the study, may be used but must be documented on the Concomitant Medication CRF. The use of all concomitant medications during the study, including all pre -, intra- and post-operative medications, including intravenous solutions, dilating drops, irrigations, viscoelastics, antimicrobials/ anti-infectives, miotics, etc. related to the surgery, will be documented. The medication name, start and stop dates, indication, dose, route of administration and any dosing alterations must be documented on the Concomitant Medications CRF through completion of the last study visit.

In case of intolerable irritation due to standard post-op open-label medication(s) prescribed by their Investigator, a study subject is to notify the Investigator immediately. If necessary, the open-label treatment regimen may be temporarily altered, or the treatment may be stopped and appropriate therapy administered at the Investigator's discretion. Any changes, discontinuation

or addition of an open-label medication(s) must be recorded on the Concomitant Medication CRF.

7.7 Prohibited Medications, Treatments and Procedures

7.7.1 Prohibited Medications

The use of any systemic, topical and/or ophthalmic NSAID or corticosteroid within 48 hours of Visit 2 or during the course of the study (Visit 2 to Visit 7) is not allowed unless medically necessary. If an NSAID, corticosteroid or an immunosuppressant is required for any condition (ocular or systemic), the study subject will be terminated from the study, have their masked punctal plug removed and will be followed through Visit 7 (Day 14) or if required until the condition has resolved or has become medically stable.

Investigational/experimental/off-label usages of drugs or devices are not permitted during the study, except as described in the protocol.

7.7.2 Prohibited Procedures

The following procedures are prohibited during the study period:

a. An LRI or AI procedure before, during or after cataract surgery

b. A blepharoplasty before or after cataract surgery

c. Nd:YAG capsulotomy (e.g., for PCO)

7.8 Prophylactic Medications

The pre- and post-operative use of antimicrobial/anti-infective and the cohesive and dispersive viscoelastics use during surgery will be used at the discretion of the Surgeon/Investigator. The use of Miochol at the conclusion of cataract surgery is recommended but can be avoided at the discretion of the Surgeon/Investigator. The use of any of the above mention medications will be documented on the Concomitant Medication CRF.

7.9 Rescue Medications

During the study some patients, as determined by the investigator, may require additional rescue medications in the study eye due to post-op ocular pain and/or inflammation the patient is experiencing. Rescue treatment will be allowed per pre-specified rescue criteria (Section 7.9.1); if the rescue criteria are not met, the medications will be considered prohibited medications. Prohibited medications, though discouraged, could be used but would be considered protocol deviations.

7.9.1 Administration of a Rescue Medication

Following cataract surgery, a rescue treatment with an ocular topical corticosteroid (prednisolone acetate 1% q.i.d.) should be administered in the study eye, at the discretion of the physician, if any of the following rescue criteria apply:

a. Anterior Chamber Cell grade is 3 (grade 3 = 16-30+ cells) or greater

b. Anterior Chamber Flare grade is 3 (grade 3 = moderate intensity) or greater

c. Subject reports moderate to severe ocular pain

A study subject will be followed through Visit 7 (Day 14) or until the study subject's post-op ocular pain and/or inflammation in the study eye has resolved or has become medically stable. The use of a rescue medication during the study will be documented on the Concomitant Medication CRF.

8 ASSESSMENT OF SAFETY

8.1 Safety Variables

Safety variable for this study include any reported AE after screening, visual acuity, slit lamp biomicroscopy finding, fundus examination findings, use of concomitant and/or rescue medications. To optimize consistency of AE reporting across centers, the study subject will be asked a standard question to elicit any AEs. At each study visit or telephone evaluation of the study subject, study personnel will ask the following question:

"Have you had any problems since your last visit?"

8.2 Definitions

8.2.1 Adverse Event

Adverse Event (AE): any unanticipated sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the administration of a medicinal product, whether or not considered related to the investigational product or device.

Medical conditions or diseases present before a subject starts study treatment are only considered AEs if they worsen after the subject starts study treatment.

8.2.2 Serious Adverse Events

Serious Adverse Event (SAE): defined as any AE that (at any dose):

- Results in death

- Is life-threatening. NOTE: The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more intense
- Requires inpatient hospitalization or prolongs existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- May jeopardize the subject or may require intervention to prevent one of the outcomes listed above. Medical and scientific judgment should be exercised in deciding if these events should be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

In addition, an AE that results in overdose or produces congenital abnormality or cancer is always considered an SAE.

A subject admitted to a hospital as a result of an AE, even if released on the same day, would qualify for inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for inpatient hospitalization. However, emergency room visits that do not result in admission to the hospital would not qualify for inpatient hospitalization and, instead, should be evaluated for one of the other criteria for SAEs (e.g., life-threatening AE or medically significant event).

Hospitalization scheduled before a subject enrolls in the study is not the result of a treatment-emergent AE, and therefore events leading to such hospitalization will not be considered study AEs or SAEs. During the study, if a subject has elective surgery for a condition present at inclusion into the study, and the condition did not worsen during the study, the reason for elective surgery (and resulting hospitalization, if applicable) should not be considered or reported as an SAE. (Surgery or hospitalization should always be reported as an outcome of an AE.) For AEs that result in persistent or significant disability/incapacity, disability/incapacity refers to a substantial disruption of a subject's ability to carry out normal life functions.

The investigator must also submit documentation of the following to the Institutional Review Board, Ethics Committee, or Research Ethics Board (collectively referred to as an IRB):

- Center-specific SAEs and follow-up: The type of serious event that must be submitted (e.g., all or only suspected), as well as the required timing of submission (e.g., within 10 days of occurrence), is defined by the IRB and regulations/guidance from regulatory authorities.
- Any documentation provided by the Sponsor regarding reportable SAEs from the study: The Sponsor will provide documentation of reportable events to the investigator, as specified in Section 8.7.

The investigator should ensure that the subject receives appropriate medical treatment and that the subject is followed up until the SAE resolves or becomes chronic, as defined in Section 8.4.

8.3 Adverse Event Descriptions

8.3.1 Intensity

The intensity of AEs will be characterized as mild, moderate, or severe, as follows:

- Mild: Usually transient, requiring no special treatment, and does not interfere with the subject's daily activities
- Moderate: Introduces a low level of inconvenience or concern to the subject and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures
- Severe: Significantly interferes with a subject's usual daily activities and requires systemic drug therapy or other treatment, if available

8.3.2 Relationship to Study Treatment

The causal relationship to study drug or treatment will be determined by the investigator according to best medical judgment, as follows:

- Suspected: There is a reasonable possibility that the AE is associated with use of the study treatment, such as a temporal relationship of the event to study treatment administration, or when other drugs, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.
- Not suspected: A relationship between the AE and the study treatment can reasonably be ruled out based on lack of any temporal relationship of the event to study treatment administration, or when the subject's underlying condition, medical history, or other therapy provide sufficient explanation for the observed event.

8.4 Follow-up for Adverse Events Definitions

Throughout the study to the final study contact, all AEs will be followed until they resolve or become chronic (as judged by the investigator).

At the final study visit, new AEs, as well as follow-up information for continuing AEs, will be recorded in the CRF and source document. If an SAE (defined in Section 8.2) is unresolved at the final study visit, it will be followed by the investigator until it resolves or becomes chronic (as judged by the investigator). Follow-up data for such SAEs will be recorded in the source document and reported to the safety monitors (refer to Section 8.7). Non-serious ongoing AEs will be followed beyond the final study visit at the discretion of the investigator and recorded in the source documents.

8.5 Pregnancy Follow-up

If a subject becomes pregnant during the study, the investigator must inform the Sponsor and collect follow-up data regarding the pregnancy, birth, and status of the child. The Sponsor will provide special CRFs for data collection in the case of pregnancy. Follow-up should be

continued until study close-out at the study center. After close-out, the Sponsor's Safety designee will continue to obtain follow-up information.

Pregnancy should be recorded as a protocol deviation. Pregnancy is not an AE; however, any complication related to pregnancy would be considered an AE.

8.6 Reporting of Technical Complaints

8.6.1 Definitions

A quality complaint is one that is received in writing, electronically, or orally that involves the use or attempted use of a N-PPDS, p-PPDS that identified any defects in the physical properties of the drug product (color, precipitates, viscosity, etc.) or its packaging. Technical complaints also include any identified customer dissatisfaction with the physical characteristic(s) of the study product (dispensing characteristics, labeling, packaging, etc.).

8.6.2 Reporting of Technical Complaints

Any technical complaint should be reported by fax to the Sponsor's Chief Scientific Officer (contact information below) within 24 hours. The complaint report should include the following information:

- Name of the study product
- Strength of study product
- Batch/lot number of study product
- Investigator name, study center name, and contact number
- Date the complaint occurred
- Brief description of the complaint
- Study subject or other individual involved (yes/no):
    - If yes and a study subject, the investigator should report whether any AEs were associated with the complaint (yes/no; if a subject AE was associated with the complaint, refer to Section 8 and attach the AE CRF page to the complaint)
    - If yes and another individual, the investigator should describe the situation and any ill effects on the health of the individual
    - If no, in the investigator's judgment, the investigator should report whether the complaint could reasonably cause an SAE if it recurred under circumstances that did involve a study subject or other person (yes/no)
- Identity of any other investigational or commercial devices involved

The study product and associated packaging that initiated the complaint should be returned to the Chief Scientific Officer (address below) for analysis.

Mati Therapeutics Inc.
Attn: Chief Scientific Officer
Deepank Utkhede
201 – 4475 Wayburne Drive
Burnaby, BC
Canada V5G 4X4

Fax: 604-637-8747
Telephone: 778-991-3301

Any complaint about a study product must be reported regardless of whether the defect or deficiency had any effect on a subject or on study personnel.

8.6.3 Punctal Plug Serious Adverse Events and Technical Complaints

The Sponsor will evaluate all SAE reports and technical complaints received in the study to determine if the report meets the definition of an unanticipated ADE. Unanticipated ADEs are defined as follows:

- any serious adverse effect on the health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

If the Sponsor determines that any SAE or technical report is an unanticipated ADE, an investigation will be begun immediately. The Sponsor will inform the investigator of any additional reporting requirements beyond those stated in Section 8.7, as applicable.

If the Sponsor determines that an unanticipated ADE presents an unreasonable risk to subjects, the Sponsor will terminate the study as soon as possible. Termination will occur not later than five working days after the Sponsor makes this determination and not later than 15 working days after the Sponsor first received notice of the effect. The Sponsor will report the results of any investigations to the FDA and to investigators, who will also submit the reports to their IRBs, within 10 working days after the Sponsor first received notice of the effect.

8.6.4 Anticipated Adverse Events

The following is a list including, but not limited to, ocular adverse events that are anticipated. Any event that is unlikely but anticipated must have an adverse event form completed and reported to Mati Therapeutics Inc. (see Section 8.7 for reporting details).

- Endophthalmitis/Intraocular infection
- Hypopyon
- IOL dislocation

- Cystoid macular edema
- Pupillary block
- Retinal detachment/tear
- Corneal edema
- Iritis
- Raised IOP requiring treatment
- Visual symptoms requiring lens removal
- Tilt and decentration requiring repositioning
- Residual refractive error resulting in a secondary intervention

NOTE: Wound burps during the first week postoperatively and suture removal are not considered adverse events for this study.

8.7 Reporting Procedures

Adverse events that occur from Visit 2 (1-2 days pre-op) through completion of the end-of-study visit must be documented. The Investigator will assess the AE severity and relationship of the AE to the study drug/device. The Investigator will follow the progress of the study subject until the AE either resolves or becomes medically stable. Treatments and medications required to treat AEs must be recorded.

All adverse events, regardless of severity and whether or not attributed to the drug or drug delivery device, are to be reported to Mati Therapeutics Inc. Adverse events are also to be reported to the site IRB per the IRB's reporting requirements.

8.7.1 Adverse Event Reporting

An adverse event that is not serious or related to the study drug or drug delivery device is to be reported to the designated Medical Monitor within 10 working days of the Investigator first becoming aware of the event. Notification will occur by recording on the appropriate CRF(s), scanning and email or faxing the CRF(s) of the visit in which the event is first noted. An adverse event is also to be reported to the reviewing IRB/IEC per their reporting requirements.

8.7.2 Serious Adverse Event Reporting

All SAEs, regardless of cause(s) or relationship to the study drug or the drug delivery device, must be reported within 24 hours of becoming aware of the event to the designated Medical Monitor by telephone, facsimile, or email. Additional contact numbers and AE/SAE reporting information will be provided to each site in a separate document.

All SAEs will be reported to:

Robert Williams, MD
Mati Therapeutics Inc.
iopdoc1@gmail.com
Phone: 360.378-7916
Phone: 360.298-5325 (cell)
Fax: 360.282-6871

The Investigator must complete the SAE Report Form and send it with other relevant pages of the CRF to the designated Medical Monitor within 24 hours of discovery of the SAE. The Investigator will also compile with urgent priority other relevant documentation (copies of test results, hospital discharge summary, autopsy report, etc.) and send this information to the designated Medical Monitor. Any SAE will be reported to the Investigator's IRB/IEC per their reporting requirements.

8.7.3 Unanticipated Problem Reporting

If during the study an adverse event occurs that may reasonably be regarded as study drug and/or study-device-related and was not previously expected in nature, severity, or degree of incidence in the investigation plan, the Investigator is to report the unanticipated adverse event to the designated Medical Monitor within 48 hours, and to the Investigator's IRB as soon as possible, but no later than 10 working days, after learning of the event as required by 21CFR812.

8.7.4 Events of Special Interest

N/A

8.7.5 Unmasking Study Treatment

Masked information on the identity of the assigned test article will be provided for each study subject. If the treatment code needs to be broken in the interest of the study subject's safety, the Investigator is encouraged to contact the Medical Monitor prior to unmasking if there is sufficient time. Dependent upon the individual circumstances (i.e., medical emergency), the individual code may be broken prior to contact with the Medical Monitor. The Medical Monitor must be informed in all cases in which the code was broken and of the circumstances involved.

The Medical Monitor for this study is: Robert Williams, MD
Phone: 360.378-7916 (office)
Phone: 360.298-5325 (cell)

Additionally, the Medical Monitor may be required to unmask a study subject's masked treatment if the AE meets criteria of a Suspected Unexpected Serious Adverse Reaction (SUSAR) in order to fulfill expedited regulatory reporting requirements.

8.8 Study Halting Rules

Collaboration between representatives of Mati Therapeutics Inc., Investigators and statisticians may stop the study if there is evidence of a lack of safety or efficacy associated with the study drug/device or if there is sufficient evidence of efficacy to warrant phase III testing.

8.9 Safety Oversight

This study will utilize a Medical Monitor for safety monitoring. The Medical Monitor will remain masked regarding the study treatment until the study has been completed. The Medical Monitor will review and assess any reports of adverse events and, if necessary, to discuss these with the reporting Investigator(s). The medical monitor will also be available to answer all questions from Investigators.

9 CLINICAL MONITORING

Mati Therapeutics Inc. representative will ensure that the investigation is conducted in accordance with the following:

a. GCPs as specified in ICH E6 (R1) and E8 (8.2) and 21 CFR. Part 50, 54, 56 and 312

b. The signed Investigators' Agreement

c. The signed protocol for the study

d. Any conditions imposed by the IRB

e. The requirements of the regulations for the Protection of Human Patients (21CFR50) and all other applicable regulations

Prior to initiation of the study at a site, the CRA will conduct a visit with the Investigator(s) and the study staff to ensure the following

a. The Investigator understand the investigational status of the study material and the requirements for its accountability

b. The Investigator understands the protocol and understands and accepts their obligations in conducting the clinical investigation

c. The Investigator has adequate facilities for conducting the study, and equipment and instrumentation required by the protocol

d. The Investigators and their staff have sufficient time and access to an adequate number of subjects to conduct the clinical investigation.

During the course of the investigation, the CRA will conduct periodic site visits and maintain telephone contact with the Investigators and their staff to ensure that the study is being conducted in accordance with the protocol, and with any specific conditions of the IRB and

clinical requirements. At such visits, the CRA will ensure that informed consent has been obtained and documented for each study subject, in accordance with 21 CFR parts 50 and 56, and the requirements of the overseeing IRB and the Sponsor. The CRA will review and compare CRFs to source records and supporting documents to ensure that data recorded on the CRFs are complete, accurate, and legible, and that any corrections to the CRFs are made with a single line strike-through of the incorrect entry, and entry of the correct information adjacent with initials of the individual making the correction and date of corrected entry. The CRA will further ensure that there are no data omissions and that any study subject withdrawals are documented. The CRA will review CRFs and source records for any unanticipated AEs, and ensure that the Investigators are complying with FDA and Sponsor requirements for reporting AEs and SAEs. The CRA will ensure that the Investigators are carrying out the agreed upon activities and have not delegated them to unauthorized staff, that the facilities and staff continue to be acceptable for the study, and that the Investigators are properly tracking study inventory and are accounting for the disposition of all study drug.

The CRA shall prepare and maintain records of each site visit, significant telephone discussion, and written communications with the site. These records will include such information as:

a. Date, name, and address of the Investigators and names of other staff members present at each meeting

b. A summary of the findings of the visit

c. A statement of any action taken by the CRA or Investigators to correct any deficiencies noted.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical and Analytical Plans

The primary analysis population will be an ITT (Intent-to-Treat) analysis for all study subjects randomized to treatment that have completed at least on post-operative follow-up visit and had no major protocol violations. Individual study subjects or individual visits may be excluded if a major protocol violation occurs (such as violation of inclusion/exclusion criteria, the use of prohibited medications or non-compliance with protocol requirements that can potentially have significant impact on efficacy).

10.2 Statistical Hypotheses

a. First Hypotheses

The Null Hypothesis: There are no differences between patients receiving an active treatment (N-PPDS) vs. a placebo (p-PPDS) in controlling post-operative ocular pain associated with cataract surgery

Alternative Hypothesis: There are differences between patients receiving an active treatment (N-PPDS) vs. a placebo (p-PPDS) in controlling post-operative ocular pain associated with cataract surgery

b. Secondary Hypotheses

The Null Hypothesis: There are no differences between patients receiving an active treatment (N-PPDS) vs. a placebo (p-PPDS) in controlling post-operative ocular inflammation associated with cataract surgery

Alternative Hypothesis: There are no differences between patients receiving an active treatment (N-PPDS) vs. a placebo (p-PPDS) in controlling post-operative ocular inflammation associated with cataract surgery.

10.3 Analysis Datasets

Data will be pooled from all study centers for data analysis, unless otherwise specified. Study dataset will be generated (keypunched) from original (white) case report forms that have been reviewed and collected from clinical sites. Dataset will contain rows of individual subject data; each row will be clear labeled with the study subject randomized study number and initials. Each column of the dataset will contain a specific parameter for all study subjects. Unmasking the treatment code will not occur until the dataset has been keypunched, data has been verified, and codes or classifications have been assigned.

10.4 Description of Statistical Methods

10.4.1 General Approach

All statistical tests will be two-sided and interpreted at a 5% significance level. Descriptive statistics (i.e., mean, standard deviation, etc.) will be provided for all continuous variables and frequency distributions will be generated for all categorical variables collected in this study.

10.4.2 Analysis of the Primary Efficacy Endpoint(s)

The primary efficacy variable will be the severity of ocular pain report at visit 4, 5, 6 and 7 (post-op days 1, 3, 7 and 14). For analyses using the intent-to-treat (ITT) data set, all data from all subjects with at least one post-operative follow-up pain evaluation will be included. For the per protocol (PP) analyses dataset, data from subjects or visits with significant protocol deviations will be excluded.

10.4.3 Analysis of the Secondary Endpoint(s)

The secondary efficacy variable will be the severity of ocular inflammation (anterior chamber cells and flare) report at visit 4, 5, 6 and 7 (post-op days 3, 7 and 14). For analyses using the intent-to-treat (ITT) data set, all data from all subjects with at least one post-operative follow-up inflammation evaluation will be included. For the per protocol (PP) analyses dataset, data from subjects or visits with significant protocol deviations will be excluded.

Efficacy analysis of primary and secondary endpoints will be based on observed data only. In the case of a significant amount of missing data, Last Observation Carried Forward may be used for sensitivity analysis.

10.4.4 Safety Analyses

All study subjects who are exposed or deemed exposed to study medication will be evaluable for safety analysis. A subject is deemed exposed to study medication if they discontinue the study prior to surgery visit and were implanted with a masked PPDS.

The safety endpoints in this study are adverse events, visual acuity, slit-lamp parameters (Lid, conjunctiva, cornea), fundus findings, and use of rescue medication. Safety variables will be summarized using descriptive statistics.

The type, severity, duration and frequency of reported adverse events will be tabulated for each treatment group, by visit. Adverse events will also be summarized for events and a comparison of the proportion of study patients reporting adverse events between groups will be made using a chi-square test. Additionally, any adverse event experienced by a subject after signing informed consent and before exposure will be presented separately in the safety analysis.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment emergent AEs (those occurring after insertion of a study PPDS) will be summarized descriptively: The number and percentage of study subjects who experienced an AE and the total number of AEs will be summarized by system organ class and preferred term. Associated AEs, defined as AEs suspected to be treatment related by the investigator, SAEs and serious associated AEs will also be summarized, if necessary. Summaries of each type of event will be prepared by severity and for all severities combined.

Concomitant medication recorded and used during the study will be coded using the World Health Organization Drug Dictionary and listed by subject. Ocular concomitant medications will be identified by each eye in the listing.

10.4.5 Adherence and Retention Analyses

N/A

10.4.6 Baseline Descriptive Statistics

Demographic and baseline characteristics will be summarized by treatment group and overall. Counts and percentages will be presented for categorical variables such as sex, age group (by decade), race, ethnicity, cataract density and type. Mean, standard deviation, median, minimum and maximum will be presented for continuous variables such as age, punctum size (non-dilated) and visual acuity scores.

10.4.7 Planned Interim Analyses

An interim analysis will be performed to confirm that positive efficacy trends are being observed and that the enrolment should continue. The interim analysis will be performed after a minimum of 25 subjects have completed visit 7 in the study. The data will be unmasked and analysis of primary and secondary endpoints will be completed along with baseline descriptive statistics.

Sites will remain masked to treatment for the remainder of the study. A summary of the results may be shared with the sites but no individual site data will be generated or shared.

10.4.8 Multiple Comparison/Multiplicity

N/A

10.4.9 Tabulation of Individual Response Data

Reports of ocular pain will be tabulated by treatment group, by number of patients reporting ocular pain as either "No Pain" or "Pain" (trace to severe) at each follow-up visit (Visit 4 through Visit 7).

10.4.10Exploratory Analyses

N/A

10.5 Sample Size

Since this is a pilot study, no formal sample size estimation was performed.

10.6 Measures to Minimize Bias

To minimize bias, the study has been designed as a randomized, double blind study.

10.6.1 Enrollment/ Randomization/Masking Procedures

Randomization will be stratified (or balanced) by study center. Patients will be randomized in a ratio of 2:1, 2 active (N-PPDS) for each placebo (p-PPDS). Treatment assignments for this study have been randomized in blocks of three (each sequential group of three, two lines are active treatment, and one line is placebo treatment), 25 blocks total. Using a random number generator (JMP 10.0 statistical software), each block is assigned three randomized numbers. The dataset is then sorted by ascending order by block, by random number. By ascending order, each line is assigned a subject number (e.g. 101-175). As a subject qualifies for enrollment, they will be sequentially assigned a subject number. The subject numbers designated what treatment group the subject will be assigned.

10.6.2 Evaluation of Success of Blinding

N/A

10.6.3 Breaking the Study Blind/Participant Code

Prior to locking the database and breaking the masked study medication code, each study subject and visit will be assessed regarding the qualification for evaluation of safety and efficacy parameters.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

11.1 Source Documentation

The Investigator must maintain adequate and accurate source documents upon which CRFs for each study subject are based. They are to be separate and distinct from the CRFs, except for cases in which the Sponsor has predetermined that direct data entry into specified pages of the subject's CRF is appropriate. Study source documents should include detailed notes on:

a. Study protocol number

b. The oral and written communication with the study subject regarding the study treatment (including the risks and benefits of the study).

c. The date that informed consent and HIPAA forms were signed must be recorded in the source documentation

d. The study subject's medical history prior to participation in the study

e. The study subject's basic identifying information, such as demographics, that links the subject's source documents with the CRFs

f. Date of all study subject visit and surgery throughout the duration of the study

g. Date the punctal plug was first inserted, removed and if applicable, dates of any plug that was extruded/loss and a new plug was re-inserted

h. Anterior chamber cells and flare values at each visit

i. Subject reports of ocular pain at each visit

j. All AEs

k. The subject's exposure to any concomitant therapy (including start and stop dates, route of administration, and dosage)

l. All relevant observations and data on the condition of the subject throughout the study.

11.2 Access and Retention of Study Records

The study is subject to audits by the Sponsor/designee, third parties, or by regulatory authorities. If such an audit occurs, the Investigator must agree to allow access to all required

study subject records. The Investigator will notify Sponsor promptly of any FDA audits that are scheduled, and must forward copies of any resultant Form 483 and/or audit reports to the Sponsor promptly.

All study records will be maintained by the Investigator at the site for a minimum of 2 years following the date a marketing application is approved for the drug for which the indication was being investigated. If no application is to be filed or the application is not approved for such indication, study records must be retained for at least 2 years after the investigation is discontinued and the FDA is notified:

11.3 Subject Confidentiality

Records identifying the study subject by name will be kept confidential. The Investigator will ensure the study subject's anonymity is maintained throughout the course of the study. A study subject will be assigned a site/subject ID number to maintain study subject confidentiality. In particular, the Investigator will keep an enrollment log with confidential identifying information that corresponds to the subject numbers and initials of each study subject. A study subject name may possibly be disclosed to Mati Therapeutics Inc. or regulatory agencies during inspection of medical records related to the study, but reasonable precautions will be taken to maintain confidentiality of personal information to the extent permitted by applicable laws and regulations. If the results of the study are published, the study subject's identity will remain confidential.

11.4 Case Report Form Completion

The Investigator is responsible for ensuring that data are properly recorded on each study subject's case report forms and related documents. An Investigator who has signed the protocol signature page should personally sign completed case report forms to ensure that the observations and findings are recorded on the case report forms correctly and completely. Following study examination, investigative sites should complete and remove the yellow NCR copy of the CRF from the study subjects' booklet leaving the white copy of the CRF intact inside the booklet. Yellow copies of completed CRFs will be mailed in on a weekly basis to the following:

D'Ellis Group, Inc.
Attn: Daniel Schwob
26741 Portola Pkwy, Suite 1E 717
Foothill, Ranch, CA 92610

The CRF data will be reviewed against the subject's source data by the study monitors to ensure completeness and accuracy. After monitoring has occurred at the clinical sites and the CRFs have been submitted, additional data clarifications and/or additions may be needed. Data clarifications and/or additions are documented and are part of each subject's CRFs.

11.5 Investigator Study Summary

A final Investigator's summary will be provided to Mati Therapeutics Inc. within approximately three months after the completion of the study. The Investigator summary should include:

a. Investigator name and title

b. Title if the protocol

c. Date the clinical study began (1st enrolled study subject) and the date the last study subject exited the study

d. Number of study subjects enrolled into the study, completed, discontinued, terminated, withdrew

e. Brief discussion regarding any reported AEs/SAEs

f. Brief discussion of clinical findings during the study.

12 QUALITY ASSURANCE AND QUALITY CONTROL

Investigator must grants permission to personnel from the Sponsor, its representatives, third parties and appropriate regulatory authorities for on-site monitoring and review of all appropriate study documentation, as well as on-site review of the procedures employed in data collection, where clinically appropriate. Study auditing, data entry, verification and validation, and subsequent analysis will be performed by the Sponsor or Sponsor's designees in accordance with GCPs and established Standard Operating Procedures.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 Ethical Standard

The Investigator agrees to conduct the study in accordance with United States Investigational New Drug regulations specified under 21 CFR 11, 50, 54, 56, and 312, the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP), and the Guidelines of the Declaration of Helsinki, Finland, 1964 and its subsequent amendments (Tokyo, Japan, 1975; Venice, Italy, 1983; Hong Kong, 1989; Republic of South Africa, 1996; Scotland, 2000). The Investigator will conduct all aspects of the study in accordance with all national, state, and local laws of the pertinent regulatory authorities.

13.2 Institutional Review Board

The protocol, Informed Consent Form (ICF), and any study subject information sheet must be approved in writing by the appropriate IRB before the study can be initiated at a site. A copy of the IRB approval must be sent to the Sponsor (or designee) along with a list of the IRB members and their occupations/affiliations. Institutional Review Board approval is also

required for any advertising or other material used for subject recruitment. If the protocol is amended, the Investigator must sign the revised protocol and submit the amendment to the IRB for review and approval prior to implementation of the changes specified in the amendment. The Investigator must report promptly to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, including all SAEs that have resulted in an expedited safety report to the FDA. No drug will be shipped to a site until IRB approval has been granted and the Sponsor or designee has been notified of this in writing.

The Investigator is responsible for obtaining continued review of the clinical study, at intervals not to exceed 1 year or otherwise specified by the IRB. The Investigator must provide the Sponsor (or designee) with written documentation of the continued review.

13.3 Informed Consent Process

13.3.1 Consent Procedures and Documentation

Each subject must provide written Informed Consent before any study-related procedures are started. It is the responsibility of the Investigator or designated staff member(s) to give a copy of the Informed Consent to each potential study subject and to be available to answer any questions the subject may have about the nature of the study and his or her participation in it. The individual responsible for explaining the consent form to the subject must witness the subject's signature on the form. It is the responsibility of the Investigator to provide a copy of the IRB-approved consent form to the Sponsor (or designee) prior to the start of the study. If a protocol amendment substantially alters a study design or increases the potential risk to the study subject, the consent form must be revised and submitted to the IRB(s) for review and approval prior to implementation. The revised consent form must be used to obtain consent from each study subject currently in the study if they are affected by the amendment and from new subjects prior to their enrollment in the study. See Appendix 7 for further details

13.3.2 Other Informational Documents Provided to Participants

A subject to be enrolled in to the study is required to review and sign a Health Insurance Portability and Accountability Act (HIPAA) of 1996 authorization document. Each study subject will receive copies of all applicable informational documents for their records.

13.4 Participant and Data Confidentiality

Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access will be required to take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

The confidentiality of records that could identify subjects will be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirement(s).

13.4.1 Research Use of Stored Human Samples, Specimens or Data

N/A

13.5 Future Use of Stored Specimens

N/A

14 DATA HANDLING AND RECORD KEEPING

14.1 Data Collection and Management Responsibilities

The nature and location of all source documents will be identified to ensure that original data required to complete the CRFs exist and are accessible for verification by the site monitor. At a minimum, source documents should include specific data, as indicated in Section 11.1 (source documentation) of the protocol, for each subject.

14.2 Study Records Retention

The Investigator must arrange for retention of study records at the site for 2 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 at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug/device. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement with the Sponsor. The Sponsor will inform the Investigator/Institution as to when these documents no longer need to be retained. The Investigator will take measures to prevent any accidental or premature destruction of these documents.

a. All adverse event information (adverse event forms, follow-up letters, etc.)

b. Study subject records (source documents/CRFs)

c. Investigational supply records/inventory

d. IRB and regulatory approval documentation

e. All study related correspondence

f. All study agreements

g. Site visit documentation

h. Protocols and the reason for any deviations from the protocol

i. Study Subject log

j. Clinical Investigator's Brochure

k. Completed study subject informed consent and HIPAA forms

l. Study subject medical chart/clinic notes.

It is required that the author of an entry in the source documents be identifiable. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the CRF are consistent with the original source data.

> **NOTE**: These documents should be retained for a longer period if required by the applicable regulatory requirements or by 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. The Investigator should take measures to prevent any accidental or premature destruction of these documents.

Mati Therapeutics Inc. requires notification if the Investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

14.3 Protocol Deviations

Any deviation from the protocol done to protect the life or physical well-being of a study subject in an emergency must be reported to Mati Therapeutics Inc. and the reviewing Institutional Review Board (IRB) as soon as possible, but no later than five working days after the deviation occurs. Unless it is an emergency, if the Investigator desires to modify any procedure and/or deviate from the design of the study, he or she must contact and obtain consent from Mati Therapeutics Inc. regarding the proposed changes prior to implementation (refer to Section 7.1 for details). If the modifications may affect the scientific soundness of the study, or the rights, safety, or welfare of the study participants, approval by the FDA and all appropriate regulatory agencies as well as approval of the IRB is also required.

14.4 Publication and Data Sharing Policy

All information related to this study is considered confidential information belonging to Mati Therapeutics Inc. Data on the use of the study drug/device and results of all clinical and laboratory studies are considered private and confidential. None of the details, results, or other information for this study shall be published or made known to a third party without written consent from Mati Therapeutics Inc., except for disclosure to regulatory agencies if required by law.

15 LITERATURE REFERENCES

Kholdebarin R, et al. Multicenter study of compliance and drop administration in glaucoma. Can J Ophthalmol. 2008;43:454–461.

Winfield AJ, et al. A study of the causes of non-compliance by patients prescribed eyedrops. Br J Ophthalmol. 1990;74:477– 480.

An JA, et al. Evaluation of eyedrop administration by inexperienced patients after cataract surgery. J Cataract Refract Surg. 2014;40:1857–1861.

16 APPENDICES

Appendix 1

PUNCTAL SIZING TECHNIQUE
With the Coroneo Punctal Gauge

INSTRUCTIONS FOR USE
CORONEO™ PUNCTAL GAUGE
NON-STERILE CE
PATENTS PENDING

Description:
The Coroneo Punctal Gauge is designed to aid the Physician in determining the proper size EaglePlug™, SuperEagle™ Plug, FlexPlug™, or SuperFlex® Plug for use. Additionally, the instrument provides a simple and controlled method for punctal dilation prior to insertion.

The system consists of a single handpiece, with gauging and dilation marks at each end. The instrument is manufactured from medical grade Titanium, and is autoclavable. All Coroneo Gauges are shipped with tip protectors which must be removed before use, cleaning, disinfecting, or sterilizing.

GAUGING & DILATION

For proper measurement and insertion of punctal plugs, the following procedure is recommended:

Note: A topical anesthetic for the punctum is recommended before proceeding with the use of this product. Always gauge before dilating. In order to achieve accurate gauging results, do not use the Coroneo Punctal Gauge with punctum plugs other than EaglePlugs, SuperEagle Plugs, FlexPlugs, or SuperFlex Plugs.

Note: Care should be taken when gauging and dilating, not to perforate the punctal ring.

Gently insert the appropriate end (one is labeled with sizes 0.5, 0.6, & 0.7, and the opposite side is labeled with sizes 0.8, 0.9, & 1.0) of the gauge/dilator into the punctum, using slight finger traction to expose the punctum (Fig. 1a). Continue inserting the gauge vertically into the canaliculus (Fig. 1b). Once the horizontal canaliculus has been reached, if necessary, gently turn the instrument horizontally to continue inserting past the vertical canaliculus (Fig. 1c). If the Coroneo Punctal Gauge inserts deeper than the third mark on the small end of the instrument, turn the gauge around and continue using the opposite end. If the gauge inserts past the third line on the large end, gauging and/or dilation should stop immediately, and a larger plug than 1.0mm may be necessary. When tightening of the punctal ring is observed around the instrument, read the appropriate size from the gauge. There are three "grooves" in each end of the gauge that correspond to the three sizes indicated on the handle. The punctum can then be simultaneously dilated, and the proper size plug can be immediately placed in the patient's punctum.

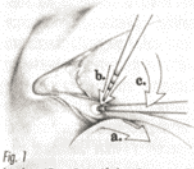


Fig. 1

CLEANING, DISINFECTION AND STERILIZATION

Note: The Coroneo Punctal Gauge is intended to contact mucous membranes only. Instruments that contact mucous membrane only, may have high level disinfection, as specified by the Center for Disease Control (CDC) and in AAMI Technical Information Report 12 (TIR 12). Instruments used under other conditions may require sterilization.

Note: The instrument should be examined for damage and wear before use.

CLEANING INSTRUCTIONS

- Instruments are to be kept moist, after usage, until cleaning is completed.
- Fresh water and an enzymatic detergent (such as Enzol®) are the cleaning agents.
- Instruments are cleaned by soaking, coupled with brushing with a soft bristled brush such as a toothbrush. Brushing should be done underwater to prevent aerosolization of microorganisms.
- After cleaning, rinse instruments with a stream of fresh water.

DISINFECTION INSTRUCTIONS

- Soak the instruments in a liquid chemical germicide solution labeled as a disinfectant/sterilant (such as Cidex®) which has been approved by a competent authority for use in disinfecting or sterilizing medical instruments.
- Soak the instruments for the time listed by the manufacturer.

Note: Some disinfectant/sterilant solutions are alkaline; i.e., high pH, and will affect anodized instruments. Do not leave anodized instruments in these solutions for protracted periods of time.

- After disinfection, rinse instruments with a stream of fresh water, and dry completely.

STERILIZATION INSTRUCTIONS

- If instruments are placed in a sterilizing tray, do not allow instruments to touch one another, or the tray sides.
- Instruments not intended for immediate use must be wrapped in an appropriate material such as a pouch to maintain sterility.
- Chemical and biological indicators should be used to verify sterilization.
- Steam sterilization has been validated for a 15 minute, gravity cycle at 270°F (132°C).

CAUTIONS

U.S Federal Law restricts this device for sale by, or on the order of, a licensed medical practitioner.

Enzol® and Cidex® are registered trademarks of J&J.

EC REP
Quality First International
11 Burford Road, Suites 317 & 318
Stratford, London E15 2ST
U.K.
Telephone: 44 208 221 2361
Telefax: 44 208 221 1912

EagleVision
AN ENTEROPTYX™ COMPANY
8500 Wolf Lake Dr., Suite 110 • P.O. Box 34877
Memphis, TN 38133 USA
(901) 380-7000 • Fax (901) 380-7001
1-800-222-7584 www.eaglevis.com

 UT0035 CID3226

Appendix 2

SLIT-LAMP EXAMINATION GRADING SYSTEMS: The biomicroscopic slit-lamp exam should be performed by the same evaluator at each study visit. Adherence to the grading scales listed below will improve consistency across study sites.

A. Evaluation of Biomicroscopy Findings (Lid/Lid Margin, Conjunctiva, Cornea)
The severity of a sign will be graded by the investigator based on the appearance at each study visit The following four-point grading scales are to be used to rate Lid/Lid Margin, Conjunctiva, and Corneal findings:

Severity	Score	Description
None	0	Finding is NORMAL
Mild	+1	Finding is FAINT but discernible and diffuse
Moderate	+2	Finding is DISTINCIVE
Severe	+3	Finding is VERY DISTINCTIVE and dense

B. Evaluation of Anterior Chamber Cells and Flare (Anterior Chamber Cells and Flare)
The severity of Anterior Chamber Cells and Flare will be graded by the investigator based on the appearance at each study visit. The following five-point grading scales are to be used to rate the following:

i. Anterior Chamber CELLS

Severity	Score	Description
None	0	No cells seen
Trace	+1	1-5 cells seen
Mild	+2	6-15 cells seen
Moderate	+3	16-30 cells seen
Severe	+4	>30 cells seen

ii. Anterior Chamber FLARE

Severity	Score	Description
None	0	No Tyndall effect
Trace	+1	Tyndall effect barely discernible
Mild	+2	Tyndall effect in anterior chamber is clearly visible
Moderate	+3	Tyndall effect in anterior chamber is moderately intense
Severe	+4	Tyndall effect in anterior chamber is very intense. The aqueous humour has a white milky appearance

Appendix 3

GRADING SYSTEMS AND METHODOLOGIES

A. Visual Acuity

Visual acuity will be measured using a Snellen chart both with (BCVA) and without correction (UCVA). The test distance and lighting conditions specified for the investigator's chart must be used and kept constant throughout the study.

B. Fundus Exam

Using an ophthalmoscope, the investigator will examine the back part of the eye (fundus), including the retina, optic disc, choroid and blood vessels. Findings will be recorded as either "Within Normal Limits" or "Abnormal". If findings are abnormal, investigator will rate the findings as either "Not Clinically Significant" or "Clinical Significant". For all Fundus Findings indicated as Clinical Significant the investigator will describe the finding in the appropriate section of the Case Report Form:

C. Cataract Density

Severity	Score	Description
None	0	No cataract
Trace	+1	Early lens opacity
Mild	+2	Intermediate lens opacity
Moderate	+3	Advanced lens opacity
Severe	+4	Hypermature lens opacity

D. Ocular Pain Evaluation

Severity	Score	Description
None	0	Absence of pain
Trace	+1	A slight, occasional awareness of an ocular sensation
Mild	+2	A noticeable, intermittent awareness of an ocular sensation that has no impact on daily activities
Moderate	+3	A prolonged, moderate ocular aching that occasionally interferes with normal daily activities
Marked (Severe)	+4	A prolonged, intense ocular pain that interferes with normal daily activities
Severe (Intolerable)	+5	A definite, continuous, unbearable ocular or periocular pain that prohibits performing normal daily activities

Appendix 4

NEVANAC® (nepafenac ophthalmic suspension) 0.1% Package Insert

NDA 21-862/S-008
Page 4

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NEVANAC® safely and effectively. See full prescribing information for NEVANAC®.

NEVANAC® (nepafenac ophthalmic suspension) 0.1%, topical ophthalmic
Initial U.S. Approval: 2005

----------INDICATIONS AND USAGE----------
NEVANAC ophthalmic suspension is a nonsteroidal, anti-inflammatory prodrug indicated for the treatment of pain and inflammation associated with cataract surgery (1).

----------DOSAGE AND ADMINISTRATION----------
One drop of NEVANAC ophthalmic suspension should be applied to the affected eye three-times-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. (2)

----------DOSAGE FORMS AND STRENGTHS----------
Sterile ophthalmic suspension: 0.1%
3 mL in a 4 mL bottle (3)

----------CONTRAINDICATIONS----------
Hypersensitivity to any of the ingredients in the formula or to other NSAIDS. (4)

----------WARNINGS AND PRECAUTIONS----------

Increased bleeding time due to interference with thrombocyte aggregation (5.1)
Delayed healing (5.2)
Corneal effects including keratitis (5.3)

----------ADVERSE REACTIONS----------
Most common adverse reactions (5 to 10%) are capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Alcon Laboratories, Inc. at 1-800-757-9195 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 06/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

Reference ID: 2966037

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NEVANAC® ophthalmic suspension is indicated for the treatment of pain and inflammation associated with cataract surgery.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing
One drop of NEVANAC should be applied to the affected eye three-times-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period.

2.2 Use with Other Topical Ophthalmic Medications
NEVANAC® may be administered in conjunction with other topical ophthalmic medications such as beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics, and mydriatics.

If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

3 DOSAGE FORMS AND STRENGTHS

Sterile ophthalmic suspension: 0.1%

3 mL in a 4 mL bottle

4 CONTRAINDICATIONS

NEVANAC® is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other NSAID.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Bleeding Time
With some nonsteroidal anti-inflammatory drugs including NEVANAC®, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that NEVANAC® ophthalmic suspension be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

5.2 Delayed Healing
Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including NEVANAC®, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

5.3 Corneal Effects
Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs including NEVANAC® and should be closely monitored for corneal health.

Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome),

rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Postmarketing experience with topical NSAIDs also suggests that use more than 1 day prior to surgery or use beyond 14 days post surgery may increase patient risk and severity of corneal adverse events.

5.4 Contact Lens Wear
NEVANAC should not be administered while using contact lenses.

6 ADVERSE REACTIONS

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to the rates in the clinical studies of another drug and may not reflect the rates observed in practice.

6.1 Ocular Adverse Reactions
The most frequently reported ocular adverse reactions following cataract surgery were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation. These reactions occurred in approximately 5 to 10% of patients.

Other ocular adverse reactions occurring at an incidence of approximately 1 to 5% included conjunctival edema, corneal edema, dry eye, lid margin crusting, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, photophobia, tearing and vitreous detachment.

Some of these reactions may be the consequence of the cataract surgical procedure.

6.2 Non-Ocular Adverse Reactions
Non-ocular adverse reactions reported at an incidence of 1 to 4% included headache, hypertension, nausea/vomiting, and sinusitis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Teratogenic Effects.
Pregnancy Category C: Reproduction studies performed with nepafenac in rabbits and rats at oral doses up to 10 mg/kg/day have revealed no evidence of teratogenicity due to nepafenac, despite the induction of maternal toxicity. At this dose, the animal plasma exposure to nepafenac and amfenac was approximately 260 and 2400 times human plasma exposure at the recommended human topical ophthalmic dose for rats and 80 and 680 times human plasma exposure for rabbits, respectively. In rats, maternally toxic doses ≥10 mg/kg were associated with dystocia, increased postimplantation loss, reduced fetal weights and growth, and reduced fetal survival.

Nepafenac has been shown to cross the placental barrier in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, NEVANAC® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects.
Because of the known effects of prostaglandin biosynthesis inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of NEVANAC® during late pregnancy should be avoided.

8.3 Nursing Mothers
NEVANAC® is excreted in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NEVANAC® ophthalmic suspension is administered to a nursing woman.

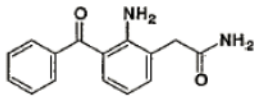
8.4 Pediatric Use

The safety and effectiveness of NEVANAC® in pediatric patients below the age of 10 years have not been established.

8.5 Geriatric Use
No overall differences in safety and effectiveness have been observed between elderly and younger patients.

11 DESCRIPTION

NEVANAC® (nepafenac ophthalmic suspension) 0.1% is a sterile, topical, nonsteroidal anti-inflammatory (NSAID) prodrug for ophthalmic use. Each mL of NEVANAC® suspension contains 1 mg of nepafenac. Nepafenac is designated chemically as 2-amino-3-benzoylbenzeneacetamide with an empirical formula of $C_{15}H_{14}N_2O_2$. The structural formula of nepafenac is:



Nepafenac is a yellow crystalline powder. The molecular weight of nepafenac is 254.28. NEVANAC®ophthalmic suspension is supplied as a sterile, aqueous 0.1% suspension with a pH approximately of 7.4.

The osmolality of NEVANAC®ophthalmic suspension is approximately 305 mOsmol/kg.

Each mL of NEVANAC® contains: Active: nepafenac 0.1% Inactives: mannitol, carbomer 974P, sodium chloride, tyloxapol, edetate disodium, benzalkonium chloride 0.005% (preservative), sodium hydroxide and/or hydrochloric acid to adjust pH and purified water, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
After topical ocular dosing, nepafenac penetrates the cornea and is converted by ocular tissue hydrolases to amfenac, a nonsteroidal anti-inflammatory drug. Amfenac is thought to inhibit the action of prostaglandin H synthase (cyclooxygenase), an enzyme required for prostaglandin production.

12.3 Pharmacokinetics
Low but quantifiable plasma concentrations of nepafenac and amfenac were observed in the majority of subjects 2 and 3 hours postdose, respectively, following bilateral topical ocular three-times-daily dosing of nepafenac ophthalmic suspension, 0.1%. The mean steady-state Cmax for nepafenac and for amfenac were 0.310 ± 0.104 ng/ml and 0.422 ± 0.121 ng/ml, respectively, following ocular administration.

Nepafenac at concentrations up to 300 ng/mL did not inhibit the *in vitro* metabolism of 6 specific marker substrates of cytochrome P450 (CYP) isozymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4). Therefore, drug-drug interactions involving CYP mediated metabolism of concomitantly administered drugs are unlikely. Drug-drug interactions mediated by protein binding are also unlikely.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Nepafenac has not been evaluated in long-term carcinogenicity studies. Increased chromosomal aberrations were observed in Chinese hamster ovary cells exposed *in vitro* to nepafenac suspension. Nepafenac was not mutagenic in the Ames assay or in the mouse lymphoma forward mutation assay. Oral doses up to 5,000 mg/kg did not result in an increase in the formation of micronucleated polychromatic erythrocytes *in vivo* in the mouse micronucleus assay in the bone marrow of mice.

Nepafenac did not impair fertility when administered orally to male and female rats at 3 mg/kg (approximately 90 and 380 times the plasma exposure to the parent drug, nepafenac, and the active metabolite, amfenac, respectively, at the recommended human topical ophthalmic dose).

14 CLINICAL STUDIES

In two double-masked, randomized clinical trials in which patients were dosed three-times-daily beginning one day prior to cataract surgery, continued on the day of surgery and for the first two weeks of the postoperative period, NEVANAC® ophthalmic suspension demonstrated clinical efficacy, compared to its vehicle in treating postoperative inflammation.

Patients treated with NEVANAC® ophthalmic suspension were less likely to have ocular pain and measurable signs of inflammation (cells and flare) in the early postoperative period through the end of treatment than those treated with its vehicle.

For ocular pain in both studies a significantly higher percentage of patients (approximately 80%) in the nepafenac group reported no ocular pain on the day following cataract surgery (Day 1) compared to those in the vehicle group (approximately 50%).

Results from clinical studies indicated that NEVANAC® has no significant effect upon intraocular pressure; however, changes in intraocular pressure may occur following cataract surgery.

16 HOW SUPPIED/STORAGE AND HANDLING

NEVANAC® (nepafenac ophthalmic suspension) is supplied in a natural, oval, low density polyethylene DROP-TAINER® dispenser with a natural low density polyethylene dispensing plug and gray polypropylene cap. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

3 mL in 4 mL bottle NDC 0065-0002-03

Storage: Store at 2 - 25˚C (36 - 77˚F).

17 PATIENT COUNSELING INFORMATION

17.1 Slow or Delayed Healing
Patients should be informed of the possibility that slow or delayed healing may occur while using nonsteroidal anti-inflammatory drugs (NSAIDs).

17.2 Avoiding Contamination of the Product
Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Use of the same bottle for both eyes is not recommended with topical eye drops that are used in association with surgery.

17.3 Contact Lens Wear
NEVANAC® should not be administered while wearing contact lens.

17.4 Intercurrent Ocular Conditions
Patients should be advised that if they develop an intercurrent ocular condition (e.g., trauma, or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multi-dose container.

17.5 Concomitant Topical Ocular Therapy

If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

17.6 Shake Well Before Use
Patients should be advised to shake the bottle well.

U.S. Patent No; 5,475,034

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Appendix 5

ILEVRO® (nepafenac ophthalmic suspension) 0.3% Package Insert

NDA 203-491/S-001
Page 3

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ILEVRO™ (nepafenac ophthalmic suspension), 0.3% safely and effectively. See full prescribing information for ILEVRO™ (nepafenac ophthalmic suspension), 0.3%.

ILEVRO™ (nepafenac ophthalmic suspension), 0.3%, topical ophthalmic
Initial U.S. Approval: 2005

----------INDICATIONS AND USAGE----------
ILEVRO™ (nepafenac ophthalmic suspension), 0.3% is a nonsteroidal, anti-inflammatory prodrug indicated for the treatment of pain and inflammation associated with cataract surgery (1).

----------DOSAGE AND ADMINISTRATION----------
One drop of ILEVRO™ (nepafenac ophthalmic suspension), 0.3% should be applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery. (2)

----------DOSAGE FORMS AND STRENGTHS----------
Sterile ophthalmic suspension 0.3%: 1.7 mL in a 4 mL bottle. (3)

----------CONTRAINDICATIONS----------
Hypersensitivity to any of the ingredients in the formula or to other NSAIDS.(4)

----------WARNINGS AND PRECAUTIONS----------
Increased bleeding time due to interference with thrombocyte aggregation (5.1)
Delayed healing (5.2)
Corneal effects including keratitis (5.3)

----------ADVERSE REACTIONS----------
Most common adverse reactions (5 to 10%) are capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Alcon Laboratories, Inc. at 1-800-757-9195 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

Reference ID: 3231062

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ILEVRO™ (nepafenac ophthalmic suspension), 0.3% is indicated for the treatment of pain and inflammation associated with cataract surgery.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

One drop of ILEVRO™ (nepafenac ophthalmic suspension), 0.3% should be applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.

2.2 Use with Other Topical Ophthalmic Medications

ILEVRO™ (nepafenac ophthalmic suspension), 0.3% may be administered in conjunction with other topical ophthalmic medications such as beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics, and mydriatics.

If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

3 DOSAGE FORMS AND STRENGTHS

Sterile ophthalmic suspension 0.3%

1.7 mL in a 4 mL bottle

4 CONTRAINDICATIONS

ILEVRO™ (nepafenac ophthalmic suspension), 0.3% is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other NSAIDs.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Bleeding Time

With some nonsteroidal anti-inflammatory drugs including ILEVRO™ (nepafenac ophthalmic suspension), 0.3%, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphema) in conjunction with ocular surgery.

It is recommended that ILEVRO™ (nepafenac ophthalmic suspension), 0.3% be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

5.2 Delayed Healing

Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including ILEVRO™ (nepafenac ophthalmic suspension), 0.3%, may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

5.3 Corneal Effects

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs including ILEVRO™ (nepafenac ophthalmic suspension), 0.3% and should be closely monitored for corneal health.

Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Postmarketing experience with topical NSAIDs also suggests that use more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events.

5.4 Contact Lens Wear

ILEVRO™ (nepafenac ophthalmic suspension), 0.3% should not be administered while using contact lenses.

6 ADVERSE REACTIONS

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to the rates in the clinical studies of another drug and may not reflect the rates observed in practice.

6.1 Serious and Otherwise Important Adverse Reactions

The following adverse reactions are discussed in greater detail in other sections of labeling.

- Increased Bleeding Time (*Warnings and Precautions 5.1*)
- Delayed Healing (*Warnings and Precautions 5.2*)
- Corneal Effects (*Warnings and Precautions 5.3*)

6.2 Ocular Adverse Reactions

The most frequently reported ocular adverse reactions following cataract surgery were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation. These reactions occurred in approximately 5 to 10% of patients.

Other ocular adverse reactions occurring at an incidence of approximately 1 to 5% included conjunctival edema, corneal edema, dry eye, lid margin crusting, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, photophobia, tearing and vitreous detachment.

Some of these reactions may be the consequence of the cataract surgical procedure.

6.3 Non-Ocular Adverse Reactions
Non-ocular adverse reactions reported at an incidence of 1 to 4% included headache, hypertension, nausea/vomiting, and sinusitis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Teratogenic Effects.
Pregnancy Category C: Reproduction studies performed with nepafenac in rabbits and rats at oral doses up to 10 mg/kg/day have revealed no evidence of teratogenicity due to nepafenac, despite the induction of maternal toxicity. At this dose, the animal plasma exposure to nepafenac and amfenac was approximately 70 and 630 times human plasma exposure at the recommended human topical ophthalmic dose for rats and 20 and 180 times human plasma exposure for rabbits, respectively. In rats, maternally toxic doses ≥ 10 mg/kg were associated with dystocia, increased postimplantation loss, reduced fetal weights and growth, and reduced fetal survival.

Nepafenac has been shown to cross the placental barrier in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ILEVRO™ (nepafenac ophthalmic suspension), 0.3% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects.
Because of the known effects of prostaglandin biosynthesis inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of ILEVRO™ (nepafenac ophthalmic suspension), 0.3% during late pregnancy should be avoided.

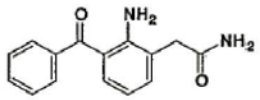
8.3 Nursing Mothers
Nepafenac is excreted in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ILEVRO™ (nepafenac ophthalmic suspension), 0.3% is administered to a nursing woman.

8.4 Pediatric Use
The safety and effectiveness of ILEVRO™ (nepafenac ophthalmic suspension), 0.3% in pediatric patients below the age of 10 years have not been established.

8.5 Geriatric Use
No overall differences in safety and effectiveness have been observed between elderly and younger patients.

11 DESCRIPTION

ILEVRO™ (nepafenac ophthalmic suspension), 0.3% is a sterile, topical, nonsteroidal anti-inflammatory (NSAID) prodrug for ophthalmic use. Each mL of ILEVRO™ (nepafenac ophthalmic suspension), 0.3% contains 3 mg of nepafenac. Nepafenac is designated chemically as 2-amino-3-benzoylbenzeneacetamide with an empirical formula of $C_{15}H_{14}N_2O_2$. The structural formula of nepafenac is:



Nepafenac is a yellow crystalline powder. The molecular weight of nepafenac is 254.28. ILEVRO™ (nepafenac ophthalmic suspension), 0.3% is supplied as a sterile, aqueous suspension with a pH approximately of 6.8.

The osmolality of ILEVRO™ (nepafenac ophthalmic suspension), 0.3% is approximately 300 mOsm/kg.

Each mL of ILEVRO™ (nepafenac ophthalmic suspension), 0.3%, contains: Active: nepafenac 0.3% Inactives: boric acid, propylene glycol, carbomer 974P, sodium chloride, guar gum, carboxymethylcellulose sodium, edetate disodium, benzalkonium chloride 0.005% (preservative), sodium hydroxide and/or hydrochloric acid to adjust pH and purified water, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
After topical ocular dosing, nepafenac penetrates the cornea and is converted by ocular tissue hydrolases to amfenac, a nonsteroidal anti-inflammatory drug. Nepafenac and amfenac are thought to inhibit the action of prostaglandin H synthase (cyclooxygenase), an enzyme required for prostaglandin production.

12.3 Pharmacokinetics
Following bilateral topical ocular once-daily dosing of ILEVRO™ (nepafenac ophthalmic suspension), 0.3%, the concentrations of nepafenac and amfenac peaked at a median time of 0.5 hour and 0.75 hour, respectively on both Day 1 and Day 4. The mean steady-state Cmax for nepafenac and for amfenac were 0.847 ± 0.269 ng/mL and 1.13 ± 0.491 ng/mL, respectively.

Nepafenac at concentrations up to 3000 ng/mL and amfenac at concentrations up to 1000 ng/mL did not inhibit the *in vitro* metabolism of 6 specific marker substrates of cytochrome P450 (CYP) isozymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4). Therefore, drug-drug interactions involving CYP mediated metabolism of concomitantly administered drugs are unlikely.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Nepafenac has not been evaluated in long-term carcinogenicity studies. Increased chromosomal aberrations were observed in Chinese hamster ovary cells exposed *in vitro* to nepafenac suspension. Nepafenac was not mutagenic in the Ames assay or in the mouse lymphoma forward mutation assay. Oral doses up to 5,000 mg/kg did not result in an increase in the formation of micronucleated polychromatic erythrocytes *in vivo* in the mouse micronucleus assay in the bone marrow of mice.

Nepafenac did not impair fertility when administered orally to male and female rats at 3 mg/kg.

14 CLINICAL STUDIES

In two double masked, randomized clinical trials in which patients were dosed daily beginning one day prior to cataract surgery, continued on the day of surgery and for the first two weeks of the postoperative period, ILEVRO™ (nepafenac ophthalmic suspension), 0.3% demonstrated superior clinical efficacy compared to its vehicle in treating postoperative pain and inflammation.

Treatment effect over vehicle for resolution of ocular pain occurred as early as day 1 post-surgery. Treatment effect over vehicle for resolution of inflammation was significantly better than vehicle in both studies at day 7 and day 14 post-surgery.

Inflammation and Ocular Pain Resolution Results of Nepafenac ophthalmic suspension, 0.3% versus Vehicle at Day 14 Post-surgery (All-Randomized Population)

Studies	Treatment	Inflammation Resolution at Postop Day 14	Ocular Pain Resolution at Postop Day 14
Study 1	Nepafenac ophthalmic suspension, 0.3% (n/N) [1]	552/851 (65%)	734/851 (86%)
	NEVANAC (n/N) [1]	568/845 (67%)	737/845 (87%)
	Vehicle (n/N) [1]	67/211 (32%)	98/211 (46%)
	Difference (95% CI) [2]	33% (26%, 40%)	40% (32%, 47%)
Study 2	Nepafenac ophthalmic suspension, 0.3% (n/N) [1]	331/540 (61%)	456/540 (84%)
	Vehicle (n/N) [1]	63/268 (24%)	101/268 (38%)
	Difference (95% CI) [2]	38% (31%, 45%)	47% (40%, 54%)

[1] n/N is the ratio of those with complete resolution of anterior chamber cell and flare by the postoperative day 14 visit over all randomized subjects.
[2] Difference is (Nepafenac ophthalmic suspension, 0.3% – vehicle). The 95% confidence interval is derived using asymptotic approximation.

16 HOW SUPPLIED/STORAGE AND HANDLING

ILEVRO™ (nepafenac ophthalmic suspension), 0.3% is supplied in a white, oval, low density polyethylene DROP-TAINER® dispenser with a natural low density polyethylene dispensing plug and gray polypropylene cap presented in an overwrap. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

1.7 mL in 4 mL bottle NDC 0065-1750-07

Storage: Store at 2 - 25°C (36 - 77°F).

Protect from light.

17 PATIENT COUNSELING INFORMATION

17.1 Slow or Delayed Healing

Patients should be informed of the possibility that slow or delayed healing may occur while using nonsteroidal anti-inflammatory drugs (NSAIDs).

17.2 Avoiding Contamination of the Product

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Use of the same bottle for both eyes is not recommended with topical eye drops that are used in association with surgery.

17.3 Contact Lens Wear
ILEVRO™ (nepafenac ophthalmic suspension), 0.3% should not be administered while wearing contact lens.

17.4 Intercurrent Ocular Conditions
Patients should be advised that if they develop an intercurrent ocular condition (e.g., trauma, or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multi-dose container.

17.5 Concomitant Topical Ocular Therapy
If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

17.6 Shake Well Before Use
Patients should be instructed to shake well before each use.

U.S. Patent Nos. 5,475,034; 6,403,609; and 7,169,767

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ALCON LABORATORIES, INC.
Fort Worth, Texas 76134 USA

Appendix 6

Study Product Components

Nepafenac Punctal Plug Delivery System (N-PPDS) Components

Component	Description
Nepafenac	GMP grade, micronized powder
poly (ξ-caprolactone)	GMP grade, pellets
PEG400	NF grade, liquid
Tyloxapol	USP grade, viscous liquid
Tubing	Polyimide tube length (0.0220" inner diameter, with 0.0010" wall–medical grade)
Loctite® 4305™ Cyanoacrylate adhesive	Medical grade ethyl cyanoacrylate with photoinitiator
L67 Punctal Plug	Silicone punctal plug (Silicone –MED-4870, colorant MED-4800-6)

Placebo Punctal Plug Delivery System (p-PPDS) Components

Component	Description
poly (ξ-caprolactone)	GMP grade, pellets
PEG400	NF grade, liquid
Tyloxapol	USP grade, viscous liquid
Tubing	Polyimide tube length (0.0220" inner diameter, with 0.0010" wall–medical grade)
Loctite® 4305™ Cyanoacrylate adhesive	Medical grade ethyl cyanoacrylate with photoinitiator
L67 Punctal Plug	Silicone punctal plug (Silicone –MED-4870, colorant MED-4800-6)

Appendix 7

GUIDELINES FOR INFORMED CONSENT

Both the written informed consent form and the discussion of informed consent with a potential study subject should include explanations of the following:

a. The study involves research

b. The purpose of the study

c. The study treatment(s) and the probability for random assignment to each treatment

d. The study procedures to be followed, including all invasive procedures

e. The subject's responsibilities

f. The aspects of the study that are experimental

g. The reasonably foreseeable risks or inconveniences to the study subject and, when applicable, to an embryo, fetus, or nursing infant

h. The reasonably expected benefits. When there is no intended clinical benefit to the study subject, the study subject should be made aware

i. The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks

j. The compensation and/or treatment available to the study subject in the event of study-related injury

k. The anticipated prorated payment, if any, to the study subject for participating in the study

l. The anticipated expenses, if any, to the subject for participating in the study

m. The study subject's participation in the study is voluntary and that they may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which they are otherwise entitled

n. The monitor(s), the auditor(s), the IRB/Independent Ethics Committee (IEC), and the regulatory authority(ies) will be granted direct access to the study subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access

o. The records identifying the study subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the study are published, the subject's identity will remain confidential.

p. The study subject or their legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.

q. The person(s) to contact for further information regarding the study and the rights of study subjects, and whom to contact in the event of study-related injury

r. The foreseeable circumstances and/or reasons under which the subject's participation in the study may be terminated

s. The expected duration of the study subject's participation in the study

t. The approximate number of study subjects involved in the study.