CONFIDENTIAL

The following contains confidential, proprietary information which is the property of Mati Therapeutics

PROTOCOL: CLINICAL STUDY TGLA-2021-01

A 90-Day, Open-Label, Multi-Site, Pilot Study Evaluating the Safety and Intraocular Lowering Effect of Delivering Travoprost using a Punctal Plug Delivery System (Evolute®) in Subjects with Elevated Intraocular Pressure

Protocol Version 3: 08 April 2022

Travoprost Punctal Plug Delivery System, 166 µg/L67

IND 114300

Mati Therapeutics Inc.
101 Colorado St., Suite 2409
Austin, TX 78701

TABLE OF CONTENTS

PROTOCOL APPROVAL

Protocol Number: TGLA-2021-01 (Version 3)

Title of Protocol: A 90-Day, Open-Label, Multi-Site, Pilot Study Evaluating the Safety and Intraocular Lowering Effect of Delivering Travoprost using a Punctal Plug Delivery System (Evolute®) in Subjects with Elevated Intraocular Pressure

Prepared by: _____ 06 Apr 22
Daniel Schwob, Consultant
D'Ellis Group Inc.
Date

Study Director: _____ 07 Apr 2022
Robert Williams, MD
Clinical Consultant
Date

Approved by: _____ 08 April 2022
Deepank Utkhede
Chief Scientific Officer, Mati Therapeutics Inc
Date

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

PROTOCOL APPROVAL

Protocol Number: TGLA-2021-01 (Version 3)

Title of Protocol: A 90-Day, Open-Label, Multi-Site, Pilot Study Evaluating the Safety and Intraocular Lowering Effect of Delivering Travoprost using a Punctal Plug Delivery System (Evolute®) in Subjects with Elevated Intraocular Pressure

Prepared by: _____ 06 Apr 22
Daniel Schwob, Consultant
D'Ellis Group Inc.
Date

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

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

Approved by: _____ 4/6/22
Robert Butchofsky
President, Mati Therapeutics Inc
Date

STATEMENT OF COMPLIANCE

Mati Therapeutics Inc. Protocol TGLA-2021-01

A 90-Day, Open-Label, Multi-Site, Pilot Study Evaluating the Safety and Intraocular Lowering Effect of Delivering Travoprost using a Punctal Plug Delivery System (Evolute®) in Subjects with Elevated Intraocular Pressure

Protocol Version 3: 08 Apr 2022

Sponsor and Medical Monitor Approval:

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

Investigator Agreement:

I have read this protocol in its entirety and agree to:

a. Implementing and conducting this study in strict compliance with this agreement; the protocol; ICH guidelines for Good Clinical Practices and all other applicable regulatory requirements.

b. 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.

c. 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.

d. Obtain authorization for use/disclosure of health information (HIPAA authorization)

e. Maintain reliable study device dispensing log, receipt and return shipping records, and to store study supplies in a secure, locked facility accessible only to authorized study personnel

f. Maintain adequate and accurate source documents in accordance with Food and Drug Administration (FDA) regulations (e.g., CRFs, consent forms, AE/SAE and ADE/SADE forms, IRB/IEC documentation, and 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

g. 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.

h. Attempt to complete the study within the time designated.

By signing this "STATEMENT OF AGREEMENT", 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:

Representative Signature: _____Date: _____
"TYPE/Print Name of Representative"

ABBREVIATIONS AND DEFINITIONS

ADE	Adverse Device Effect
AE	Adverse Effect
BCDVA	Best-Corrected Distance Visual Acuity
BP	Blood Pressure
BT	Body Temperature (Fahrenheit)
CDC	Center for Disease Control
CRA	Clinical Research Associate
CFR	Code of Federal Regulations
CRF	Case Report Form
CRC	Clinical Research Coordinator
Evolute®	Punctal Plug Delivery System
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICH E6	International Conference on Harmonisation Guidance for Industry Good Clinical Practice: Consolidated Guidance
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
IRB	Investigational Review Board
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeters of Mercury
NCR	No Carbon Required
NDE	Non-drug eluting
NSR	Non-Significant Risk
PP	Per Protocol
QC	Quality Control
OH	Ocular Hypertension
OTC	Over-the-Counter
POAG	Primary Open-Angle Glaucoma
PPDS	Punctal Plug Delivery System
SADE	Serious Adverse Device Event
SAE	Serious Adverse Event
Study Subject	An individual that has signed a HIPAA and study consent form
Subject	Individual being considered for enrollment in to the study
UP	Unanticipated Problem
VA	Visual Acuity

STUDY SYNOPSIS

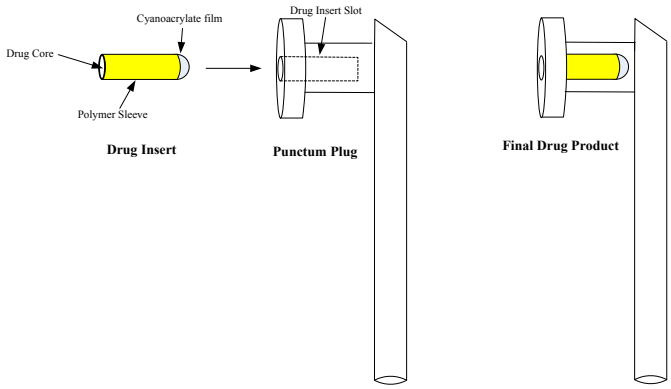
STUDY PROTOCOL NUMBER: TGLA-2021-01

STUDY PROTOCOL TITLE: A 90-Day, Open-Label, Multi-Site, Pilot Study Evaluating the Safety and Intraocular Lowering Effect of Delivering Travoprost using a Punctal Plug Delivery System (Evolute®) in Subjects with Elevated Intraocular Pressure

SPONSOR: Mati Therapeutics Inc.

INVESTIGATIONAL PRODUCT, OPEN-LABEL: The Travoprost Evolute (Travoprost Punctal Plug Delivery System) is an L-shaped, silicone punctal plug with a drug eluting core that contains travoprost (active). The Travoprost Evolute is pre-loaded onto a disposable inserter tip and individually packaged and sterilized to prevent contamination. The Travoprost Evolute is stored at refrigerated temperature.

Travoprost Evolute System



NUMBER OF SITES: Up to 8 sites within the U.S.A.

STUDY POPULATION: Up to 30 qualified male or female subjects (~30 qualified eyes) who have given HIPAA and informed consent, have met all screening, washout and treatment phase inclusion/exclusion criteria of the study, will be enrolled and will receive a Travoprost Evolute inserted in to the lower punctum of each eye.

STUDY OBJECTIVE: Using a punctal plug delivery system (Evolute) to deliver a hypotensive (travoprost) drug to the eye, evaluate the safety and ocular effects of a Travoprost Evolute system in reducing intraocular pressure in individuals diagnosed with OAG or OH.

STUDY DESIGN: This is a pilot, open-label, multi-center clinical study. Each potential subject that has given HIPAA and informed consent and has meet all screening inclusion/exclusion criteria will undergo a six-week washout phase where they will discontinue the use of their topical hypotensive medication. In addition, during the washout phase, each potential study subject will also discontinue the use of all prohibited systemic medications.

After the six-week washout, each potential subject will return for a baseline visit (Visit 2). Investigators will verify that a potential subject has discontinued the use of their topical hypotensive medication(s) and all their prohibited systemic medications for the last 6 weeks. In addition, each subject will have discontinued the use of all other ocular drops, gels or ointments 24 hours prior to the visit (Visit 2) and continues to meet all screening and washout criteria. After completing the baseline examination, each potential subject that meet all baseline

inclusion/exclusion for the treatment phase of the study will have his/her lower puncta of each eye inserted with a Travoprost Evolute®. Each study subject will be instructed to return to the investigator's office the next day, seven, 28, 60 and 90 after the insertion of their plugs for follow-up examinations.

SUBJECT SELECTION: The following are inclusion and exclusion criteria for a prospective study subject

i. Screening Phase

a. INCLUSION Criteria**:** The following are requirements a subject must meet in order to be considered for inclusion into the screening phase of the study:

1. Male or female subject, 18 years of age or older at the time of the screening examination and has been diagnosed with bilateral OAG or OH
2. A subject must be able and willing to read, comprehend and give authorization for Use/Disclosure of Health Information (HIPAA) and informed consent
3. A subject must not have taken any ocular hypertension medication(s) within the last 12 hours of the screening visit unless in the opinion of the screening physician it poses an undue risk.
4. A subject must be willing to have the **lower puncta of each eye** inserted with a study plug
5. A subject's screening visit (pre-washout) IOPs, measured between 8:00 and 10:00 AM, is less than 22 mmHg in both eyes
6. A subject IOPs are currently controlled (< 22 mm Hg) with a topical prostaglandin or in conjunction with one other topical ocular hypotensive drug, not including any fixed-combination formulations (i.e., Cosopt, Combigan, Azarga, etc.), in both eyes for at least one month
7. A subject must be willing to comply with study instructions and agree to complete the entire course of the study
8. A subject must agree to make all office appointments and have all office visits occur between 8:00 and 10:00 AM
9. Women 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, including intrauterine device (IUD); oral, dermal ("patch"), implant or injected contraceptives; tubal ligation; or barrier methods with spermicide
10. A subject has a Best-Corrected Distance (Glasses), pinhole visual acuity of 20/100 (Snellen) or better in both eyes
11. A subject has documented perimetry results within the last 6 months prior to the Screening Visit for both eyes

NOTE: If perimetry measurement are older than 6 months, perform automated perimetry at the screening visit

12. A subject has documented central corneal thickness measurements between >500 µm and <600 µm in both eyes

NOTE: if corneal thickness data is not available, measure corneal thickness of each eye using pachymetry at the screening visit

b. EXCLUSION Criteria**:** If any of the below criteria apply to a potential study subject, the subject does not qualify for enrollment into the screening phase of the study:

1. A subject with a history of non-response to topical prostaglandin eye drops for OAG/OH
2. A subject with angle-closure glaucoma, neovascular glaucoma, traumatic glaucoma or iridocorneal endothelium syndrome in either eye
3. A subject with a known sensitivity to travoprost, fluorescein, topical anesthetic, silicone, any inactive ingredient of the Travoprost Evolute® or any other products required for study procedures
4. A subject with $\geq$ 0.9 vertical cup or completely notched optic nerve head rim in either eye
5. A subject with any functionally significant visual field loss or progressive field loss within the last year in either eye
6. A subject with a history of complications, AEs, 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
7. A subject with a history of intolerance to punctal plugs or a known sensitivity to any inactive ingredient of the punctal plug, silicone, topical anesthetic, or any other products required for the study
8. A subject with structural lid abnormalities (i.e., ectropion, entropion) in either eye
9. A subject with an active lid disease in either eye (i.e., moderate or severe blepharitis, meibomianitis) that requires medical treatment
10. A subject with any clinically significant (moderate or severe) lid, conjunctival or corneal findings in either eye at the screening visit
11. A subject with a history of chronic/recurrent inflammatory eye disease (i.e., scleritis, uveitis, herpes keratitis) in either eye
12. A subject who would require the use of any ocular medication(s), an over-the-counter drop(s), ointment(s) or gel(s), other than the study hypotensive medication(s) in either eye during the study period
13. A subject who has had any ophthalmic surgical procedures (i.e., glaucoma laser, minimally invasive glaucoma surgery, cataract, refractive, etc.) in either eye within the last six months or will require ophthalmic surgery before completing the study
14. A subject with a history of penetrating keratoplasty in either eye
15. A subject requiring the use of a contact lens in either eye at any time during the study period
16. A subject with advanced diabetic retinopathy, branch retinal vein occlusion or central retinal vein occlusion in either eye
17. A subject with a history of macular edema in either eye
18. A subject currently on any systemic medication [i.e., beta-blocker, carbonic anhydrase inhibitors, corticosteroids (including dermal), etc.] that may have an effect on the subject's IOP, or who will require its use during the study period
    NOTE: An inhaled steroid, systemic beta-blocker or β-adrenoceptor antagonist may be permitted, providing the subject has maintained a stable dosage regimen for at least the last three months
19. A subject with an uncontrolled systemic disease or a medical condition that may increase the risk associated with study participation or administration of study treatment or that may interfere with the interpretation of study results (e.g.,

autoimmune disease if the subject is on chronic medications and has ocular involvement; host-versus-graft disease)

20. A subject currently participating or has participated within the last 30 days prior to the start of this study in a drug, device or other investigational research study.

ii Washout Phase

After the screening phase (process), each subject meeting all screening inclusion/exclusion criteria must be willing to:

1. DISCONTINUE the use of his/her topical hypotensive medication(s) for the next six-weeks and not to use his/her hypotensive medication for the duration of the study
2. DISCONTINUE the use of all other ocular drops, gels or ointments that have not been prescribed by the investigator, 24 hours prior to Visit 2 and for the duration of the study
3. DISCONTINUE the use of all systemic medication that are PROHIBITED by the protocol for the duration of the study. Systemic medication(s) being used by a subject at the Screening visit and is permitted by the protocol, may continue the medication(s), however the **concentration and dosing frequency** must remain the same throughout the washout and treatment phases of the study.

iii. Treatment Phase

a. INCLUSION Criteria**: After the washout phase, t**he following are requirements a subject must meet in order to be considered for enrollment into the treatment phase of the study:

1. After the six-week washout phase, the subject continues to meet all screening and washout inclusion/exclusion study criteria
2. After the six-week washout phase, subject's Baseline (Visit 2) IOP measured between 8:00 and 10:00 AM, is between $\geq$ 23 and $\leq$ 34 mmHg in at least one eye
3. Subject's Baseline (Visit 2, morning average) IOP is $\geq$ 5 mmHg from the subject's SCREENING (pre-washout) IOP in at least one eye whose Baseline IOP is between $\geq$ 23 and $\leq$ 34 mmHg
4. Investigator is able to dilate the lower puncta of each eye to 1.0 mm, and insert a study plug into each puncta.

b. EXCLUSION Criteria**:** If any of the below criteria apply to a study subject that has completed the washout period, the subject does not qualify for enrollment into the treatment phase of the study:

1. A subject who no longer meets all the screening and washout study criteria
2. A subject who **cannot be successfully inserted** with a Travoprost Evolute® **in the lower puncta of each eye**, even if only one eye qualifies for enrollment.

STUDY VARIABLES: The following will be performed and/or recorded during the course of the study:

a. Obtain written HIPAA and Informed Consent
b. Verify a subject has not used any hypotensive ocular drops within the last 12 hours prior to the screening visit or at any time during the washout or treatment phases of the study
c. Record any changes in the subject's use of any concomitant medications or ocular drops, gels or ointments during the course of the study
d. Record subject's demographic data and medical history for past 6 months

e. Perform a urine pregnancy test on a female subject of child-bearing potential at their screening and last study visits
f. Measure subject's temperature, heart rate and blood pressure
g. Record subject's Best-Corrected (Glasses) Distance or Pinhole Visual Acuity
h. Verify documented automated perimetry results have been measured in the last 6 months
   NOTE: If perimetry measurement are older than 6 months, perform automated perimetry at the screening visit.
i. Verify corneal thickness measurements are documented in the subject's chart
   NOTE: if corneal thickness data is not available, measure corneal thickness of each eye using pachymetry at the screening visit
j. Perform a slit-lamp examination of each eye
k. Perform a non-dilated fundus exam of each eye, including the evaluation of the lens
l. Perform IOP measurements of each eye
m. Dilate lower punctum to 1.0 mm and insert a study plug in to the lower puncta of each eye
n. Evaluate the study plug position in each eye using the slit-lamp
o. Record any Adverse Events/Adverse Device Events.

Study Duration: The approximate study duration is 12 months. Study projected to start 1st Qtr. 2021

Study Outcome Endpoint:

Primary Endpoint: Change in IOP from the baseline visit to Days seven, 28, 60 and 90.

Other Collected Data: Changes in IOP and percent change between the screening and the baseline visits (after washout phase, prior to insertion of any Travoprost Evolute®), percent of screened patients that qualified for washout phase, percent of patients that entered the washout phase that qualified for the treatment phase, enrollment rates (rates in to each phase of the study), number and percent of study subjects whose IOPs were ≥34 mmHg at Visit 2, number and percent of eyes that extruded a study plug, number of eyes investigators were unable to dilate or insert a study plug, listing of reasons why patients failed to qualify.

Safety Endpoint Safety variables include any reported AEs/SAEs. Safety variables will also include any clinically significant changes in IOP, BCDVA, slit-lamp findings, ocular tearing and comfort, blood pressure, heart rate, temperature, Travoprost Evolute® inspections/extrusions. Safety analyses will be performed on all subjects who enter the washout phase of the study. Subjects that were inserted with a study plug will be subgrouped and summarized separately.

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

Schedule of Assessments, Events

Visit Examination Parameters	Visit 1 Screening	Visit 2 (Day 0)	Visit 3 (Day1)	Visit 4 (Day 7)	Visit 5 (Day28)	Visit 6 (Day 60)	Visit 7 (Day 90)
Informed Consent/HIPAA	❶						
Medical Hx (past 6 months)/Demographic Data	❶	❷[A]					
Urine Pregnancy Test (Only women of childbearing potential)	❶[B]						❼[B]
Concomitant Med Use	❶	❷	❸	❹	❺	❻	❼
BT (temperature), BP (blood pressure), HR (heart rate)	❶	❷	❸	❹	❺	❻	❼
Evaluate study plug position prior to any eye exam		❷*	❸	❹	❺	❻	❼
Best-Corrected Distance (Glasses) or Pinhole VA	❶	❷	❸	❹	❺	❻	❼
Automated Perimetry (**Not required** if measured in last 6 months)	⦿						
Pachymetry (**Not required** if documented in patient's chart)	⦿						
Slit-Lamp Examination	❶	❷	❸	❹	❺	❻	❼
IOP (Goldmann) Evaluation (To be measured between 8 and 10 am)	❶	❷	❸	❹	❺	❻	❼
Non-Dilated Fundus Examination (Include evaluation of the LENS)	❶						
Begin Six-Week Washout (D/C all topical drops, gels, ointments)	❶						
Punctal Size Evaluation, Dilation of Lower Puncta		❷					
Insertion of Punctal Plugs		❷					
Punctal Plug **Extrusion			☆[C]	☆[C,D]	☆[C,D]	☆[C,D]	❼
Removal of Punctal Plugs after eye exam completed‡							❼‡
Adverse Event/Adverse Device Event Recording		❷	❸	❹	❺	❻	❼

Keys to Abbreviations:

A = Verify no change in medical history, subject still meets all study inclusion/exclusion criteria
B = If performed at the screening visit, must be performed when subject exit the study
C = In a subject where both eyes qualified at Visit 2, if a plug is extruded in one eye, **plug is to be replaced** and subject continues in the study
D = In a subject where only one eye qualified at Visit 2, if the plug is extruded in the qualified eye, the subject will be DISCONTINUED and replaced. In a subject where both eyes qualified, if a plug is extruded in one eye, then extruded again or in the fellow eye, the subject will be DISCONTINUED and replaced
* = Plug position evaluated after eye exam and plug insertion
‡ = If subject EXITs the study after visit 2, but before visit 7, subject must return to Investigator's office to have plugs removed

Body Temperature:	Temperature maybe taken using a non-contact (Infrared) thermometer or orally. Oral temperatures should not be taken within five minutes of ingestion of any food or drink
Heart Rate:	Heart rate taken in the sitting position after subject has rested for 5 minutes. Recorded values can be obtained electronically (automated) or manually (observed for 30 seconds or more)
Blood Pressure:	Blood pressure, taken in the sitting position after subject has rested for 5 minutes. Recorded values can be obtained electronically (automated) or manually
Plug Position Evaluation:	Position of the plug will be evaluated as either: Normal, Present but requires adjustment, Extruded/Recovered, Extruded/Lost, Other
Slit-Lamp Exam:	Evaluation will include the Lids (Upper & Lower), Conjunctiva (Bulbar & Palpebral) and the Cornea. SL Findings will be graded on a 5-point scale: 0 = None, 1 = Trace, 2 = Mild, 3 = Moderate, 4 = Severe
IOP Evaluation:	Goldmann applanation tonometry will be used for measuring IOP. Just prior to the start of the study, the tonometer should be calibrated. IOP of each eye will be measured twice, alternating between the eyes. The average of the two measurements will be used for analysis. However, if there is a $\geq \pm$ 3 mmHg difference between the 1st and 2nd measurement for an eye, a 3rd measurement will be taken and the average of the two closest values of the three will be used for analysis for that eye.

1 KEY ROLES

Sponsor: Mati Therapeutics Inc. (Headquarters)
101 Colorado, Apt 2409
Austin, TX 78701
512 329-6360

Sponsor Personnel:

Clinical Trial Coordinator:	Deepank Utkhede Chief Scientific Officer Mati Therapeutics Canada Inc. (R&D Branch) 201-4475 Wayburne Drive Burnaby, BC V5G 4X4 Cell: 778.991-3301 Fax: 604 637-8747 dutkhede@matitherapeutics.com
Study Monitor/ Biostatistician:	Daniel Schwob D'Ellis Group, Inc. 26741 Portola Pkwy, Ste 1E 717 Foothill Ranch, CA 92610 Office: 949.916-2800 Cell: 949.735-1320 dschwob@dellisgroup.com
Regulatory Specialist:	Caroline Stokl, Ph.D., Consultant, Regulatory Affairs 201-4475 Wayburne Drive Burnaby, BC V5G 4X4 Office: 604.983-9103 cstokl@matitherapeutics.com
Medical Monitor:	Robert Williams, MD 89 Wilks Way Friday Harbor, WA 98250 Office: 360.378-7916 Cell: 360.298-5325 iopdoc1@gmail.com
Emergency FAX Number:	24-hour Adverse Event/Adverse Device Event FAX: 360.282-6871 Robert Williams, MD Office: 360.378-7916 Cell: 360.298-5325 Deepank Utkhede Cell: 778.991-3301 Fax: 604 637-8747 Daniel Schwob Office: 949.916-2800 Cell: 949.735-1320

2 INTRODUCTION: BACKGROUND AND 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

Open-angle glaucoma (OAG) is a chronic ocular disorder characterized by elevated intraocular pressure (IOP) with clinical signs of visual field loss and/or optic nerve damage with patients rarely experience any ocular symptoms. If the condition is left untreated, irreversible vision loss due to optic nerve damage will occur. The effect of elevated IOP on the optic nerve is gradual, leading to vision loss that patients may not realizes until they have irreversibly lost a majority of their vision.

Based on estimates from the World Health Organization and the Glaucoma Foundation, this chronic disease is believed to affect approximately 67 to 105 million people worldwide (Leonard 2002) and is the leading cause of irreversible blindness worldwide. In 2011, 2.71 million people in the United States had OAG, by 2050 it is estimated that 6.3 million people in the United States will have OAG.

Treatment however of OAG/OH by nature is a disease where compliance tends to be a significant problem due to the fact patients lack positive feedback from treatment. Treatment benefits with topical hypotensive medications are designed to prevent worsening rather than improving visual function by reducing IOP, which is not noticeable by patients.

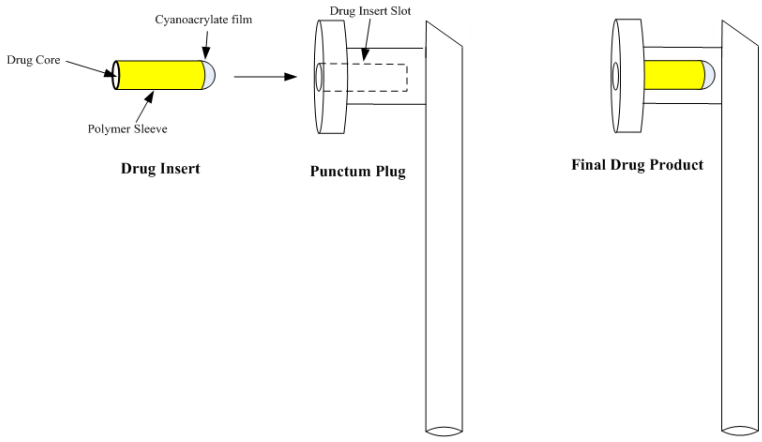
Treatment compliance is therefore a key issue in the successful control of OAG/OH and the prevention of vision loss. Traditionally, the term compliance has been employed to mean the extent to which a patient remembers and complies with the physician's advice of when, and amount of medication to use. When treating a condition with an ocular drop from a bottle, treatment also depends upon the patients' physical ability to properly instill/place the correct amount of the medication/drop on the eye. A patients' ability to correctly self-administer ocular drops can be affected by a number of factors such as coordination, manual dexterity, n, good vision, all of which tend to decrease in aging glaucoma patients, and the presence of co-morbid conditions (Choy et al. 2019). Study has also shown that adding a second medication is associated with a statistically significant decrease in compliance (Robin 2005).

Effective treatment of OAG/OH is compounded if the drop is not appropriately placed on the eye. The ideal location for instilling/placing of an eye drop is in the eyelid cul-de-sac, or directly onto the surface of the eye. Due to patients having difficulty holding the eyelid open or unable to control reflex blinking during installation, results in many missed glaucoma eye drops over time and can lead to suboptimal treatment or costly wasting of medication. In addition, many OAG/OH patients, find it difficult applying the correct amount of pressure to the bottle to release only one drop at a time.

A promising new way to treatment OAG/OH is the use of punctal plugs to deliver an accurate and consistent dosage of an ocular medication. This eliminates the need for a patient to instill an eye drop on a daily basis. Punctal plugs are medical devices designed to block the drainage of tear fluid from the eye; several models are FDA cleared and are commercially available. Punctal plugs are cleared to treat ocular dryness secondary to contact lens use, prevent complications due to dry eyes after surgery, and treat the dry eye component of ocular surface diseases.

Mati Therapeutics has developed a novel punctal plug design that can be used to deliver a drug to the ocular surface, a punctal plug delivery system (PPDS). Although Mati's PPDS plug design is novel, the types of materials and techniques used to insert and remove a PPDS are the same as other FDA cleared and commercially available silicone punctal plugs. Mati's PPDS consist of an L-shaped plug, made of medical-grade silicone with a green colorant, and a bore in the cap of the plug that contains a drug insert (see Figure 1). When a PPDS is placed in the inferior punctum of an eye, the proximal end of the drug insert is exposed to the tear fluid. As the tears come in contact with the exposed proximal surface of the insert, drug is slowly eluted into the tear film (refer to the Investigator Brochure, sections 1.1 - 1.5 for details). Based on the formulation of the drug insert, it is estimated that a PPDS containing an insert with an active compound, will be able to elute an efficacious concentration of a therapeutic drug continuously for up to 90 days.

Figure 1: Travoprost Punctal Plug Delivery System



2.2 Rationale

Past clinical studies with once-daily topical dosing of travoprost 0.004% and 0.003% ophthalmic solutions (TRAVATAN®, TRAVATAN Z® or IZBA®) have demonstrated reductions in intraocular pressure (IOP) in patients with OAG/OH (see Appendices I, J & K for package inserts). The objective of this study is to evaluate the use of a punctal plug delivery system, with a drug eluting insert containing 166 µg travoprost (Travoprost Evolute®), can deliver a sustained, safe and effective concentration of travoprost to the eye that reduces the IOP in subjects with OAG/OH. In addition, delivering a continuous lower ocular dose of travoprost vs a bolus application (drop), may reduce the severity and incidence of ocular side effects and/or adverse events (AEs).

2.3 Potential Risks and Benefits

2.3.1 Known Potential Risks

Potential risks associated with the use of a Travoprost Evolute is not fully known. The risk associated with using a study plug to deliver a sustained release of travoprost are anticipated to be similar than those observed for travoprost ophthalmic solutions (TRAVATAN®, TRAVATAN Z® or IZBA®) or the use of silicone punctal plugs. However, the combination of travoprost with a punctal plug may have unforeseen risks.

In a 3-month clinical trial involving 422 patients exposed to QD dosing of travoprost ophthalmic solution, 0.004% and 442 patients exposed to QD dosing of travoprost ophthalmic solution 0.003%, the most common ocular adverse reaction noted during the trial was ocular hyperemia. Other reported ocular adverse events reported at lower incident rates are listed in Table 1.

TABLE 1

Ocular Adverse Events Observed in Controlled Clinical Trial with Travoprost Ophthalmic Solutions 0.004% and 0.003% (TRAVATAN®, TRAVATAN Z® or IZBA®)

30-50% of Subjects	5 to 10% of Subjects	1 to 4% of Subjects
• Ocular Hyperemia *Ocular hyperemia in IZBA controlled studies noted at 12%	• Decreased VA • Eye Discomfort • Foreign Body Sensation • Pain • Pruritus	• Abnormal Vision • Blepharitis • Blurred Vision • Cataract Cells • Conjunctivitis • • Dry Eye • Iris Discoloration • Keratitis • Lid Margin Crusting • Ocular Inflammation • Photophobia • Subconjunctival Hemorrhage • Tearing

TRAVATAN® may gradually change eye color, increasing the amount of brown pigmentation in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long-term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for months to years. Patients should be informed of the possibility of iris color change. TRAVATAN, TRAVATAN Z® or IZBA® product labels are provided in Appendices I, J & K.

Primary risk factors for silicone punctal plugs for use in humans are 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 canalicula requiring irrigation or surgery. In previous studies using models of the proprietary plugs, adverse reactions (AEs) were noted in subjects, including device migration, lacrimation increased, ocular discomfort, eye irritation, conjunctival hyperemia, inflammation of lacrimal passage, eye pain, and eyelid edema.

2.3.2 Known Potential Benefits

The potential benefit of the Travoprost Evolute® is the ability to deliver a sustain release of travoprost over a 90-day period, reducing a patient's elevated IOP while eliminating his/her need to remember to correctly self-administer an eye drop on a daily basis at a specific time of day. Additional benefits would include, relieving the difficulty some patients have instilling an ocular drop, or the uncertainty they may have if they properly instilled his/her drops. Uncertainty of drop instillation can lead to either under dosing (drop instilled improperly) or overdosing, patient instilled first drop properly however, believes drop was not dosed properly and instills a second drop.

A summary of known benefits to humans of 0.004% or 0.003% travoprost ophthalmic drops can be found in the TRAVATAN®, TRAVATAN Z® or IZBA® prescribing information (see Appendices I, J & K).

3 OBJECTIVES AND PURPOSE

Past clinical studies with topical dosing of 0.004% and 0.003% ophthalmic solutions of travoprost (TRAVATAN/TRAVATAN Z and IZBA) have demonstrated the safety and efficacy of travoprost ocular drops in the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The objective for this study is to evaluate the use of a punctal plug delivery system that can deliver a sustained, safe and effective concentration of travoprost to a subject with OAG/OH that can reduce elevated intraocular pressure.

4 STUDY DESIGN AND ENDPOINTS

4.1 Description of the Study Design

This is a pilot, open-label, multi-center clinical study. Each potential subject that has given HIPAA and informed consent and has meet all screening inclusion/exclusion criteria will discontinue the use of his/her topical hypotensive medication(s) for the next six-weeks. In addition, during this period a potential study subject will also discontinue the use of all prohibited systemic medications, and all other ocular drops, gels or ointments that have not been prescribed by the investigator 24-hours prior to Visit 2.

4.2 Study Endpoints

The study will be complete when up to 30 study subjects (~30 qualified eyes) have been evaluated at Visit 7 (Day 90 ± 7 days post plug insertion) or have been terminated from the study.

4.2.1 Primary Endpoint

The primary variable will be IOP changes from baseline to Days seven, 28, 60 and 90. Primary analysis time point will be IOPs obtain between 8:00 and 10:00 am. Observed IOP and percent change from baseline in IOP will also be analyzed.

4.2.2 Other Data Endpoints

Secondary variables will look at changes in IOP and percent change between the screening and the baseline visits (after washout phase, prior to insertion of any Travoprost Evolute®), percent of screened patients that qualified for washout phase, percent of patients that entered the washout phase that qualified for the treatment phase, enrollment rates (rates in to each phase of the study), number and percent of study subjects whose IOPs were $\geq$34 mmHg at Visit 2, number and percent of eyes that extruded a Travoprost Evolute, number of eyes investigators were unable to dilate or insert a study plug, listing of reasons why patients failed to qualify.

4.2.3 Safety Endpoints

Safety variables include any reported AEs/SAEs. Safety variables will also include clinically significant changes in IOP, BCDVA, slit-lamp findings, ocular tearing and comfort, blood pressure, heart rate, temperature, and Travoprost Evolute® inspections/extrusions. Safety analyses will be performed on all subjects who enter the washout phase of the study. Subjects that were inserted with a study plug will be subgrouped and summarized separately.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Study Population

Up to 30 qualified male or female subjects (~30 qualified eyes) who have given HIPAA and informed consent, have met all screening and washout criteria, will be enrolled into the treatment phase of the study and have a Travoprost Evolute inserted into the lower punctum of each eye. All study plugs will remain in the study subject's lower puncta for a period of 90 $\pm$ 7 days after insertion.

5.2 Study Inclusion/Exclusion Criteria

5.2.1 Study Screening Phase Criteria

The following are criteria a potential study subject must meet in order to be considered for enrollment into the study screening phase of the study.

5.2.1.1 Screening Phase - Inclusion Criteria

The following are requirements a subject must meet in order to be considered for inclusion into the study screening phases of the study:

1. Male or female subject, 18 years of age or older at the time of the screening examination and has been diagnosed with bilateral OAG or OH
2. A subject must be able and willing to read, comprehend and give Authorization for Use/Disclosure of Health Information (HIPAA) and informed consent
3. A subject must not have taken any ocular hypertension medication(s) within 12 hours of the screening visit
4. A subject must be willing to have the lower puncta of each eye inserted with a study plug
5. A subject's screening visit (pre-washout) IOPs, measured between 8:00 and 10:00 AM, is less than 22 mmHg in both eyes
6. A subject IOPs are currently controlled (< 22 mm Hg) with a topical prostaglandin or in conjunction with one other topical ocular hypotensive drug, not including any fixed-combination formulations (i.e., Cosopt, Combigan, Azarga, etc.), in both eyes for at least one month
7. A subject must be willing to comply with study instructions and agree to complete the entire course of the study
8. A subject must agree to make all office appointments and have all office visits occur between 8:00 and 10:00 AM
9. Women 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, including intrauterine device (IUD); oral, dermal ("patch"), implant or injected contraceptives; tubal ligation; or barrier methods with spermicide
10. A subject has a Best-Corrected Distance (Glasses), pinhole visual acuity of 20/100 (Snellen) or better in both eyes
11. A subject has documented perimetry results within the last 6 months prior to the Screening Visit for both eyes

    NOTE: If perimetry measurement are older than 6 months, perform automated perimetry at the screening visit

12. A subject has documented central corneal thickness measurements between >500 µm and <600 µm in both eyes

    NOTE: if corneal thickness data is not available, measure corneal thickness of each eye using pachymetry at the screening visit

5.2.1.2 Screening Phase - EXCLUSION Criteria

If any of the below criteria apply to a potential study subject, the subject does not qualify for enrollment into the screening phase of the study:

1. A subject with a history of non-response to topical prostaglandin eye drops for OAG/OH
2. A subject with angle-closure glaucoma, neovascular glaucoma, traumatic glaucoma or iridocorneal endothelium syndrome in either eye
3. A subject with a known sensitivity to travoprost, fluorescein, topical anesthetic, silicone, any inactive ingredient of the Travoprost Evolute® or any other products required for study procedures
4. A subject with $\geq$ 0.9 vertical cup or completely notched optic nerve head rim in either eye
5. A subject with any functionally significant visual field loss or progressive field loss within the last year in either eye
6. A subject with a history of complications, AEs, 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
7. A subject with a history of intolerance to punctal plugs or a known sensitivity to any inactive ingredient of the punctal plug, silicone, topical anesthetic, or any other products required for the study
8. A subject with structural lid abnormalities (i.e., ectropion, entropion) in either eye
9. A subject with an active lid disease in either eye (i.e., moderate or severe blepharitis, meibomianitis) that requires medical treatment
10. A subject with any clinically significant (moderate or severe) lid, conjunctival or corneal findings in either study eye at the screening visit
11. A subject with a history of chronic/recurrent inflammatory eye disease (i.e., scleritis, uveitis, herpes keratitis) in either eye
12. A subject who would require the use of any ocular medication(s), an over-the-counter drop(s), ointment(s) or gel(s), other than the study hypotensive medication(s) in either eye during the study period
13. A subject who has had any ophthalmic surgical procedures (i.e., glaucoma laser, minimally invasive glaucoma surgery, cataract, refractive, etc.) in either eye within the last six months or will require ophthalmic surgery before completing the study
14. A subject with a history of penetrating keratoplasty in either eye
15. A subject requiring the use of a contact lens in either eye at any time during the study period
16. A subject with advanced diabetic retinopathy, branch retinal vein occlusion or central retinal vein occlusion in either eye
17. A subject with a history of macular edema in either eye

18. A subject currently on any systemic medication [i.e., beta-blocker, carbonic anhydrase inhibitors, corticosteroids (including dermal), etc.] that may have an effect on the subject's IOP, or who will require its use during the study period (**NOTE:** an inhaled steroid, systemic beta-blocker or β-adrenoceptor antagonist may be permitted, providing the subject has maintained a stable dosage regimen for at least the last three months)
19. A subject with an uncontrolled systemic disease or a medical condition that may increase the risk associated with study participation or administration of study treatment or that may interfere with the interpretation of study results (e.g., autoimmune disease if the subject is on chronic medications and has ocular involvement; host-versus-graft disease)
20. A subject currently participating or has participated within the last 30 days prior to the start of this study in a drug, device or other investigational research study.

5.2.2 Washout Phase - Criteria

After the screening phase (process), each subject meeting all screening inclusion/exclusion criteria must be willing to:

1) DISCONTINUE the use of his/her hypotensive medication for the next six-weeks (Note: If desired, an investigator can perform the six-week washout by placing the subject on mono-therapy with a topical CAI for 5 weeks, then during the last week, discontinue the use of the topical CAI). Each subject will be instructed not to use his/her hypotensive medication for the duration of the study
2) DISCONTINUE the use of all other ocular drops, gels or ointments that have not been prescribed by the investigator, 24 hours prior to Visit 2 and for the duration of the study
3) DISCONTINUE all systemic medication that are PROHIBITED by the protocol for the duration of the study. Systemic medication(s) being used by a subject at the Screening visit and is permitted by the protocol, may continue the medication(s), however the **concentration and dosing** frequency should remain the same throughout the washout and treatment phase of the study

5.2.3 Study Treatment Phase Criteria

5.2.3.1 Treatment Phase - <u>INCLUSION</u> Criteria:

After the washout phase, the following are requirements a subject must meet in order to be considered for enrollment into the treatment phase of the study:

1) After the six-week washout phase, the subject continues to meet all screening phase inclusion/exclusion criteria
2) After the six-week washout phase, subject's Baseline (Visit 2) IOP, measured between 8:00 and 10:00 AM, is $\geq$ 23.0 and $\underline{\leq}$ 34.0 mmHg in at least one eye

3) Subject's Baseline (Visit 2, morning average) IOP is ≥ 5 mmHg from the subject's SCREENING (pre-washout) IOP in at least one eye whose Baseline IOP is between ≥ 23 and ≤ 34 mmHg.

4) Investigator is able to dilate the lower puncta of each eye to 1.0 mm, and insert a study plug into each puncta.

5.2.3.2 Treatment Phase - EXCLUSION Criteria

If any of the below criteria apply to a study subject that has completed the washout period, the subject does not qualify for enrollment into the treatment phase of the study:

1) A subject who no longer meets all the screening and washout study criteria

2) A subject who **cannot be successfully inserted** with a Travoprost Evolute® **in the lower puncta of each eye**, even if only one eye qualifies for enrollment.

5.3 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 as his/her 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 (e.g. Uber, Lyft) and a stipend for his/her 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 to instilling his/her medication over the study period.

5.4 Study Subject Withdrawal or Termination Criteria

Each study subject will be informed that they are free to withdraw from the study at any time however, if they have been inserted with study plugs, they must return to the investigator's office to have the study plugs removed. 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 90 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.

5.4.1 Reasons for Termination, Discontinuation or Disqualified

At a study subject's last visit (scheduled or unscheduled), a study subject will have his/her study punctal plugs 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 90 ± 7 post-insertion). 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 5.4.2 below).

5.4.2 Reasons 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) a lack of efficacy, b) reported a serious AE/ADEs, regardless of relation to the study drug/device or has died.

5.4.2.1 Reasons for Discontinuation

A study subject will be discontinued from the study: a) if the Investigator is unable to sufficiently dilate the punctum or insert a punctal plug in to the lower punctum of either eye, b) if a subject has extruded a plug and a new plug cannot be re-inserted, c) if during the course of the study a subject has extruded a plug from each eye, d) if a subject has extruded a plug more than once from the same eye e) in a subject where only one eye qualified at Visit 2, if the plug is extruded in the qualified eye, f) if a subject has used a prohibited concomitant ocular or systemic (OTC/prescription) medication/therapy, g) if a subject is non-compliant and has missed scheduled study visits, h) for personal reasons, i) 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.

5.4.2.2 Reasons 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 study inclusion/exclusion criteria), had a positive pregnancy test (at Visit 1).

5.4.3 Handling of Study Subject Termination, Discontinued or Disqualified

5.4.3.1 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 his/her punctal plugs. 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**.

5.4.3.2 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 treatment phase, 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 subject's punctal plugs. A study subject who is discontinued from the study **will be replaced**.

5.4.3.3 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 punctal plugs, 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 punctal plugs. A study subject disqualified from the study **will be replaced**.

5.5 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 should be halted or that participation by the study center should 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 AND PROCEDURES

6.1 Study Treatment

Each investigational site will be assigned a site ID number (e.g., 100, 200 . . . 500). As a study subject qualifies for enrollment in to the screening phase of the study, they will be sequentially assigned a study ID number that corresponds with the site ID number (e.g., site ID = 100, subject sequentially assign numbers 101, 102, . . . 110). If the potential subject does not qualify after the washout phase, the subject ID number will be retired. A subject that has a Travoprost Evolute® successfully inserted into the lower puncta of each eye, will be identified throughout the treatment period of the study by his/her assigned subject ID number and initials.

6.1.1 Route of Administration

Each study subject that qualifies for the treatment phase of the study will have the lower puncta of each eye inserted with a Travoprost Evolute® (see Appendices F and G for plug insertion details). Each study plug has a drug insert which contains a drug load of 166 µg of travoprost.

If the investigator is unable to insert a study plug in both eyes, the subject will be discontinued from the study and his/her subject ID number will be retired.

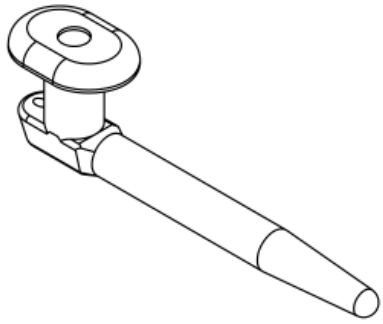
6.1.2 Formulation, Appearance, Packaging and Labeling

6.1.2.1 Formulation

The punctal plug components of the Travoprost Evolute (Figure 2) device consist of an inactive medical-grade silicone with a 2% green colorant throughout the plug (colorant allows for ease of

identification and evaluation of plug placement). The drug insert components of the study plug is a thin-walled polyimide tube (core) filled with a solid sustained release matrix containing a drug load of 166 µg of travoprost (active ingredient). The drug insert is held in place via an interference fit between its outer and inner diameters of the punctal plug bore.

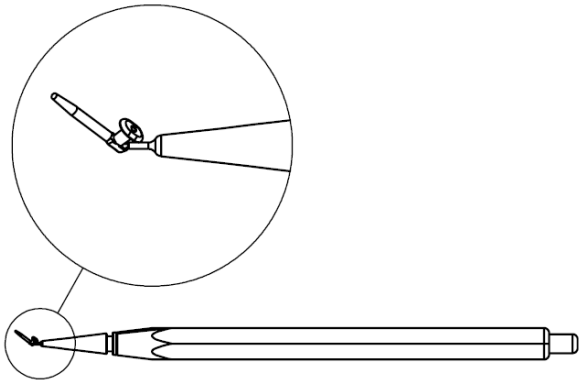
Figure 2: Travoprost Evolute System (L-shape plug Model L67)



6.1.2.2 Appearance

All Travoprost Evolute are L-shaped and will be provided preloaded on a two-part insertion tool, as shown in Figure 3.

Figure 3: Preloaded Insertion Tool with an L-Shaped Travoprost Evolute



6.1.2.3 Packaging

A pre-loaded Travoprost Evolute® will be supplied preloaded onto the inserter tip in a preformed rigid tray. Tray will be sealed with a foil laminate lid, heat sealed onto the tray and sterilized.

6.1.2.4 Labeling

Each tray containing a Travoprost Evolute will be labeled with an investigational drug statement in accordance with applicable regulations.

6.1.3 Product Storage and Stability

All used and unused study plug products must be stored in a secure area with controlled access. All plugs must be stored at refrigerated temperature (2° - 8°C). All study punctal plug delivery system products have a retest date indicated on their label.

6.1.4 Starting Dose

Upon insertion of a Travoprost Evolute, the drug insert contains a drug load of 166 µg with a drug elution rate of 1 to 2 µg per day.

6.1.5 Preparations and Insertion of a Travoprost Evolute

The Travoprost Evolute is for single-patient use only. The procedures for inserting a study plug are similar to those for commercial silicone plugs and procedures for insertion of a study plug are detailed in Appendices F & G. If the size of the study subject puncta has not be measured, gauge (Appendix E) the size of each punctum prior to dilating.

6.1.5.1 Determining Punctum Size (see Appendix E for detailed instructions)

Anesthetize the area around the lower punctum of each eye. Use a Coroneo Punctal Gauge (Figure 5) to determine the size of the punctum.

NOTE: Measurement of the punctum size should be evaluated prior to dilating the punctum.

6.1.5.2 Dilation of the Lower Punctum (Appendix F for detailed instructions)

Prior to inserting a Travoprost Evolute, it is required that the **lower punctum must be dilated to at least 1.0 mm**. While dilating, prepare the study plug to be inserted in the lower punctum of the study subject's eye.

a. If required, measurement of the punctum size should be evaluated prior to dilating the punctum.
b. Procedure for dilating the punctum to at least 1.0 mm and inserting a study punctal plug should be performed on one eye at a time
c. Anesthetize the area around the lower punctum, place a drop of topical anesthetic on the eye to be inserted. Then add lidocaine gel on a cotton-tipped swab and placing the swab directly on the lower punctum
d. Use the Coroneo Punctal Gauge to dilate the punctum. **The punctum must be 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 small puncta, hold and rotate the dilator in the punctum and canaliculus for as long as required to achieve dilation to 1.0 mm. This may take some considerable

time. Dilation may require very firm pressure however; care must be taken **NOT to apply excessive force** to dilate the punctum. Add more anesthesia if needed.

6.1.5.3 Procedure for Insertion of a Travoprost Evolute® (Appendix G **for detailed instructions**)

Lubricants are NOT to be used to insert a Travoprost Evolute. Physicians inserting the study plug will have been briefed with the instructions and guidelines. It is recommended that the punctum be dilated to at least 1 mm prior to attempting insertion. After insertion, a slit-lamp will be used to verify the Travoprost Evolute is appropriately positioned.

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 margin) the plug should be removed and the punctum re-dilated or dilated to a larger diameter.

If the Travoprost Evolute cannot be inserted after a few attempts with gentle dilation, the subject is not eligible for the study.

6.1.6 Instructions for Study Subjects after Travoprost Evolute Insertion

A subject should be instructed not to attempt to remove or adjust the Travoprost Evolute on his/her own. In addition, instruct the subject to restrict eye rubbing, swimming, scuba diving, or other actions or activities that may result in physical manipulation of the eye region.

6.1.7 Procedure for the Removal of a Travoprost Evolute (Appendix E for detailed instructions)

The Travoprost Evolute should be removed from the study subject's lower puncta using sterile ophthalmic forceps, such as Castroviejo Suture forceps (Appendix H, Figure 6) or similar toothed forceps, with a gentle tugging motion. A drop of anesthetic may be administered if necessary.

NOTE: Removal of a Travoprost Evolute 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 study plug. Use of a jeweler's forceps is not advisable

a. 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

b. The motion to remove the plug should be towards the medial canthus (not up or temporally)

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 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. Referral to tertiary care is advised in cases where the plug cannot be retrieved by massaging/milking through the punctal opening or by irrigation.

6.1.8 Unable to Insert/Extruded/Lost Travoprost Evolute®

If either eye of a study subject cannot be dilated to at least 1 mm, the subject will not be eligible for the study.

6.1.8.1 Unable to Insert Travoprost Evolute

If a Travoprost Evolute cannot be inserted after a few attempts with dilation, the subject will not be eligible for the study. **Lubricants are NOT to be used**.

NOTE: If the first attempt to insert a plug was successful however, the investigator is unable to insert the second plug, the first plug will be removed and the subject will be discontinued from the study. **Removal of a Travoprost Evolute immediately after insertion may result in the cap of the plug being torn off**; the Investigator should wait at least 24 hours after insertion of the study plug. Retain the plug for accountability of investigational supplies.

6.1.8.2 Extrusion of a Travoprost Evolute

A study subject that has noticed a study plug has been extruded or lost during the treatment phase, the study subject should immediately contact the Investigator and/or his/her staff and return to the Investigator's office as soon as possible. If the study subject can find the extruded plug, they should return with the plug where the Investigator and/or his/her staff will collect and retained the plug for investigational supply accountability. If the return plug has torn or has separated, report this as a technical complaint (Section 8.6). If a study 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.

If a single plug has been extruded during the study, the Investigator will re-insert a new plug and instruct the study subject to return to the investigator office based on their originally study visit(s) scheduled. At any time during the study, a study subject experiences a second extrusions or an extrusion in the fellow eye, the study subject will return to the Investigator's office as soon as possible and will have the remaining plug removed. The study subject will be discontinued from the study and WILL be replaced.

6.1.9 Duration of Therapy

Each subject will have a Travoprost Evolute® inserted in to the lower punctum of each eye. The study plug will remain in the study subject's lower puncta for a period of 90 ± 7 days.

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 a study plug, noting the suspected date the study plug was lost/extruded.

All used and unused 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 Delegation of Authority form 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 are required during the course of the study include (Appendix C 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. WOMEN OF CHILDBEARING POTENTIAL, urine pregnancy tests are required at the screening visit and when the female subject exits the study

c. Record subject's demographic data and medical history for the previous 6 months

d. Concomitant Medication use: All prescription systemic, ophthalmic and over-the-counter concomitant medications that will be used by the study subject will be documented. The medication name, start and stop dates, indication, dose, route of administration and any dosing alterations during the study period must be documented on the Concomitant Medications CRF

e. Verify a subject has followed all instructions regarding the discontinuation of any hypotensive ocular medication during the course of the study

f. Vital Signs (Temperature, Blood Pressure and Heart Rate): Throughout the study vital signs will be taken with the subject in the sitting position after the subject has rested five minutes. Techniques used to collect vital signs should remain consistent throughout the study

- Temperature maybe taken using a non-contact (Infrared) thermometer or orally. Oral temperatures should not be taken within five minutes of ingestion of any food or drink
- Blood pressure may be determined manually with a blood pressure cuff and auscultation or with an automated Blood Pressure monitor
- Heart rates may be determined electronically with an automated Blood Pressure monitor. Manually obtained heart rates should be recorded after a minimum of 30 seconds of observation.

g. Best-Corrected Distance Visual Acuity testing: Visual acuity with correction (e.g., wearing glasses) will be measured using a Snellen chart. Pinhole visual acuity will be measured using a Snellen chart while the subject is looking through a pinhole occluder. The test distance and lighting conditions specified for the Investigator's chart must be used and kept constant throughout the study

h. Automated Perimetry (visual fields) will be measured using a Humphrey's Visual Field Analyzer (manufactured by Carl Zeiss Meditec Inc., Dublin, CA) with at least a standard full-threshold 24-2 program or Swedish interactive threshold algorithm (SITA) program. **Visual fields measured and documented up to SIX months before the Screening Visit are acceptable** to fulfill the screening criteria

i. Pachymetry can be measured by contact methods, such as ultrasound and confocal microscopy (CONFOSCAN), noncontact methods such as optical biometry with a single Scheimpflug camera (such as SIRIUS or PENTACAM), dual Scheimpflug camera (such as GALILEI), or Optical Coherence Tomography (OCT), such as Visante. **Past corneal thickness measurement documented in the subject's chart** are acceptable to fulfill the screening criteria

j. Slit-Lamp Examination: Examination will include assessment of the lid, conjunctiva and cornea. Grading of slit-lamp findings are defined in Appendix C.

k. Perform a NON-DILATED fundus exam of each eye. Using an ophthalmoscope, the investigator will examine the back part of the eye (fundus), including the retina, optic disc, choroid and blood vessels and evaluation of the lens

l. Goldmann applanation tonometry will be used for measuring IOP. IOPs will be measured in the morning between 8:00 and 10:00 am. The IOP of each eye will be measured twice, alternating between the eyes. However, if the second measurement is $\geq \pm$ 3 mmHg from the first measurement for an eye, a third measurement will be taken. All measurements taken will

be recorded. In the case of two measurements, the average of the two values will be used for analysis, and in the case of three measurements, the average of the two closest values of the three will be used for analysis for that eye at that specific time point.

NOTE: **Just prior to the start of the study, the tonometer should be calibrated.**

m. Punctal size evaluation and dilation of the punctum (see Appendices E & F for details),

n. Insertion and removal of study punctal plugs (see Appendix G & H for details)

o. Adverse Event/Adverse Device Event reporting, Section 8.7 of the protocol for details: To optimize consistency of AE/ADE reporting across centers, the study subject will be asked a standard question to elicit any AE/ADEs. 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?**"

7.2.2 Standard of Care Procedures

At any study visit (scheduled or unscheduled), in addition to study specific examinations the Investigator will perform their standard evaluations for an OAG or OH patient.

7.3 Laboratory Procedures/Evaluations

Not applicable

7.4 Study Visit Phases/Schedule

7.4.1 Visit 1 - Screening Phase (Qualification Visit)

At this visit, prior to any study specific procedure or examination, a subject must read, comprehend and give written Authorization for Use/Disclosure of Health Information (HIPAA) and Informed Consent to participate in the study. Once all forms have been signed, the investigator and/or his or her staff will perform the following screening assessments/examinations.

a. Verify a subject has not used any hypotensive ocular drops within the last 12 hours of the screening visit

b. A female subject of child-bearing potential will have a urine pregnancy test performed

c. Record subject's demographic data and medical history for past 6 months

d. Measure subject's temperature, heart rate and blood pressure

e. Record subject's Best-Corrected (Glasses) Distance or Pinhole Visual Acuity

f. Verify automated perimetry results have been measured and documented in the subject's chart within the last 6 months

NOTE: If perimetry measurement are older than 6 months, perform automated perimetry at the screening visit

g. Verify corneal thickness measurements are documented in the subject's chart

NOTE: If corneal thickness data is not available, measure corneal thickness of each eye using contact or non-contact pachymetry at the screening visit

h. Perform a slit-lamp examination of each eye

i. Perform a non-dilated fundus exam of each eye, including the evaluation of the lens

j. Record IOP measurement of each eye

k. Record concomitant medication use

If at any time during the screening examination it is determined a subject does not meet a screening inclusion/exclusion criterion, at that point any additional screening assessments-examinations will be discontinued.

After the screening procedures and examinations have been completed, each qualified subject that meets all study inclusion/exclusion criteria will be asked to enter the washout phase of the study and will be sequentially assigned an ID number (Section 6.1). In addition, the ID number and the study subject initials will be recorded on study case report forms, in lieu of recording his/her name, in order to maintain subject confidentiality.

7.4.2 Washout Phase (Six-week duration)

During the washout phase of the study, each subject will be instructed to discontinue the use of his/her topical hypotensive medication(s) for the next six-weeks. In addition, the subject will be instructed not to use any other ocular drops, gels or ointments 24 hours prior to the Baseline visit (Visit 2) in his/her eyes that have not been prescribed by the investigator.

Systemic or topical medications that are being used at the Screening Visit, that are considered necessary for the subject's welfare and are PERMITTED by the protocol (Sections 5.2.1), may continue to be used as long as the concentration and dosing frequency of the medication(s) will remain the same throughout the entire duration of the study.

Systemic medications that are PROHIBITED by the protocol, must be discontinued during the washout phase. All ocular drops, gels or ointments being used by the subject must be discontinued 24 hours prior to Visit 2. Should the subject qualify for the treatment phase of the study, they will be asked to continue for an additional 90 ± 7 days not to use any systemic or topical medications during the treatment phase of the study.

7.4.3 Treatment Phase (Visits 2, 3, 4, 5, 6 & 7)

At the completion of the washout phase (6-weeks) each subject that continues to meet all study screening, washout and baseline criteria will have the lower puncta of each eye inserted with a Travoprost Evolute® and scheduled to return to the investigator's office for follow-up examinations at one, seven, 28, 60 and 90 days after insertion of the study plugs.

7.4.3.1 Visit 2 - Day 0, Plug Insertion Visit (Baseline)

Qualified subject will undergo the following:

a. Verify a subject has not used any hypotensive ocular drops during the washout phase
b. Verify whether there are any changes in the medical history and confirm the subject still meets all study inclusion/exclusion criteria
c. Record any addition, discontinuation or changes in the subject's use of any concomitant medications or ocular drops, gels or ointments during study washout phase
d. Record subject's temperature, heart rate and blood pressure
e. Record subject's Best-Corrected (Glasses) Distance or Pinhole Visual Acuity
f. Perform a slit-lamp examination of each eye
g. Record IOP measurement for each eye
h. Record any Adverse Events/Adverse Device Event.

After the baseline procedures and examinations have been completed, a subject that meets the baseline IOP inclusion criteria (Section 5.2.3) will have their punctal size of each eye evaluated and will be inserted with a Travoprost Evolute into the lower puncta of each eye even if only one eye qualifies.

i. Dilate the lower puncta to 1.0 mm and insert a study plug into the lower punctum of each eye (refer to Sections 6.1.5.2 & 6.1.5.3 for details regarding punctum dilation and punctal plug insertion techniques)
j. Evaluate after insertion, the position of the study plugs in each eye using the slit-lamp

NOTE: At the conclusion of the visit a subject does not meet all treatment inclusion/exclusion criteria or the investigator is unable to insert a Travoprost Evolute into the lower puncta of each eye, the study subject will be discontinued from the study. The subject ID number will be retired. If the investigator was able to insert only one study plug, the one inserted study plug must be removed (Section 5.4)

Each study subject will be instructed not to attempt to remove or adjust the punctal plug on his/her own. In addition, encourage each study subject to restrict eye rubbing, swimming, scuba diving, or other actions or activities that may result in physical manipulation of the eye region

Each study subject will be scheduled to return the next day for a follow-up study examination (Visit 3, day 1 post-plug insertion).

NOTE: At any time during the treatment phase, a study subject has noticed a plug has been extruded or lost they should immediately contact the Investigator and/or his/her staff and return to the Investigator's office as soon as possible (Section 6.1.8.2).

7.4.3.2 Visit 3 - Day 1, Post-Plug Insertion

a. Verify a subject has not used any hypotensive ocular drops since his/her last visit
b. Record any addition, discontinuation or changes in the subject's use of any concomitant medications or ocular drops, gels or ointments since his/her last visit
c. Record subject's temperature, heart rate and blood pressure
d. Record subject's Best-Corrected (Glasses) Distance or Pinhole Visual Acuity
e. Evaluate the position of each Travoprost Evolute® using the slit-lamp
f. Perform a slit-lamp examination of each eye
g. Record IOP measurement for each eye
h. Record any Adverse Events/Adverse Device Event

NOTE: Should a study subject exit the study early (after Visit 2 and before Visit 7), the subject must undergo all test and procedures scheduled for Visit 7 (Final Visit).

7.4.3.3 Visit 4 - Day 7 ± 1, Post-Plug Insertion

a. Verify a subject has not used any hypotensive ocular drops since his/her last visit
b. Record any addition, discontinuation or changes in the subject's use of any concomitant medications or ocular drops, gels or ointments since his/her last visit
c. Record subject's temperature, heart rate and blood pressure
d. Record subject's Best-Corrected (Glasses) Distance or Pinhole Visual Acuity
e. Evaluate the position of each Travoprost Evolute® using the slit-lamp
f. Perform a slit-lamp examination of each eye
g. Record IOP measurement for each eye
h. Record any Adverse Events/Adverse Device Event

NOTE: Should a study subject exit the study early (after Visit 2 and before Visit 7), the subject must undergo all test and procedures scheduled for Visit 7 (Final Visit).

7.4.3.4 Visit 5 - Day 28 ± 3, Post-Plug Insertion

i. Verify a subject has not used any hypotensive ocular drops since his/her last visit
j. Record any addition, discontinuation or changes in the subject's use of any concomitant medications or ocular drops, gels or ointments since his/her last visit
k. Record subject's temperature, heart rate and blood pressure
l. Record subject's Best-Corrected (Glasses) Distance or Pinhole Visual Acuity
m. Evaluate the position of each Travoprost Evolute® using the slit-lamp

n. Perform a slit-lamp examination of each eye

o. Record IOP measurement for each eye

p. Record any Adverse Events/Adverse Device Event

NOTE: Should a study subject exit the study early (after Visit 2 and before Visit 7), the subject must undergo all test and procedures scheduled for Visit 7 (Final Visit).

7.4.3.5 Visit 6 - Day 60 ± 5, Post-Plug Insertion

q. Verify a subject has not used any hypotensive ocular drops since his/her last visit

r. Record any addition, discontinuation or changes in the subject's use of any concomitant medications or ocular drops, gels or ointments since his/her last visit

s. Record subject's temperature, heart rate and blood pressure

t. Record subject's Best-Corrected (Glasses) Distance or Pinhole Visual Acuity

u. Evaluate the position of each Travoprost Evolute® using the slit-lamp

v. Perform a slit-lamp examination of each eye

w. Record IOP measurement for each eye

x. Record any Adverse Events/Adverse Device Event

NOTE: Should a study subject exit the study early (after Visit 2 and before Visit 7), the subject must undergo all test and procedures scheduled for Visit 7 (Final Visit).

7.4.3.6 Visit 7 - Day 90 $\pm$ 7, Post-Plug Insertion (Final Study Visit)

At this visit the following will be performed and recorded:

a. Verify a subject has not used any hypotensive ocular drops since his/her last visit

b. Record any addition, discontinuation or changes in the subject's use of any concomitant medications or ocular drops, gels or ointments since his/her last visit

c. If performed at SCREENING Visit, perform a urine pregnancy test on a female subject of child-bearing potential

d. Record subject's temperature, heart rate and blood pressure

e. Record subject's Best-Corrected (Glasses) Distance or Pinhole Visual Acuity

f. Evaluate the position of each Travoprost Evolute using the slit-lamp prior to removal of the plug

g. Perform a slit-lamp examination of each eye prior to study plug removal

h. Record IOP measurement for each eye before study plug removal

i. Removal of the study plug from each eye (refer to Section 6.1.7 for details regarding removal of a punctal plug)

j. Record any reported Adverse Events/Adverse Device Event

An exit form will be completed at the final study examination (Visit 7), or whenever the study subject completes or leaves the study for any reason.

NOTE: The day each Travoprost Evolute® are removed with no addition follow-up required, will be the study subject's official exit date from the study. However**, if the subject is exiting from the study due to an AE/SAE or ADE/SADE, the study subject will be followed and exam findings recorded by the investigator until the AE/SAE or ADE/SADE has resolved or has become medically stable**.

Schedule of Assessments, Events

Visit Examination Parameters	Visit 1 Screening	Visit 2 (Day 0)	Visit 3 (Day1)	Visit 4 (Day 7)	Visit 5 (Day28)	Visit 6 (Day 60)	Visit 7 (Day 90)
Informed Consent/HIPAA	❶						
Medical Hx (past 6 months)/Demographic Data	❶	❷[A]					
Urine Pregnancy Test (Only women of childbearing potential)	❶[B]						❼[B]
Concomitant Med Use	❶	❷	❸	❹	❺	❻	❼
BT (temperature), BP (blood pressure), HR (heart rate)	❶	❷	❸	❹	❺	❻	❼
Evaluate study plug position prior to any eye exam		❷*	❸	❹	❺	❻	❼
Best-Corrected Distance (Glasses) or Pinhole VA	❶	❷	❸	❹	❺	❻	❼
Automated Perimetry (**Not required** if measured in last 6 months)	⦿						
Pachymetry (**Not required** if documented in patient's chart)	⦿						
Slit-Lamp Examination	❶	❷	❸	❹	❺	❻	❼
IOP (Goldmann) Evaluation (To be measured between 8 and 10 am)	❶	❷	❸	❹	❺	❻	❼
Non-Dilated Fundus Examination (Include evaluation of the LENS)	❶						
Begin Six-Week Washout (D/C all topical drops, gels, ointments)	❶						
Punctal Size Evaluation, Dilation of Lower Puncta		❷					
Insertion of Punctal Plugs		❷					
Punctal Plug **Extrusion			☆[C]	☆[C,D]	☆[C,D]	☆[C,D]	❼
Removal of Punctal Plugs after eye exam completed‡							❼‡
Adverse Event/Adverse Device Event Recording		❷	❸	❹	❺	❻	❼

Keys to Abbreviations:

A = Verify no change in medical history, subject still meets all study inclusion/exclusion criteria
B = If performed at the screening visit, must be performed when subject exit the study
C = In a subject where both eyes qualified at Visit 2, if a plug is extruded in one eye, **plug is to be replaced** and subject continues in the study
D = In a subject where only one eye qualified at Visit 2, if the plug is extruded in the qualified eye, the subject will be DISCONTINUED and replaced. In a subject where both eyes qualified, if a plug is extruded in one eye, then extruded again or in the fellow eye, the subject will be DISCONTINUED and replaced
* = Plug position evaluated after eye exam and plug insertion
‡ = If subject EXITs the study after visit 2, but before visit 7, subject must return to Investigator's office to have plugs removed

Body Temperature:	Temperature maybe taken using a non-contact (Infrared) thermometer or orally. Oral temperatures should not be taken within five minutes of ingestion of any food or drink
Heart Rate:	Heart rate taken in the sitting position after subject has rested for 5 minutes. Recorded values can be obtained electronically (automated) or manually (observed for 30 seconds or more)
Blood Pressure:	Blood pressure, taken in the sitting position after subject has rested for 5 minutes. Recorded values can be obtained electronically (automated) or manually
Plug Position Evaluation:	Position of the plug will be evaluated as either: Normal, Present but requires adjustment, Extruded/Recovered, Extruded/Lost, Other
Slit-Lamp Exam:	Evaluation will include the Lids (Upper & Lower), Conjunctiva (Bulbar & Palpebral) and the Cornea. SL Findings will be graded on a 5-point scale: 0 = None, 1 = Trace, 2 = Mild, 3 = Moderate, 4 = Severe
IOP Evaluation:	Goldmann applanation tonometry will be used for measuring IOP. Just prior to the start of the study, the tonometer should be calibrated. IOP of each eye will be measured twice, alternating between the eyes. The average of the two measurements will be used for analysis. However, if there is a $\geq \pm$ 3 mmHg difference between the 1st and 2nd measurement for an eye, a 3rd measurement will be taken and the average of the two closest values of the three will be used for analysis for that eye.

7.5 Unscheduled Visit

The investigator has the option of bringing a study subject back in for an unscheduled visit any time during the washout or treatment phase of the study for safety reasons (e.g., subject complaint of moderate or severe ocular symptoms, an AE). An unscheduled visit CRF should be completed. At minimum the investigator should record the following:

a. Record any change in concomitant medication use
b. Inspection of both punctal plugs via the slit-lamp
c. Slit-Lamp examination, both eyes
d. Measure IOP, both eyes
e. Recording of any reported adverse events/adverse device events

7.6 Early Exit Visit (Disqualified, Discontinued or Terminated Study Subject)

Any study subject exiting the study early must undergo all test and procedures scheduled for Visit 7 (Day 90 ± 7 days, post-plug insertion) and all results recorded on the appropriate CRFs.

> **NOTE:** Refer to Section 7.4.3.6 for details on procedures and examination to take place on the final study subject visit

An exit CRF (Case Report Form) will be completed whenever the study subject completes or leaves the study for any reason. A study subject will be exited from the study on the day the Travoprost Evolute® are removed from both eyes with no additional follow-up required. However**, if the subject is exiting from the study due to an AE/ADE, the study subject will be followed and exam findings recorded by the investigator until the AE/ADE has resolved or has become medically stable**.

7.7 Emergency Anaphylactic or Overdose Procedures, Dose Modifications

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

> **NOTE**: Use caution when inserting a study plug 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 travoprost ophthalmic solutions 0.004% & 0.003% (TRAVATAN®, TRAVATAN Z®, IZBA®). Refer to the Investigator Brochure and Appendices I, J & K 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 topical or systemic medication(s) must be recorded on the Concomitant Medication CRF.

7.8 Concomitant Medication

During the washout and treatment phases of the study, each 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 or topical medications that are being used at the Screening Visit, that are considered necessary for the subject's welfare and are permitted by the protocol (Section 5.2.1.2 for details), may continue to be used as long as the concentration and dosing frequency of the medication(s) remains the same throughout the entire washout and treatment phases of the study.

7.8.1 Pre-Study Concomitant Medication Use

Pre-study concomitant medication is defined as a prescription and/or an over-the-counter (OTC) medication taken within **2 months** (whether continuing or not) prior to Visit 1 (Screening Visit). All prior medications must be documented on the Concomitant Medications CRF.

7.8.2 Concomitant Medication Use during Study

Each study subject will be instructed not to use any other ocular drops, gels or ointments in his/her eyes that have not been prescribed by the Investigator. Systemic medications being used at screening visit 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 during the washout and treatment phase of the study, 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, except for routine medications given for ocular study procedures required by the protocol (i.e., topical anesthetic for plug insertion), 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.

Systemic or topical medications that are being used at the Screening Visit, that are considered necessary for the subject's welfare and are permitted by the protocol (Section 5.2.1.2, criteria 12 & 18, for details), may continue to be used as long as the concentration and dosing frequency of the medication(s) will remain the same throughout the entire duration of the study.

7.9 Prohibited Medications, Treatments and Procedures

7.9.1 Prohibited Medications

After the screening visit, the use of any ocular drops, gels or ointments in either eye is prohibited, with the exception for routine topical medication given for an ocular study procedure(s) that is required by the protocol (i.e., topical anesthetic). Systemic or topical medications being used at

the Baseline Visit that are permitted by the protocol (Section 5.2.1.2, criteria 12 & 18, for details), are considered necessary for the subject's welfare, and will not interfere with the study may be used.

7.9.2 Prohibited Treatments

The following are prohibited during the study washout and treatment periods:

a. Use of homeopathic remedies (e.g., gingko biloba, cayenne pepper, bilberry, etc.)
b. Significant changes to eating or drinking habits (i.e., begin a diet, increase or decrease alcohol, caffeine or water intake, etc.)
c. Significant changes in physical exercise/yoga
d. Use of marijuana

7.9.3 Prohibited Procedures

The following procedures are prohibited during the study washout and treatment periods:

a. Laser trabeculoplasty
b. Trabeculectomy
c. Tube shunt surgery
d. Cataract surgery

7.10 Rescue Medication(s)

7.10.1 Administration of a Rescue Medications

A subject with an elevated IOP (>34 mmHg) or undue medical risk in either eye should be prescribed his/her glaucoma regimen they were using prior to entering the study The use of a rescue medication will be considered prohibited medication and will be considered a protocol deviation and the study subject will be terminated from the study. Reason for termination on the exit form should be listed as "due to lack of efficacy".

8 ASSESSMENT OF SAFEETY

8.1 Safety Variables

Safety variables for this study will include any reported AE/ADE and rescue medication use. Safety variables will also include clinically significant changes in IOP, BCDVA, slit-lamp findings, ocular tearing and comfort, blood pressure, heart rate, temperature, extrusion of a Travoprost Evolute®, or technical issues with the study plug (e.g., cap of study plug tears or becomes separated during plug removal.

To optimize consistency of AE/SAE reporting across sites, the study subject will be asked a standard question to elicit any AE/SAE. 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 Event

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 screening 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, 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):

- Site-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 Event 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 8.2.2) 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 8.7.2). 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 site. 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 Complaint

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 Travoprost Evolute® plug that identifies any defect 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 site name, and contact number
- Date the complaint occurred
- Brief description of the complaint
- Identity of any other investigational or commercial devices involved.
- Study subject or another 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 Sections 8.6 & 8.7 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).

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
Phone: 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 Delivery System 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 a subject.

If the Sponsor determines that any SAE or technical report is an unanticipated ADE, an investigation will begin immediately. The Sponsor will inform the investigator of any additional reporting requirements beyond those stated in Sections 8.6 & 8.7 as applicable.

If the Sponsor determines that an unanticipated ADE presents an unreasonable risk to a subject, the Sponsor will terminate the study as soon as possible. Termination will occur no later than five working days after the Sponsor makes this determination and no 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 his/her IRBs, within 10 working days after the Sponsor first received notice of the effect.

8.6.4 Anticipated Adverse Event

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. (Section 8.7 for reporting details).

Listing of Anticipated Ocular Adverse Events

DRUG:

Incidence rate 30-50%:	Hyperemia (*Hyperemia in IZBA controlled studies noted at 12%)
Incidence rate 5-10%:	Decreased VA, Eye Discomfort, Foreign Body Sensation, Pain, Pruritus
Incidence rate 1-4%:	Abnormal Vision, Blepharitis, Blurred Vision, Cataract, cells, Conjunctivitis, Corneal Staining, Dry Eye, eye disorder, Iris Discoloration, Keratitis, Lid Margin Crusting, Ocular Inflammation, Photophobia, Subconjunctival Hemorrhage, Tearing

DEVICE:

The main risks of commercial silicone punctal plugs are ocular discomfort, epiphora (watery eyes), loss of plug (extrusion), ocular inflammation, and subconjunctival hemorrhage. Less common, but serious, side effects include but are not limited to pyogenic granuloma, damage to the muscle at the opening of the punctum, canaliculiti or migration of the plug into the canalicula (requiring irrigation or surgery)

NOTE: Patient treated with an ophthalmic solution of travoprost should be informed of the potential for increased brown pigmentation of the iris, periorbital and/or eyelid tissue, and increase growth of eyelashes in the treated eye

8.7 Reporting Procedures

AEs/ADEs that occur from Visit 2 through completion of the end-of-study visit must be documented. The Investigator will assess the AE/ADE severity and relationship to the travoprost Evolute®. The Investigator will follow the progress of the study subject until the AE/ADE either resolves or becomes medically stable. Treatments and medications required for treatment must be recorded.

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

8.7.1 Adverse Event Reporting

For each reported AE, investigators should record the following on the appropriate CRF and in the subject's source documents: whether an AE is serious (yes/no), the date of onset, date resolved (date or ongoing), duration (minutes/hours/days), frequency (single/intermittent), severity (mild/moderate/severe), relationship to study treatment (suspected/not suspected), and if treatment was required (medication prescribed, stopped treatment, etc.).

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

Any severe, serious or unexpected AE occurring during or within 15 days after the completion of the study, regardless of cause(s) or relationship to the study drug or the drug delivery device, an initial report must be made immediately (within 24 hours) once becoming aware of the event by telephone, facsimile, or email to the study Medical Monitor, Robert Williams, MD or the Study Monitor, Daniel Schwob (see contact information below).

The Investigator must complete an SAE Report Form and send it with other relevant pages of the CRF to the designated Medical Monitor within 24 hours of the initial discovery of the event. 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.

All SAEs will be reported to:

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

Daniel Schwob (back up contact)
Study Monitor
D'Ellis Group, Inc.
email: dschwob@dellisgroup.com
Phone: (Office): 949.916-2800
Phone: (Cell) 949.735-1320

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

Not Applicable

8.8 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 review and assess any reports of adverse events/adverse device 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 (R2) and E8 (8.2) and 21 CFR. Parts 50, 54, 56, 312 and 812
b. The signed Investigators' Agreement
c. The signed IRB approved 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, a Mati representative will conduct a visit with the Investigator(s) and the study staff to ensure the following

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

b. The Investigator understands the protocol and understands and accepts his/her 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 his/her staff have sufficient time and access to an adequate number of subjects to conduct the clinical investigation.

During the course of the investigation, a Mati representative may conduct periodic site visits and maintain telephone contact with the Investigators and his/her staff to verify 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, a Mati representative will:

a. Verify 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.
b. Review and compare CRFs to source records and supporting documents to ensure that data recorded on the CRFs are complete, accurate, and legible
c. Verify 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
d. Verify that there are no data omissions and that any study subject withdrawals are documented.
e. Review CRFs and source records for any unanticipated AEs/ADEs, and ensure that the Investigators are complying with FDA and Sponsor requirements for reporting AEs/ADEs and SAEs/SADEs.
f. Verify that the Investigator(s) is carrying out the agreed upon activities and has not delegated them to unauthorized staff and that the facilities and staff continue to be acceptable for the study.
g. Verify the Investigator(s) is properly tracking study inventory and is accounting for the disposition of all study devices.
h. Prepare and maintain records of each site visit, significant telephone discussion, and written communications with the site. These records will include such information as:
    i. Date, name, and address of the Investigator(s) and names of other staff members present at each meeting
    ii. A summary of the findings of the visit
    iii. A statement of any action taken by a Mati representative or Investigator(s) 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 who had the lower puncta of each eye inserted with a study punctal plug 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 or non-compliance with protocol requirements that can potentially have significant impact on study outcomes).

10.2 Statistical Hypotheses

The Null Hypothesis: There are no differences between baseline and follow-up visit intraocular pressure values

Alternative Hypothesis: There are differences between baseline and follow-up visit intraocular pressure values

10.3 Analysis of Datasets

Data will be pooled from all study sites for data analysis, unless otherwise specified. Study dataset will be generated (keypunched) from original (white) case report forms (CRFs) that have been reviewed and collected from clinical sites. Dataset will contain rows of individual subject data; each row will be clearly labeled with the study subject assigned study number and initials. Each column of the dataset will contain a specific parameter for all study subjects.

10.4 Description of Statistical Methods

10.4.1 General Approach

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. Analyses of the intent-to-treat (ITT) data set, will include all data from all subjects with a recorded screening visit IOP OU. Per protocol (PP) analyses dataset, will exclude data from subjects or visits with significant protocol deviations (e.g., IOPs obtained before 8:00 AM and after 10:00 AM will be excluded).

10.4.2 Analysis of Primary Study Variable

The primary study outcome variable will be the change in IOP at Visits 4, 5, 6 and 7 (Days 7, 28, 60 and 90 days post-insertion) compared with the Baseline IOP (Visit 2, Day 0), obtained between 8:00 and 10:00 AM. The unit of analysis will be the study eye at visit 2 with the highest post-washout IOP. Observed IOP and percent change from baseline in IOP will also be analyzed.

10.4.3 Other Data Endpoints

The following will be evaluated:

- Mean and percent change in Baseline IOP (post-washout) compared with Screening IOP (pre-washout)
- Mean and percent of patients screened vs patients that qualified for the study washout phase
- Mean and percent of patient entered in the washout phase that qualified for the treatment phase
- Evaluate enrollment rate of patients in to the various phases of the study (avg. number of patients by day/week/month)
- Mean and percent of patients and eyes with IOPs > 34 mmHg post-washout
- Mean and percent of patients and eyes that extruded a plug during the study treatment phase
- Mean and percent of patients and eyes the investigator was unable to dilate to at least 1.0 mm
- Mean and percent of patients and eyes the investigator was unable to insert with a Travoprost Evolute®
- Listing of reasons why patient failed to qualify for various phases of the study

10.4.4 Safety Analyses

All subjects that qualify for the washout phase of the study will be evaluated. Safety variables will include any clinically significant changes in IOP, BCDVA, slit-lamp findings, ocular tearing and comfort, blood pressure, heart rate, temperature, study plug inspections/extrusions, and incidence and severity of any reported AEs/SAEs and ADEs/SADEs.

10.4.5 Adherence and Retention Analyses

Not Applicable

10.4.6 Baseline Descriptive Statistics

Demographic and baseline characteristics will be summarized. Counts and percentages will be presented for categorical variables such as gender, age group (by decade), race and ethnicity. Mean, standard deviation, median, minimum and maximum will be presented for continuous variables such as age and non-dilated punctum size.

10.4.7 Planned Interim Analyses

Data will be analyzed on an ongoing basis. The final analyses will be completed after the last study subject has completed his/her final visit and the study database has been closed.

10.4.8 Tabulation of Individual Response Data

Not Applicable

10.4.9 Exploratory Analyses

Not Applicable

10.5 Sample Size

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

10.6 Measures to Minimize Bias

Not Applicable.

10.6.1 Enrollment

Each investigational site will be assigned a site ID number (e.g., 100, 200 . . . 500). As a potential study subject qualifies to enter the study washout period, they will be sequentially assigned a study number that corresponds with the site ID number (e.g., 101, 102, . . . 110). If the potential subject does not qualify after the washout period, the subject ID number will be retired. Those subjects that do qualify will be identified throughout the treatment period of the study by his/her assigned subject ID number and initials.

10.6.2 Evaluation of the Success of Blinding/Masking Treatment

Not Applicable

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 visits 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. Intraocular Pressure values and slit-lamp findings at each visit

i. The subject's exposure to any concomitant therapy (including start and stop dates, route of administration, and dosage) at each visit
j. Blood pressure, temperature and heart rate values at each visit
k. All reported AEs/ADEs and SAEs/SADEs
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

All 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, 1E 717
Foothill, Ranch, CA 92610

The white copy of the CRF data will be reviewed against the subject's source data by the study monitor(s) to ensure completeness and accuracy. After monitoring has occurred at the clinical site(s) and the CRFs have been submitted, additional data clarifications and/or additions may be needed. Data clarifications and/or additions are to be documented and will be 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 of 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 and ADEs/SADEs
f. Brief discussion of clinical findings during the study.

12 QUALITY ASSURANCE AND QUALITY CONTROL

Investigator must grant 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/SADEs 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 enrollment in the study.

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 his/her 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 a subject 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

Not Applicable

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. 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 (refer to Section 13.2 for details).

14.4 Publications 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

Bengtsson B, Heijl A. 2005. A long-term prospective study of risk factors for glaucomatous visual field loss in patients with ocular hypertension. J Glaucoma. 14(2):135-138.

Choy BNK et al. 2019. Factors Associated with Poor Eye Drop Administration Technique and the Role of Patient Education among Hong Kong Elderly Population. Journal of Ophthalmology, vol. 2019, Article ID 5962065, 5 pages.

Gordon MO, Beiser JA, Brandt JD, et al. 2002. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol. 120(6):714-720.

Kass MA, Heuer DK, Higginbotham EJ, et al. 2002. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 120(6):701-713.

Leonard R. 2002. Statistics on Vision Impairment: A Resource Manual (5th Edition). New York: Arlene R Gordon Research Institute of Lighthouse International.

Leske MC, Heijl A, Hyman L, Bengtsson B, Komaroff E. 2004. Factors for progression and glaucoma treatment: the Early Manifest Glaucoma Trial. Curr Opin Ophthalmol. 15(2):102-106.

Maier PC, Funk J, Schwarzer G, Antes G, Falck-Ytter YT. 2005. Treatment of ocular hypertension and open angle glaucoma: meta-analysis of randomised controlled trials. BMJ. 331(7509):134. Epub 2005 Jul 1.

Robin AL, Covert D. 2005. Does Adjunctive Glaucoma Therapy Affect Adherence to the Initial Primary Therapy? Ophthalmology. 112:863-8

16 APPENDICES

Appendix A

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)
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 a study subject, 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.

Appendix B

HIPAA Form

PATIENT AUTHORIZATION FOR USE AND RELEASE OF HEALTH AND RESEARCH STUDY INFORMATION

Study Number: **TGLA-2021-01**

Study Title: A 90-Day, Open-Label, Multi-Site, Pilot Study Evaluating the Safety and Intraocular Lowering Effect of Delivering Travoprost using a Punctal Plug Delivery System (Evolute®) in Subjects with Elevated Intraocular Pressure

By signing this Authorization, you agree to permit the disclosure of your confidential medical information by the Physician and others involved in the research to affiliates, agents and contractors (Sponsor) and Regulatory Authorities [e.g., the United States Food and Drug Administration (FDA)] for the purpose of conducting a study on a punctal plug delivery system design to deliver a glaucoma medication to your eye and the effect the medication has on reducing the pressure within your eye. Outcomes from this study may include publication of anonymous patient data. Such information may include, without limitation, your initials, age, race and gender. The Sponsor has provided financial assistance to the Physician to support these purposes.

Furthermore, such information may be used, along with medical information of other individuals, in the creation and maintenance of a research database or repository for follow-up or retrospective research and/or statistical purposes. Such information may also be transferred to another country, which may have different privacy laws. Once your information has been released to the Sponsor, it will continue to be protected by the Sponsor's privacy policy or by privacy policies that, in the Sponsor's judgments, provide protection that is equivalent to the Sponsor's privacy policy. It will not, however, have the protection of the federal privacy regulations.

Unless another date is required by applicable law(s) your authorization will NOT expire because this information will be compiled into clinical research data and used for research purposes in the future, and you consent to the retention and future processing of your data. If your information is obtained in California, USA, this authorization will expire in 20 years.

You have the right to revoke this authorization at any time, so long as you do so in writing. If you wish to revoke this authorization, please send a letter in which you refer to this authorization by the date of your signature below, to the physician conducting this trial (Doctor's name and address listed below). However, please be advised that your revocation may not be effective if, in the meantime, the Physician has taken action in reliance on this authorization. We will honor your revocation to the greatest extent possible without diminishing the purposes of the trial.

You have the right to access your data, subject to reasonable limitations, and to submit corrections to the Physician at the address listed below. You understand that you will not be allowed access to the information about you if we believe that disclosure of this information would jeopardize the integrity of the research efforts or other purposes of the trial. Following the conclusion of the trial, upon your request and under reasonable terms, you may access your

personal information that we retain. This information may be most readily available from the Physician, but the Sponsor will endeavor to provide you access to your information if necessary. The Physician and Sponsor will ensure that reasonable and appropriate physical, procedural, and technological safeguards are in place in order to protect your information from inadvertent destruction, disclosure or unauthorized access.

The Physician may condition your participation in the trial on whether or not you sign this authorization or revoke it at a future date.

One copy of this authorization will be kept by the Physician and the Sponsor may retain another copy in their files. You will receive a copy of the authorization that you have signed and dated.

Physician's Name: TBD, MD

Address: TDB (Street 1)
TDB (Street 2)
City, State Zip Code

I have read and understand this Authorization, and agree that my medical information may be used and released according to the terms written above.

_____	_____	_____
Print Name of Study Subject	Study Subject's Signature	Date of Signature

OR

_____	_____	_____
Print Name of Legally Authorized Representative	Signature of Legally Authorized Representative	Date of Signature

_____
Indicate Relationship to Study Subject

Acknowledged by Physician

_____	_____	_____
Print Name of Physician	Physician Signature	Date of Signature

Appendix C

Examination Tests/Procedures and Equipment

1. TESTS/PROCEDURES

a. Blood Pressure and Heart Rate

Throughout the study, vital signs (blood pressure, heart rate) will be taken with the subject in the sitting position after the subject has rested for at least five minutes. Blood pressures may be determined manually with a blood pressure cuff and auscultation or with an automated Blood Pressure monitor. Heart rates may be determined electronically with an automated Blood Pressure monitor. Manually obtained heart rates should be recorded after a minimum of 30 seconds of observation.

b. Temperature

Temperature maybe taken using a non-contact (Infrared) thermometer or orally. Oral temperatures should not be taken within five minutes of ingestion of any food or drink

c. Visual Acuity

Best-corrected distance visual acuity will be measured using a Snellen chart while the subject is wearing his or her glasses. Pinhole visual acuity will be measured using a Snellen chart while the subject is looking through a pinhole occluder. The test distance and lighting conditions specified for the investigator's chart must be used and kept constant throughout the study.

d. Automated Perimetry

Full threshold visual fields will be measured using a Humphrey's Visual Field Analyzer (manufactured by Carl Zeiss Meditec Inc., Dublin, CA) with at least a standard full-threshold 24-2 program or Swedish interactive threshold algorithm (SITA) program. Visual fields measured up to **SIX months** before the Screening Visit are acceptable to fulfill the screening procedure.

e. Pachymetry

Corneal thickness can be measured by contact methods, such as ultrasound and confocal microscopy (CONFOSCAN), noncontact methods such as optical biometry with a single Scheimpflug camera (such as SIRIUS or PENTACAM), dual Scheimpflug camera (such as GALILEI), or Optical Coherence Tomography (OCT), such as Visante. Corneal thickness data that is documented in the patient chart is acceptable to fulfill the screening procedure.

f. Evaluation of Slit-Lamp Findings (Lids, Cornea, Conjunctiva)

The severity of a sign will be graded by the investigator based on the appearance at each study visit using the following scale:

NONE (0) = Normal;
TRACE (1) = Slightly visible;
MILD (2) = Somewhat visible and diffuse;

MODERATE (3) = Visible and diffuse;
SEVERE (4) = Extremely visible and dense

g. **Intraocular Pressure Measurements**
(see Appendix D for details)

h. **Dilated Fundus Examination**
Using an ophthalmoscope, the investigator will examine the back part of the eye (fundus), including the retina, optic disc, choroid and blood vessels.

i. **Position Evaluation of the Study Plug**
Study plug position will be evaluated as either:

- Normal
- Present but requires adjustment
- Extruded/Recovered
- Extruded/Lost
  Other

j. **Punctal Measurements**
(see Appendix E for details)

k. **Adverse Event**/Adverse Device Event
To optimize consistency of AE reporting across centers, the subject will be asked a standard question to elicit any AEs. At each study visit or telephone evaluation of the subject, study personnel (non-observer) will ask the following question:

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

2. EQUIPMENT

a. Coroneo Punctal Gauge

Description

The Coroneo Punctal Gauge (Figure 5) is designed to aid the physician in determine the size of the punctum. In addition, the instrument provides a simple and controlled method for punctal dilation prior to plug 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.

For proper measurement and insertion of punctal plugs, the following procedures are recommended. A topical anesthetic for the punctum is recommended before proceeding with the use of this instrument. ALWAYS measure the punctum first before dilation. See

Appendix E for procedures to gauge the size of a punctum and Appendix F for procedures to dilate the punctum to at least 1.0 mm.

Cleaning, disinfection and sterilization of punctal gauge

Prior to use, the Punctal Gauge should be examined for damage and wear

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 the AAMI Technical Information Report 12 (TIR 12). Instruments used under other conditions may require sterilization.

i. **Cleaning Instructions**

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

ii. **Disinfecting Instructions**

- Soak the punctal gauge in a liquid chemical germicide solution labeled as a disinfection/sterilant (e.g., Cidex®) which has been approved by a competent authority for use in disinfecting or sterilizing medical instruments
- Soak the punctal gauge for the time listed by the manufacture of the disinfection/sterilant solution

  NOTE: Disinfection/sterilant solutions are alkaline (e.g., high pH) and will affect anodized instruments. Do not leave anodized instruments in these solutions for a protracted period of time.
- After disinfection, rinse instrument with a stream of fresh water, and dry completely

iii. **Sterilization Instructions**

- If the punctal gauge is placed in a sterilizing tray, do not allow the punctal gauge to touch other instruments or the sides of the tray
- After sterilization, if the punctal gauge is not intended for immediate use, gauge 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 15 minutes, gravity cycle at 270°F (132°C).

b. Castroviejo Corneal Suturing Forceps

Description

Castroviejo Corneal Suturing Forceps are designed for handling both corneal tissue and suture materials during eye surgery procedures. Castroviejo Corneal Suturing Forceps have tying platform with Tungsten Carbide dust for additional grip and reliability.

Manual disinfection

Due to the potential for residual chemicals to remain on the instrument and cause an adverse reaction, do not use an enzymatic or liquid chemical disinfectant or sterilant when manually cleaned instrument.

Drying

Dry the instrument with a lint-free surgical wipe or blow the instrument dry with micro-filtered pressurized medical grade air. When blowing dry with pressurized air, ensure a secure grip on the instrument to avoid damage to the instrument from air pressure.

Maintenance, Inspection and Testing

Following cleaning, inspect the instrument to ensure that all visible soil has been removed and that the instrument operates as intended. A microscope should be used whenever possible.

Packaging

Package the instrument in a suitable sterilization pouch or instrument tray lined with soft silicone mats. Protective tips made of soft silicone of the proper size and thickness are recommended. Instruments should not be touching each other.

Appendix D

Procedure for Performing Applanation Tonometry

Goldmann applanation tonometry will be used for measuring the intraocular pressures (IOP) of each eye. **Just prior to the start of the study, the tonometer should be calibrated and at least once every month during the duration of the study.**

Accurate and precise IOP readings are imperative, studies have found tight collars, ties or other restrictive clothing around the neck may cause an increase in venous pressure when the patient extends his or her neck forward, resulting in an inaccurately high IOP reading. Have a patient loosen any collars or neckties that may be restrictive to obtain an accurate measurement.

The IOP of each eye will be measured by a qualified evaluator [Study investigator, Co-investigator(s) or Sub-investigator(s)]. If there is more than one evaluator in the office, the same individual and the same Goldmann applanation tonometer used to measure the screening IOPs should be used to take measurements at all study visits.

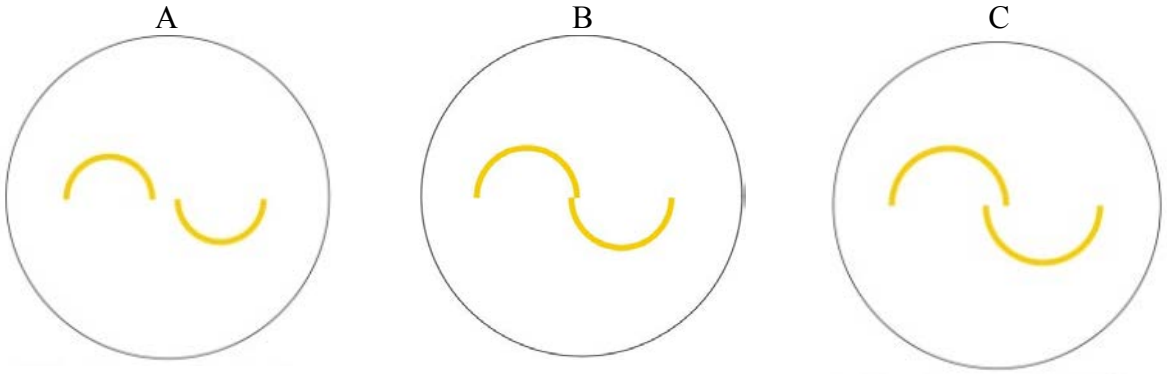
NOTE: Study subjects IOP measurements must be evaluated between 8:00 and 10:00 AM

Measuring and Recording of IOPs

A topical anesthetic will be instilled on each eye. Afterwards a fluorescein strip or drop will be placed onto the cul-de-sac of each eye. The IOP will be measured by the evaluator by placing the applanator tip on the corneal apex. When the evaluator has obtained a desired endpoint (i.e., mires of equal size, centered in the field, with the inner surfaces of the circles "kissing"), the tip can be withdrawn from the cornea (Figure 4-B).

Figure 4

Applanation tonometry semi-circles viewed through the Goldmann Prism



Correct end point:(diagram “B”):
Inner edges of the semi-circles
are just touching (“kissing”)

After the tonometer has been withdrawn, read and record the pressure from the scale on the knob on the side of the tonometer, then reset the tonometer knob to "10" (NOTE: Whenever possible,

the same individual should perform and record the pressure values from the tonometry, at each time point for all subjects).

The IOP of each eye will be measured twice, alternating between eyes. However, if the second measurement is $\geq \pm$ 3 mmHg from the first measurement for an eye, a third measurement will be taken. All measurements taken will be recorded. In the case of two measurements, the average of the two values will be used for analysis, and in the case of three measurements, the average of the two closest values of the three will be used for analysis for that eye at that specific time point.

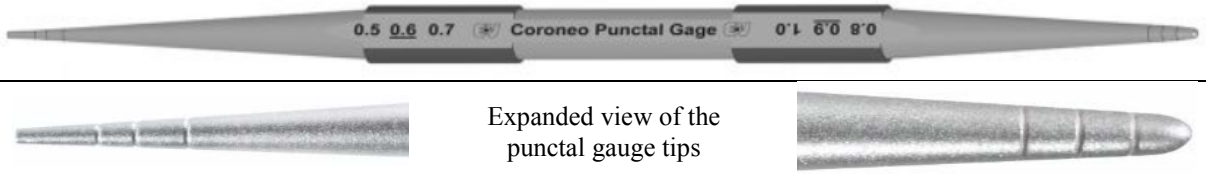
Appendix E

PROCEDURE FOR GAUGING (MEASURING) PUNCTUM SIZE

The Coroneo Punctal Gage (Figure 5) is a reusable double-ended instrument that allows you to gauge the size of the puncta from 0.5 mm to 1.0 mm. Do not dilate the punctum before gauging the size of the punctum.

Figure 5

Coroneo Punctal Gage



NOTE: Care should be taken when gauging the punctum not to perforate the punctal sphincter. If the size of the study subject puncta has not be measured, gauge) the size of each punctum prior to dilating.

1. The study subject may be seated at the slit-lamp or placed in a reclined position
2. Anesthetize the area around the lower punctum

   NOTE: Placing a drop of topical anesthetic such as proparacaine or lidocaine on the eye to be inserted. Then adding lidocaine gel on a cotton-tipped swab and placing the swab directly on the lower punctum of the eye for 5 seconds and wait a few minutes. Past investigators have found this to be effective in numbing the area around the lower punctum
3. Use slight finger traction to expose and stabilize the punctum
4. Begin with the smallest gauge tip (0.5, 0.6, 0.7) of the Coroneo gage
5. Gently insert the tip of the gauge in to the punctum vertically
6. Once the horizontal canaliculus has been reached, if necessary, gently turn the instrument horizontally to continue inserting past the vertical canaliculus.
7. If the instrument can be inserted past the third ring on the tip of the Coroneo gage without observing tightening of the punctal ring – stop and remove the gauge
8. Repeat the above procedure using the larger end of the Coroneo gage (0.8, 0.9, 1.0)
9. 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
10. Record the punctal size in the appropriate section of the case report form.

If gauging the size of the punctum is immediately followed by dilating and inserting the study plug (PPDS), refer to Appendix F for details regarding the dilation of the lower punctum.

Appendix F

PROCEDURE FOR DILATION OF THE PUNCTUM

Use the Coroneo Punctal Gage (Figure 5) to dilate the punctum. If the size of the study subject puncta have not been measured, gauge (Appendix E) the size of each punctum prior to dilating.

NOTE: Care should be taken when dilating the punctum not to perforate the punctal sphincter. Dilating and inserting the punctal plug delivery system (PPDS) should be **performed on <u>ONE</u> eye at a time**.

1. The study subject may be seated at the slit-lamp or placed in a reclined position. The following steps 1-6 are the same procedure used to measure (gauge) the size of the punctum

2. Anesthetize the area around the lower punctum

   NOTE: Placing a drop of topical anesthetic such as proparacaine or lidocaine on the eye to be inserted. Then adding lidocaine gel on a cotton-tipped swab and placing the swab directly on the lower punctum of the eye for 5 seconds and wait a few minutes. Past investigators have found this to be effective in numbing the area around the lower punctum

3. Use slight finger traction on the lower lid to expose and stabilize the punctum

4. Begin with the smallest gauge tip (0.5, 0.6, 0.7) of the Coroneo gage

5. Gently insert the tip of the gauge in to the punctum vertically

6. Once the horizontal canaliculus has been reached, if necessary, gently turn the instrument horizontally to continue inserting past the vertical canaliculus as you gently dilate

7. Once the instrument is inserted past the third ring on the tip of the Coroneo gage, repeat the above procedure using the larger end of the Coroneo gauge (0.8, 0.9, 1.0)

8. **The punctum must be dilated to at least 1.0 mm**. Once the punctum is dilated to 1.0 mm, leave dilator in place for 20 to 30 seconds to allow the sphincter to fully relax. During this time prepare the PPDS to be inserted.

   NOTE: For small puncta, hold and rotate the dilator in the punctum and canaliculus for as long as required to achieve dilation to 1.0 mm. This may take some considerable time (1-2 minutes). Dilation may require very firm pressure however; care must be taken **<u>NOT to apply excessive force</u>** to dilate the punctum. Add more anesthesia if needed.

Refer to Appendix G for detailed procedure for inserting the PPDS

Appendix G

PROCEDURES FOR INSERTION OF A PPDS

The procedure for inserting Mati's PPDS punctal plug is similar to those for commercial plugs. Mati's PPDS is for **single-patient use only**.

NOTE: Do not use a lubricant when inserting the plug, this may facilitate inadvertent plug intrusion below the punctal opening.

1. Once the punctum has been dilated to 1.0 mm, leave the dilator in place for 20 to 30 seconds to allow the sphincter to fully relax. During this time prepare the PPDS to be inserted by removing the foil laminate lid and release the pre-loaded PPDS from the preformed rigid tray

2. Remove the dilator from the punctum and immediately attempt to insert the PPDS before the sphincter starts to close

3. Use slight finger traction on the lower lid to expose and stabilize the punctum, and position the plug end of the insertion instrument over the study subject's punctum

4. Insert the plug, coming straight down perpendicular to the punctum until the cap of the plug is flush with the lid margin

5. Once the plug is in the proper position, release the lower lid and press the release button and pull the insertion instrument away from the study subject's punctum

After insertion, the punctal opening should be visually inspected using a slit-lamp to confirm the retention and proper placement of the PPDS, with the cap still visible. The position of the PPDS may be adjusted with forceps or the tip of the inserter if necessary. However, if unable to position the cap of the plug flush with the lid margin, 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

NOTE: Removal of a properly positioned PPDS immediately after insertion may result in the cap of the plug being torn off. Investigator should wait until the following day to allow the punctal sphincter to adjust (relax) before attempting to remove a PPDS. If the plug tears or separates, report this as a technical complaint (Section 8.6.3). Retain all removed or damaged PPDS for accountability of investigational supplies.

If the PPDS cannot be inserted after a few attempts with gentle dilation, the subject is not eligible for the study.

Appendix H

PROCEDURES FOR REMOVAL OF A PPDS

The PPDS should be removed from the study subject's lower puncta using sterile ophthalmic forceps, such as Castroviejo Suture forceps (Figure 6) or similar toothed forceps. When removing a PPDS, if necessary, a drop of anesthetic may be administered.

Figure 6

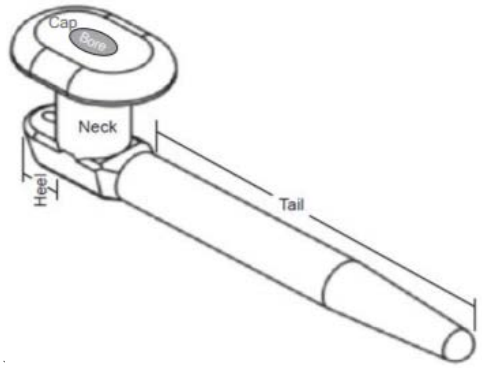
Castroviejo Corneal Suturing Forceps 1x2 0.12mm 90° Straight, Titanium

a. 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

b. The teeth of the forceps should **NOT** be used to grasp the neck of the PPDS, but are placed on the far sides of the plug with the blades straddling the neck. The teeth of the forceps are used instead to prevent the blades of the forceps from sliding off the neck. Grasping the neck of the plug with the teeth may fracture or tear the plug

Figure 7

Punctal Plug Delivery System
(L-shape Model L67)



c. The first motion to remove the plug should be towards the medial canthus (not up or temporally), which is necessary to disengage the heel of the plug, pulling the plug out with a tugging motion towards the medial canthus

NOTE: 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.

If the cap becomes separated, removal of the plug can be attempted 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 does not appear that the plug will lodge in the canal, and only if the investigator feels comfortable doing so, he or she may attempt to irrigate the canal until the plug flushes out of the nasolacrimal duct.

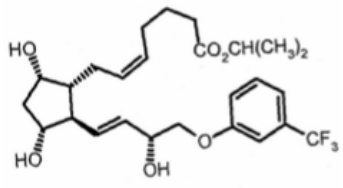
NOTE: A PPDS is larger than commercially available silicone plugs and may become lodged in the canal more easily. Clinical judgment should be exercised when proceeding. Referral to tertiary care is advised in cases where the plug cannot be retrieved by massaging/milking through the punctal opening or by irrigation. Plug intrusion at removal, or spontaneous migration of a PPDS beyond the punctal opening such that massage, irrigation, or punctoplasty is required to remove it should be recorded as an AE.

Appendix I

TRAVATAN® (travoprost ophthalmic solution) 0.004% Sterile

DESCRIPTION

TRAVATAN® (travoprost ophthalmic solution) 0.004% Sterile DESCRIPTION Travoprost is a synthetic prostaglandin F2α analogue. Its chemical name is isopropyl (Z)-7[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(1E,3R)-3-hydroxy-4-[(α,α,α- trifluoro-m-tolyl)oxy]-lbutenyl]cyclopentyl]-5-heptenoate. It has a molecular formula of C26H35F3O6 and a molecular weight of 500.56. The chemical structure of travoprost is:



Travoprost is a clear, colorless to slightly yellow oil that is very soluble in acetonitrile, methanol, octanol, and chloroform. It is practically insoluble in water.

TRAVATAN® Ophthalmic Solution 0.004% is supplied as sterile, buffered aqueous solution of travoprost with a pH of approximately 6.0 and an osmolality of approximately 290 mOsmol/kg.

Each mL of TRAVATAN® 0.004% contains 40 ug travoprost. Benzalkonium chloride 0.015% is added as a preservative. Inactive Ingredients are: polyoxyl 40 hydrogenated castor oil, tromethamine, boric acid, mannitol, edetate disodium, sodium hydroxide and/or hydrochloric acid (to adjust pH) and purified water.

CLINICAL PHARMACOLOGY

Mechanism of Action

Travoprost free acid is a selective FP prostanoid receptor agonist which is believed to reduce intraocular pressure by increasing uveoscleral outflow. The exact mechanism of action is unknown at this time.

Pharmacokinetics/Pharmacodynamics

Absorption: Travoprost is absorbed through the cornea and is hydrolyzed to the active free acid. Data from four multiple dose pharmacokinetic studies (totaling 107 subjects) have shown that plasma concentrations of the free acid are below 0.01 ng/ml (the quantitation limit of the assay) in two-thirds of the subjects. In those individuals with quantifiable plasma concentrations (N=38), the mean plasma Cmax was 0.018 ± 007 ng/ml (ranged 0.01 to 0.052 ng/mL) and was reached

within 30 minutes. From these studies, travoprost is estimated to have a plasma half-life of **45** minutes. There was no difference in plasma concentrations between Days 1 and 7, indicating steady-state was reached early and that there was no significant accumulation.

Metabolism: Travoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to its biologically active free acid. Systemically, travoprost free acid is metabolized to inactive metabolites via beta-oxidation of the α (carboxylic acid) chain to give the 1,2-dinor and 1,2,3,4-tetranor analogs, via oxidation of the 15-hydroxyl moiety, as well as via reduction of the 13,14-double bond.

Elimination: The elimination of travoprost free acid from plasma was rapid and levels were generally below the limit of quantification within one hour after dosing. The terminal elimination half-life of travoprost free acid was estimated from fourteen subjects and ranged from 17 minutes to 86 minutes with the mean half-life of 45 minutes. Less than 2% of the topical ocular dose of travoprost was excreted in the urine within 4 hours as the travoprost free acid.

Clinical Studies

In clinical studies, patients with open-angle glaucoma or ocular hypertension and baseline pressure of 25 - 27 mmHg who were treated with TRAVATAN® Ophthalmic Solution 0.004% dosed once-daily in the evening demonstrated 7 - 8 mmHg reductions in intraocular pressure. In subgroup analyses of these studies, mean IOP reduction in black patients was up to 1.8 mmHg greater than in non-black patients. It is not known at this time whether this difference is attributed to race or to heavily pigmented irides. In a multi-center, randomized, controlled trial, patients with mean baseline intraocular pressure of 24 - 26 mmHg on TIMOPTIC* 0.5% BID who were treated with TRAVATAN® 0.004% dosed QD adjunctively to TIMOPTIC* 0.5% BID demonstrated 6 - 7 mmHg reductions in intraocular pressure.

TRAVATAN® has been studied in patients with hepatic impairment and also in patients with renal impairment. No clinically relevant changes in hematology, blood chemistry, urinalysis laboratory data were observed in these patients.

INDICATIONS AND USAGE

TRAVATAN® Ophthalmic Solution is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

CONTRAINDICATIONS

TRAVATAN® is contraindicated in patients with hypersensitivity to travoprost, benzalkonium chloride or any other ingredients in this product.

WARNINGS

TRAVATAN® has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris and periorbital tissue (eyelid) and increased pigmentation and growth of eyelashes. These changes may be permanent.

TRAVATAN® may gradually change eye color, increasing the amount of brown pigmentation in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long-term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for months to years. Patients should be informed of the possibility of iris color change.

Eyelid skin darkening has been reported in association with the use of TRAVATAN®.

TRAVATAN® may gradually change eyelashes in the treated eye; these changes include increased length, thickness, pigmentation, and/or number of lashes.

Patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation of the iris, periorbital and/or eyelid tissue, and eyelashes in the treated eye and thus heterochromia between the eyes. They should also be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes.

PRECAUTIONS

General

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent cornea1 disease or a disruption of the epithelial surface (see Information for Patients).

Patients may slowly develop increased brown pigmentation of the iris. This change may not be noticeable for months to years (see Warnings). Iris pigmentation changes may be more noticeable in patients with mixed colored irides, i.e., blue-brown, grey-brown, yellow-brown, and green-brown; however, it has also been observed in patients with brown eyes. The color change is believed to be due to increased melanin content in the stromal melanocytes of the iris. The exact mechanism of action is unknown at this time. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may

become more brownish. Until more information about increased brown pigmentation is available, patients should be examined regularly and, depending on the situation, treatment may be stopped if increased pigmentation ensues.

TRAVATAN® should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation.

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin $F_{2\alpha}$ analogues. These reports have mainly occurred in aphakic patients, pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. TRAVATAN® should be used with caution in these patients.

TRAVATAN® has not been evaluated for the treatment of angle closure, inflammatory or neovascular glaucoma.

TRAVATAN® Ophthalmic Solution should not be administered while wearing contact lenses.

Patients should be advised that TRAVATAN® contains benzalkonium chloride which may be absorbed by contact lenses. Contact lenses should be removed prior to the administration of the solution. Lenses may be reinserted 15 minutes following administration of TRAVATAN®.

Information for Patients

Patients should be advised concerning all the information contained in the Warnings and Precautions sections.

Patients should also 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.

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

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should immediately seek his/her physician's advice.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies in mice and rats at subcutaneous doses of 10, 30, or 100 µg/kg/day did not show any evidence of carcinogenic potential. However, at 100 µg/kg/day, male rats were only treated for 82 weeks, and the maximum tolerated dose (MTD) was not reached in the mouse study. The high dose (100 µg/kg) corresponds to exposure levels over 400 times the human exposure at the maximum recommended human ocular dose (MRHOD) of 0.04 µg/kg, based on plasma active drug levels. Travoprost was not mutagenic in the Ames test, mouse micronucleus test and rat chromosome aberration assay. A slight increase in the mutant frequency was observed in one of two mouse lymphoma assays in the presence of rat S-9 activation enzymes.

Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 ug/kg/day [250 times the maximum recommended human ocular dose of 0.04 ug/kg/day on a ug/kg basis (MRHOD)]. At 10 ug/kg/day, the mean number of corpora lutea was reduced, and the postimplantation losses were increased. These effects were not observed at 3 ug/kg/day (75 times the MRHOD).

Pregnancy: Teratogenic Effects

Pregnancy Category: C Travoprost was teratogenic in rats, at an intravenous (IV) dose up to 10 ug/kg/day (250 times the MRHOD), evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, such as fused sternebrae, domed head and hydrocephaly. Travoprost was not teratogenic in rats at IV doses up to 3 ug/kg/day (75 times the MRHOD), and in mice at subcutaneous doses up to 1.0 ug/kg/day (25 times the MRHOD). Travoprost produced an increase in postimplantation losses and a decrease in fetal viability in rats at IV doses > 3 ug/kg/day (75 times the MRHOD) and in mice at subcutaneous doses > 0.3 ug/kg/day (7.5 times the MRHOD).

In the offspring of female rats that received travoprost subcutaneously from Day 7 of pregnancy to lactation Day 21 at the doses of ≥ 0.12 ug/kg/day (3 times the MRHOD), the incidence of postnatal mortality was increased, and neonatal body weight gain was decreased. Neonatal development was also affected, evidenced by delayed eye opening, pinna detachment and preputial separation, and by decreased motor activity.

There are no adequate and well-controlled studies in pregnant women. TRAVATAN® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

A study in lactating rats demonstrated that radiolabeled travoprost and/or its metabolites were excreted in milk. It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRAVATAN® is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS

The most common ocular adverse event observed in controlled clinical studies with TRAVATAN® 0.004% was ocular hyperemia which was reported in 35 to 50% of patients. Approximately 3% of patients discontinued therapy due to conjunctival hyperemia.

Ocular adverse events reported at an incidence of 5 to 10% included decreased visual acuity, eye discomfort, foreign body sensation, pain, and pruritus.

Ocular adverse events reported at an incidence of 1 to 4% included, abnormal vision, blepharitis, blurred vision, cataract, cells, conjunctivitis, dry eye, eye disorder, flare, iris discoloration, keratitis, lid margin crusting, photophobia, subconjunctival hemorrhage, and tearing.

Nonocular adverse events reported at a rate of 1 to 5% were accidental injury, angina pectoris, anxiety, arthritis, back pain, bradycardia, bronchitis, chest pain, cold syndrome, depression, dyspepsia, gastrointestinal disorder, headache, hypercholesterolemia, hypertension, hypotension, infection, pain, prostate disorder, sinusitis, urinary incontinence, and urinary tract infection.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once-daily in the evening. The dosage of TRAVATAN® should not exceed once-daily since it has been shown that more frequent administration may decrease the intraocular pressure lowering effect. Reduction of intraocular pressure starts approximately 2 hours after administration, and the maximum effect is reached after 12 hours.

TRAVATAN® may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

HOW SUPPLIED

TRAVATAN® (travoprost ophthalmic solution) 0.004% is a sterile, isotonic, buffered, preserved, aqueous solution of travoprost (0.04 mg/mL) supplied in Alcon's oval DROP-TAINER® package system. TRAVATAN® is supplied as a 2.5 mL solution in a 4 mL and a 5 mL solution in a 7.5 mL natural polypropylene dispenser bottle with a natural polypropylene dropper tip and a turquoise polypropylene overcap. Tamper evidence is provided with a shrink band around the closure and neck area of the package. NDC 0065-0266-25, 2.5 mL fill NDC 0065-0266-17, 2 units, 2.5 mL fill each NDC 0065-0266-34, 5 mL fill

Storage

Store at 2° - 25°C (36° - 77°F). Rx Only

Rx Only

U.S. Patent Nos. 5,631,287; 5,849,792; 5,889,052; 6,011,062, and 6,235,781.

*TIMOPTIC is a registered trademark of Merck & Co., Inc.

ALCON LOGO

ALCON LABORATORIES, INC.

Fort Worth, Texas 76134 USA

Appendix J

TRAVATAN Z® PACKAGE INSERT

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TRAVATAN Z® (travoprost ophthalmic solution) 0.004% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

2 DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening. TRAVATAN Z should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogs may decrease the IOP lowering effect.

Reduction of the IOP starts approximately 2 hours after the first administration with maximum effect reached after 12 hours.

TRAVATAN Z may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

3 DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing travoprost 0.04 mg/mL.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Pigmentation

Travoprost ophthalmic solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as travoprost is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of travoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long-term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to

be affected by treatment. While treatment with TRAVATAN Z can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

5.2 Eyelash Changes
TRAVATAN Z may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

5.3 Intraocular Inflammation
TRAVATAN Z should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

5.4 Macular Edema
Macular edema, including cystoid macular edema, has been reported during treatment with travoprost ophthalmic solution. TRAVATAN Z should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

5.5 Angle-closure, Inflammatory or Neovascular Glaucoma
TRAVATAN Z has not been evaluated for the treatment of angle-closure, inflammatory or neovascular glaucoma.

5.6 Bacterial Keratitis
There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

5.7 Use with Contact Lenses
Contact lenses should be removed prior to instillation of TRAVATAN Z and may be reinserted 15 minutes following its administration.

6 ADVERSE REACTIONS

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

The most common adverse reaction observed in controlled clinical trials with TRAVATAN and TRAVATAN Z was ocular hyperemia, which was reported in 30% to 50% of patients. Up to 3% of patients discontinued therapy due to conjunctival hyperemia. Ocular adverse reactions reported at an incidence of 5% to 10% in these clinical trials included decreased visual acuity, eye discomfort, foreign body sensation, pain, and pruritus.

Ocular adverse reactions reported at an incidence of 1% to 4% in clinical trials with TRAVATAN

or TRAVATAN Z included abnormal vision, blepharitis, blurred vision, cataract, conjunctivitis, corneal staining, dry eye, iris discoloration, keratitis, lid margin crusting, ocular inflammation, photophobia, subconjunctival hemorrhage, and tearing.

Non-ocular adverse reactions reported at an incidence of 1% to 5% in these clinical studies were allergy, angina pectoris, anxiety, arthritis, back pain, bradycardia, bronchitis, chest pain, cold/flu syndrome, depression, dyspepsia, gastrointestinal disorder, headache, hypercholesterolemia, hypertension, hypotension, infection, pain, prostate disorder, sinusitis, urinary incontinence, and urinary tract infections.

6.2 Postmarketing Experience

Additional adverse reactions have been identified during post approval use of TRAVATAN or TRAVATAN Z in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to TRAVATAN or TRAVATAN Z, or a combination of these factors, include: arrhythmia, vomiting, epistaxis, tachycardia, and insomnia.

In postmarketing use with prostaglandin analogs, periorbital and lid changes including deepening of the eyelid sulcus have been observed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies in pregnant women to inform a drug-associated risk.

In animal reproduction studies, subcutaneous (SC) administration of travoprost to pregnant mice and rats throughout the period of organogenesis produced embryo-fetal lethality, spontaneous abortion, and premature delivery at potentially clinically relevant doses.

Advise pregnant women of a potential risk to a fetus. Because animal reproductive studies are not always predictive of human response, TRAVATAN Z should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown; however, in the U.S. general population, the estimated background risk of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Data

Animal Data

An embryo-fetal study was conducted in pregnant rats administered travoprost once daily by SC injection from gestation day (GD) 6 to 18, to target the period of organogenesis. At 10 mcg/kg (60

times the maximum recommended human ocular dose [MRHOD], based on estimated plasma Cmax), travoprost was teratogenic in rats, evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, including fused sternebrae, domed head and hydrocephaly. Travoprost caused post-implantation loss at 10 mcg/kg. The no observed adverse effect level (NOAEL) for post-implantation loss was 3 mcg/kg (18 times the MRHOD, based on estimated plasma Cmax). The maternal NOAEL was 10 mcg/kg.

An embryo-fetal study was conducted in pregnant mice administered travoprost once daily by SC injection from GD 6 to 11, to target the period of organogenesis. At 1 mcg/kg (6 times the MRHOD, based on estimated plasma Cmax), travoprost caused postimplantation loss and decreased fetal weight. The no observed adverse effect level (NOAEL) for malformations was 0.3 mcg/kg (2 times the MRHOD, based on estimated plasma Cmax). The maternal NOAEL was 1 mcg/kg.

Pre/postnatal studies were conducted in rats administered travoprost once daily by subcutaneous injection from GD 7 (early embryonic period) to postnatal Day 21 (end of lactation period). At doses of greater than or equal to 0.12 mcg/kg/day (0.7 times the MRHOD, based on estimated plasma Cmax), adverse pregnancy outcomes (embryo-fetal lethality, abortion, and early delivery), low-birth weight and developmental delays were observed. The NOAEL for adverse pregnancy outcomes, low-birth weight and developmental delay was 0.1 mcg/kg (0.6 times the MHROD, based on estimated plasma Cmax). The NOAEL for maternal toxicity was 0.72 mcg/kg (4 times the MHROD, based on estimated plasma Cmax).

8.2 Lactation

Risk Summary

There are no data on the effects of travoprost on the breastfed child or milk production. It is not known if travoprost is present in human milk following ophthalmic administration. A study in lactating rats demonstrated that radio-labeled travoprost and/or its metabolites were excreted in milk following subcutaneous administration.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRAVATAN Z and any potential adverse effects on the breast-fed child from TRAVATAN Z.

8.4 Pediatric Use

Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

8.5 Geriatric Use

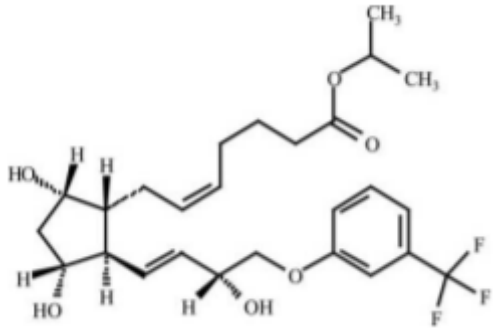
No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

8.6 Hepatic and Renal Impairment

Travoprost ophthalmic solution 0.004% has been studied in patients with hepatic impairment and also in patients with renal impairment. No clinically relevant changes in hematology, blood chemistry, or urinalysis laboratory data were observed in these patients.

11 DESCRIPTION

Travoprost is a synthetic prostaglandin F analog. Its chemical name is [1R-[1α(Z),2β(1E,3R*),3α,5α]]-7-[3,5- Dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl) phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1- methylethylester. It has a molecular formula of C26H35F3O6 and a molecular weight of 500.55 g/mol. The chemical structure of travoprost is:



Travoprost is a clear, colorless to slightly yellow oil that is very soluble in acetonitrile, methanol, octanol, and chloroform. It is practically insoluble in water.

TRAVATAN Z is supplied as sterile, buffered aqueous solution of travoprost with a pH of approximately 5.7 and an osmolality of approximately 290 mOsmol/kg.

TRAVATAN Z contains Active: travoprost 0.04 mg/mL; Inactives: polyoxyl 40 hydrogenated castor oil, sofZia® (boric acid, propylene glycol, sorbitol, zinc chloride), sodium hydroxide and/or hydrochloric acid (to adjust pH), and purified water, USP. Preserved in the bottle with an ionic buffered system, sofZia®.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Travoprost free acid, a prostaglandin analog is a selective FP prostanoid receptor agonist, which is believed to reduce IOP by increasing uveoscleral outflow. The exact mechanism of action is unknown at this time.

12.3 Pharmacokinetics

Travoprost is absorbed through the cornea and is hydrolyzed to the active free acid. Data from 4 multiple dose pharmacokinetic studies (totaling 107 subjects) have shown that plasma concentrations of the free acid are below 0.01 ng/mL (the quantitation limit of the assay) in two-thirds of the subjects. In those individuals with quantifiable plasma concentrations (N = 38), the mean plasma Cmax was 0.018 ± 0.007 ng/mL (ranged 0.01 to 0.052 ng/mL) and was reached

within 30 minutes. From these studies, travoprost is estimated to have a plasma half-life of 45 minutes. There was no difference in plasma concentrations between Days 1 and 7, indicating steady-state was reached early and that there was no significant accumulation.

Travoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to its biologically active free acid. Systemically, travoprost free acid is metabolized to inactive metabolites via beta-oxidation of the α (carboxylic acid) chain to give the 1,2-dinor and 1,2,3,4-tetranor analogs, via oxidation of the 15-hydroxyl moiety, as well as via reduction of the 13, 14 double bond.

The elimination of travoprost free acid from plasma was rapid and levels were generally below the limit of quantification within one hour after dosing. The terminal elimination half-life of travoprost free acid was estimated from fourteen subjects and ranged from 17 minutes to 86 minutes with the mean half-life of 45 minutes. Less than 2% of the topical ocular dose of travoprost was excreted in the urine within 4 hours as the travoprost free acid.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies in mice and rats at subcutaneous doses of 10, 30, or 100 mcg/kg/day did not show any evidence of carcinogenic potential. However, at 100 mcg/kg/day, male rats were only treated for 82 weeks, and the maximum tolerated dose (MTD) was not reached in the mouse study. The high dose (100 mcg/kg) corresponds to exposure levels 326 times (mouse) and 547 times (rat) the human exposure at the MRHOD of 0.04 mcg/kg, based on estimated plasma Cmax for active travoprost free acid.

Travoprost was not mutagenic in the Ames test, mouse micronucleus test or rat chromosome aberration assay. A slight increase in the mutant frequency was observed in one of two mouse lymphoma assays in the presence of rat S-9 activation enzymes.

Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 3 mcg/kg/day (18 times the MRHOD based on estimated plasma Cmax). At 10 mcg/kg/day (60 times the MRHOD, based on estimated plasma Cmax), the mean number of corpora lutea was reduced, and the post-implantation losses were increased.

14 CLINICAL STUDIES

In clinical studies, patients with open-angle glaucoma or ocular hypertension and baseline pressure of 25 to 27 mmHg, who were treated with TRAVATAN or TRAVATAN Z dosed once daily in the evening, demonstrated 7 to 8 mmHg reductions in IOP. In sub-group analyses of these studies, mean IOP reduction in black patients was up to 1.8 mmHg greater than in non-black patients. It is not known at this time whether this difference is attributed to race or to heavily pigmented irides.

In a multi-center, randomized, controlled trial, patients with mean baseline IOP of 24 to 26 mmHg on TIMOPTIC** 0.5% twice daily who were treated with TRAVATAN dosed daily adjunctively to TIMOPTIC** 0.5% twice daily demonstrated 6 to 7 mmHg reductions in IOP.

16 HOW SUPPLIED/STORAGE AND HANDLING

TRAVATAN Z is a sterile, isotonic, buffered, preserved, aqueous solution of travoprost (0.04 mg/mL).

TRAVATAN Z is supplied as a 2.5 mL solution in a 4 mL and a 5 mL solution in a 7.5 mL oval natural polypropylene dispenser bottle with a natural polypropylene dropper tip and a turquoise polypropylene or high-density polyethylene overcap. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

2.5 mL fill	NDC 0065-0260-25
5 mL fill	NDC 0065-0260-05

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

After opening, TRAVATAN Z can be used until the expiration date on the bottle.

17 PATIENT COUNSELING INFORMATION

Potential for Pigmentation

Advise the patient about the potential for increased brown pigmentation of the iris, which may be permanent. Inform the patient about the possibility of eyelid skin darkening, which may be reversible after discontinuation of TRAVATAN Z [*see Warnings and Precautions (5.1)*].

Potential for Eyelash Changes

Inform the patient about the possibility of eyelash and vellus hair changes in the treated eye during treatment with TRAVATAN Z. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment [*see Warnings and Precautions (5.2)*].

Handling the Container

Instruct the patient to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions [*see Warnings and Precautions (5.6)*].

When to Seek Physician Advice

Advise the patient that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of TRAVATAN Z [*see Warnings and Precautions (5.3, 5.4, 5.5)*].

Use with Contact Lenses

Contact lenses should be removed prior to instillation of TRAVATAN Z and may be reinserted 15

minutes following its administration [*see Warnings and Precautions (5.7)*].

Use with Other Ophthalmic Drugs

If more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes between applications.

TIMOPTIC** is a registered trademark of Merck & Co., Inc.

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

T2020-40

Appendix K

IZBA® PACKAGE INSERT

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
IZBA (travoprost ophthalmic solution) 0.003% is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

2 DOSAGE AND ADMINISTRATION
The recommended dosage is one drop in the affected eye(s) once daily in the evening. IZBA (travoprost ophthalmic solution) 0.003% should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogs may decrease the intraocular pressure lowering effect.

Reduction of the intraocular pressure starts approximately 2 hours after the first administration with maximum effect reached after 12 hours.

IZBA may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

3 DOSAGE FORMS AND STRENGTHS
Ophthalmic solution containing travoprost 0.03 mg/mL.

4 CONTRAINDICATIONS
None

5 WARNINGS AND PRECAUTIONS

5.1 Pigmentation
Travoprost ophthalmic solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes. Pigmentation is expected to increase as long as travoprost is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of travoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long-term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with IZBA (travoprost ophthalmic solution) 0.003% can be continued in patients who develop noticeably increased iris pigmentation, these patients should

be examined regularly. (See Patient Counseling Information, 17.1).

5.2 Eyelash Changes
IZBA may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

5.3 Intraocular Inflammation
IZBA should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

5.4 Macular Edema
Macular edema, including cystoid macular edema, has been reported during treatment with travoprost ophthalmic solution. IZBA should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

5.5 Bacterial Keratitis
There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (See Patient Counseling Information, 17.3).

5.6 Use with Contact Lenses
Contact lenses should be removed prior to instillation of IZBA and may be reinserted 15 minutes following its administration.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience
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 rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Different methodologies were used to collect adverse reactions during the development of travoprost. The most common adverse reaction observed in controlled clinical studies with travoprost 0.004% was ocular hyperemia. Ocular hyperemia was reported in 30 to 50% of patients by physician rating the severity of patient's post treatment ocular hyperemia compared to standardized reference photographs and/or patients who discontinued therapy due to ocular hyperemia.

In a 3-month clinical trial involving 442 patients exposed to IZBA (travoprost ophthalmic solution, 0.003%) and 422 control patients exposed to travoprost ophthalmic solution, 0.004%, the most common adverse drug reaction was ocular hyperemia. This was reported in 12% of patients treated

with IZBA based on clinical observations and/or patient complaints. One patient (0.2%) discontinued treatment with IZBA due to ocular hyperemia. Rates observed in the control patients were comparable.

Ocular adverse reactions reported in clinical studies with travoprost ophthalmic solutions including IZBA at an incidence of 5% to 10% included decreased visual acuity, eye discomfort, foreign body sensation, pain and pruritus. Ocular adverse reactions reported at an incidence of 1 to 4% included abnormal vision, blepharitis, blurred vision, cataract, conjunctivitis, corneal staining, dry eye, iris discoloration, keratitis, lid margin crusting, ocular inflammation, photophobia, subconjunctival hemorrhage and tearing.

Nonocular adverse reactions reported at an incidence of 1 to 5% in these clinical studies were allergy, angina pectoris, anxiety, arthritis, back pain, bradycardia, bronchitis, chest pain, cold/flu syndrome, depression, dyspepsia, gastrointestinal disorder, headache, hypercholesterolemia, hypertension, hypotension, infection, pain, prostate disorder, sinusitis, urinary incontinence and urinary tract infections.

In post marketing use with prostaglandin analogs, periorbital and lid changes including deepening of the eyelid sulcus have been observed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of IZBA (travoprost ophthalmic solution 0.003%) administration in pregnant women. Malformations were observed in rats at doses that were 1500 times higher the maximum recommended human ocular dose (MRHOD) based on estimated Cmax values for the active free acid. Embryo lethality and decreased fetal/neonate viability were observed in mice at subcutaneous doses 9-fold higher than the MRHOD based on estimated Cmax for the active free acid. IZBA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Travoprost was teratogenic in rats, at an intravenous (IV) dose up to 10 mcg/kg/day (1500 times the MRHOD, evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, such as fused sternebrae, domed head and hydrocephaly. Travoprost did not produce malformations in rats at IV doses up to 3 mcg/kg/day (470 times the MRHOD), or in mice at subcutaneous doses up to 1 mcg/kg/day (9 times the MRHOD). Travoprost produced an increase in post-implantation losses and a decrease in fetal viability in rats at IV doses of 10 mcg/kg/day (1500 times the MRHOD) and in mice at subcutaneous doses of 1 mcg/kg/day (9 times the MRHOD).

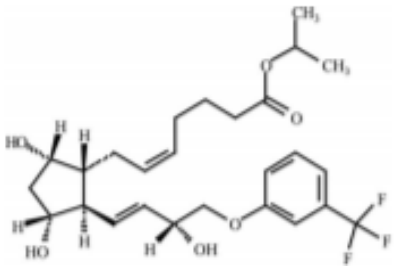
In the offspring of female rats that received travoprost subcutaneously from Day 7 of pregnancy to lactation Day 21 at doses of $\geq$ 0.12 mcg/kg/day (3.2 times the MRHOD), the incidence of postnatal mortality was increased, and neonatal body weight gain was decreased. Neonatal development was also affected, evidenced by delayed eye opening, pinna detachment and preputial separation, and by decreased motor activity.

8.3 Nursing Mothers
A study in lactating rats demonstrated that radiolabeled travoprost and/or its metabolites were excreted in milk. It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when IZBA is administered to a nursing woman.

8.4 Pediatric Use
Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long term chronic use.

8.5 Geriatric Use
No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

11 DESCRIPTION Travoprost is a synthetic prostaglandin F2α analog. Its chemical name is [1R-[1 (Z),2 (1E,3R*),3α ,5 α]]-7-[3,5-Dihydroxy-2-[3- hydroxy-4-[3-(trifluoromethyl) phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-methylethylester. It has a molecular formula of C26H35F3O6 and a molecular weight of 500.55. The chemical structure of travoprost is:



Travoprost is a clear, colorless to slightly yellow oil that is very soluble in acetonitrile, methanol, octanol, and chloroform. It is practically insoluble in water.

IZBA (travoprost ophthalmic solution) 0.003% is supplied as sterile, isotonic, buffered aqueous solution of travoprost with a pH of approximately 6.8 and an osmolality of approximately 290 mOsmol/kg.

IZBA contains Active: travoprost 0.03 mg/mL; Preservative: POLYQUAD® (polyquaternium-1) 0.01mg/mL; Inactives: boric acid, mannitol, polyoxyethylene 40 hydrogenated castor oil, propylene glycol, sodium chloride, sodium hydroxide and/or hydrochloric acid (to adjust pH) and purified water, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Travoprost free acid, a prostaglandin analog is a selective FP prostanoid receptor agonist which is believed to reduce intraocular pressure by increasing uveoscleral outflow. The exact mechanism

of action is unknown at this time.

12.3 Pharmacokinetics

Travoprost is absorbed through the cornea and is hydrolyzed to the active free acid. Data from four multiple dose pharmacokinetic studies using travoprost ophthalmic solution, 0.004% (totaling 107 subjects) have shown that plasma concentrations of the free acid are below 0.01 ng/mL (the quantitation limit of the assay) in two-thirds of the subjects. In those individuals with quantifiable plasma concentrations (N=38), the mean plasma Cmax was 0.018 ± 0.007 ng/mL (ranged 0.01 to 0.052 ng/mL) and was reached within 30 minutes. From these studies, travoprost is estimated to have a plasma half-life of 45 minutes. There was no difference in plasma concentrations between Days 1 and 7, indicating steady-state was reached early and that there was no significant accumulation.

Travoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to its biologically active free acid. Systemically, travoprost free acid is metabolized to inactive metabolites via beta-oxidation of the α(carboxylic acid) chain to give the 1,2-dinor and 1,2,3,4-tetranor analogs, via oxidation of the 15-hydroxyl moiety, as well as via reduction of the 13,14 double bond.

The elimination of travoprost free acid from plasma was rapid and levels were generally below the limit of quantification within one hour after dosing. The terminal elimination half-life of travoprost free acid was estimated from fourteen subjects and ranged from 17 minutes to 86 minutes with the mean half-life of 45 minutes. Less than 2% of the topical ocular dose of travoprost was excreted in the urine within 4 hours as the travoprost free acid.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies in mice and rats at subcutaneous doses of 10, 30, or 100 mcg/kg/day did not show any evidence of carcinogenic potential. However, at 100 mcg/kg/day, male rats were only treated for 82 weeks, and the maximum tolerated dose (MTD) was not reached in the mouse study. The high dose (100 mcg/kg) corresponds to exposure levels over 400 times (for the mouse) and 700 times (for the rat) of the human exposure at the maximum recommended human ocular dose (MRHOD) of 0.03 mcg/kg, based on estimated plasma Cmax for active free acid.

Travoprost was not mutagenic in the Ames test, mouse micronucleus test or rat chromosome aberration assay. A slight increase in the mutant frequency was observed in one of two mouse lymphoma assays in the presence of rat S-9 activation enzymes.

Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 mcg/kg/day (40 times the MRHOD based on estimated plasma Cmax for active free acid). At 10 mcg/kg/day, the mean number of corpora lutea was reduced, and the post implantation losses were increased. These effects were not observed at 3 mcg/kg/day (12 times the MRHOD).

14 CLINICAL STUDIES

A single clinical trial of 3 months duration was conducted to compare the IOP-lowering effect of IZBA (travoprost ophthalmic solution) 0.003% to TRAVATAN (travoprost ophthalmic solution) 0.004%, with both dosed once daily in the evening in adult patients with open angle glaucoma or ocular hypertension. Patient age ranged from 21 to 92 years, with a mean age of 65 years. A total of 864 patients (IZBA, 442 patients; TRAVATAN, 422 patients) were enrolled, with 840 (97%) completing through Month 3.

Analysis was based on the intent-to-treat (ITT) population defined as all patients who received study drug and completed at least one scheduled on-therapy study visit.

The least squares mean IOP (mmHg), the difference in mean IOP (IZBA minus TRAVATAN), and the 95% CI for the treatment difference in mean IOP at visit and time point are presented in Table 1. The differences in the mean IOP at all visits and time points were within ±1 mmHg, demonstrating equivalence of IZBA to TRAVATAN in lowering intraocular pressure.

Table 2 presents the mean IOP change from baseline at Week 2, Week 6, and at Month 3. IZBA demonstrated comparable IOP reductions at all on-therapy visits and time points; the mean IOP reduction from baseline in the IZBA group ranged from 7.1 to 8.2 mmHg and in the TRAVATAN group ranged from 7.1 to 8.4 mmHg. In both treatment groups, the greatest mean IOP reduction was observed at the 8 AM assessment time point.

Table 1 Mean IOP (mmHg) by Treatment Group and Treatment Difference in Mean IOP

Visit/ Time Point	IZBA (Travoprost 0.003%)	TRAVATAN (Travoprost 0.004%)	Difference
	Mean (SE)	Mean (SE)	Mean (95% CI) *
Baseline	(N = 442)	(N = 418)	
8 AM	26.9 (0.12)	27.1 (0.14)	-0.2 (-0.5, 0.2)
10 AM	25.4 (0.13)	25.6 (0.15)	-0.2 (-0.6, 0.2)
4 PM	24.6 (0.14)	24.8 (0.16)	-0.2 (-0.6, 0.2)
Week 2	(N = 442)	(N = 416)	
8 AM	19.4 (0.16)	19.5 (0.17)	-0.1 (-0.5, 0.3)
10 AM	18.6 (0.16)	18.6 (0.16)	-0.0 (-0.4, 0.4)
4 PM	18.0 (0.16)	18.3 (0.16)	-0.3 (-0.7, 0.1)
Week 6	(N = 440**)	(N = 413)	
8 AM	19.3 (0.16)	19.3 (0.17)	-0.0 (-0.4, 0.4)
10 AM	18.5 (0.16)	18.6 (0.17)	-0.1 (-0.5, 0.3)
4 PM	18.0 (0.16)	18.1 (0.17)	-0.2 (-0.6, 0.2)
Month 3	(N = 432**)	(N = 408)	
8 AM	19.2 (0.17)	19.3 (0.18)	-0.1 (-0.5, 0.3)
10 AM	18.3 (0.17)	18.6 (0.18)	-0.3 (-0.7, 0.1)
4 PM	18.0 (0.16)	18.0 (0.17)	0.0 (-0.4, 0.4)

SE = Standard Error; CI = Confidence Interval * Estimates for Week 2, Week 6, and Month 3 are based on least squares means derived from a statistical model that accounts for correlated IOP measurements within patient where site and 8 AM baseline IOP stratum are in the model; estimates for Baseline visit at each time point are based on a two-sample independent t-test procedure. **One subject had missing data at 8 AM at Week 6; one subject had missing data at 4 PM at Month 3.

Table 2. IOP Change from Baseline (mmHg)

		IZBA				TRAVATAN			
Visit		N	8 AM	10 AM	4 PM	N	8 AM	10 AM	4 PM
Week 2	Mean	442	-8.0	-7.3	-7.1	416	-8.1	-7.5	-7.1
	95% CI		(-8.3, -7.7)	(-7.6, -7.0)	(-7.4, -6.8)		(-8.4, -7.8)	(-7.8, -7.2)	(-7.4, -6.8)
Week 6	Mean	440*	-8.1	-7.4	-7.2	413	-8.3	-7.5	-7.2
	95% CI		(-8.4, -7.9)	(-7.6, -7.1)	(-7.5, -6.9)		(-8.7, -8.0)	(-7.9, -7.2)	(-7.5, -6.9)
Month 3	Mean	432*	-8.2	-7.5	-7.1	408	-8.4	-7.6	-7.3
	95% CI		(-8.6, -7.9)	(-7.9, -7.2)	(-7.4, -6.8)		(-8.7, -8.1)	(-7.9, -7.2)	(-7.7, -7.0)

*One subject had missing data at 8 AM at Week 6; one subject had missing data at 4 PM at Month 3.

16 HOW SUPPLIED/STORAGE AND HANDLING

IZBA (travoprost ophthalmic solution) 0.003% is a sterile, isotonic, buffered, preserved, aqueous solution of travoprost (0.03 mg/mL) supplied in Alcon's oval DROP-TAINER® package system.

IZBA is supplied as a 2.5 mL solution in a 4 mL bottle and a 5 mL solution in a 7.5 mL bottle. The dispenser bottles are made of polypropylene and fitted with a natural color polypropylene dropper tip and a turquoise polypropylene over cap. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

2.5 mL fill NDC 0065-0000-00

5 mL fill NDC 0065-0000-00

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

17 PATIENT COUNSELING INFORMATION

17.1 Potential for Pigmentation

Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent. Advise patients about the possibility of eyelid skin darkening, which may be reversible after discontinuation of IZBA (travoprost ophthalmic solution 0.003%).

17.2 Potential for Eyelash Changes

Advise patients about the possibility of eyelash and vellus hair changes in the treated eye during treatment with IZBA. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

17.3 Handling the Container

Instruct patients to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

17.4 When to Seek Physician Advice
Advise patients that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of IZBA.

17.5 Use with Contact Lenses
Contact lenses should be removed prior to instillation of IZBA and may be reinserted 15 minutes following its administration.

17.6 Use with Other Ophthalmic Drugs
If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

Rx Only
U.S. Patent Nos. 5,631,287; 5,849,792; 5,889,052; 6,011,062; 8,178,582

ALCON®

ALCON LABORATORIES, INC. Fort Worth, Texas 76134 USA

9007509-1111

PRINCIPAL DISPLAY PANEL

NDC 0065-0000-00 Rx Only

IZBA (travoprost ophthalmic solution) 0.003%

Alcon® 2.5 mL