Clinical Study Protocol

A Single Center Open Label Early Feasibility Study to Evaluate the Efficacy and Safety of the RenewalNail™ Plasma Treatment System in Patients with Mild to Moderate Onychomycosis (Fungal Nail) of the Hallux caused by *Trichophyton rubrum* or *Trichophyton mentagrophytes*.

Protocol Number: DFCR-0003

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TITLE PAGE

Study Title A Single Center Open Label Early Feasibility Study to Evaluate the Efficacy and Safety of the RenewalNail™ Plasma Treatment System in Patients with Mild to Moderate Onychomycosis (Fungal Nail) of the Hallux caused by *Trichophyton rubrum* or *Trichophyton mentagrophytes*.		
Project Name DeviceFarm Early Feasibility Study	**Protocol Number** DFCR-0003	**Clinical Phase** I
Investigational Product RenewalNail™ Plasma Treatment System		
Subject Population/Indication Patients with mild to moderate distal subungual onychomycosis of one hallux nail who fulfill the inclusion/exclusion criteria		**Duration** 6 months
Design Single-center, open-label		

This study will be performed in compliance with Good Clinical Practices (GCPs). This Protocol follows guidelines outlined by the International Council on Harmonization. All the data furnished to the Investigator and his/her staff and all data obtained through this Protocol will be regarded as confidential and proprietary in nature and will not be disclosed to any third party without the written consent of DeviceFarm, Inc.

PROTOCOL APPROVAL PAGE

A Single Center Open Label Early Feasibility Study to Evaluate the Efficacy and Safety of the RenewalNail™ Plasma Treatment System in Patients with Mild to Moderate Onychomycosis (Fungal Nail) of the Hallux caused by *Trichophyton rubrum* or *Trichophyton mentagrophytes*.

SPONSOR: DeviceFarm, Inc.
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Newark, CA 94560

Approvals	**Signature**	**Date**
Jeffrey Roe, PhD CEO DeviceFarm, Inc.		

SYNOPSIS

Title of Study:
A Single Center Open Label Early Feasibility Study to Evaluate the Efficacy and Safety of the RenewalNail™ Plasma Treatment System in Patients with Mild to Moderate Onychomycosis (Fungal Nail) of the Hallux caused by *Trichophyton rubrum* or *Trichophyton mentagrophytes*.

Objective:
To determine if a three-treatment protocol with the RenewalNail™ plasma treatment system over a week will result in mycological cure and/or clear nail growth on the treated hallux toe.

Methodology:
Single-center, open-label

Number of Subjects (planned):
5 Subjects

Number of Sites and Number of Subjects Per Site:
One (1) site, 5 Subjects

Diagnosis and Main Criteria for Inclusion:
Laboratory confirmed diagnosis of mild to moderate onychomycosis on at least one hallux toe caused by *Trichophyton rubrum* or *Trichophyton mentagrophytes*

Male and female Subjects of any race between 21 and 75 years of age meeting specific inclusion/exclusion criteria

Investigational Product:
RenewalNail™ Plasma Treatment System (DFPD-003)
Mode of Administration: topical
Number of treatments: 3
Duration of each treatment: 45 minutes

Criteria for Evaluation:
Efficacy:
Mycological Cure: Two consecutive negative mycology cultures
Clinical Cure: Photographic evidence of clear nail growth
Safety:
Adverse Events

STUDY CONTACTS

SPONSOR/SITE PERSONNEL		
Name/Title	**Affiliation/Address/Tel.**	**Responsibilities**
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1.0 INTRODUCTION

Background and Rationale: Onychomycosis, the most common nail disease, accounts for 30% of all cutaneous fungal infections. The disease is a progressive chronic recurring fungal infection affecting an estimated 35 million people in the United States. Approximately 50% of elderly over the age of 70 are infected as well as 30% of diabetics. Although dermatophyte infections are rarely life threatening, their high incidence and prevalence makes them an important health problem. Onychomycosis is not just a cosmetic problem, but can cause pain, difficulty walking, and susceptibility to secondary infections such as cellulitis and osteomyelitis.

Distal subungual onychomycosis (DSO) is the most common form of onychomycosis. DSO is characterized by nail discoloration, onycholysis, dystrophy of the nail plate, and accumulation of subungual debris. There is an average of 4.4 to 5.3 involved toes per patient, with an average of about 2.4 per foot. Approximately 75% of patients have both feet involved.

There are currently three groups of FDA-approved approaches to the treatment of onychomycosis: oral treatments, topical therapy, and laser treatments. Oral terbinafine (Lamisil®, Novartis Pharmaceuticals) is the lead therapy among oral medications consisting of a 250-mg tablet per day for 12 weeks for the treatment of toenail onychomycosis. Oral terbinafine yields the highest complete cure rates, between 38 and 76% depending on the clinical trial design. Oral therapy might be adequate if not for the relatively high risk of liver toxicity and drug-drug interactions. Many patients and their physicians choose not to select oral therapy due to the associated risk. Rare cases of liver failure and serious skin reactions have been reported with oral terbinafine use (Lamisil® package insert).

Topical treatment options have been researched/under development by many companies in order to provide an effective antifungal drug therapy without exposing the patient to the side effects and toxicity associated with oral antifungal drug therapy. FDA-approved topical treatments for onychomycosis include Jublia® (Valeant Pharmaceuticals), Penlac® Nail Lacquer (Dermik Laboratories) and Kerydin® (Anacor Pharmaceuticals). Topical formulations address the toxicity problem caused by the oral medications and are easy to apply. However, topical therapy has a much lower cure rate than oral therapy at 5-17% and requires significant compliance by the patient since the treatment is so long in duration (typically one year), and relatively labor intensive compared to oral therapy. Topical drug permeation can be enhanced by surgically removing the nail or disrupting the nail plate using physical techniques (manual or electrical nail abrasion, acid etching, and ablation by lasers) but the pain and inconvenience makes these unpopular choices.

Laser treatments are relatively safe, but only offer temporary cosmetic improvement (i.e., no cure). Recent publications that review the most widely used laser treatments available on the market today have concluded that they are not effective in the treatment of onychomycosis. Examples include Clearsense® laser (Sciton), Pinpointe® Footlaser (Nuvolase), Noveon® laser (Nomir Medical Technologies), GenesisPlus® laser (Cutera), and Harmony® laser (Alma Laser).

Despite improvements in outcomes with new topical antifungals and other treatment options, there is still no topical treatment that is greater than 20% effective. As a result, numerous strategies have evolved to improve efficacy and reduce reoccurrence while maintaining safety.

The Sponsor DeviceFarm, Inc. has developed the RenewalNail™ plasma treatment system to topically treat

fungal infected toenails. The goal of the RenewalNail™ therapy is to overcome the shortcomings of both topical and oral therapies by combining the safety of a topical treatment with the efficacy of an oral treatment. Thus, the RenewalNail™ plasma treatment system may avoid systemic adverse events, achieve high efficacy rates, and provide a method of therapy that is not dependent on labor-intensive, long-term patient compliance as are other topical applications on the market today.

Please review the *DeviceFarm Device Description-0003* document for more details on the technology and the RenewalNail™ plasma treatment system.

2.0 STUDY OBJECTIVES

The purpose of this study is to assess the clinical feasibility of DeviceFarm, Inc.'s RenewalNail™ system and the treatment protocol that was developed based on extensive laboratory testing on human cadaver nails.

The primary objective of this study is to evaluate the efficacy and safety of the RenewalNail™ plasma treatment system and Protocol in achieving mycological cure for the patient. The Protocol calls for three 45-minute treatments performed over a week to achieve mycological cure. Mycological cure will be assessed with two consecutive mycological culture tests done over a week. Two consecutive negative mycology culture results confirm the elimination of fungus causing onychomycosis infection, as recommended by recent FDA guidance. There will be no placebo arm in the study.

Secondary objectives include:

- Will the treatment protocol result in clear nail growth for the patient over a 5-month interval?
- Is the instrument functional in a clinical setting as related to user instructions, user interface and human factor analysis?
- Are there treatment protocol or instrument changes that would improve the treatment results, patient safety, or patient comfort?
- Are there fungal species beyond *Trichophyton rubrum* and *Trichophyton mentagrophytes* that are not affected by the treatment, as seen in species identification from the nail scrapings?

3.0 INVESTIGATIONAL PLAN

3.1 Overall Study Design

DeviceFarm, Inc.'s Early Feasibility Study will be conducted as a Single-center open-label study in Subjects who meet the specified inclusion/exclusion criteria. Informed consent will be obtained. Characteristics of patients including age, gender, disease severity, and disease history will be documented during the screening visit.

Five Subjects with Distal Subungual Onychomycosis (mild to moderate DSO) infection of their big toe (hallux) nail infected by the dermatophytes *Trichophyton (T.) rubrum* or *T. mentagrophytes* will be enrolled.

Treatments will be performed at the office of the Investigator as elaborated in the *3.4* ***Conduct of Study*** section below. The treatment protocol outlines three 45-minute treatments over the course of the first week (within 7 calendar days).

Primary study endpoint will be mycological cure, which is defined as two consecutive negative cultures following treatment. Mycological cultures will be collected (1) during screening, (2) after the third treatment, and (3) around a week (5-15 calendar days) after the third treatment.

Secondary study endpoint will be clear nail growth. Photographs of the target toes will be taken throughout the study to track clear nail growth.

3.2 Discussion of Study Design

This study will be conducted as a Single-center, open-label, pilot study involving 5 Subjects. After giving informed consent, each Subject will be screened for eligibility according to inclusion/exclusion criteria. A Subject will be considered evaluable if he or she satisfies all admission criteria for entry into the study and completes the treatment protocol.

3.3 Selection of Study Population

Five adult Subjects will be prospectively enrolled in the study by the study site. There are no restrictions based on gender, race, or ethnicity. No diabetics or immunocompromised people will be enrolled. No minors under the age of 21 will be enrolled. No pregnant women will be enrolled.

3.3.1 Inclusion Criteria

- Subjects who are between 21 to 75 years (inclusive) of age;
- Subjects who are in good general health and free from any clinically significant disease that might interfere with the study evaluations;
- Subjects with established clinical diagnosis of distal subungual onychomycosis;
- Subjects with at least one big toe nail involved with 20-75% infection;
- Subjects with both positive KOH and culture for onychomycosis dermatophytes in screening of nail samples;
- Subjects whose infection is confirmed to be caused by *T. rubrum* or *T. mentagrophytes*;
- Subjects who are willing and able to refrain from employing other (non-study) treatments (traditional or alternative) for his or her toenail onychomycosis throughout study participation;
- Subjects who are willing and able to refrain from the use of nail cosmetics such as clear and/or colored nail lacquers during the week of treatment (from Study Visits 1 through 3);
- Subjects who are willing and able to give written informed consent and able to adhere to procedures and visit schedules;
- Women of childbearing potential who are currently sexually active must agree to use a medically accepted method of contraception while receiving protocol specified treatment. Methods include condoms (male or female), diaphragm or cervical cap with spermicide, medically prescribed intrauterine device, oral or systemic hormonal contraceptive, surgical sterilization (e.g., hysterectomy or tubal ligation);
- Women of childbearing potential who are not currently sexually active must agree to use a

medically accepted method of contraception should they become sexually active while participating in the study;

- Women of childbearing potential must have a negative pregnancy test prior to start of study.

3.3.2 Exclusion Criteria

- Subjects with onychomycosis infection involving lunula of the affected toenail(s) or spikes of disease extending to nail matrix in the affected big toenail;
- Subjects whose foot is too large (larger than US men's size 13) or too small (smaller than US women's size 3) to properly fit into the plasma treatment device;
- Subjects whose affected big toenail cannot become normal in the opinion of the investigator;
- Subjects who received topical antifungal treatment of the nails within 2 weeks before study initiation;
- Subjects who received systemic antifungal treatment within 3 months before study initiation;
- Simultaneous participation in another clinical study or participation in another clinical study in the 30 days directly preceding treatment;
- Subjects who are immunocompromised (e.g. adrenal insufficiency, diabetes mellitus, febrile neutropenia, and the human immunodeficiency virus infected);
- Subjects with any pacemakers, or any metallic implants or prostheses in the vicinity of the treatment site (such as ankle, foot, etc.);
- Subjects with any clinically significant condition or situation, other than the condition being studied that, in the opinion of the investigator, would interfere with study evaluations or optimal participation in the study;
- Subjects who feel they cannot sit for 45 minutes at a time during the treatment;
- Subjects who are part of the staff personnel directly involved with this study or who are family members of the investigational study staff;
- Subjects with known allergy to any of the tested treatment products [i.e. perfluorocarbons and plastic polycarbonate];
- Women who are pregnant, breastfeeding, or planning pregnancy prior to the end of study participation;

3.3.3 Withdrawal Criteria

Withdrawal criteria include but are not limited to the following:

- Investigator's request;
- Safety reasons (e.g., severe adverse reactions);
- Subject's request;
- Poor compliance;
- Subjects lost to follow-up. The Investigator will try to reach the Subject, twice by telephone and once by certified letter, before considering the Subject lost-to-follow-up. These actions will be reported on the Final Case Report Form and a copy of the follow-up letter will be maintained in the Investigator's file.

Treatment may be discontinued at any time by the investigator if, in his/her clinical judgment, it is in the best interest of the Subject, treatment is deemed inappropriate by a physician evaluation, or if the Subject cannot comply with the protocol. All premature discontinuations and their causes must and will be carefully documented by the Investigator on the Final Case Report Form and, if need be, on the Adverse Event Case Report Form.

Subjects who did not complete the entire study should be fully evaluated when possible. The procedures designated for the Final Visit should be completed for all Subjects discontinuing. Subjects are free to withdraw from participating in this study at any time and for whatever reason, specified or unspecified, and without prejudice.

3.3.4 Subject Identifiers

Upon screening, the Subject will be assigned a unique 3-digit Subject number that increments sequentially at the site (i.e., 001, 002). At Study Visit 1/Day 1, Subjects who are eligible for participation will retain the same Subject number for the remainder of the study. This Subject number is to be recorded on the Case Report Form for future identification and outcomes reporting.

3.4 Conduct of Study

3.4.1 Study Overview by Visit

3.4.1.1 Screening Visit

Subjects are to be screened at the Investigator's facility to determine eligibility for the study. Written informed consent is to be obtained after a careful description of the study. Written, witnessed, informed consent will be obtained from each Subject prior to participation in the study. The Subject will be given adequate time to review the informed consent document as well as address questions and concerns.

Once written informed consent is granted, Screening Visit activities will be carried out as specified in 3.4.2.1. Namely, a medical history is taken and a brief physical examination is conducted. If the Subject is confirmed to meet the inclusion/exclusion criteria besides positive mycological testing, they are assigned a Subject number and results are recorded on the Case Report Form (CRF) for each Subject. Nail scrapings are collected for fungal infection testing by KOH assay and mycological culture. Culture results will be obtained within 4 weeks of Subject's initial screening visit.

A screen failure is a Subject who received information about the study, including signing an informed consent, and possibly performing some study related procedures but was not enrolled, and did not receive study treatment**.** Only the Subject number, date of visit, date of consent, reason for screen failure, and study status (screen failure) will be captured in the CRF for every screen failure Subject.

3.4.1.2 Study Visit 1

The Subject will be scheduled for the first treatment as soon as positive mycological testing results are available and the Subject is confirmed to meet all inclusion/exclusion criteria. A Subject meeting all of the entry criteria is enrolled into the study. Day 1 activities will be carried out as specified in 3.4.2.2.

3.4.1.3 Study Visits 2-6

The Subject reports back to the Investigator's facility for the remainder of treatments. Investigator inquires with Subject regarding compliance, adverse events and for clinical assessment of the treated area of the foot.

Visit 2 and Visit 3 activities will be carried out as specified in 3.4.2.3 and 3.4.2.4, respectively. Mycological culture collected at Visit 3 will be the first of the two consecutive cultures for assessing mycological cure.

Visit 4 activities are specified in 3.4.2.5. Mycological culture collected at this visit will be the second of the two consecutive cultures for assessing mycological cure.

On Visit 5, mycological cultures will be collected to measure rates of reinfection/recurrence. Visit 5 activities will be carried out as specified in 3.4.2.6.

Visit 6 will be the last visit of the study and activities will be carried out as specified in 3.4.2.7.

3.4.1.4 Discontinuation

If an eligible Subject drops out of the study for any reason, the Investigator must make every reasonable effort to obtain clinical assessments of adverse events. All data should be recorded in the CRF for the Subject and the reason for the drop out should be documented.

In the event that a Subject drops out of the study due to an adverse event, the nature of the event and its clinical course must be fully documented. The Investigator must attempt to follow the Subject until the adverse event has resolved, become clinically insignificant, stabilized, or the Subject is lost to follow-up.

Subjects who drop out of the study without completing the three 45-minute treatments over the course of the first week (within 7 calendar days) will be considered premature drop out. The Sponsor will take reasonable action to replace any of the Subjects who drop out prematurely to maintain the 5-Subject enrollment.

3.4.2 Study Procedures by Visit

Activities to be performed at each visit are listed below. Please review the *DeviceFarm Device Description* and the *Instructions for Use* documents for details about using the Device and taking photographs with the camera.

3.4.2.1 Screening Visit – Baseline

- Obtain Subject's written informed consent prior to initiating any study procedures.
- Document Subject's Informed Consent in the Subject's medical record.
- Screen potential Subject according to the study inclusion/exclusion criteria.
- Take the Subject's medical history.
- Perform a brief physical exam.
- Perform urine pregnancy test on women of childbearing potential.
- Photograph the infected hallux nail(s).
    - If both hallux nails are infected and meet the inclusion/exclusion criteria, both nails can be photographed and tested for KOH and mycology. If both are positive for KOH and culture, the Investigator will choose one and only treat that one in the study.
- Perform KOH testing of infected hallux nail(s): Before obtaining a specimen, make sure the nail is clipped and cleansed with an alcohol swab to remove bacteria and debris.
- Collect mycology sample for lab culture: Prepare and ship the mycology samples according to the instructions from the designated mycology laboratory.

3.4.2.2 Study Visit 1 - Day 1

- Check for conformance to inclusion/exclusion criteria.
- Perform debridement on the infected nail to be treated.
- Notch the nail.
- Measure distance between proximal nail fold and notch.
- Insert the Disposable into the RenewalNail™ plasma treatment device.
- Brush the top, edges, and underside of the infected nail with the Nail Penetration Enhancer.
- Insert the Subject's foot into the opening of the Disposable that was placed the device.
- Ensure that the Subject's foot is properly inserted into the device with a seal of the Disposable flexible material around the foot.
- Push the device power button to start the treatment.
- Complete the 45-minute plasma treatment.
- Perform clinical evaluation of the toes after plasma treatment as specified in "*5.0 Safety Assessment/Risks*"
- Check on occurrence of adverse events. Stop protocol if any serious adverse events occur.
- Photograph the treated nail.

3.4.2.3 Study Visit 2

Study Visit 2 should occur no sooner than 36 hours after Study Visit 1. In no circumstance should the Subject receive treatment on two (2) consecutive days.

- Check on occurrence of adverse events.
- Perform a plasma treatment per instructions in the *Instructions for Use of the DeviceFarm RenewalNail Plasma Generator DFPD-003* document.
- Perform clinical evaluation of the toes after plasma treatment as specified in "*5.0 Safety Assessment/Risks*"
- Photograph the treated nail.

3.4.2.4 Study Visit 3

Study Visit 3 should occur no sooner than 36 hours after Study Visit 2, but within 7 calendar days from Study Visit 1. In no circumstance should the subject receive treatment on two (2) consecutive days

- Check on occurrence of adverse events.
- Perform a plasma treatment per instructions in the *Instructions for Use of the DeviceFarm RenewalNail Plasma Generator DFPD-003* document.
- Perform clinical evaluation of the toes after plasma treatment as specified in "*5.0 Safety Assessment/Risks*"
- Perform fungal scrapings for mycological culture as instructed by the laboratory.
- Photograph the treated nail.

3.4.2.5 Study Visit 4 - Day 12 (+/- 3 days)

- Check on occurrence of adverse events.
- Perform fungal scrapings for mycological culture as instructed by the laboratory.
- Photograph the treated nail.

3.4.2.6 Study Visit 5 - Day 42 (+/- 3 days)

- Check on occurrence of adverse events.
- Perform fungal scrapings for mycological culture as instructed by the laboratory.
- Measure nail growth (renotch, if needed)
- Photograph the treated nail.

3.4.2.7 Study Visit 6 - Day 168 (+/- 5 days)

- Check on occurrence of adverse events.
- Measure nail growth
- Photograph the treated nail.

3.4.3 After-Treatment Instructions

After-treatment care will be discussed in detail with each Subject as follows:

- Nail polish or gels should not be applied to treated nails between treatments.
- Do not pick at the treated nail or the skin surrounding the nail.
- Do not use abrasive cleansers, exfoliants, or scrubs on the treated nail or skin around the nail.

4.0 EFFICACY ASSESSMENT

4.1 Photographic Documentation

Baseline photographs will be taken of the infected nails at the Screening Visit prior to KOH and mycology sampling since these sampling procedures require much of the infected nail to be removed in order to reach the site of active infection.

Photographs will be taken of the treated nail at the end of each Study Visit to document the appearance

of the nail following each visits' procedures and to allow for photographic assessment of clear nail growth over the course of the study.

All photographs should be done with the digital camera provided by the Sponsor and following the instructions provided in the *Instructions for Use of the DeviceFarm Nail Photography* document.

4.2 Mycological Cure Assessment

Mycological culture assays will be performed at an accredited mycology laboratory after Investigator has acquired a specimen of subungual debris obtained from the area as close to the cuticle as possible. This specimen will be shipped to the mycological lab according to the laboratory instructions. A mycological cure is defined as two consecutive negative cultures following completion of the week of treatment.

4.3 Clear Nail Growth Assessment

Clinical improvement is assessed by clear nail growth. Clear nail growth is ultimately a more successful aesthetic outcome for a patient than mycological cure, though the former is more important for preventing secondary infections.

Clinical improvement will be judged by analyzing the nail photographs and assessing the amount of clear nail distance from the proximal end of the nail plate towards the distal end. Clearance will be quantified through the Investigator's recording of nail growth measurements and serial digital photography of the affected nail.

<u>Nail Marking Protocol</u>

Marking a notch with a blade or file at the base of the nail dystrophy is helpful to more easily quantify clear nail growth when analyzing serial nail photographs.

At Study Visit 1, a superficial notch will be made using a scalpel, triangular file or equivalent instrument, approximately 5 mm long on the target surface at the midline of the nail plate proximal to the onychomycotic border.

At Study Visits 2-6, prior to taking photographs, the Investigator will refer to the previously marked notch. If the notch cannot be easily seen in the photographs, the Investigator will deepen the notch and/or use ink, marker or other means to improve the visibility of the notch. If a notch is not present, a superficial notch will be made as previously done at Study Visit 1. A comment will be added on the CRF that a new notch was made at that specific visit.

5.0 SAFETY ASSESSMENT/ RISKS

Safety will primarily be measured by the occurrence of adverse events. Adverse Events will be assessed at every study visit.

Possible risks from the RenewalNail™ plasma treatment system include: edema, erythema, heat, discomfort, itching, or blistering. The use of the Device is not expected to present any new or different risks to those known to be associated with other FDA approved plasma devices for skin resurfacing or for other energy-based onychomycosis treatments such as lasers.

Clinical evaluations of treated toes will be assessed at each visit, using scores for each of the two parameters (erythema and edema); each parameter will be rated as none, mild, moderate or severe (0-3) by the investigator.

Definitions:

Sign/Symptom	Description
Erythema	Redness around the toe(s)
Edema	Swelling around the toe(s)

Signs and Symptoms Scoring:

Score	Assessment	Description
0	None	Absent; symptom not present
1	Mild	Slight, barely perceptible; symptom does not interrupt normal daily activities nor does it require medical management
2	Moderate	Distinctive presence; symptom causes some interruption of normal daily activities but does not require medical management
3	Severe	Marked, intense; symptom interrupts normal daily activities and requires some medical management

5.1 Adverse Events

An adverse event (AE) is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the treatment.

Each subject will be monitored for the occurrence of AEs, including SAEs, immediately after treatment initiation. At each visit, the investigator or other site staff will question the Subject about adverse events using an open question taking care not to influence the Subject's answers (e.g., "Have you had any medical problems since your last visit?").

Any adverse event, whether or not it is related to the treatment procedure, will be reported on the Adverse Event form along with the date of onset, the severity, the relationship to the treatment, and the outcome. Under certain circumstances, additional information may be requested.

When an adverse event persists at the end of the study, the Investigator will ensure a follow-up of the Subject until the Investigator agrees the event is satisfactorily resolved or no further follow-up is required. The study requires that Subjects be actively monitored for adverse events up to and including 14 days after last day of the study.

The severity of an adverse event will be scored according to the following scale:

Score Interpretation

1	Mild	Awareness of sign or symptom, but easily tolerated
2	Moderate	Discomfort enough to cause interference with usual activity
3	Severe	Incapacitation with inability to perform usual activity

The relationship of an adverse event to RenewalNail™ plasma treatment is to be assessed according to the following definitions:

Not related – no temporal association, or the cause of the event has been identified, or the RenewalNail™ plasma treatment cannot be implicated based upon available information.

Possibly related – temporal association, but other etiologies are likely to be the cause. However, involvement of the RenewalNail™ plasma treatment cannot be excluded, based upon available information.

Probably related – temporal association, other etiologies are possible, but unlikely, based upon available information.

Related – established temporal or other association to the event is not reasonably explained by the Subject's known clinical state or any other factor, based on available information.

5.2 Serious Adverse Events

A serious adverse event (SAE) or reaction is defined as any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening, (the term "life-threatening" in the definition of "serious" 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 severe);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect.

Any SAE occurring in a Subject receiving study solution, and any SAE occurring during the 30 days post-treatment that the Investigator becomes aware of, must and will be reported by the Investigator or designee to the Study Medical Monitor within 24 hours even if the SAE does not appear to be RenewalNail™ plasma treatment related. This should be done by telephone and by sending a copy of the Serious Adverse Event form plus other supporting documentation, as required.

All additional follow-up evaluations must be reported to the Sponsor immediately. All SAEs will be followed until the Investigator/Sponsor agrees the event is satisfactorily resolved or no further follow-up is required.

The Investigator/Sponsor will be responsible for notifying the relevant authorities of any SAE, as outlined in the ICH Guidelines. The Sponsor will also ensure that the appropriate IRB is notified of the SAE.

5.3 Risk Management

Subjects will be followed closely during the course of the trial and will have access to the Investigator and/or study staff at all times via provision of after-hours telephone. All known risks will be disclosed to

the Subject via the informed consent process. Subjects will be informed both verbally and in writing in a timely manner of any new information that might relate to safety or their willingness to continue in the study.

6.0 BENEFITS

There is no guarantee of success for the treatment. To the extent that a Subject may be uncertain if they have a fungal nail infection, the screening in this study may provide them with a laboratory result that positively or negatively supports this diagnosis. Being in this study may reduce or eliminate their fungal nail infection, but this is an experimental study and there is limited information about the safety and effectiveness of plasma treatment for fungal nail infections.

There may be a societal benefit from what is learned leading to improved onychomycosis treatment in the future.

7.0 Test Materials

7.1 Administration

Device Name	RenewalNail™ Treatment System DFPD-003
Treatment Schedule	45-minute treatments on Study Visits 1, 2 and 3
Route of Administration	Topical

7.2. Packaging and Labeling

Study Device (RenewalNail™ plasma treatment device) will be packaged to ensure safe transportation from the Sponsor's site to the study site. Each Device and Disposable will be labeled with a unique ID number for tracking purposes. *Instructions for Use* and warnings will be included.

Study Device label will include the Sponsor's name, study protocol number, and warning: "Caution: Limited by Federal (United States) law to investigational use only."

7.3 Subject Treatment and Use Instructions

Each Subject receiving treatment will receive verbal instructions as part of the informed consent regarding the treatment protocol. All site personnel taking part in the study will be trained on handling and use of the device. Each Subject's plasma gas treatment will be done automatically and under the supervision of the Investigator.

7.4 Accountability

The Sponsor will provide the study Device, Disposables, Nail Penetration Enhancer (perfluorodecalin), and *Instructions for Use* documents to the Investigator. Receipt of all study supplies will be confirmed and documented by the site. In accordance with federal regulations, the Investigator must agree to keep all clinical supplies in a secure location with restricted access. All supplies provided to the Investigator must not be used in any unauthorized manner. All used and unused supplies will be appropriately inventoried and returned to the Sponsor.

7.5 Prior and Concomitant Therapy

Therapies used within six months of signing the Informed Consent Form should be recorded on the Previous/Concomitant Therapy Form of the CRF. Washout medications should be listed on the Previous/Concomitant Therapy Form when applicable.

Information on concomitant therapy should be recorded on the Previous/Concomitant Therapy Form of the CRF. Any therapy used by the Subject will be considered concomitant therapy (e.g., antifungal therapy, birth control pills, immunosuppressant therapy, etc.). Every attempt should be made to keep concomitant therapy dosing constant during the study. Any change to concomitant therapy should be noted on the Previous/Concomitant Therapy Form. An Adverse Event Form should be completed for any Subject starting a concomitant therapy (except therapies used prophylactically) to treat any health condition/event not identified in the Subject's baseline medical history.

8.0 Monitoring

8.1 Clinical Monitoring/Auditing

The Sponsor will ensure that a qualified monitor is available to oversee the conduct of the trial and that monitoring is performed in accordance with applicable procedures and regulations. The monitor will evaluate compliance with the investigational plan, FDA regulations, IRB guidelines, and the signed Investigator agreement. In addition, inspections or on-site audits may be carried out by the FDA or by the Sponsor's independent Quality Assurance Department. The Investigator will allow the Sponsor's representatives and any regulatory agency to examine all study records, CRFs, corresponding Subject medical records, and any other documents considered source documentation. The Investigator will allow a representative of the Sponsor to observe the treatment as part of a technical assessment about the performance of the instrument, as long as the Subjects have provided optional consent for this observation. The Investigator also agrees to assist the representative, if required.

8.2 Regulatory Obligations

The RenewalNail™ plasma treatment device is a Non-Significant Risk Investigational Device and as such is Subject to the abbreviated IDE regulations, including records and reporting, device disposition, and study monitoring.

9.0 Statistical Methods Planned

Due to the nature of the study and the small number of Subjects, no inferential statistical analyses will be performed. The results from this study will be used to determine whether the treatment can achieve mycological cure for onychomycosis Subjects fulfilling the inclusion/exclusion criteria.

Mycological cure is defined as an achievement of negative culture results for both *Trichophyton rubrum* and *Trichophyton mentagrophytes* from both Visit 3 and Visit 4.

The data is too small to summarize with descriptive statistics; therefore, Subject listings will be presented.

9.1 Safety Analyses

The type, severity, duration, and frequency of reported adverse events will be tabulated. Adverse events will also be summarized for events that were considered treatment-related. Adverse events will be presented in Subject listings to include the start date and time, stop date and time, relationship to study procedure, severity, and action taken. Serious adverse events will be presented in a separate listing. The safety endpoints will be an assessment of:

- Device-related adverse events
- Overall rate and severity of all reported adverse events

9.2 Changes in Study Conduct/Statistical Analyses /Amendments

No change in the conduct of the study should be instituted without written approval from the Sponsor and the IRB.

10.0 ETHICS AND GENERAL STUDY CONDUCT CONSIDERATIONS

10.1 Institutional Review Board (IRB)

This study and all appropriate amendments will be reviewed and approved by an Institutional Review Board according to the established IRB procedures.

10.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki and GCPs.

10.2.1 Principal Investigator

The Principal Investigator is responsible for conducting this study in accordance with all applicable laws and IRB approved documents. The Investigator must ensure adherence to the procedures outlined in this Study Protocol. The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Investigator abides by GCP as described in the ICH Guidelines Topic E6: “Guideline for Good Clinical Practice.” Compliance with these regulations also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. The study will also be carried out in keeping with local legal and regulatory requirements.

10.3 Record Keeping

10.3.1 Data Collection

Data for this study will be recorded in the Subject’s chart and transcribed onto the Subject Case Report Forms (CRFs) provided by the Sponsor. Data will be captured and compiled using procedures developed by the Sponsor or designee. Data must be recorded promptly, completely and accurately on the CRFs. Whenever possible, record the reason for missing data in the source document. Only individuals who are identified on the study personnel responsibility log and who have received appropriate training on the CRF

or data entry system may enter or correct data on the CRFs.

10.3.2 Data Corrections

Corrections of data entered on original CRFs must be made using standard good documentation practice. Incomplete or inconsistent data on CRFs will result in data queries that require resolution by the Investigator or designee. Corrections to the CRFs, including reasons for change, will be documented through the audit trail. The Sponsor Monitor will review the CRFs, evaluate them for completeness and accuracy, and ensure that all appropriate corrections are made.

10.3.3 Source Documentation

The Investigator must maintain detailed source records on all study Subjects. Subject source data must be maintained as original records or a certified copy. The Investigator and institution should take measures to prevent accidental or premature destruction of documents. Investigators must keep accurate separate records (other than the Case Report Forms) of all Subject visits which include all pertinent study related information including the original signed/dated Informed Consent Forms. As a minimum, a statement should be made indicating that the Subjects have been enrolled in the study and that they signed an Informed Consent Form prior to administration of any study-related procedure. Any and all side effects and adverse events must be thoroughly documented. Results of any diagnostic tests conducted during the study should also be included in the source documentation. Telephone conversations with the Subjects and/or Sponsor concerning the study must also be documented.

10.3.4 Archives

Case Report Forms will identify Subjects only by assigned study number and will be stored on site in a secure location. All pertinent data, correspondence, original or amended protocol, all reports and all other material relating to the study will be maintained securely in Sponsor/Investigator archives for either:

(a) a period of at least 2 years following the date on which the treatment device is approved by FDA for marketing for the purposes that were the Subject of the clinical investigations, or
(b) a period of at least 2 years after the date on which the entire investigation (all clinical trials) is terminated and FDA is notified.

Access will be granted only to the clinical investigators, study staff, study Sponsor, and associated regulatory authorities. If the Principal Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian.

DEVICE ACCOUNTABILITY

The Devices to be used in this study are the sole property of the Sponsor. All provided products to be used for this study and their receipt, inventory, dispensing, and reconciliation records will be maintained in compliance with federal regulations. Upon completion or termination of the study the site will be responsible for returning or disposing of all partial and unused products under FDA regulations.

11.0 INVESTIGATOR AGREEMENT

I have read Protocol No: DFCR-0003 "**A Single Center Open Label Early Feasibility Study to Evaluate the Efficacy and Safety of the RenewalNail™ Plasma Treatment System in Patients with Mild to Moderate Onychomycosis (Fungal Nail) of the Hallux caused by *Trichophyton rubrum* or *Trichophyton mentagrophytes*.**" and agree that it contains all of the information necessary to conduct the study. I agree to conduct the study as described herein, and will complete the study within the time designated. In addition, I agree to conduct all my activities related to the study in accordance with ICH Guidelines for Good Clinical Practice, the Code of Federal Regulations, the Health Insurance Portability and Accountability Act (HIPAA) and local regulatory guidelines. I will discuss study-related information with all study personnel responsible to me to ensure that they are adequately informed regarding conduct of the study. I agree to keep records on all Subject information (case report forms, shipment and device return forms and all other information collected during the study) in accordance with FDA regulations. I will ensure that the rights, safety and welfare of Subjects under my care are protected. Only an Investigator designated on the Statement of Investigator (Form FDA 1572) may sign Case Report Forms. I will not enroll any Subjects into this protocol until proper regulatory, IRB and Sponsor approval is obtained.

I will provide copies of the proposal and all information available on the RenewalNail™ plasma treatment system relating to preclinical and prior clinical experience, which was furnished to me by the Sponsor to all physicians, nurses and other personnel responsible to me who will participate in this study. I will discuss this material with them to assure that they are fully informed regarding the device and the conduct of the study.

I agree that the conduct and results of this study will be kept confidential. I agree that the case report forms and other data pertinent to this study are the property of DeviceFarm, Incorporated, who may utilize the data in various ways, such as for submission to government regulatory agencies, or in publication of the results of the study, if applicable. To prevent premature disclosure of trade secrets or other confidential information, I agree that the timing of a separate presentation or publication of the study by me will be subject to mutual agreement in advance with DeviceFarm, Incorporated.

I further agree that DeviceFarm, Incorporated shall have access to any source documents from which case report form information may have been generated.

_____ _____

Principal Investigator Signature Date

_____

Printed Name