STATISTICAL ANALYSIS PLAN

DFCR-0002: RenewalNail™ Plasma Treatment System
Version 1.0
May 02, 2017

A Multi 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

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List of Abbreviations

AE	Adverse Event
MedDRA	Medical Dictionary for Regulatory Activities
DSO	Distal Subungual Onychomycosis
PD	Protocol Deviation
PV	Protocol Violation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
T. rubrum	Trichophyton rubrum
T. mentagrophytes	Trichophyton mentagrophytes
WHO Drug	World Health Organization Drug Dictionary

Statistical Analysis Plan

1 Purpose of Statistical Analysis Plan

The purpose of the statistical analysis plan is to describe in detail all the data, statistical methods, and summary tables required to implement the statistical analysis of Clinical Study Protocol DFCR-0002 (Section 9 in the study protocol Version 2.0 (Amendment 01), dated January 06, 2017).

2 Study Objectives

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.

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.

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 Study Design and Sample Size

3.1 Study Design

This is an early feasibility study. It will be conducted as a multi-center open-label study in Subjects who meet the specified inclusion/exclusion criteria. Informed consent will be obtained. Characteristics of subjects including age, gender, disease severity, and disease history will be documented during the screening visit.

Thirty Subjects with 20-75% 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. Enrollment will be paused after the first five Subjects are enrolled. These five Subjects will serve as a sentinel group to monitor treatment safety and efficacy for this group prior to enrolling the remaining 25 Subjects.

Treatments will be performed at the office of the Investigator as elaborated in the Conduct of Study section from the protocol. The treatment protocol outlines three 45-minute treatments over the course of the first week (within 7 calendar days). Cultures will be collected during screening, after the third treatment and a week after third treatment. A final treatment will be performed in week 7 (i.e. 6 weeks after the initial week of treatment). This final treatment is a

preventative maintenance treatment to minimize potential spore release or reinfection of the toenail during the growth of new nail.

3.2 Sample Size

Thirty adult subjects will be prospectively enrolled in the study. Potentially eligible subjects presenting for onychomycosis treatment at the clinic will be invited to participate in the study and may be included so long as they give informed consent to participate and meet inclusion and exclusion requirements. Investigators will be asked to document all subjects approached for the study by maintaining a prescreening log.

Enrollment will be paused after five subjects are enrolled. Once safety and efficacy data from mycology results from study visit 4 is obtained for all 5 subjects, an interim evaluation will be performed. If the interim evaluation shows safety concerns, the study will be suspended for all subjects pending an assessment of the safety event(s) and appropriate action to prevent the event(s) from reoccurring. If the interim evaluation shows no safety concerns, the enrollment of subjects will resume and the subjects already enrolled will complete the remainder of their study visits per protocol.

4 Populations To Be Analyzed

All enrolled subjects will be included for evaluation.

5 Planned Analyses

5.1 Methodological Considerations

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.

The data is too small to summarize with descriptive statistics; therefore, Subject listings will be presented. SAS software will be used for all data listings.

5.2 Handling of Dropouts or Missing Data

Original data will be presented in the data listing. No data manipulation will be applied for dropouts or missing data.

5.3 Demographics and Baseline Characteristics

Data listings will be presented for demographics and baseline characteristics.

5.4 Subject Accountability

Data listings will be presented for subject disposition and reason for discontinuation.

5.5 Efficacy Variables and Evaluations

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. It will be summarized using frequency and percentage.

All the efficacy data will be presented in subject data listings.

5.6 Safety Variables and Evaluations

Adverse Events

Adverse events (AEs) will be coded in MedDRA, version 18.1 or higher. Treatment-Emergent Adverse Event (TEAE) is defined as any AE occurring on or after application of the first study product. Overall rate of subjects with at least one TEAE, the severity of the TEAE, and the device related TEAE will be tabulated. In the summaries of incidence rates (frequencies and percentages), severity and relationship to study device, subjects who report more than one event that are mapped to the same preferred term will be counted only once under the strongest severity and relationship, accordingly.

Serious adverse events (SAEs) will be listed by subject and will be discussed within the clinical study report. In addition, a list of subjects whose study treatment interrupted/ discontinued due to an AE will be provided.

All information pertaining to AEs noted during the study will be listed by subject, detailing verbatim term given by the Investigator, preferred term, system organ class, onset date, resolution date, severity, seriousness, action taken for the AE, outcome, and study treatment relatedness. The event onset will also be shown relative (in number of days) to date of first administration of study product.

Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary, version March 2016 or higher, and will be presented in data listings.

Clinical Evaluations of Treated Toes

Clinical evaluations of treated toes for each subject will be listed by study visits.

6 Appendices

6.1 Handling of Missing or Incomplete Dates for Adverse Events and Concomitant Medications

Adverse Events

Handling of partial dates is only considered for the start date. An adverse event with a partial start date is considered treatment emergent if:

- only the day is missing and the start month/year is the same or after the month/year of the first dose
- the day and month are missing and the start year is the same or greater than the year of the first dose date

- the start date is completely missing

Concomitant Medications

Handling of partial dates is only considered for the stop date. A medication with a partial stop date is considered concomitant if:

- only the day is missing and the stop month/year is the same or after the month/year of the first dose
- the day and month are missing and the stop year is the same or greater than the year of the first dose date
- the stop date is completely missing or the medication is ongoing

7 Tables and Listings

The following is an example of tables and listings that will be included in the clinical study report. Tables and listings may be modified as needed during the data analyses.

Summary Tables

Table 14.1 – Summary of Mycological Cure

		RenewalNail
All subjects	Subjects who completed both Visits 3 and 4	XX
	Subjects with mycological cure	XX (XX.X%)
Subjects who met the entrance criteria	Subjects who completed both Visits 3 and 4	XX
	Subjects with mycological cure	XX (XX.X%)

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.
Percentage is based on number of subjects who completed both Visits 3 and 4.
Source: Listing 16.2.6.1
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Table 14.2 - Overall Summary of Treatment Emergent Adverse Events (TEAE)

	RenewalNail (N=XX)
Subjects with at least one TEAE	XX (XX.X%)
Subjects with at least one Serious TEAE	XX (XX.X%)
Subjects with at least one Related TEAE[2]	XX (XX.X%)
Subjects with TEAE Leading to Study Treatment Interrupted/Discontinued	XX (XX.X%)
Number (%) of deaths	XX (XX.X%)
Overall TEAEs	
Number of Subjects with at least one Mild TEAE	XX (XX.X%)
Number of Subjects with at least one Moderate TEAE	XX (XX.X%)
Number of Subjects with at least one Severe TEAE	XX (XX.X%)
Number of Subjects with at least one Not Related TEAE	XX (XX.X%)
Number of Subjects with at least one Possibly Related TEAE	XX (XX.X%)
Number of Subjects with at least one Probably Related TEAE	XX (XX.X%)
Number of Subjects with at least one Related TEAE	XX (XX.X%)

For summary by severity and relationship to study medical device, subjects reporting more than one TEAE are only counted once under the greatest reported severity and the most likely relationship to study product, accordingly.
[1]Related category includes Possible, Probable, and Related TEAE.
Source: Listing 16.2.7.1
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Subject Listings

Listing 16.2.1.1 – Subject End-of-Study Status and Study Compliance for Enrolled Subjects

Site-Subject	Subject Completed Study?	Date Completed or Discontinued	Reason, if Discontinued	Used any prohibited med.?	Same wedge selected?

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Listing 16.2.1.2 – Dates of Visits for Enrolled Subjects

Site-Subject	Screening Visit [Day #]	Visit 1/ Day 1 (Baseline)	Visit 2/Day 3 or/4 [Day #]	Visit 3/ Day 6 or 7 [Day #]	Visit 4/ Day 12 ±3 days [Day #]	Visit 5/ Day 42 ±3 days [Day #]	Visit 6/ Day 168 ±5 days [Day #]

Day # is calculated from Baseline (Visit11) Date. Day 1 is the Baseline on date while Day -1 is the day prior to the Baseline visit.
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Listing 16.2.2.1 – Violation of Inclusion Criteria* for Enrolled Subjects

Site-Subject	1	2	3	4	5	6	7	8	9	10	11	12	13

* Please see section 3.3.1 of study protocol for description of the inclusion criteria.
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Listing 16.2.2.2 – Violation of Exclusion Criteria* for Enrolled Subjects

Site-Subject	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24

*Please see section 3.3.2 of study protocol for description of the inclusion criteria.
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Listing 16.2.2.3 – Comments for Enrolled Subjects

Site-Subject	Date of Comments	CRF Page No.	Comment(s)	Initials of Author

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Listing 16.2.4.1 – Demographics and Informed Consent for Enrolled Subjects

Site-Subject	Age (yrs)	Birth Date	Sex	Race	Ethnicity	California Bill of Rights Signed?	Informed Consent	
							Signed?	Date

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Listing 16.2.4.2 – Brief Physical Examination and Urine Pregnancy Test for Enrolled Subjects

				Urine Pregnancy Test	
Site-Subject	Heart	Lungs	Abdomen	Date	Result
	Abnormal: xxxxxxxxx	Normal	Normal		

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Listing 16.2.4.3 – Vital Signs for Enrolled Subjects

	Sitting Blood Pressure (mmHg)		Heart Rate	Temp.	Resp. Rate	Height	Weight	Continued to meet entry
Site-Subject	Systolic	Diastolic	(bpm)	(°F)	(breath/min)	(inches)	(lbs)	criteria at Visit 1?

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Listing 16.2.4.4 – Medical History (With Past and Current Findings) for Enrolled Subjects

Site-Subject	Body System	Diagnosis/Procedure	Onset Date	Stop Date	Concomitant Medication?
	xxx	xxxx	-----2002	Ongoing	Yes
	xxxxxxx	xxxxxxxxxxxx	-----1997	Ongoing	No

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Listing 16.2.4.5 – Previous or Concomitant Medications for Enrolled Subjects

Site-Subject	WHO Class	WHO Name	Medication	Indication	Start Date [Day #]	Stop Date [Day #]	Dose	Unit	Route	Frequency

Note: Medications coded using the WHO Drug Dictionary, version xxx.
Day # is calculated from Baseline (Visit 1) Date. Day 1 is the Baseline date while Day -1 is the day prior to the Baseline visit.
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Listing 16.2.5.1 – Nail Photographs for Enrolled Subjects

Site-Subject	Visit	Target Big Toenail?	Photo before debridement?	Debridement performed on target toe?	Thinning nail performed?	Photo before treatment?	Photo after treatment?	Photo uploaded?

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Listing 16.2.5.2 – Nail Notching/Treatment for Enrolled Subjects

Site-Subject	Visit	Notch Measurement		Nail Measurement (mm)	New nail growth (mm)*	Plasma treatment performed per instructions?	Treatment Start Time	Treatment End Time	Photo after treatment?	Photo uploaded?
		Re-Notch?	Distance (mm)							

*New nail growth = nail measurement at Visit 5/Visit 6 - notch measurement at Visit 1. If at anytime during the study the nail has to be re-notched, then new nail growth = nail measurement at Visit 5/Visit 6 – the last re-notch measurement.
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Listing 16.2.6.1 – Mycological Culture for Enrolled Subjects

			Mycological Culture								
Site-Subject	Visit	Sample submit to lab	T. Rubrum	T. Mentag.	No Growth	Bacterial Overgrowth	Other Fungi	Other Dermatophyte	Other	Mycological Culture	Mycological Cure*
01-001	Scr	Y	X							T. Rubrum	
	3	Y						Xxxxxx		Other Dermatophyte	Yes
	4	Y				X	X			Bacterial Overgrowth; Other Fungi	Yes
	5				X					No Growth	Yes
01-002											

*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.
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Listing 16.2.6.2 – Clinical Evaluation of Treated Toes and KOH Preparation for Enrolled Subject

		Clinical Evaluation			KOH Result	
Site-Subject	Visit	Erythema	Edema	Evaluator	Left Hallux	Left Hallux

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Listing 16.2.7.1 – Adverse Events for Enrolled Subjects

Site-Subject	System Organ Class // Preferred Term// Verbatim Term	Start Date/Time [Day #]	Stop Date/Time [Day #]	Severity	Relation to Study Treatment	Action Taken[1]	Outcome[2]	SAE?

Day # is calculated from the Baseline (Visit 1) date. Day 1 is the Baseline date while Day -1 is the day prior to the Baseline visit.
[1] Action Taken: 1=None, 2=Study treatment interrupted/discontinued, 3=Non-drug therapy, 4=New OTC or Rx drug added, 5=Hospitalized (includes ER visits).
[2] Outcome: 1=Resolved, 2= Improved, 3= Stabilized, 4= Worsened, 5= Unchanged, 6=Lost to follow-up/Unknown, 7=Fatal.
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Repeat Listing16.2.7.1 for –

Listing 16.2.7.2 – Adverse Events Leading to Study Treatment Interruption/Discontinuation for Enrolled Subjects
Listing 16.2.7.3 – Serious Adverse Events for Enrolled Subjects