Clinical Study Protocol Number DBI-201- Open Label, Single-dose, Dose Escalating Evaluation of the Safety and Tolerability of DBI-001 in Patients with Tinea Pedis

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DermBiont® Inc.

CLINICAL STUDY PROTOCOL

Protocol Number DBI-201

Open label, single-dose, dose escalating evaluation of the safety and tolerability of DBI-001 in patients with Tinea pedis

Development Phase of Study:	**Phase 2 A**
Study Design:	**Open Label**
Date of Original Protocol:	**26 November 2018**
Date of Amendment 1:	**05 March 2019**
Sponsor Representative:	**International Dermatology Research, Inc. (IDR)**
Sponsor:	**DermBiont Inc.**

CONFIDENTIAL

This protocol will be conducted in compliance with procedures outlined in this document, Good Clinical Practice (GCP) guidelines and applicable regulatory requirements. This study will not be initiated without the approval of the Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Any changes to the protocol will be approved in writing by the IRB/IEC before implementation except where necessary to eliminate an immediate harm to the patient.

PROTOCOL REVIEW AND APPROVALS

Open label, single-dose, dose escalating evaluation of the safety and tolerability of DBI-001 in patients with Tinea pedis

Reviewed and approved by:

[redacted]
Chief Executive Officer,
Chief Medical Officer

_____ _____
Signature Date

[redacted]
Vice President, CMC
and Technical Operations

_____ _____
Signature Date

[redacted]
Medical Director

_____ _____
Signature Date

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Table 1. List of Definitions & Abbreviations

TERM	DEFINITION
AE	Adverse Event
CRF / eCRF	Case Report Form / electronic Case Report Form
DBI-001	Investigational Product, [redacted]
Dermatophytes	A pathogenic fungus that grows on skin, mucous membranes, hair, nails, feathers, and other body surfaces, causing ringworm and related diseases.
DNA	Deoxyribonucleic Acid
Dysbiosis	Microbial imbalance on or inside the body.
EC	Ethics Committee
e-Swab	e-Swab is a liquid-based, multipurpose, collection and preservation system that maintains viability of aerobic, anaerobic and fastidious bacteria.
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Inform Consent Form
IRB	Institutional Review Board
IP	Investigational Product aka Test Product
ISGA	Investigators static global assessment
Microbiome	Microorganisms in a particular environment
PHI	Protected Health Information
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
Sponsor	DermBiont

SYNOPSIS

NAME OF SPONSOR: DermBiont Inc. **NAME OF FINISHED PRODUCT**: DBI-001 **NAME OF ACTIVE INGREDIENT(S):** [redacted]	
Title of Study	Open label, single-dose, dose escalating evaluation of the safety and tolerability of three dose levels of DBI-001 in patients with Tinea pedis.
Investigator(s)	[redacted]
Study centre(s)	Santo Domingo, DR
Publication	N/A
Phase of development	Phase 2A
Objectives	Primary Objective: Evaluate the safety and tolerability of DBI-001 in patients with Tinea pedis. Secondary Objectives: • Evaluation of presence or persistence of [redacted] of DBI-001 following a single application of DBI-001 • Effect of a single application of DBI-001 on the abundance of *T. rubrum* • Effect of a single application of DBI-001 on the signs and symptoms of interdigital T. pedis.
Study Design and Evaluation Methods	A single-center, open label, dose escalating design will be used in a population of patients with interdigital Tinea pedis. The test product will be applied by study personnel at the investigational site. Each subject will have a single application of approximately 0.5 ml of the test article applied to each foot. Both affected and unaffected feet will be treated covering the web spaces, toes, toe nails as well as the plantar and lateral aspect of both feet. Each of the three groups will have 4 subjects. After the first cohort has completed their day 7 visits, if no significant tolerability or safety issues identified the second cohort will be enrolled. After the second cohort has completed the day 7 visits and if no significant tolerability of safety issues is identified the third cohort will be enrolled.

Methodology	Open label, dose escalating
Number of patients	N=12 (3 cohorts) 4 patients per treatment group
Inclusion Criteria	Subjects must meet all of the following criteria to be included in the study: 1. Witnessed, signed informed consent approved by Institutional Review Board/Independent Ethics Committee. 2. A signed Health Information Portability and Accountability Act (HIPAA) authorization form which permits the use and disclosure of subject's individually identifiable health information. 3. Male Subjects of any race 18 years of age and older. 4. Subjects with a clinical diagnosis of interdigital T. pedis *T. pedis interdigital defined as lesions localized to the interdigital spaces or predominantly interdigital, but may extend to other areas of the foot (the non-interdigital lesions should not be hyperkeratotic, i.e., characteristic of tinea pedis moccasin).* 5. Provisionally confirmed diagnosis at baseline by a positive potassium hydroxide (KOH) wet mount at the clinical site. 6. The sum of the clinical signs and symptoms scores of the target lesion is at least 4 using the Grading and signs and symptoms of T. pedis detailed in section 6.6.1, including a minimum score of at least 2 for erythema AND a minimum score of 2 for either scaling/fissures or pruritus/burning (on a scale of 0-3, where 2 indicates moderate severity).

Exclusion Criteria

Subjects with the following will be excluded from this study:

1. Any dermatological conditions that could interfere with clinical evaluations.

2. Any underlying disease(s) or some other dermatological condition that requires the use of interfering topical or systemic therapy.

3. Subjects that have not undergone the specified washout period(s) for the following topical preparations or subjects who require the concurrent use of any of the following topical medications **applied to the foot**:

Topical astringents and abrasives (e.g. Burrow's solution)	1 week
Topical antibiotics and antifungal on the affected area (e.g. Neomycin, Miconazole, Clotrimazole, Terbinafine)	2 weeks
Anti-inflammatories, corticosteroids, topical immunomodulators (e.g. Pimecrolimus, Tacrolimus)	4 weeks

4. Subjects that have not undergone the specified washout period(s) for the following systemic medications or subjects who require the concurrent use of any of the following **systemic medications:**

Corticosteroids (including intramuscular injections) (e.g. Triamcinolone acetonide)	4 weeks
Antibiotics (e.g. Tetracycline, Cephalosporins, etc.) and/or Antifungal agents (e.g. Fluconazole, Itraconazole, Terbinafine, etc.)	4 weeks
Systemic immunomodulators (e.g. Cyclophosphamide, Azathioprine, Biologicals-Monoclonal Antibodies)	4 weeks

5. Treatment of any type of cancer within the last 6 months.

6. History of any significant internal disease (which contraindicates use of live microbiome e.g. leukemia, liver failure, cardiovascular disease)

	7. Subjects who are known to be allergic to any of the test product(s) or any components in the test product(s) or history of hypersensitivity or allergic reactions to any of the study preparations as described in the Investigator's Brochure. 8. AIDS or AIDS related complex by medical history. 9. Known or suspected immune suppressive medications or diseases. 10. Diabetes mellitus Type I or II by medical history. 11. Peripheral vascular disease based on medical history. 12. Any subject not able to meet the study attendance requirements. 13. Subjects who have participated in any other trial of an investigational drug or device within 30 days prior to enrollment or participation in a research study concurrent with this study.
Test product, dose and mode of administration	The test product will be applied by study personnel at the investigational site. Each subject will have a single application of approximately 0.5 ml of the test article applied to both affected and unaffected feet covering the web spaces, toes, toe nails as well as the plantar and lateral aspect of both feet. The product is formulated in a low viscosity aqueous gel and approximately 0.5 ml will be applied to each foot. The three dose groups are: Cohort 1 dose10^6 /ml CFUs of [redacted] Cohort 2 dose 10^7/ml CFUs of [redacted] Cohort 3 dose 10^8/ml CFUs of [redacted]
Duration of treatment	A single application will be applied and then patients will be followed for 28 days

Criteria for evaluation	Evaluations will be made at Screening, Day 1 / Baseline prior to the application of the test article and then 1 hour after application and study days 2, 3+1 ,7+/-1, 14+/-2 and 28+/-2. Subjects will also be queried for adverse events starting after the informed consent is signed and all timepoints following application. Primary: • Signs and symptoms of irritation Secondary: • Data listing showing duration of time over which DBI-001 can be detected by molecular diagnosis • Change in abundance of *T. rubrum* by molecular diagnosis • Changes in the signs and symptoms of T. pedis • Changes in the T. pedis ISGA • Frequency of conventional culture negative • Frequency of KOH negative
Statistical methods	Descriptive

Safety Results:	Dermal Safety and Tolerability: Tolerability will be evaluated through assessment of selected local signs and symptoms (pain / burning, pruritus, erythema, edema, and scabbing/ crusting). Any local skin reaction that requires use of a concomitant therapy or causing study drug interruption or discontinuation should be reported as an AE. The scales to be used for assessing local skin reactions follow
Adverse Events:	During the study, subjects will be assessed for the occurrence of new and ongoing AEs. Descriptions of AEs will include the dates of onset and resolution (if resolved), maximum severity, and seriousness, corrective treatment, outcome, and the Investigator's assessment of causality. AEs present at any visit will be followed to resolution (return to normal or to the baseline state) or until clinically stable as determined by the Investigator.

Efficacy Results:	• Proportion of samples at each time point in which [redacted] can be detected by molecular diagnosis. • Proportion of samples at each time point in which *T. rubrum* can be detected by molecular diagnosis • Relative abundance of *T. rubrum* at each time point • Change in abundance of *T. rubrum* • Changes in the signs and symptoms of T. pedis • Changes in the T. pedis ISGA • Change from dermatophyte culture positive to culture negative • Change from KOH positive to KOH negative

1. INTRODUCTION

1.1 Background Information

DBI-001 is a live bacterial product containing [redacted] This product is being developed as a topical probiotic for the treatment of fungal infections of the skin and nails. [redacted] is an aerobic Gram-negative bacterium commonly found in the soil, water, vegetables and grains from the human food chain, and on the skin of healthy humans. DBI-001 is a human derived commensal organism being employed as a topical probiotic. The strain of [redacted] in the DBI-001 product is a strain [redacted] that DermBiont isolated from the skin of a healthy young adult. Based on DNA sequencing this strain has no know virulence factors nor genes that would indicate antimicrobial resistance. In vitro the [redacted] strain has been shown to inhibit the growth of T. rubrum. The [redacted] strain is sensitive to commonly used antibiotics.

New strains of probiotics and their applicability for curing disease through topical application has been reviewed (Kerry et al 2018). The microbiome in health and disease was initially studied as it related to the microbiome of the gut. It is now well recognized that all human epithelial surfaces have a microbiome community that can contribute to health and diseases. There are distinct microbial communities in the gut, the skin, the respiratory tract, the oral cavity, and the genital urinary tract.

The use of topical live bacterial products to treat skin diseases is a new and rapidly advancing therapeutic approach. To date at least three live bacterial products have been studied in the clinic. An ammonia oxidizing bacterium has been used in Phase 2 trials to treat acne patients (https://clinicaltrials.gov/ct2/show/NCT02832063). A coagulase-negative Staphylococcus has been used to treat patients with atopic dermatitis (Williams and Gallo 2017). A strain of *P. acnes* has been used to treat acne patients.
(https://www.clinicaltrials.gov/ct2/show/NCT03450369?term=Naked+Biome&rank=2).

Application of [redacted] to the skin of amphibians has been shown to be able to treat and prevent the acquisition of a lethal cutaneous fungal infection(Brucker et al. 2008). [redacted] produces at least two anti-fungal compounds violacein and indole-3 carboxaldehyde.

In vitro [redacted] has been shown to inhibit the growth of *T. rubrum*, a dermatophytic fungus commonly associated with diseases of the skin and nails in humans.

There are a number of recognized skin diseases associated with a group of fungi called dermatophytes. These include various forms of Tinea pedis (athlete's foot), onychomycosis (toe nail fungus), Tinea cruris (jock itch) and Tinea corporis (ring worm). Traditionally these are

thought to be caused by an "infection" with a dermatophyte. The current thinking is that when the dermatophyte is present there is disease and when it is absent there is no disease.

There are numerous antifungal drugs both oral and topical that in vitro are very potent and effective in inhibiting or even killing fungi. Despite these potent drugs the complete clinical and mycologic response rate in most clinical trials is well under 50%, most about 30%. It is not uncommon to see subjects who do respond, even complete clinical responses will still have positive cultures or microscopic evidence by KOH examination demonstrating the presence of a dermatophyte. There are also subjects with all of the signs and symptoms of disease from whom a dermatophyte cannot be cultured.

The human epithelial surfaces of the skin, gut, genital tract, and respiratory tract are at the interface with the outside world. These areas have long been known to be inhabited by microorganisms previously referred to as "the normal flora" which for the most part was thought to neither contribute much to health or disease. But in recent years with the availability of DNA sequencing what had been called the normal flora is also called the microbiome. The DNA sequencing was needed to establish this because many of the organisms are either difficult or impossible to grow using routine culture techniques. It has become apparent that a normal microbiome can contribute to health while an abnormal microbiome can be associated with disease. An abnormal microbiome associated with disease is called a dysbiosis.

Recent studies have focused in large part on the bacterial component of the cutaneous microbiome and little is known about the fungal component, the mycobiome.

It is possible that the skin diseases of the foot associated with dermatophytes represent a dysbiosis rather than an "infection" in the traditional sense. It is known that using conventional culture techniques dermatophytes can be cultured from the feet of people with no signs or symptoms of skin disease. In addition, the diseases of the foot associated with dermatophytes are seen far more commonly in people who wear shoes than in people who are barefoot.

It is possible that dermatophytes are in fact part of the cutaneous microbiome in at least some individuals. As part of the community of organisms that make up the cutaneous microbiome of the foot dermatophyte are kept in balance by other organisms such as bacteria. However, wearing shoes especially in warm climates and/or by people with sweaty feet changes the "micro climate" tipping the environmental condition to favor the dermatophyte resulting in the Tinea pedis and onychomycosis.

Current antimicrobial treatments do nothing to correct a dysbiosis and may in fact contribute to the dysbiosis resulting in these conditions frequently being chronic recurrent.

This is analogues to the better known vulvar vaginal candidiasis associated with uses of systemic antibiotics. A normal healthy vagina has a mixture of yeast and bacterial that keep each other in balance. By taking an oral antibiotic that decreased the bacterial component thus favor the growth of yeast can result in vulvar vaginal candidiasis.

It is also possible that subjects with the clinical features of disease who are culture and/or KOH negative may not be actually be false negative, but their disease could be associated with organisms other than the traditional dermatophytes or dermatophytes that are difficult if not impossible to culture with routine mycology cultures. There is a substantial literature implicating molds, yeast, and other organisms in these cases. Using DNA sequencing may more accurately characterize the community of organisms associated with these condition that has been accomplished to date with routine dermatophyte culture and KOH examinations.

It is hoped that the topical probiotic DBI-001 will improve the treatment of common diseases of the skin and nails associated with dermatophytes. Assuming good safety and tolerability in this trial the sponsor will then enroll patients with T. pedis and onychomycosis into larger vehicle-controlled efficacy trials.

The purpose of the current protocol is to establish the safety and tolerability of a single application of [redacted] to the feet of patients with proven T. pedis. In addition, the effect of [redacted] on the T. pedis will also be evaluated.

1.2 Rationale

A single application of [redacted] to the skin of three different species of amphibians in two independent laboratories has been shown to treat and prevent a lethal cutaneous fungal infection. In-vitro [redacted] has been shown to significantly inhibit the growth of the fungus, *T. rubrum* most frequently associated with T. pedis. Based on these observations' topical application of the probiotic [redacted] could treat T. pedis. This protocol intends to enroll only males because T. pedis is far more common in men than women.

2. POTENTIAL RISKS AND BENEFITS

2.1 Potential Risks

Despite the fact that [redacted] is found in the cutaneous microbiome of some people as well as in the human food chain it is possible that application of [redacted] could result in a worsening of the T. pedis, impetigo, or cellulitis. A mild detergent solution will be used to collect samples and it could cause a local irritant reaction.

2.2 Potential Benefits

In amphibians a single application of [redacted] has been shown to treat their cutaneous infection. It is possible that a single application of [redacted] could result in improvement even a clinical and microbiologic cure of the subject's T. pedis. Upon subject's study completion, subjects who continue to have signs and symptoms of T. pedis will be given an approved topical anti-fungal agent with application instructions.
It should be noted that if worsening of the T. pedis, impetigo, or cellulitis were to occur, [redacted] is susceptible to commonly used topical and oral antimicrobials and antibiotics.

3. STUDY OBJECTIVES AND PURPOSE

The purpose of the study is to evaluate the safety and tolerability of DBI-001 in patients with Tinea pedis. Secondly to evaluate presence or persistence of [redacted] of DBI-001 following a single application of DBI-001. Thirdly to see the effect on the abundance of *T. rubrum*. Lastly to see the effect of a single application of DBI-001 on the signs and symptoms of interdigital T. pedis.

4. STUDY DESIGN AND ENDPOINTS

4.1 Description of the Study Design

A single center open label dose escalating study design will be used in a population of patients with interdigital Tinea pedis. Each subject will have a single application of approximately 0.5 ml of the test article applied to each foot covering the web spaces of both feet as well as the plantar and lateral aspect of both feet as well as on and around all toes and toe nails. The three test articles will be 10^6 CFUs/ml, 10^7 CFUs/ml, and 10^8 CFUs/ml. Each of the three groups will have 4 subjects. After the first cohort has completed their day 7 visits and if no significant tolerability of safety issues is identified the second cohort will be enrolled. After the second cohort has completed the day 7 visits and if no significant tolerability or safety issues are identified the third cohort will be enrolled.

Evaluations will be followed according to Table 2 Schedule of Events for Subjects. At all evaluations, signs and symptoms of application site reactions (local tolerability at sites unaffected by T.pedis interdigital) will be recorded. At baseline, days 2, 3 (+1),7 (+/-1) ,14 (+/-2), and 28 (+/-2), the signs and symptoms of T. pedis will be recorded. The investigators static global assessment (ISGA) of the interdigital T. pedis will be recorded at baseline, days 2, 3(+1) ,7 (+/-1) ,14 (+/-2), and 28 (+/-2). Subjects will also be queried for adverse events during their follow up visits or by self-reporting while on study until Day 28.

4.2 Study Endpoints

4.2.1 Primary Endpoints

a. Safety

- Tolerability will be evaluated through assessment of selected local signs and symptoms (pain / burning / stinging, pruritus, erythema, edema, and scabbing / crusting). Any local skin reaction that requires use of a concomitant therapy or study discontinuation should be reported as an AE on the Case Report Forms.

4.2.2 Secondary Endpoints

a. Efficacy

- Proportion of samples at each time point in which [redacted] can be detected by molecular diagnosis
- Proportion of samples at each time point in which *T. rubrum* can be detected by molecular diagnosis
- Relative abundance of *T. rubrum* at each time point
- Change in abundance of *T. rubrum*
- Changes in the signs and symptoms of T. pedis
- Change from dermatophyte culture positive to culture negative
- Change from KOH positive to KOH negative

4.2.3 Exploratory Endpoints

Changes in the T. pedis ISGA

5. INVESTIGATIONAL PRODUCT (IP) / STUDY MATERIALS

5.1 Investigational Product / Test Articles

Investigational Product	Doses per Subject
Cohort 1- dose10^6/ml CFUs of [redacted]	1 dose
Cohort 2- dose 10^7/ml CFUs of [redacted]	1 dose
Cohort 3- dose 10 ^{8}/ ml CFUs of [redacted]	1 dose

5.2 Study Materials

Study Materials Provided by Investigational Site	Study Materials Provided by Sponsor	
Gloves	Dermapak for Fungal Culture	Bio Hazard Bags
Supplies for KOH Wet Mount (On site)	e-Swabs/vials or Zymo DNA Shield Collection Tubes	Cover Slips
Computer with internet access	Cotton Tip Applicators	Pipettors and Tips
	Supplies for KOH Wet Mount KOH + DSMO	Diluent Vials & Cohort Vials
	Topical anti-fungal agent	Racks (Mixing & Application)
	Subject Labels (Source Docs)	Cryoboxes
	Sample Labels (swabs / Dermapaks)	Study Binder and Study Forms/Logs
	Kimwipes	Curettes
	Absorbent bench surface liners	Polypropylene Cleanroom Wipes
	Racks	Photographs Equipment (Laptop & camera)
		Shipping Materials

6. STUDY PROCEDURES

6.1 Inclusion Criteria

Subjects must meet all of the following criteria to be **included** in the study:

1. Witnessed, signed informed consent approved by EC / IRB.
2. If required by local authorities a signed Health Information Portability and Accountability Act (HIPAA) authorization form which permits the use and disclosure of subject's individually identifiable health information.
3. Male Subjects of any race 18 years of age and older.
4. Subjects with a clear diagnosis of interdigital T. pedis: T. pedis interdigital defined as lesions localized to the interdigital spaces or predominantly interdigital, but interdigital but may extend to other areas of the foot (the non-interdigital lesions should not be hyperkeratotic, i.e., characteristic of Tinea pedis moccasin).

5. Provisionally confirmed diagnosis at baseline by a positive potassium hydroxide (KOH) wet mount at the clinical site.
6. The sum of the clinical signs and symptoms scores of the target lesion is at least 4, including a minimum score of at least 2 for erythema AND a minimum score of 2 for either scaling, fissures/ cracking or pruritus/burning (on a scale of 0-3, where 2 indicates moderate severity).

6.2 Exclusion Criteria

Subjects with the following will be **excluded** from this study:

1. Any dermatological conditions that could interfere with clinical evaluations.
2. Any underlying disease(s) or some other dermatological condition that requires the use of interfering topical or systemic therapy.
3. Subjects that have not undergone the specified washout period(s) for the following topical preparations or subjects who require the concurrent use of any of the following topical medications **applied to the foot:**

Topical astringents and abrasives	1 week
Topical antibiotics on the affected area	2 weeks
Anti-inflammatories, corticosteroids, topical immunomodulators	4 weeks

4. Subjects that have not undergone the specified washout period(s) for the following systemic medications or subjects who require the concurrent use of any of the following systemic medications:

Corticosteroids (including intramuscular injections)	4 weeks
Antibiotics	4 weeks
Antifungal agents	4 weeks
Systemic immunomodulators	4 weeks

5. Treatment of any type for cancer within the last 6 months.
6. History of any significant internal disease.
7. Subjects who are known to be allergic to any of the test product(s) or any components in the test product(s) or history of hypersensitivity or allergic reactions to any of the study preparations as described in the Investigator's Brochure.
8. AIDS or AIDS related complex by medical history
9. Known or suspected immune suppressive medications or diseases
10. Diabetes mellitus Type I or II by medical history

11. Peripheral vascular disease based on medical history.
12. Any subject not able to meet the study attendance requirements.
13. Subjects who have participated in any other trial of an investigational drug or device within 30 days prior to enrollment or participation in a research study concurrent with this study.

6.3 Recruitment and Retention

Subjects will be recruited from the Investigator's clinical dermatology practice. The investigator may also recruit subjects using Ethics Committee approved recruitment materials. Retention is not anticipated to be an issue for this short 4-week trial.

6.4 Withdrawal or Termination

6.4.1 Subject Withdrawal

Participation in the study is strictly voluntary. A subject has the right to withdraw from the study at any time for any reason and is under no obligation to disclose the reason. If a subject withdraws, the Investigator and Sponsor are to be informed immediately and the withdrawal noted on the Case Report Form. Subjects may be replaced at the discretion of the Investigator and Sponsor.

The Investigator has the right to terminate participation of a subject at any time for any of the following:

- Use of non-permitted concomitant medication
- Lack of subject compliance
- Protocol violation
- Disease progression
- Any perceived safety risks

6.4.2 Study Discontinuation

There is only a single application per subject of the test article and drug product discontinuation is not anticipated.

Study discontinuation is at the discretion of the Sponsor or the Investigator in any of, but not limited to, the following events:

- Occurrence of unusual AEs in terms of their nature, severity, causality, duration, or unexpected incidence.
- Medical or ethical reasons affecting the continued performance of the study.
- Difficulties in the recruitment of the subjects.

6.4.3 Stopping Rules

With a single application per subjects there is no need for stopping rules for individual subjects. However, the sponsor may terminate dosing new subjects if there are safety concerns noted for any reason.

Table 2 Schedule of events for Subjects

Evaluation	*Screen (-28 day to day 1)	Day 1 / Baseline	1 Hr. after application	Day 2	Day 3 (+1)	Day 7 (+/-1)	Day 14 (+/-2)	Day 28 (+/-2)
			Treatment period	Follow up period				
Informed consent	X	X						
Demographics	X	X						
Inclusion/Exclusion	X	X						
Medical History	X	X						
ISGA of T. pedis	X	X		X	X	X	X	X
Clinical assessment of signs and symptoms of T. pedis		X		X	X	X	X	X
Application of Investigational Product		X						
Concomitant Medication inquiry	X	X		X	X	X	X	X

Evaluation	*Screen (-28 day to day 1)	Day 1 / Baseline	1 Hr. after application	Day 2	Day 3 (+1)	Day 7 (+/-1)	Day 14 (+/-2)	Day 28 (+/-2)
Application Site Reactions (local tolerability for areas unaffected by T. pedis		X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X
e-Swab		X	X	X	X	X	X	X
KOH Wet Mount (On Site)	X							
Fungal Culture & KOH (Mycology Central Lab)		X				X		X
Photos of T. Pedis		X				X	X	X

*Washout

6.5 Study Visits

The study will be conducted with a Screening visit that may also be Day 1 / Baseline visit, 1-hour after application evaluation and five follow-up visits. Further details on timing, administration of the assessment, and processes are provided in the Study Operation Manual (SOM).

6.5.1 Screening Visit

Following written informed consent from each subject, the Investigator will determine whether subjects are eligible to participate in the study by performing screening tests and evaluations. This would include collecting demographic information, review of Inclusion and Exclusion criteria, medical history, concomitant medications, a KOH examination at the site and ISGA.

Screening and baseline visits can occur on the same day if no washout period is necessary. The baseline visit must be completed within 28 days of the screening visit.

At the Screening visit, continuous monitoring of concomitant medications, therapies and AEs throughout the study period will begin.

6.5.2 All Other Visits

Study visit assessments will be conducted as presented in Tables 2 and 3.

a. Baseline (Day1) visit:

For subjects **who did not have a screening washout period** will have the following tasks completed at baseline Day 1:

1. Informed consent.
2. Record demographics.
3. Review of Inclusion/Exclusion Criteria.
4. Medical history.
5. Concomitant medication.
6. T. pedis ISGA of each web space on both feet.
7. T. pedis signs and symptoms.
8. Classification toe web space. As not all web spaces are equally affected and the act of collecting samples from a web space could affect the laboratory results. Web spaces on both feet will be classified based on the ISGA as clear, almost clear, mild T. pedis, moderate T. pedis, severe T. pedis. In addition, one representative web space classified

as moderate will be designated as the target sampling web space. Representative web space should be marked on each subject's paperwork for reference.

9. Signs and symptoms of local tolerability of the areas other than the web spaces.
10. Collect sample for onsite KOH from the target sampling web space.
11. Collect sample for reference mycology laboratory from the target sampling web space.
12. Collect an e-swab from the target sampling web space.
13. Obtain digital photograph of the target sampling web space.
14. Assigned test article will then be applied to both feet. Approximately 0.5 ml of the test article will be applied to each foot spreading the test article over all web spaces, on and around all toe nails, the entire plantar and lateral aspects of the foot.
15. Record any adverse event, if any.
16. **One hour after application of the test article, the following activities will be done:**
    a. E-Swab from an affected web space other than target sampling web space.
    b. Signs and symptoms of local tolerability of the areas other than the web spaces.
    c. Record adverse event, if any.
    d. Give an appointment for Day 2 visit.

For subjects **who had a screening** visit prior to a baseline visit before the test article is applied will have the following tasks completed:

1. Review of Inclusion/Exclusion Criteria.
2. Update Medical History.
3. Concomitant medications.
4. Record Adverse events, if any.
5. T. pedis ISGA of each web space on both feet.
6. T. pedis signs and symptoms.
7. Classification toe web space. As not all web spaces are equally affected and the act of collecting samples from a web space could affect the laboratory results. Web spaces on both feet will be classified based on the ISGA at clear, almost clear, mild T. pedis, moderate T. pedis, severe T. pedis. In addition, one representative web space classified as moderate will be designated as the target sampling web space.
8. Signs and symptoms of local tolerability of the areas other than the web spaces.
9. Collect sample for reference mycology laboratory from the target sampling web space
10. Collect an e-swab from the target sampling web space.
11. Obtain digital photograph of the target sampling web space.
12. Assigned test article will then be applied to both feet. Approximately 0.5 ml of the test article will be applied to each foot spreading the test article over all web spaces, on and around all toe nails, the entire plantar and lateral aspects of the foot
13. **One hour after application of the test article, the following activities will be done:**

a. E-Swab from an affected web space other than target sampling web space.
b. Signs and symptoms of local tolerability of the areas other than the web spaces
c. Record adverse event, if any.
d. Given an appointment for Day 2 visit.

Detailed instruction for sample collection and processing are in the Study Operation Manual, provided separately.

Day 2 Approximately 24 hours after the test article was applied:

1. Concomitant medications.
2. Adverse events.
3. T. pedis ISGA of each web space on both feet.
4. T. pedis signs and symptoms.
5. Signs and symptoms of local tolerability of the areas other than the web spaces.
6. Collect an e-swab from an affected but previously not sampled web space. If none available collect e-swab from an unaffected but previously not sampled web space.
7. Give subject appointment for Day 3 visit.

Detailed instruction for sample collection and processing are in the Study Operation Manual, provided separately.

Day 3 Approximately 48 hours after the test article was applied:

1. Concomitant medications.
2. Adverse events.
3. T. pedis ISGA of each web space on both feet.
4. T. pedis signs and symptoms.
5. Signs and symptoms of local tolerability of the areas other than the web spaces.
6. Collect an e-swab from an affected but previously not sampled web space. If none available collect e-swab from an unaffected but previously not sampled web space.

Detailed instruction for sample collection and processing are in the Study Operation Manual, provided separately.

Day 7

1. Concomitant medications.
2. Adverse events.
3. T. pedis ISGA of each web space on both feet.
4. T. pedis signs and symptoms.
5. Signs and symptoms of local tolerability of the areas other than the web spaces.

6. Collect sample for routine mycology from the target sampling web space.
7. Collect an e-swab from the target sampling web space.
8. Obtain digital photograph of the target sampling web space.

Detailed instruction for sample collection and processing are in the Study Operation Manual, provided separately.

Day 14

1. Concomitant medications.
2. Adverse events.
3. T. pedis ISGA of each web space on both feet.
4. T. pedis signs and symptoms.
5. Signs and symptoms of local tolerability of the areas other than the web spaces.
6. Collect an e-swab from the target sampling web space.
7. Obtain digital photograph of the target sampling web space.

Detailed instruction for sample collection and processing are in the Study Operation Manual, provided separately.

Day 28

1. Concomitant medications.
2. Adverse events.
3. T. pedis ISGA of each web space on both feet.
4. T. pedis signs and symptoms.
5. Signs and symptoms of local tolerability of the areas other than the web spaces.
6. Collect for routine mycology from the target sampling web space.
7. Collect an e-swab from the target sampling web space.
8. Obtain digital photograph of the target sampling web space.

Detailed instruction for sample collection and processing are in the Study Operation Manual, provided separately.

6.6 Study Specific Procedures

6.6.1 Grading of signs and symptoms of T. pedis

Will be graded as follows:

Fissuring/Cracking score:

0=none (complete absence),
1=mild (slight)

2=moderate (definitely present)
3=severe (marked, intense)

Erythema score:

0=none (complete absence)
1=mild. (slight),
2=moderate. (definitely present)
3=severe (marked, intense)

Maceration score:

0=none (complete absence)
1=mild (slight)
2=moderate (definitely present)
3=severe (marked, intense)

Scaling score:

0=none (complete absence)
1=mild (slight)
2=moderate (definitely present),
3=severe (marked, intense)

Pruritus score:

0=none (complete absence)
1=mild (slight)
2=moderate (definitely present)
3=severe (marked, intense)

Burning/Stinging score:

0=none (complete absence)
1=mild (slight)
2=moderate (definitely present),
3=severe (marked, intense)
Composite (total) signs and symptoms score

6.6.2 T. pedis Investigator's Static Global Assessment (ISGA)

Clear - possible faint erythema and a hint of scale

Almost clear - slight scale and minimal erythema

Mild - definite scale and erythema but no maceration, cracking or fissuring

Moderate - definite (mild to moderate) scale, erythema, maceration, and cracking or fissuring

Severe - at least moderate or severe scale, erythema, maceration, and cracking or fissuring

6.6.3 Local Tolerability for Areas Not Affected by T. Pedis

Local tolerability for areas to which the test article is to be applied but without T. pedis such as the unaffected web spaces on and around the toes, toe nails, the plantar and lateral aspects of the foot tolerability will be evaluated based on these signs and symptoms:

Pain/Burning: as reported by the subject as being the greatest intensity they have experienced within the last 24 hours at Baseline or since the last visit at subsequent visits.

0	None	No pain/burning
1	Mild	Slight burning/stinging sensation; not really bothersome
2	Moderate	Definite warm, burning/stinging that is somewhat bothersome
3	Severe	Hot burning/stinging sensation that causes definite discomfort and may interrupt daily activities and/or sleep

Pruritus: as reported by the subject as being the greatest intensity they have experienced within the last 24 hours at Baseline or since the last visit at subsequent visits.

0	None	No pruritus
1	Mild	Slight pruritus, not really bothersome
2	Moderate	Definite pruritus that is somewhat bothersome
3	Severe	Intense pruritus that may interrupt daily activities and/or sleep

Erythema: as assessed by the Investigator

0	None	No erythema present
1	Mild	Slight pink coloration
2	Moderate	Definite redness
3	Severe	Marked erythema, bright red to dusky dark red in color

Edema: as assessed by the Investigator

0	None	No edema
1	Mild	Slight, but definite edema
2	Moderate	Definite edema
3	Severe	Marked edema

Scabbing/Crusting: as assessed by the Investigator

0	None	No scabbing/crusting
1	Mild	Slight, but definite scabbing/crusting
2	Moderate	Definite scabbing/crusting
3	Severe	Marked scabbing/crusting

6.6.4 Sample Collection

One representative web space, according to the grading of signs and symptoms of T. pedis, must be classified as at least moderate to be designated as the Target Sampling (or target lesion) web space.

Subjects who have both feet affected, will have samples collected from each foot separately. Subjects that have one foot affected and the other foot unaffected, sample will only be collected from the affected foot. Indicate on the CRF if samples were collected from Left and/or Right foot.

For Microbial Sampling
If one foot is moderate and the contralateral foot is less than moderate the less than moderate foot will also be sampled.

For Drug Product Application
Both feet are treated even if one foot is not affected

Baseline Web space ISGA Grading	**Microbial Sampling**	**Drug Product Application**
Clear	No	Yes
Almost Clear	Yes, if contralateral is moderate	Yes
Mild	Yes, if contralateral is moderate	Yes
Moderate	Yes	Yes
Severe	Yes	Yes

Detailed instruction for sample collection and processing are in Table 3 below.

Table 3 Microbiological Samples

	Onsite KOH	Routine Mycology (Fungal Culture & KOH At Central Lab)	Molecular Diagnostics (e-swab)
Day 1 (Baseline -Prior to dose)	Target Sampling Web space	Target Sampling Web space	Target Sampling Web space
1hour after dose			Affected Web space other than Target Sampling Web space
Day 2			Previously not sampled affected Sampling Web space. If not available, then previously not sampled unaffected space.
Day 3			Previously not sampled affected Sampling Web space. If not available, then previously not sampled unaffected space.
Day 7		Target Sampling Web space	Target Sampling Web space
Day 14			Target Sampling Web space
Day 28		Target Sampling Web space	Target Sampling Web space

Throughout the study, continuous monitoring of concomitant medications, therapies and AEs will occur.

6.7 Study Drug Product Administration

All subjects will have a single application of their assigned test article applied by study personnel at the baseline visit. Details of test article preparation are in the Study Operation Manual, in brief, there is a vial with [redacted] in an aqueous gel vehicle. Then approximately 0.5 ml of the test article will be applied to each foot covering the toe web spaces, on and around the toe nails as well as the plantar and lateral aspects of the foot. The product will be allowed to air dry.

6.8 Concomitant medication and Excluded Therapy

Usage of prescription or over the counter topical or systemic medications will be reported during the subject's participation in the study. The use of anti-fungal or antibacterial treatments in the past 4 weeks is an exclusion criterion.

6.9 Investigational Product

The test product will be applied by the Investigator or study personnel at the investigational site. Each subject will have a single application of approximately 0.5 ml of the test article applied to each foot. Both affected and unaffected feet will be treated covering the web spaces, toes, toe nails as well as the plantar and lateral aspect of both feet. The product is formulated as a suspension in a low viscosity aqueous gel. The three dose groups are:

Cohort 1 dose 10^6 /ml CFUs of [redacted]
Cohort 2 dose 10^7/ml CFUs of [redacted]
Cohort 3 dose 10^8/ml CFUs of [redacted]

The cohort 1 dose is comparable to the dose that has been shown to be effective against cutaneous fungal infection of amphibians. It has been estimated that the density of bacteria on normal skin is approximately 1 x 10^5/cm^2. At our highest dose of 10^8 CFUs/ ml applying 0.5 ml to each foot, this volume will cover approximately 500 cm^2. The cohort 1, 2, and 3 doses then we would be adding 10^3 CFUs ,10^4 CFUs, 10^5 CFUs / cm^2, respectively.

The doses in this trial are comparable to the doses used in the study of other topical live bacterial products. An ammonia oxidizing bacterium has been used in Phase 2 trials to treat acne at a dose of 10^9/ml (Aobiome Inc. patent #9738870), a coagulase-negative Staphylococcus at a dose of 10^7/ml CFUs (Williams and Gallo 2017) has been used in atopic dermatitis patients, and a strain P. acnes has been applied to the face of acne patients at a dose of 10^8/ml CFUs. (https://www.clinicaltrials.gov/ct2/show/NCT03450369?term=Naked+Biome&rank=2).

Each of the three groups will have 4 subjects. After the first cohort has completed their day 7 visits, if no significant tolerability or safety issues identified the second cohort will be enrolled. After the

second cohort has completed the day 7 visits and if no significant tolerability of safety issues is identified the third cohort will be enrolled.

6.10 Treatment Compliance

All subjects will receive only a single application of the test article applied at the investigational site by designated study personnel. This will allow for well document compliance, Investigator or designee will record the time, date and dose of drug product administration. Data Analysis and Statistical Consideration.

6.11 General Statistical Considerations

As this is an open label safety and tolerability trial all of the collected data will be presented in listings, tables, and figures in a descriptive fashion.

Primary Objective:
Evaluate the safety and tolerability of DBI-001 in patients with Tinea pedis

Secondary Objective:
Evaluation of presence or persistence of [redacted] of DBI-001 following a single application of DBI-001.

Effect of a single application of DBI-001 on the abundance of *T. rubrum*
Effect of a single application of DBI-001 on the signs and symptoms of interdigital T. pedis.

6.12 Analysis of Data for Objectives

a. Primary Objective: Evaluation of presence or persistence of [redacted] following a single application of DBI-001.
b. Secondary Objective: Effect of a single application of DBI-001 on the abundance of *T. rubrum.*
c. Exploratory Objectives: Effect of a single application of DBI-001 on the signs and symptoms of interdigital T. pedis.

6.13 Analysis Populations

All subjects treated will be included in the analysis

6.14 Sample Size Determination

As there is no formal statistical analysis planned there were no assumption made in selection of the sample size.

7. ASSESSMENT OF SAFETY

7.1 Safety Evaluations and Criteria

Upon completion of the day 7 visit by the first cohort, the Medical Monitor and Investigator will review the safety results and determine if the trial is to proceed with dosing the second cohort. The same process will be completed upon completion of Day 7 for Cohort 2 to determine if Cohort 3 will be enrolled.

As detailed in section 6.6.3, local tolerability will be evaluated by recording the severity of the signs of T. pedis as well as the signs and symptoms of local tolerability on treated areas not involved with T. pedis. In addition, adverse events will be documented.

7.2 Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug product, whether or not it is considered to be study drug product related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug product (treatment-emergent).

7.3 Serious Adverse Event

A serious adverse event (SAE) is any AE, occurring at any dose level and regardless of causality that:

- Results in death.
- Is life-threatening: Life-threatening means that the subject was at immediate risk of death from the reaction as it occurred, (i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.

- Is an important medical event: an important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- A hospitalization for an elective procedure will not be considered a SAE

7.4 Unexpected Adverse Event

An unexpected AE is an AE that is not reported in the Investigator's Brochure (IB).

7.5 Relationship of Adverse Events to Study Drug Product

The following classifications should be used when evaluating the relationship of AEs and SAEs to the investigational drug product.

1. **None**: No relationship between the experience and the administration of study drug product; related to other etiologies such as concomitant medications or subject's clinical state.
2. **Unlikely**: The current state of knowledge indicates that a relationship is unlikely.
3. **Possibly**: A reaction that follows a plausible temporal sequence from administration of the study drug product and follows a known response pattern to the suspected study drug product. The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject.
4. **Probably**: A reaction that follows a plausible temporal sequence from administration of the study drug product and follows a known response pattern to the suspected study drug product. The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.
5. **Definitely**: A reaction that follows a plausible temporal sequence from administration of the study drug product and follows a known response pattern to the suspected study drug product and can be confirmed with a positive re-challenge test or supporting laboratory data.

Severity:

1. Mild: Awareness of sign or symptom, but easily tolerated
2. Moderate: Discomfort enough to cause interference with normal daily activities
3. Severe: Inability to perform normal daily activities
4. Life-threatening: Immediate risk of death from the reaction as it occurred

8. PROCEDURES FOR ADVERSE EVENT RECORDING AND REPORTING

8.1 Emergency Sponsor Contact

In the event of a medical emergency (i.e., an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug product), investigational site personnel must immediately contact the Medical Monitor.

Medical Monitor Contact	
Name:	[redacted]
Telephone:	
Email:	
Name:	[redacted]
Telephone:	
Email:	

8.2 Other Required Safety Assessments

A clinically significant worsening from Baseline of any abnormal study assessment, such as laboratory test, physical examination, or vital signs, should be considered an AE and recorded accordingly. If possible, a diagnosis for the clinically significant study assessment should be provided by the Investigator (e.g., urinary tract infection or anemia). In the absence of a diagnosis, the abnormal study assessment itself should be listed as the AE (e.g., bacteria in urine or decreased hemoglobin).

An abnormal study assessment is considered clinically significant if the subject has one or more of the following related to the abnormal study assessment:

1. Concomitant clinical signs or symptoms.
2. Further diagnostic testing or medical/surgical intervention.
3. Discontinued from the study.

Repeat testing to determine whether the result is abnormal, in the absence of any of the above criteria, does not necessarily meet clinically significant criteria. The determination of whether the study assessment results are clinically significant must be made by the Investigator.

9. SPECIAL REQUIREMENTS AND PROCEDURES

9.1 Study Monitoring

The Clinical Monitor and/or the Sponsor representative will arrange to visit the Investigator sites at regular intervals during the study. The monitoring visits must be conducted according to the applicable International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities. During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be resolved. The Clinical Monitor will be given access to study relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality assurance officers named by DermBiont or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and aid and documentation (including source data) as requested.

9.2 Audits and Inspections

The Investigators and clinical sites will permit study related monitoring, audits, IRB/IEC review, and regulatory inspections as requested by FDA, DermBiont or designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed Informed Consent Forms (ICFs), etc.) in addition to eCRFs.

9.3 Data Quality Control and Quality Assurance

The Investigator is responsible for ensuring the study is conducted according to the protocol, Code of Federal Regulations (CFR), GCP, and applicable regulatory requirements. The responsibilities outlined in these documents along with the identification that a signed informed consent must be obtained prior to a subject participation in the study.

9.4 Confidentiality

To maintain subject privacy, all eCRFs, banked study samples, study drug accountability records, study reports and communications will identify the subject by the assigned subject identification number. The Investigator will grant monitor(s) and auditor(s) from DermBiont or designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

All information regarding the investigational product supplied by DermBiont to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from DermBiont Inc. It is understood that there is an obligation to provide DermBiont with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

9.5 Subject Rights

Study subjects can withdraw their consent to have their clinical samples banked even after the sample has been shipped to the clinical laboratory. A study subject should contact their Investigator or the Investigator's designee and ask for his/her sample to be withdrawn from the bank and destroyed. For samples that have been partially analyzed the remaining sample will be destroyed but the clinical site and DermBiont shall be entitled to retain and use any research results obtained prior to the withdrawal of consent.

9.6 Protocol Amendments

Protocol amendments that impact subject safety, change the scope of the investigation, or affect the scientific quality of the study must be approved by the IRB/IEC and submitted to the appropriate regulatory authorities before implementation of such modifications to the study.

In the event that the protocol needs to be modified immediately to eliminate an apparent hazard to a subject, DermBiont will amend and implement the protocol change and subsequently notify the regulatory authorities and/or the IRB/IEC, as appropriate.

The Investigator should not modify the protocol without agreement from DermBiont and prior review or approval by the IRB/IEC. Any deviations from the protocol should be documented by the Investigator or designee.

9.7 Obligations of the Clinical Investigator

The Investigator will agree to be responsible for the overall conduct of the study; for completing regulatory documents and documentation of training; for ensuring that the study is conducted according to the study protocol; for protecting the rights, safety and welfare of study subjects under their care; and for insuring data quality and integrity.

If any study responsibilities are delegated, the Investigator will be responsible for maintaining written documentation of who is designate to perform the specific responsibilities.

The study will be conducted by qualified study Investigators.

The Investigator or designees are responsible for qualified subjects and collecting samples. The Investigator or designees will be responsible for maintaining records of all samples collected and investigational drug administrations; recording the subject's data on the source documents and eCRFs; documenting the presence of absence of AEs following sample collection and study drug applications and following the reporting requirements of any SAEs to the Sponsor and IRB/IEC.

9.8 Institutional Review Board/Independent Ethics Committee

The Investigator must obtain written IRB/IEC approval of the protocol, approval for relevant supporting information and all types of subject recruitment and advertisement and the ICF prior to starting the study. The IRB/IEC will meet all US FDA requirements governing IRBs/IECs (21 CFR Part 56).

DermBiont or the designee must approve the ICF submitted to the investigational site's IRB/IEC. All subject recruitment and advertisements must be submitted to DermBiont or designee prior to submission to the IRB/IEC, for review.

9.9 Ethical Conduct of the Study

DermBiont and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines and must also conduct the study in accordance with local regulations.

9.10 Written Informed Consent

Written informed consent is required from each subject prior to any testing under this protocol, including screening tests and evaluations. The ICF, as specified by the investigational site's IRB/IEC, must follow the Protection of Human Subjects regulations listed in 21 CFR Part 50.

The background of the proposed study and the benefits and risks of the procedures and study must be explained to the subjects. It is the responsibility of the Investigator to obtain consent and to provide the subject with a copy of the signed and dated ICF. Confirmation of a subject's informed consent must also be documented in the subject's medical record prior to any testing under this protocol, including screening tests and evaluations.

All ICFs used in this study must be approved by the appropriate IRB/IEC and by DermBiont or designee. The ICF must not be altered without the prior agreement of the relevant IRB/IEC and DermBiont.

9.11 Subject Data Protection

Prior to any testing under this protocol, including screening tests and evaluations, subjects must authorize the release and use of protected health information (PHI), as required by local law.

10. DATA HANDLING AND RETENTION OF RECORDS

10.1 Paper and Electronic Case Report Form Completion

Paper CRF and eCRFs will be completed for each enrolled subject. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's paper and eCRF. Source documentation supporting the paper and eCRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject status.

Investigators will maintain copies of the paper CRF and eCRFs at the clinical site. The paper CRF eCRFs will be completed as much as possible for subjects who discontinue or are terminated from the study by the investigator, and the reason for the discontinuation or termination must be clearly and concisely specified on the appropriate paper CRF and eCRF.

10.2 Retention of Records

The Investigator will maintain all study records according to ICH GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. DermBiont must be notified in writing if a custodial change occurs.

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