An Open-Label, Multi-Center, Clinical Study Evaluating the Effect of the NDE L68 StableFit® Punctal Plug on the Tear Lake

Clinical Study Protocol-NDE 68-19-01

NCT Number: NCT04280653

Protocol Version 1: July 31, 2019

Mati Therapeutics Inc.

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Mati Therapeutics Inc.
4317 Dunning Lane
Austin, TX 78746

PROTOCOL APPROVAL

Protocol Number: NDE68-19-01

Title of Protocol: An Open-Label, Multi-Center, Clinical Study Evaluating the Effect of the NDE L68 StableFit® Punctal Plug on the Tear Lake

Prepared by: _____ 30 July 2019
Daniel Schwob, Consultant
D'Ellis Group Inc.
Date

Study Director: _____ 30 Jul 19
Robert Williams, MD
Clinical Consultant
Date

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

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

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

Approved by: _____ 7-30-19
Robert Butchofsky — Date
President,
Mati Therapeutics Inc.

STATEMENT OF COMPLIANCE

Mati Therapeutics Inc. Protocol NDE68-19-01

An Open-Label, Multi-Center Clinical Study Evaluating the Effect of the NDE L68 StableFit® Punctal Plug on the Tear Lake

Protocol Version Date: July 31, 2019

Sponsor and Medical Monitor Approval:

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

Investigator Agreement:

I have read this protocol. I agree to:

a. Implement and conduct this study in strict compliance with this agreement; the protocol; ICH guidelines for Good Clinical Practices and all other applicable regulatory requirements.
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, ADE/SADE forms, IRB/IEC documentation, study supply records). Keep source documentation for the maximum period of time permitted by the hospital, institution, or private practice. In addition, 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.
i. By signing this protocol, the Investigator grants permission to personnel from the Sponsor, its representatives, third parties and appropriate regulatory authorities for on-site monitoring and review of all appropriate study documentation, as well as on-site review of the procedures employed in data collection, where clinically appropriate.

Signature of Investigator: _____Date:_____

Print Name of Investigator: _____

Acknowledged By/Sponsor's Representative Signature:

Signature of Sponsor's Representative: _____Date:_____

Print Name of Sponsor's Representative: _____

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

ADE	Adverse Device Effect
CRA	Clinical Research Associate
CFR	Code of Federal Regulations
CRF	Case Report Form
CRC	Clinical Research Coordinator
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
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
IDE	Investigational Device Exemption
IRB	Investigational Review Board
ITT	Intent-to-treat
L68 StableFit®	Mati punctal plug design
MedDRA	Medical Dictionary for Regulatory Activities
NCR	No Carbon Required
NDE	Non-drug eluting
NSR	Non-Significant Risk
PP	Per Protocol
QC	Quality Control
SADE	Serious Adverse Device Event
Study Subject	An individual that has signed a HIPAA form and an IRB approved study consent form
Subject	Individual being considered for enrollment in to the study
UP	Unanticipated Problem

STUDY SYNOPSIS

Study Protocol Number: NDE68-19-01

Study Protocol Title: An Open-Label, Multi-Center Clinical Study Evaluating the Effect of the NDE L68 StableFit® Punctal Plug on the Tear Lake

Sponsor: Mati Therapeutics Inc.

Investigational Product, Open-Label: Mati's Non-Significant Risk, Non-Drug Eluting (NDE) L68 StableFit® punctal plug design. The NDE L68 StableFit® punctal plug is pre-loaded onto a disposable inserter and individually packaged and sterilized to prevent contamination. The L68 StableFit® plug consists of medical grade silicone and 2% green colorant. The L68 StableFit® plug is stored at room temperature.

Number of sites: Up to 4 sites within the U.S.A.

Study Population: Up to 40 male or female subjects in good general health with a mild to moderate dry eye condition. A subject will be allowed to use ocular drops during the study however, the subject must discontinue the use of all drops at least one hour prior to a study examination.

Study Objective: To evaluate the effect of the NDE L68 StableFit® punctal plug on the tear lake. In addition, evaluate the insertion/removal characteristics and the investigator's evaluation of the subjects' acceptance of the NDE L68 StableFit® punctal plug.

Study Design: This is a Non-Significant Risk (NSR) medical device, multi-center, open-label clinical study. Each study subject that qualifies at the baseline visit will receive an NDE L68 StableFit® punctal plug in the lower punctum in one of their eyes. All study plugs will remain in the study subject's lower punctum for a period of 28 + 4 days after insertion.

> **Note**: The investigator has the option of inserting the plug in either the left or right eye of the subject. However, if the investigator is unable to insert the plug in the first eye chosen, the investigator can insert the plug in the fellow eye as long as the fellow eye meets all study inclusion/exclusion criteria.

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

Study Inclusion Criteria: The following are inclusion criteria for potential study subjects' wishing to participate in this study

a. A male or female subject, 18 years of age or older, in good general health at the time of the baseline examination, who may or may not have a mild to moderate dry eye condition

b. A subject must be able to read, comprehend and be willing to give HIPAA authorization and informed consent

c. A subject must be willing to have a punctal plug inserted in the lower punctum of one of their eyes

d. A subject must be willing to comply with all study instructions, agree to make all office appointments, and complete the entire course of the study

Subject Exclusion Criteria: The following are exclusion criteria for potential study subjects' wishing to participate in this study:

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

b. A subject with a history of intolerance to punctal plugs

c. A subject with structural lid abnormalities (e.g., ectropion, entropion) in the planned study eye

d. A subject with any clinically significant lid, conjunctival or corneal findings in the planned study eye at the baseline visit

e. A subject with a puncta >0.9 mm prior to dilation in the planned study eye

f. A subject with a severe dry eye condition

g. A subject experiencing epiphora in the planned study eye

h. A subject experiencing any clinically significant ocular pain or discomfort in or around either eye at the baseline visit

i. A subject with a known sensitivity to any inactive ingredient of the punctal plug, silicone, topical anesthetic, or any other products required for the study

j. A subject currently participating or has participated in a clinical trial involving the use of an investigational medication within 30 days prior to enrollment.

Study Duration: The approximate study duration is eight months. The study is projected to start the 3rd quarter of 2019

Study Variables: The following will be performed and/or recorded during the course of the study

Visit 1: Screening/Baseline (Day 0)

a. Obtain written Consent and HIPAA

b. Subject demographic data and medical history for past 7 days

c. Verify a subject has not used any ocular drops within the last hour prior to their baseline visit

d. Record subject reports of any ocular signs or symptoms they are currently experiencing, prior to the sizing and dilation of the lower punctum

e. Slit-Lamp examination of the planned study eye, prior to the sizing and dilation of the lower punctum

f. Tear lake evaluation of the planned study eye, prior to the sizing and dilation of the lower punctum

g. Size evaluation of the lower puncta of the planned study eye, prior to dilation of the lower punctum

h. After dilation of the punctum to at least 1.0 mm, insert the study punctal plug

i. Inspection of the punctal plug after insertion via slit-lamp

j. Record any Adverse Device Events

k. After a study subject has been inserted with the NDE L68 StableFit® punctal plug, the Investigator will evaluate the insertion characteristics of the punctal plug

NOTE: After the last study subject has been inserted with a study punctal plug, based on all subjects enrolled in the study, the investigator will give an overall assessment on the insertion characteristics of the study punctal plug.

Visit 2: Follow-up (Day 7 + 1 post plug insertion)

a. Verify a subject has not used any ocular drops, in their study eye, within the last hour prior to their scheduled visit

b. Slit Lamp examination

c. Inspection of the plug via slit-lamp

d. Tear lake evaluation

e. Record any Adverse Device Events

Visit 3: Follow-up (Day 28 + 4 post plug insertion)

a. Verify a subject has not used any ocular drops, in their study eye, within the last hour prior to their scheduled visit

b. Investigator evaluation of the subject's acceptability of the punctal plug, prior to removal of the study plug

c. Slit Lamp examination, prior to removal of the study plug

d. Inspection of plug via slit-lamp, prior to removal of the study plug

e. Tear lake evaluation, prior to removal of the study plug

f. Remove study punctal plug

g. After the plug has been removed, the Investigator will evaluate the removal characteristics of the inserted punctal plug

h. Record any Adverse Device Events

NOTE: After the last study subject has had their punctal plug removed, based on all subjects that completed the study, the investigator will give an overall assessment on the removal characteristics of the punctal plug.

Study Outcome Variables:

Primary Study Endpoint:	Investigators' evaluation of the tear lake
Secondary Study Endpoint:	Investigator's evaluation of epiphora, insertion/ removal characteristics and Investigators' evaluation of the subject's acceptance of the NDE L68 StableFit® punctal plug.
Study Safety Variables:	Safety assessments will include any clinically significant slit-lamp biomicroscopy findings, any extrusions of a punctal plug and incidence and severity of any reported ADEs after punctal plug insertion.

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

Schedule of Assessments, Events

EXAM PARAMETERS	v1	v2	V3
Inform Consent/HIPAA	❶		
Demographic Data/Medical Hx	❶ A		
Subject Reports of any Ocular Signs or Symptoms	❶ B		
Verify No Ocular Drop use **One Hour** Prior to Visit	❶	❷	❸
Inv. Evaluation of Subject's Acceptance of Study Plug			❸ C
Slit Lamp Examination	❶ B	❷	❸ C
Tear Lake Evaluation	❶ B	❷	❸ C
Size Evaluation of Lower Puncta, Prior to Dilation	❶ B		
Dilation of Lower Puncta	❶		
Insertion of a Punctal Plug	❶		
Inspection of the Placement of the Punctal Plug	❶ D	❷	❸ C
Investigator Device Assessment of Insertion	❶ E		
Removal of Punctal Plug			❸
Investigator Device Assessment of Removal			❸ F
Adverse Device Event Recording	❶	❷	❸

Keys to Abbreviations:

A = Record medical history for the past 7 days
B = PRIOR to **INSERTION** of punctal plug
C = PRIOR to **REMOVAL** of punctal plug
D = Slit-Lamp Evaluation of Punctal Plug **AFTER INSERTION**
E = After EACH Study Subject and after **ALL** Study Subjects have had their Punctal Plug Inserted
F = After EACH Study Subject and after **ALL** Study Subjects have had their Punctal Plug Removed

Visit Schedule:

v1 = Screening/Baseline
v2 = 7 ± 1 days post plug insertion
v3 = 28 ± 4 days post plug insertion

1 KEY ROLES

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2 INTRODUCTION: BACKGROUND AND 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

A punctal plug, also known as tear duct plug or lacrimal plug, is a small medical device that is inserted into the nasolacrimal duct (puncta) of an eye to block (occlude) the drainage of tear fluid. Over the years several models of punctal plugs have been approved and are commercially available. Punctal plugs are classified by the FDA as a Class II Pre-Amendment medical device. Furthermore, plugs are not identified as significant risk devices on the FDA Information Sheet titled "Significant Risk and Non-Significant Risk Medical Device Studies."

Occlusion of the puncta with punctal plugs has been a treatment for lacrimal deficiency in patients with dry eye for over the last 30 years (Freeman 1975). Since then, punctal plugs have been used extensively in primary eye care and are considered safe and effective in the treatment of dry eye (Freeman 1975; Willis et al. 1987; Tuberville et al. 1982; Fayet et al. 1990). Since the inception of punctal plugs, several materials and designs have been developed with a host of products available on the market. While the designs have slight differences in architecture, the basic mechanism of action in treating dry eye with punctal plugs is basically the same, the conservation of naturally produced tears by physical occlusion of the lacrimal punctum.

Although Mati's punctal plug designs are novel, the types of materials and techniques for insertion of the plugs are the same as other commercially marketed punctal plugs. Therefore Mati punctal plugs do not represent any more risk to human subjects than the risk associated with currently marketed punctal plugs however; the unique design of Mati punctal plug has shown a significant improvement in plug retention when compared to other marketed plugs.

2.2 Rationale

To evaluate the effect of Mati's non-significant risk, non-drug eluting (NDE) L68 StableFit® punctal plug on the tear lake. In addition, evaluate the insertion/removal characteristics and subjects' acceptance of Mati's NDE L68 StableFit® punctal plugs.

2.3 Potential Risks and Benefits

The risks of the NDE L68 StableFit® punctal plug is not fully known but are expected to be similar to those observed for commercial punctal plugs, which are considered to be low. Some risks associated with punctal plug use are discomfort, epiphora, loss of plug, 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 controlled clinical trials of the Mati punctal plugs, rates of serious adverse device events have been less than 1 percent (Fayet 1990, Balaram 2001, Kim 2005).

There are no treatment benefits to study participants. Study subjects will receive regular eye exams.

3 OBJECTIVES AND PURPOSE

To evaluate the effect of the NDE L68 StableFit® punctal plug on the tear lake. In addition, evaluate the insertion/removal characteristics and assess the subjects' acceptance of the NDE L68 StableFit® punctal plug.

4 STUDY DESIGN AND ENDPOINTS

4.1 Description of the Study Design

This is a Non-Significant Risk (NSR) medical device, multi-center, open-label clinical study. Each study subject that qualifies at the baseline visit will receive an NDE L68 StableFit® punctal plug in the lower punctum in one of their eyes. All study plugs will remain in the study subject's lower punctum for a period of 28 + 4 days after insertion.

4.2 Study Endpoints

The study will be complete when up to 40 study subjects (40 eyes) have been evaluated at Visit 3 (28 + 4 days post-insertion) or have been terminated from the study.

4.2.1 Primary Study Endpoint

The primary study endpoint will be the comparison of the tear lake volume at baseline with the tear lake volume at each follow-up visit.

4.2.2 Secondary Study Endpoints

Secondary study endpoints will evaluate the investigator's evaluation of epiphora, insertion/removal characteristics of the NDE L68 StableFit® punctal plug, and Investigators' evaluation of the study subjects' acceptance of the NDE L68 StableFit® punctal plug.

4.2.3 Safety Endpoints

Safety assessments will include any clinically significant slit-lamp biomicroscopy findings, any extrusions of a punctal plug, and incidence and severity of any reported ADEs after punctal plug insertion.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Study Population

Up to 40 normal healthy volunteers who meet all study inclusion/exclusion criteria will be enrolled in to the study. A subject will be allowed to use ocular drops during the study however, the subject must discontinue the use of all drops at least one hour prior to a study examination.

5.2 Study Subject Inclusion Criteria

The following are inclusion criteria for potential study subjects' wishing to participate in this study:

a. A male or female subject, 18 years of age or older, in good general health at the time of the baseline examination, who may or may not have a mild to moderate dry eye condition

b. A subject must be able to read, comprehend and be willing to give HIPAA authorization and informed consent

c. A subject must be willing to have a punctal plug inserted in the lower punctum of one of their eyes

d. Subject must be willing to comply with all study instructions, agree to make all office appointments, and complete the entire course of the study.

5.3 Study Subject Exclusion Criteria

The following are exclusion criteria for potential study subjects' wishing to participate in this study:

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

b. A subject with a history of intolerance to punctal plugs

c. A subject with structural lid abnormalities (e.g., ectropion, entropion) in either eye

d. A subject with any clinically significant lid, conjunctival or corneal findings in either eye at the baseline visit

e. A subject with a puncta >0.9 mm prior to dilation in either eye

f. A subject with a severe dry eye condition

g. A subject experiencing epiphora in either eye

h. A subject experiencing any clinically significant ocular pain or discomfort in or around either eye at the baseline visit

i. A subject with a known sensitivity to any inactive ingredient of the punctal plug, silicone, topical anesthetic, or any other products required for the study

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

5.4 Strategies for Recruitment and Retention

To increase study subject enrollment and retention in the study, sites should dedicate an individual [Clinical Research Coordinator (CRC)] who is well informed regarding the study design, study specific 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 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.

5.5 Study Subject Withdrawal or Termination Criteria

After insertion of a study plug, the Investigator may withdraw a study subject from the study if in their medical judgment it is in the study subject's best interest.

Each study subject will be informed that they are free to withdraw from the study at any time. If a study subject is prematurely withdrawn from the study, the reason(s) for withdrawal must be recorded on the relevant page of the subject's case report form (CRF). Study subjects who withdraw from the study will be replaced.

The Investigator, the Investigator in consultation with the Medical Monitor, or the Medical Monitor may exercise his or her medical judgment to terminate a study subject's participation in the study if it is in the best interest of the study subject. A terminated study subject will be followed through Visit 3 (28 days after insertion of the punctal plug) 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 termination of a study subject.

5.5.1 Reasons for Termination, Discontinuation or Disqualified

At a study subject last visit (scheduled or unscheduled), they will have their punctal plug removed and a study exit case report form (CRF) must be completed, whether or not the study subject completed the final study visit (Visit 3, 28 days after plug insertion). The reason for any early exit 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's early exit from the study should be selected from the following standard categories.

5.5.1.1 Termination from the study

A study subject will be terminated from the study if in the Investigator's medical judgment, it was in the best interest of the study subject that developed or reported: a) a clinically significant ocular sign(s) or symptom(s) b) reported serious ADE, regardless of relation to the study device or has died or c) extrusion of a punctal plug.

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

5.5.1.2 Discontinued from the study

A study subject will be discontinued from the study if the Investigator is unable to insert the study punctal plug in to either eye of the study subject's lower punctum, has personal reasons, 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 – if the study subject was discontinued for a reason other than those listed above, the Investigator must specify the reason.

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

5.5.1.3 Disqualification from the study

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

Notification of disqualification will be clearly documented on the appropriate Case Report Form. The Investigator must 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 plug. A study subject disqualified from the study will be replaced.

5.6 Premature Termination or Suspension of Study or Study Site

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

If representatives of Mati Therapeutics Inc., the Principal Investigator, the Study Monitor [Clinical Research Associate (CRA)], the Medical Monitor, or the FDA officials discover conditions arising during the study that indicate that the study will be halted or that participation by the study center will be terminated, this action may be taken after appropriate consultation with representatives of

Mati Therapeutics Inc., the Principal Investigator, the CRA, and the Medical Monitor. Conditions that may warrant termination of the study include, but are not limited to the following:

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

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

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

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

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

f. Insufficient adherence to protocol requirements.

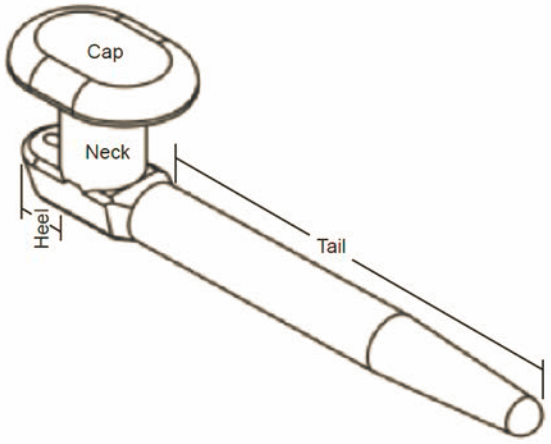
Study termination and follow-up will be performed in compliance with the conditions set forth in 21 CFR 812.40 and 21 CFR 812.43.

6 STUDY DEVICE

6.1 Mati's Non-Significant Risk, Non-Drug Eluting (NDE) L68 StableFit® punctal plug

The NDE L68 StableFit® punctal plug consists of inactive medical grade silicone and 2% green colorant. The NDE L68 StableFit® punctal plug design is shown in Figure 1. The NDE L68 StableFit® punctal plug is provided pre-loaded on an insertion tool, packaged in a preformed rigid tray with a foil laminate lid heat sealed onto the tray and sterilized.

Figure 1: Proprietary NDE L68 StableFit® Punctal Plug Design



6.2 Procedure for Insertion of the NDE L68 StableFit® Punctal Plug

The procedure for inserting a Mati's NDE L68 StableFit® punctal plug is similar to those for commercial plugs. In preparation for the insertion of the NDE L68 StableFit® punctal plug, the subject may be seated at the slit lamp, or placed in a reclined position:

a. To anesthetize the area around the lower punctum, place a drop of topical anesthetic such as proparacaine or lidocaine on the eye. Then use a proparacaine or lidocaine soaked cotton-tipped swab. Place the swab directly on the lower punctum of the eye to be inserted for ~30 to 60 seconds (proparacaine or lidocaine can be irrigated into the canaliculus for better anesthesia if desired)

b. Using the Coroneo punctal dilator, the dilator is engaged vertically (straight down) in the punctum with a gentle twisting motion. The dilator is then quickly moved 90 degrees parallel to the lid margin passing it into the proximal canaliculus dilating the punctum

c. 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. It is very important to fully dilate the punctum to 1.0 mm.

While dilating, prep the study punctal plug to be inserted in the lower punctum of the study subject's eye.

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. Add more anesthesia if needed.

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

e. Position the plug end of the insertion instrument over the study subject's punctum

f. Gently insert the plug, coming straight down perpendicular to the punctum until the cap of the plug is flush with the lid margin

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

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

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. Placement of the plug can then be re-attempted. Multiple attempts are sometimes necessary however; lubricants are not to be used.

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

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

6.3 Instruction for Study Subjects

Instruct each study subject not to attempt to remove or adjust the punctal plug on his/her own. If a punctal plug is extruded and the subject can recover it, the plug must be returned to the study center. In addition, encourage each study subject to restrict eye rubbing and be mindful of his/her study eye when swimming or in other activities.

6.4 Procedure for Removal of Punctal a Plug

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

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

b. It is recommended that a 0.12 1x2 teeth Castroviejo Suture forceps or similar toothed forceps with platforms should be used for plug removal.

   NOTE: Using a jeweler's forceps is not advisable

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

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

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

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

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

> **NOTE**: Please exercise clinical judgment 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 migrations are to be reported as an ADE however, a superficial migration, in which the plug is temporarily displaced, is visible with the slit lamp and can be easily repositioned, is not considered an ADE.

Removal of the study punctal plug immediately after insertion may result in the cap of the plug being torn off; if possible the Investigator should wait 30 to 60 minutes after insertion before attempting to remove a study punctal plug. However, if the plug tears or separates, report this as a technical complaint. Retain the plug for accountability of investigational supplies.

6.5 Punctal Plug – Unable to Insert / Extruded

6.5.1 Unable to Insert a Punctal Plug in Either Punctum

If a punctal plug cannot be inserted in to each eye after dilation, the study subject will be discontinued from the study and replaced.

6.5.2 Extrusion of the Punctal Plug after the Baseline Visit

A study subject that has noticed a plug has been extruded or lost during the follow-up period should immediately contact the Investigator and/or his/her staff and return to the Investigator's office as soon as possible. The Investigator will terminate the study subject from the study and will NOT be replaced.

6.6 Study Plug Accountability and Storage Procedures

The Investigator is responsible for maintaining the study treatment (punctal plug) 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 his/her 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 study plugs will be verified by the Sponsor and/or his/her 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:

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

b. Record subject's demographic data and medical history for the previous 7 days

c. Record any subject reports of any ocular signs or symptoms they may be experiencing

d. Slit-Lamp Examination: Slit-lamp examination will include assessment of the lid, conjunctiva and cornea as normal or abnormal. If a finding is indicated as abnormal, the investigator will indicate if the finding is clinically significant. If the finding is considered clinical significant, the investigator will describe the finding in the section provided on the Case Report form

e. Evaluation of the subject tear lake: Using a slit lamp micrometer, the micrometer will be oriented vertically and centered on the lower lid margin at the middle of the lower lid. The tear lake will be measured using the slit lamp micrometer from the lid margin to the superior border of the lower tear lake and measured to 0.1 mm.

f. Punctum size evaluation prior to dilation: Using the Coroneo punctum dilator, the narrow end of the dilator has calibrated rings that correspond to punctum diameters of 0.5, 0.6 and 0.7 mm. The rings on the wide end of the dilator correspond to punctum diameters of 0.8, 0.9 and 1.0 mm. Prior to measuring the punctum diameter, the eye should be anesthetized (see Section 6.2 of the protocol for details) with a topical anesthetic. The narrow end of the dilator is them introduced vertically into the punctum and advanced until the punctum starts to invert. The diameter is recorded as the nearest ring to the edge of the punctum when inversion begins. If the punctum diameter is larger than 0.7 mm, the narrow end of the dilator is removed, and the wider end inserted and advanced in the same way. Again, the diameter is recorded as the nearest ring when inversion begins.

g. Insertion of a study punctal plug (see Section 6.2 of the protocol for details)

h. Removal of a study punctal plug (see Section 6.6 of the protocol for details)

i. Adverse Device Event reporting, see Section 8.5 of the protocol for details: To optimize consistency of ADE reporting across centers, the study subject will be asked a standard question to elicit any 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?"

7.3 Study Visit Schedule

7.3.1 Visit 1: Day 0 - Screening (Prior to punctal plug insertion)

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

a. Obtain informed consent and HIPAA authorization release

b. Record the subject's demographic data and prior 7 days medical history

c. Verify a subject has not used any ocular drops within the last hour prior to their baseline visit

d. Record any subject reports of ocular signs or symptoms they are currently experiencing

e. Slit-lamp examination of the planned study eye

7.3.2 Visit 1:Baseline - Day 0 (Insertion of a punctal plug - refer to Section 6.2 for details regarding the insertion of the NDE punctal plug)

After the screening examination, a qualified study subject will be sequentially assigned an ID number. 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.

Note: The investigator has the option of inserting the plug in either the left or right eye of the subject. However, if the investigator is unable to insert the plug in the first eye chosen, the investigator can insert the plug in the fellow eye as long as the fellow eye meets all study inclusion/exclusion criteria.

f. Tear lake evaluation of the planned study eye prior to the sizing and dilation of the lower punctum

g. Size evaluation of the punctum of the planned study eye prior to the dilation of the lower punctum

h. After dilation, the study punctal plug is inserted in to the lower punctum of study eye, inspect the punctal plug using the slit-lamp, the position of a study punctal plug may be adjusted with forceps.

i. Record any reported adverse device event(s)

j. After the study plug has been inserted in the lower puncta, the investigator will assess the insertion characteristics of the plug.

NOTE: After the last study subject has been inserted with a study punctal plug, based on all subjects enrolled in the study, the investigator will give an overall assessment on the insertion characteristics of the study punctal plug.

7.3.3 Visit 2: Follow-Up (Day 7 + 1 post plug insertion)

At this visit the following will be performed and recorded:

a. Verify a subject has not used any ocular drops, in their study eye, within the last hour prior to their scheduled visit

b. Slit-lamp examination of the study eye

c. Inspection of the punctal plug via the slit lamp

d. Tear lake evaluation of the study eye

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

7.3.4 Visit 3: Follow-Up (Day 28 + 4 post plug insertion)

At this visit the following will be performed and recorded:

a. Verify a subject has not used any ocular drops, in their study eye, within the last hour prior to their scheduled visit

b. Investigator evaluation of subject's acceptability of the punctal plug, prior to the removal of the punctal plug

c. Slit-lamp examination, prior to the removal of the punctal plug

d. Inspection of the punctal plug via the slit lamp, prior to removal of the plug

e. Tear lake evaluation of the eye prior the removal of the punctal plug

f. Removal of the punctal plug (refer to Section 6.6 for details regarding the removal of a punctal plug)

g. Recording of any reported adverse device event

h. After removal of the study subject punctal plug, the investigator will assess the removal characteristics of the plug.

NOTE: After the last study subject has had their punctal plug removed, the investigator will give an overall assessment on the removal characteristics of all punctal plugs that were inserted during the study.

An exit form will be completed at the final study examination (Visit 3), or whenever the study subject completes or leaves the study for any reason.

Schedule of Assessments, Events

EXAM PARAMETERS	v1	v2	V3
Inform Consent/HIPAA	❶		
Demographic Data/Medical Hx	❶ A		
Subject Reports of any Ocular Signs or Symptoms	❶ B		
Verify No Ocular Drop use **One Hour** Prior to Visit	❶	❷	❸
Inv. Evaluation of Subject's Acceptance of Study Plug			❸ C
Slit Lamp Examination	❶ B	❷	❸ C
Tear Lake Evaluation	❶ B	❷	❸ C
Size Evaluation of Lower Puncta, Prior to Dilation	❶ B		
Dilation of Lower Puncta	❶		
Insertion of a Punctal Plug	❶		
Inspection of the Placement of the Punctal Plug	❶ D	❷	❸ C
Investigator Device Assessment of Insertion	❶ E		
Removal of Punctal Plug			❸
Investigator Device Assessment of Removal			❸ F
Adverse Device Event Recording	❶	❷	❸

Keys to Abbreviations:

A = Record medical history for the past 7 days
B = PRIOR to **INSERTION** of punctal plug
C = PRIOR to **REMOVAL** of punctal plug
D = Slit-Lamp Evaluation of Punctal Plug **AFTER INSERTION**
E = After EACH Study Subject and after **ALL** Study Subjects have had their Punctal Plug Inserted
F = After EACH Study Subject and after **ALL** Study Subjects have had their Punctal Plug Removed

Visit Schedule:

v1 = Screening/Baseline
v2 = 7 ± 1 days post plug insertion
v3 = 28 ± 4 days post plug insertion

7.3.5 Early Exit

Any study subject exiting the study early, the Investigator must record/perform the following:

a. Verify a subject has not used any ocular drops, in their study eye, within the last hour prior to their scheduled visit

b. Investigator evaluation of subject's acceptability of the punctal plug, prior to the removal of the punctal plug, if the plug has not been extruded

c. Slit-lamp examination, prior to the removal of the punctal plug, if the plug has not been extruded

d. Inspection of the punctal plug via the slit lamp, prior to removal of the plug, if the plug has not been extruded

e. Tear lake evaluation of the study eye prior the removal of the punctal plug, if the plug has not been extruded

f. Removal of the punctal plug (refer to Section 6.6 for details regarding the removal of a punctal plug), if the plug has not been extruded

g. Recording of any reported adverse device event(s)

h. After a study subject has had the punctal plug removed, the investigator will assess the removal characteristics of the plug.

An exit form will be completed whenever the study subject completes or leaves the study for any reason.

A study subject that has exited the study due to an adverse device event will be followed by the investigator until the ADE has resolved or has become medically stable.

7.3.6 Unscheduled Visit

The investigator has the option of bringing a study subject back in for an unscheduled visit during the course of the study for safety reasons (e.g., subject complaint of moderate or severe ocular symptoms, and ADE). An unscheduled visit CRF should be completed. At minimum the investigator should record the following"

a. Inspection of the punctal plug via the slit-lamp, if applicable

b. Slit-Lamp examination

c. Recording of any reported adverse device events

8 ASSESSMENT OF SAFETY

8.1 Safety Variables

Safety variable for this study include any clinically significant slit-lamp biomicroscopy findings, any extrusions of a punctal plug, and incidence and severity of any reported ADEs after punctal plug insertion. To optimize consistency of ADE reporting across centers, the study subject will be asked by study personnel the following question:

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

All ADEs either observed by the Investigator or one of his/her medical collaborators, or reported by the subject spontaneously, or in response to the direct question above, will be noted in the ADEs section of the subject's CRF and in the source document. Only treatment emergent ADEs (those occurring during or after the insertion of the investigational punctal plug) should be recorded as ADEs. Events reported before the initial screening period should be recorded as medical history.

If any ADE is reported, the date of onset, intensity, relationship to study device or treatment, action taken, date of resolution (or the fact that it is still continuing or has become chronic), and whether the ADE is serious or not will be recorded (see Section 8.5).

Plug migrations are to be reported as an ADE; however, a superficial migration, in which the plug is temporarily displaced, is visible with the slit lamp and can be easily removed, is not considered an ADE.

8.2 Definitions

8.2.1 Adverse Device Event (ADE)

Any unfavorable and unintended effect on health or safety of a study subject involving the use of a medical device. Medical conditions or diseases present before a subject starts the study are only considered adverse device events if they worsen during or after use of the medical device. Any new medical conditions or diseases that present during the course of the study will be recorded as an adverse device event.

8.2.2 Serious Adverse Device Event (SADE)

Defined as any ADE that:

- Results in death
- Is life-threatening even if temporary in nature.

  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 permanent impairment of a body function or permanent damage to a body structure
- Necessitates medical or surgical intervention to prevent a life-threatening situation or preclude permanent impairment of a body function or permanent damage to a body structure

8.2.3 Unexpected Adverse Device Event

An ADE that is not identified in nature, instructions for use or clinical study protocol.

8.3 Adverse Device Event Descriptions

8.3.1 Intensity

The intensity of ADEs 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 Device

The causal relationship to study device will be determined by the investigator according to his/her best medical judgment, as follows:

Suspected: There is a reasonable possibility that the ADE is associated with use of the study device, such as a temporal relationship of the event to study device insertion, 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 ADE and the study device can reasonably be ruled out based on lack of any temporal relationship of the event to study device insertion, 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 Device Event

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

At the final study visit, new ADEs, as well as follow-up information for continuing ADEs, will be recorded in the CRF and source document. If an SADE (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 SADEs will be recorded in the source document and reported to the safety monitors (refer to Section 8.5.2). Non-serious ongoing ADEs will be followed beyond the final study visit at the discretion of the Investigator and recorded in the source documents.

8.5 Reporting Procedures

Adverse device events that occur from Visit 1 through completion of the end-of-study visit must be documented. The Investigator will assess the ADE severity and relationship of the ADE to the study device. The Investigator will follow the progress of the study subject until the ADE either resolves or becomes medically stable. Treatments and medications required to treat ADEs must be recorded.

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

8.5.1 Adverse Device Event Reporting

An adverse device event that is not serious or related to the study 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 device event is also to be reported to the reviewing IRB/IEC per his/her reporting requirements.

8.5.2 Serious Adverse Device Event Reporting

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

All SADEs will be reported to:

Robert Williams, MD or	Deepank (Deeps) Utkhede
Mati Therapeutics Inc.	Mati Therapeutics Canada Inc. (R&D Branch)
iopdoc1@gmail.com	dutkhede@matitherapeutics.com
Phone: 360.378-7916	Phone: 778 991-3301
Phone: 360.298-5325 (cell)	
Fax: 360.282-6871	

The Investigator must complete the SADE Report Form and send it with other relevant pages of the CRF to the designated Medical Monitor within 24 hours of discovery of the SADE. 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 SADE will be reported to the Investigator's IRB/IEC per his/her reporting requirements.

8.5.3 Unanticipated Problem Reporting

If during the study an adverse device event occurs that may reasonably be regarded as 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 device 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.

8.6 Reporting of Technical Complaints about Investigational Device

8.6.1 Definitions

A quality complaint received in writing, electronically, or orally that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device product. (In this definition, "effectiveness" refers to the actual function of the device, not to how

the subject responds to the action of the device. Also in this definition, "device product" refers only to devices provided by the Sponsor for clinical studies and to investigational devices.)

In this definition, safety includes the safety of a subject, user, or other person associated with the use of a medical device.

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 device
- Model of the study device
- Identification numbers (i.e. serial or part number) for a device
- Investigator name, study center name, and contact number
- Date the complaint occurred
- Brief description of the complaint
- Study subject or other individual involved (yes/no):
    - If yes and a study subject, the investigator should report whether any ADEs were associated with the complaint (yes/no; if a subject ADE was associated with the complaint, refer to Section 8 and attach the ADE 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 SADE if it recurred under circumstances that did involve a study subject or other person (yes/no).
- Identity of any other investigational or commercial devices involved.

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

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

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

Any complaint about a study device 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 SADE and Technical Complaints

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

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

If the Sponsor determines that any SADE or technical report is an unanticipated ADE, an investigation will be begun immediately. The Sponsor will inform the investigator of any additional reporting requirements beyond those stated in Section 8.5.3 as applicable.

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

8.6.4 Anticipated Adverse Device Events

Due to the duration of the study, the only anticipated ADE would be extrusion of the punctal plug. Any event that is unlikely but anticipated must have an adverse device event form completed and reported to Mati Therapeutics Inc. (see Section 8.5 for reporting details).

8.7 Study Halting Rules

Collaboration between representatives of Mati Therapeutics Inc., Investigators and statisticians may stop the study if there is evidence of a lack of safety associated with the study device.

8.8 Safety Oversight

This study will utilize a Medical Monitor for safety monitoring. The Medical Monitor will review and assess any reports of 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 (R1) and E8 (8.2) and 21 CFR. Parts 50, 54, 56 and 812

b. The signed Investigators' Agreement

c. The signed protocol for the study

d. Any conditions imposed by the IRB

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

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

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

b. The Investigator understands the protocol and understands and accepts 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, the CRA may conduct periodic site visits and maintain telephone contact with the Investigators and his/her staff to ensure that the study is being conducted in accordance with the protocol, and with any specific conditions of the IRB and clinical requirements. At such visits, the CRA will ensure that informed consent has been obtained and documented for each study subject, in accordance with 21 CFR parts 50 and 56, and the requirements of the overseeing IRB and the Sponsor. The CRA will review and compare CRFs to source records and supporting documents to ensure that data recorded on the CRFs are complete, accurate, and legible, and that any corrections to the CRFs are made with a single line strike-through of the incorrect entry, and entry of the correct information adjacent with initials of the individual making the correction and date of corrected entry. The CRA will further ensure that there are no data omissions and that any study subject withdrawals are documented. The CRA will review CRFs and source records for any unanticipated ADEs, and ensure that the Investigators are complying with FDA and Sponsor requirements for reporting ADEs and SADEs. The CRA will ensure that the Investigators are carrying out the agreed upon activities and have not delegated them to unauthorized staff, that the facilities and staff continue to be acceptable for the study, and that the Investigators are properly tracking study inventory and are accounting for the disposition of all study devices.

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

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

b. A summary of the findings of the visit

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

10 STATISTICAL CONSIDERATIONS

10.1 Statistical and Analytical Plans

The primary analysis population will be an ITT (Intent-to-Treat) analysis for all study subjects who had a lower puncta 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

10.2.1 Primary Hypotheses

The Null Hypothesis: There are no differences between baseline and follow-up tear lake evaluations

Alternative Hypothesis: There are differences between baseline and follow-up tear lake evaluations

10.2.2 Secondary Hypotheses

The Null Hypothesis: There are no differences in the frequency or severity of study subjects exhibiting of epiphora

Alternative Hypothesis: There are differences in the frequency or severity of study subjects exhibiting of epiphora

10.3 Analysis Datasets

Data will be pooled from all study centers for data analysis, unless otherwise specified. Study dataset will be generated (keypunched) from original (white) case report forms that have been reviewed and collected from clinical sites. Dataset will contain rows of individual subject data; each row will be clearly labeled with the study subject ID 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

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

10.4.2 Analysis of the Primary Endpoint(s)

The primary study variable will be based on the change from baseline in tear lake values. For analyses, using the intent-to-treat (ITT) data set, all data from all subjects with at least one follow-up evaluation of the tear lake will be evaluated. For the per protocol (PP) analyses dataset, data from subjects or visits with significant protocol deviations will be excluded.

10.4.3 Analysis of the Secondary Endpoint(s)

Secondary endpoints will be based on changes from baseline in the severity of epiphora. For the investigator's evaluation of the subject's acceptance of the punctal plug, data from all subjects will be evaluated. Investigator evaluation of insertion and removal characteristics will be tabulated by study subject and overall evaluation. For analyses using the intent-to-treat (ITT) data set, all data from all subjects with at least one assessment of epiphora, subject acceptability and punctal plug characteristics evaluations will be included. For the per protocol (PP) analyses dataset, data from subjects or visits with significant protocol deviations will be excluded.

10.4.4 Safety Analyses

All study subjects who were inserted with a punctal plug will be evaluable for safety analysis. The safety endpoints in this study are clinically significant slit lamp biomicroscopy findings (lid, conjunctiva, and cornea), incident rate of plug extrusions, and the frequency and severity of any reported adverse device events. Safety variables will be summarized using descriptive statistics.

The type, severity, duration and frequency of reported adverse device events will be tabulated by visit. Additionally, any adverse device event experienced by a subject after signing informed consent and before exposure will be presented separately in the safety analysis.

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

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

10.4.5 Baseline Descriptive Statistics

Demographic and baseline characteristics will be summarized. Counts and percentages will be presented for categorical variables such as sex, 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.

10.4.6 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.

10.5 Sample Size

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

10.5.1 Enrollment Procedures

Qualified subjects that meet all inclusion and exclusion criteria and complete the screening process will be sequentially assigned a study number.

11 SOURCE DOCUMENTS AND ACCESS

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

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

h. Subject reports of signs and symptoms at each visit

i. All ADEs and SADE

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

k. 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 device for which the indication was being investigated. If no application is to be filed or the application is not approved for such indication, study records must be retained for at least 2 years after the investigation is discontinued and the FDA is notified.

11.3 Subject Confidentiality

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

11.4 Case Report Form Completion

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

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

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

11.5 Investigator Study Summary

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

a. Investigator name and title

b. Title 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 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 regulations specified under 21 CFR 11, 50, 54, 56, and 812, 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 his/her 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 SADEs that have resulted in an expedited safety report to the FDA. No device 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 his/her enrollment in the study. See Section 7.1 for further details.

13.3.2 Other Informational Documents Provided to Participants

A subject to be enrolled in to the study is required to review and sign a Health Insurance Portability and Accountability Act (HIPAA) of 1996 authorization document. Each study subject will receive copies of all applicable informational documents for 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 subjects will be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirement(s).

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 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 device event information (adverse device 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. Investigator Brochure

k. Completed study subject informed consent and HIPAA forms

l. Study subject medical chart/clinic notes.

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

> **NOTE**: These documents should be retained for a longer period if required by the applicable regulatory requirements or by agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained. The Investigator should take measures to prevent any accidental or premature destruction of these documents.

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

14.3 Protocol Deviations

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

14.4 Publication and Data Sharing Policy

All information related to this study is considered confidential information belonging to Mati Therapeutics Inc. Data on the use of the study 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 REFERENCES

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Kim BM, Osmanovic SS, Edward DP. 2005. Pyogenic granulomas after silicone punctal plugs: a clinical and histopathologic study. Am J Ophthalmol. 139:678-684.

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