A Randomized, Observer-Blinded, within Subject Bilateral Comparison to Study the Safety and Efficacy of Daily Application for 4 weeks of DBI-001 Gel Versus Aqueous Gel in Subjects with Atopic Dermatitis

NCT Number: NCT05253755

Document Date: 12/16/2021

DermBiont

CLINICAL STUDY PROTOCOL

Protocol Number: [redacted]

A Randomized, Observer-Blinded, within Subject Bilateral Comparison to Study the Safety and Efficacy of Daily Application for 4 weeks of DBI-001 Gel Versus Aqueous Gel in Subjects with Atopic Dermatitis

Investigational Product:	DBI-001
Development Phase of Study:	Phase 2
US IND Number:	26068
Protocol:	Version 5.0 (16 December 2021)
Supersedes	Version 4.0 (18 November 2021) Version 3.0 (11 April 2021) Version 2.0 (25 March 2021) Version 1.0 (17 July 2020)
Sponsor:	DermBiont, Inc. 451 D Street, Suite 908 Boston, MA 02210
Primary Medical Monitor:	[redacted] Senior Medical Director [redacted]
Secondary Medical Monitor:	[redacted] Chief Medical Officer [redacted]

Property of DermBiont, Inc.

Confidential
May not be used, divulged, published, or otherwise disclosed without the consent of DermBiont, Inc.

DermBiont

SPONSOR PROTOCOL REVIEW AND APPROVAL PAGE

Review and approval by:

[redacted]
Chief Medical Officer

[redacted]
Signature

12/17/2021
Date

[redacted]
Chief Development Officer

[redacted]
Signature

12/17/2021
Date

[redacted]
Chief Scientific Officer

[redacted]
Signature

12/17/2021
Date

[redacted]
Senior Medical Director

[redacted]
Signature

12/17/2021
Date

[redacted]
Vice President of Clinical Operations

[redacted]
Signature

12/17/2021
Date

Protocol Number: DBI-207

DermBiont

INVESTIGATOR AGREEMENT

I have fully discussed the objectives of this study and the contents of this protocol with the sponsor's representative.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Conference on Harmonisation guidelines on Good Clinical Practice (ICH E6), and applicable regional regulatory requirements.

I agree to make available to sponsor personnel, their representatives and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the case report forms. I am aware of my responsibilities as a principal investigator as provided by the sponsor.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the sponsor.

_____ _____

Print Name Signature

_____ _____

Title Date

_____

Institution Name

Signature on this page assures the sponsor that, to the best of the investigator's knowledge, the affiliated Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) operates in accordance with the governing regulations, and that the investigator understands, and agrees to abide by, all governing regulatory obligations and the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) and country and regional (local) requirements while conducting this clinical investigation. Additionally, investigator gives access to all relevant data and records to DermBiont monitors, auditors, DermBiont Clinical Quality Assurance representatives, designated agents of DermBiont, IRBs/IECs/REBs, and regulatory authorities as required.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF DEFINITIONS AND ABBREVIATIONS

TERM	DEFINITION
AD	Atopic Dermatitis
ADSI	Atopic Dermatitis Severity Index
AE	Adverse Event
Aqueous Gel	Water made into a gel with a common gelling agent
CFU	Colony-forming unit, a unit used to estimate the number of viable bacteria or fungal cells in a sample
CFR	Code of Federal Regulations
CRF / eCRF	Case Report Form / electronic Case Report Form
CSSSP	Collection Sampling, Storage & Shipment Plan
DBI-001	Investigational Product, Study Drug- [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.
Swab	It 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
Genodermatoses	Geno dermatoses are genetic diseases with cutaneous expression.
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IEC	Independent Ethics Committee
ICH	International Code of Harmonisation
IRB	Institutional Review Board
IP	Investigational Product
LAR	Legally Authorized Representative
Microbiome	Microorganisms in a particular environment
MITT	Modified intent to treat
PBS	Phosphate Buffered Saline
PHI	Protected Health Information

qPCR	Quantitative polymerase chain reaction
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
Sponsor	DermBiont Inc.
TEAEs	Treatment-emergent Adverse Events
Telemedicine	An audiovisual communication that remotely connects investigators at site with subjects at home

SYNOPSIS

NAME OF SPONSOR: DermBiont Inc. **NAME OF FINISHED PRODUCT**: DBI-001 **NAME OF ACTIVE INGREDIENT(S):** [redacted]	
Title of Study	A Randomized, Observer-blinded, Within Subject Bilateral Comparison to Study the Safety and Efficacy of Daily Application for 4 weeks of DBI-001 Gel Vs. Aqueous Gel in Subjects with Atopic Dermatitis
Investigator(s)	TBD
Study centre(s)	Multiple centres
Publication	N/A
Phase of development	Phase 2b
Objectives	**Primary Objective:** • Effect of daily application of DBI-001 on the signs and symptoms of atopic dermatitis (AD). **Secondary Objectives:** • Determine the antibacterial effect of daily applications of DBI-001 on the abundance of *S. aureus* in the cutaneous microbiome. • To determine the safety and tolerability of DBI-001 Gel vs. Aqueous Gel in subjects with AD. • Evaluation of the presence and persistence of strain [redacted] following daily applications of DBI-001 for 4 weeks. • Characterize changes in abundance and diversity of the microbiome during and following 4 weeks of daily applications of DBI-001. • [redacted] before and after treatment with 4 weeks of daily applications of DBI-001.

Study Design and Evaluation Methods	• A randomized, Observer-blinded, daily application, bilateral study of DBI-001 Gel vs. Aqueous Gel in subjects with AD. • Approximately 20 subjects will be enrolled with clinically stable AD according to the criteria of Hanifin and Rajka[i] with comparable anatomically symmetrical, bilateral target lesions (Hanifin and Rajka 1980). • Subjects meeting the inclusion/exclusion criteria will be enrolled into the study. • Subjects will be instructed to adhere to treatment site restrictions to avoid specific activities 12 hrs. prior to clinic visits and 12 hrs. after test article application that could adversely impact the quality of samples or remove the test articles from the treated sites. Showering or rinsing with water is acceptable. • Each subject will have 1 site identified on comparable anatomically symmetrical, bilateral areas spanning approximately 100 cm^2, which is approximately the area of the palm of the hand. • Clinical evaluations of two sites of AD will be done by an evaluating investigator(s) who is blinded to treatment assignments. • The Atopic Dermatitis Severity Index (ADSI) (Van Leent et al. 1998) is the sum of the severity scores of the signs and symptoms of AD including erythema, pruritus, exudation, excoriation and lichenification. • At Baseline (prior to test article application) and then at, Day 7 (±2),14 (±2), 21 (±2), 28 (±2), 35 (±4) and 42 (±4), samples will be collected using PBS swabs for microbiologic evaluation from both treatment sites. • At Baseline (prior to test article application) and then again at the end of treatment, [redacted] • Both treated sites on all subjects will be treated with 27 daily doses (once daily application for 4 weeks) of the assigned test articles applied by study personnel at the baseline visit, Days 7 (±2),14 (±2), and 21 (±2). Between visits on weekdays, subjects, or legally authorized representative (LAR), will apply the daily doses during telemedicine visits with a treating investigator, or qualified delegate. On weekends subjects or LAR will apply doses unsupervised.
Methodology	Observer-Blinded, Randomized, Aqueous Gel-Controlled, Bilateral
Number of subjects	Approximately 20 Subjects
Study Population	Males and females ages 12-65, in general good health with AD and comparable anatomically symmetrical bilateral AD lesions areas.

Inclusion Criteria	Subjects must meet all of the following criteria to be included in the study: 1. Ability to understand, agree to, and sign the study Informed Consent. If the subject is unable to provide consent for him/herself, the subject's legally authorized representative may provide written consent. 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 or Female Subjects of any race 12-65 years of age. 4. Physician diagnosed clinically stable AD according to the criteria of Hanifin and Rajka[ii] with comparable anatomically symmetrical, bilateral target lesions (Hanifin and Rajka 1980). Lesions must have an Atopic Dermatitis Severity Index (ADSI) ≥6. The two sites need to be comparable anatomically symmetrical sites. It will be in the opinion of the Investigator based on subject's medical history whether the lesions are clinically stable. 5. Female subjects of child-bearing potential must use at least one method of birth control that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence or vasectomized partner for the duration of study participation. 6. Technical ability and willingness to self-apply, or LAR to apply, test articles during telemed visits with the study staff and unsupervised on weekends. 7. Willingness to discontinue use of systemic AD treatments and topical treatments to the target areas for the duration of the study unless specifically permitted by the Investigator. 8. Willingness to comply with test site restriction for 12 hours prior to all office visits including the Baseline visit and for 12 hours after each treatment application. These treatment site restrictions include: a. No washing of test sites with any cleansers or soaps at any time from the Baseline visit to completion of the Day 42 Follow up Visit. Water passing over the areas during showering is acceptable. b. No rubbing the test sites with a washcloth, towel, luffas. Pat dry after showering is acceptable. c. No recreational activities in chlorinated or chemically treated water such as swimming pools, hot tubs, and spas. d. No tight or form fitting clothing covering the treatment areas. e. No sunbathing or use of suntan parlors or tanning beds. f. If participating in physical activities resulting in heavy perspiration only pat dry test site areas with towel if needed. g. Any activity that in the opinion of the investigator might alter the quality of the samples collected or risk removal of the test article.

	9. Willingness to undergo the following washout periods: a. Washout of 2 weeks prior to the Baseline visit for topical treatments used on the two treatment target sites, including but not limited to: antibacterial products, anti-inflammatories (e.g., corticosteroids, tacrolimus, Pimecrolimus). Other than the two treatment sites, topical medications may be **used** before/during the duration of the study. Subjects will be provided 1% hydrocortisone for treating non-target areas during the trial. b. Washout of 4 weeks prior to the Baseline visit for systemic treatments for AD, including but not limited to corticosteroids (oral or intramuscular injections), systemic immunomodulators or immunosuppressive agents (e.g., methotrexate, cyclosporine, hydroxychloroquine), antibiotics (oral or injected, if required to treat a medical condition short duration of oral antibiotics (≤10 days) are permitted after randomization) c. Washout of 2 weeks prior to the Baseline visit for bleach baths. d. Washout of 2 weeks prior to the Baseline visit for phototherapy. 10. No history of allergy to at least two of the following classes of antibiotics: Cephalosporins, Quinolones, Tetracyclines, Aminoglycosides Macrolides, Carbapenems and Lipopeptides. 11. Willingness to allow digital photos of treatment areas to be taken and stored.
Exclusion Criteria	1. Women who are pregnant, planning a pregnancy, breastfeeding or have a positive pregnancy test at screening. 2. Any dermatological conditions that could interfere with clinical evaluations or any disease state or physical condition which might expose the subject to an unacceptable risk by study participation. 3. Any underlying disease(s) or other dermatological conditions that require the use of exclusionary topical or systemic therapy. 4. Spontaneously improving or rapidly deteriorating dermatitis anywhere on the body. 5. Netherton's syndrome or other genetic dermatoses that result in defective epidermal barrier function. 6. Treatment of any type of cancer within the last 6 months other than cutaneous basal cell carcinoma. 7. History of any significant internal disease (which contraindicates use of live microbiome e.g., leukemia, liver failure, cardiovascular disease). 8. 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. 9. AIDS or AIDS related complex by medical history. 10. Known or suspected immune suppressive medications or diseases or any condition that in the opinion of the investigator would increase the subject's susceptibility to opportunistic infections. 11. Treatment with systemic immune modulating or anti-inflammatory biologic agents within 16 weeks of Baseline Visit. 12. Poorly controlled diabetes mellitus Type I or II by medical history. 13. Peripheral vascular disease based on medical history. 14. Any subject not able to meet the study attendance and telemed visit requirements. 15. Participants with a history of psychiatric disease or history of alcohol or drug abuse that would interfere with the ability to comply with the study protocol. 16. 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 articles will be applied by designated unblinded treating investigator(s) at respective the investigational site(s) on Baseline/Day 1 followed by weekly applications on Days 7 (+/-2), 14 (+/-2), and 21 (+/-2).) The daily applications between visits will be applied by the subjects, or LAR, under the supervision of a designated treating investigator(s), or delegate(s), during a telemed visit on weekdays and unsupervised on weekends. Approximately 0.1ml of the assigned test articles will be applied to designated treatment sites. 1mL vial of DBI-001 gel contains 10^7-10^9 CFU/mL of [redacted] Approximately 0.1mL applied to a treatment area that is approximately 100 cm^2 will contain approximately 10^{4-6} CFU per cm^2 of [redacted]
Duration of Trial	Approximately 56 days (+/-4) including up to 14 days from Screening Visit to Baseline Visit, a 28 (+/-2) day treatment period followed by a 14 (+/-4) day post treatment follow up.
Statistical methods	All subjects who are randomized and treated with test article will be included in the Intent-to-Treat analysis set. All subjects who are randomized, receive at least one (1) confirmed dose of test article, and have at least one (1) post-baseline safety assessment will be included in the Safety analysis set.

	The evaluation of *S. aureus* qPCR and CFU abundance will be performed on all subjects and separately in a modified intent to treat (MITT) population defined as subjects with bilateral abundant S. aureus at baseline as detected by qPCR. A MITT population defined as all subjects with [redacted] detected by qPCR at one or more time points in samples obtained from one treatment targeted site but no [redacted] detected in any sample from the contralateral treatment targeted site at any time point during the trial will also be evaluated. Linear interpolation of efficacy variables will be performed using observed data that precedes and follows the off-schedule visit, if present. The last observation will be carried forward if all the data subsequent to the off-schedule value is missing. No adjustments for multiplicity will be made; p-values are primarily presented for descriptive purposes.
Safety Evaluation	Tolerability will be evaluated through assessment of the severity of the signs and symptoms of the disease state (erythema, pruritus, exudation, excoriation and lichenification) as well as pain, burning, or stinging and review of adverse events. 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 (CRFs).
Sample Size	Sample size is based on clinical judgement and published literature on this type of trial and is deemed adequate to successfully demonstrate the stated goals.

Study Endpoints	**Primary Study Endpoint:** The hypothesis of this trial related to clinical effect is that 4 weeks of daily dosing with DBI-001 will improve AD based on evaluation of signs and symptoms of AD in the comparison of sites treated with DBI-001 DP or Aqueous Gel on the following: • Change from baseline in ADSI score at days 7 (±2), 14 (±2), 21 (±2), 28 (±2), 35 (±4) and 42 (±2). • Change from baseline in individual signs and symptoms of AD (components of ADSI score) at days, 7 (±2), 14 (±2), 21 (±2), 28 (±2) 35 (±4) and 42 (±2). **Secondary Endpoints:** In the *S. aureus* MITT population, comparison of sites treated with DBI-001 or Aqueous Gel on the following microbial metrics: • Change from baseline in signs and symptoms of local tolerability (erythema, pruritus, exudation, excoriation and lichenification as well as pain, burning or stinging) for the DBI-001-treated sites vs. the Aqueous Gel-treated sites. • Change from baseline in abundance of *S. aureus* based on molecular diagnostic qPCR on samples obtained from lesioned skin at days 7, 14, 21, 28, 35 and 42. • Change from baseline in abundance of *S. aureus* based on CFU counts on samples obtained from lesioned skin at days 7, 14, 21, 28, 35, and 42. • The proportion of subjects with a greater decrease in ADSI for the DBI-001-treated site than the Aqueous Gel-treated site. • Changes in the abundance and diversity of the microbiome for the DBI-001-treated sites vs. the Aqueous Gel-treated sites**.** • [redacted] before and after treatment with 4 weeks of daily applications of DBI-001.

Analysis of Efficacy	**Primary:** The primary analysis will compare the differences from baseline in ADSI score between DBI-001 and Aqueous Gel treated sites will be done using a two-sided Wilcoxon sign rank test at each of Days 7, 14, 21, 28, 35 and 42. The proportion of subjects with a greater decrease in ADSI for the DBI-001-treated sites than the Aqueous Gel-treated sites will be summarized descriptively for Days, 7, 14, 21, 28, 35, and 42. Comparison of differences at Day 28 between DBI-001 and Aqueous Gel of abundance of [redacted] on treated sites will be done using a two-sided Wilcoxon sign rank test. Comparison of differences at Day 28 between DBI-001 and Aqueous Gel of abundance and diversity of the microbiome based on DNA sequencing will be done using a two-sided Wilcoxon sign rank test. Comparisons at Days 7, 14, 21, 35, and 42 will also be done. Additionally, a repeated measures model will be used to compare DBI-001 to Aqueous Gel for the secondary endpoints. P-values will be provided for descriptive purposes. **Secondary:** The secondary analysis of the S. aureus MITT population will compare the differences in change from baseline and Day 28 between DBI-001 and Aqueous Gel treated sites in abundance of *S. aureus* based on qPCR and CFU counts using a 2-sided Wilcoxon sign rank test, alpha = 0.05, with a null hypothesis of median difference equal to zero. Comparisons at Days 7, 14, 21, 35, and 42 will also be done. Additionally, a repeated measures model will be used to compare DBI-001 to Aqueous Gel for the secondary endpoint. P-values will be provided for descriptive purposes. [redacted] **Exploratory:** Comparison in changes in the overall microbiome as defined by 16s and/or whole genome sequencing of samples obtained prior to, during, and after treatment.

	Comparison of change from baseline in individual signs and symptoms of AD (components of ADSI score) between DBI-001 and Aqueous Gel treated sites will be done using a two-sided sign test at each of Days 7, 14, 21, 28, 35, and 42. Additionally, a repeated measures model will be used to compare DBI-001 Gel to Aqueous Gel for the above exploratory endpoints.
Analysis of Safety	Signs and symptoms of local tolerability (erythema, pruritus, exudation, excoriation and lichenification as well as pain, burning, or stinging) will be summarized with changes from baseline. 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, seriousness, action taken regarding the investigational product, corrective treatment, outcome, and Investigator's assessment of causality. All reported treatment-emergent AEs (TEAEs), defined as any AE with an onset on or after the date of first investigational product application, will be summarized by treatment group, the number of subjects reporting TEAEs, system organ class, preferred term, severity, and relationship to investigational product. When summarizing TEAEs by severity or relationship to investigational product, each subject will be counted only once within a system organ class or a preferred term using the event with the greatest severity or causality, respectively, within each category. All reported serious adverse events (SAEs) will be summarized by treatment group, the number of subjects reporting SAEs, system organ class, preferred term, severity, and relationship to investigational product. All information pertaining to AEs noted during the study will be listed by subject and will include a verbatim description of the event as reported by the Investigator, as well as the preferred term, system organ class, start date, stop date (if stopped), seriousness, severity, action taken regarding the investigational product, corrective treatment, outcome and relationship to the investigational product. In addition, a listing of subjects who prematurely discontinue from the study due to AEs will be provided as well as a listing of subjects who reported an SAE.
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.

Study Design/Type	This is a randomized, observer blinded, Aqueous Gel-controlled, daily application for 4 weeks, within-subject, bilateral comparison trial examining the effect of DBI-001 Gel vs. Aqueous Gel on the clinical ADSI scores and the abundance of *S. aureus* of comparable bilateral target sites of AD as well as signs and symptoms of local tolerability on treated sites in subjects. Subjects meeting the inclusion/exclusion criteria and having moderate to severe AD lesions at screening and baseline/Day 1 will be enrolled into the study. In an observer-blinded fashion, each subject will have two sites randomly assigned to have either DBI-001Gel or Aqueous Gel applied to the designated treatment targeted sites. After Screening, Study visits will occur at Day 1 Baseline then Days 7 (±2), 14 (±2), 21 (±2), 28 (±2), 35 (±4), and 42 (±4). At each study visit, the following procedures will be conducted: clinical assessment of signs and symptoms of AD, ADSI clinical scoring, clinical signs and symptoms of erythema, pruritus, exudation, excoriation, lichenification. pain, burning, or stinging, and collection of microbiologic samples. [redacted] Photos of both treatment sites will be taken on all visits except the Screening Visit.

Table 1. Schedule of Events.

Evaluation	[a]Screen (- 14 Day to day 0)	Day 1 Baseline	Day 7 (±2)	Day 14 (±2)	Day 21 (±2)	Day 28 (±2)	Day 35 (±2)	Day 42 (±4)
	Treatment						Follow-up	
Demographics	X							
Inclusion/Exclusion	X							
Urine Pregnancy test (For Women of childbearing potential)	X			X				X
Confirm Compliance with Treatment Site Restrictions[b]		X	X	X	X	X	X	X
Medical History	X							
Concomitant Medication Query	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X
Clinical Assessment of Local Tolerability		X[c]	X	X	X	X	X	X
Calculate ADSI Scores based on Signs and Symptoms of AD	X	X	X	X	X	X	X	X
Digital Images of Both Treatment Sites		X	X	X	X	X	X	X
PBS Swabs from both Sites		X	X	X	X	X	X	X
Sample both Sites [redacted]		X				X		
Apply Test Articles After all Evaluations and Sampling		X	X	X	X			
Collect Returned Used and Unused Test Articles			X	X	X	X		
Dispense Test Articles for Home Application		X	X	X	X			
Review Treatment Site Restrictions		X	X	X	X			
Review Procedures for Telemed Visits		X						
Dispense 1% Hydrocortisone Ointment as Needed		X	X	X	X	X	X	X
Appointment for Next Clinic Visit and Telemed[a] Visits	X[a]	X	X	X	X	X	X	

[a] Screening and Baseline visits can be on the same day only if *all* eligibility criteria are met and *all* required Screening and Day 1/Baseline tests and tasks are completed on the same day.

[b] Except for the Day 28, 35, or 42 visits, if violations of treatment site restrictions prior to the visit are reported, details of the violation should be recorded in the CRF and the visit should be completed including evaluations and sampling.

[c] On Baseline/Day 1, local tolerability is to be assessed 30-minutes after application of test articles.

For the Day 28, 35, and 42 Visits:
If violations of treatment site restrictions reported occurred more than 24 hours prior to the visit at the Day 28, 35, or 42 visits, details of the violation should be recorded in the CRF and the evaluations and sampling completed as scheduled.

If violations of treatment site restrictions less than 24 hours prior to the visit is reported at the Day 28, 35, or 42 visits, details of the violation should be recorded in the CRF. Evaluations can be completed but an additional visit 24-48 hours after the violation should be scheduled for sample collections.

Details on sampling sites are in Table 2 and the Collection Sampling, Storage, Shipping Procedure, provided separately.

1. INTRODUCTION

Background Information

DBI-001 is a topical live bacterial product containing [redacted] (a strain isolated from humans, [redacted]). This product is being developed as a topical probiotic for the treatment of diseases of the skin. [redacted] is an aerobic Gram-negative bacterium commonly found in the soil, water, vegetables and grains from the human food chain (Asakura et al. 2016; DR001 2019; DR002 2019) and on the skin of healthy humans (DR001 2019; DR002 2019). The strain of [redacted] is a strain that DermBiont isolated from the skin of a healthy young adult. Based on c DNA sequencing, this strain has no known virulence factors nor genes that would indicate antimicrobial resistance. In vitro, the [redacted] strain has been shown to inhibit the growth of *S. aureus* and dermatophytes. This strain is sensitive to commonly used antibiotics.

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 not thought to contribute to health or disease. In recent years, enabled by the availability of DNA sequencing, what had been called the normal flora is now called the microbiome. DNA sequencing is able to detect the many organisms that are either difficult or impossible to grow using routine culturing techniques. A normal microbiome can contribute to health while an abnormal microbiome, a dysbiosis, can be associated with disease.

Atopic dermatitis (AD) is a common skin disease that affects a large proportion of the adult and pediatric population worldwide. *S. aureus* presence in the cutaneous microbiome of AD patients has been directly correlated to disease severity (Blazewicz et al. 2017; Hepburn et al. 2017). In the case of *S. aureus* and AD, it now appears this is not an "infection" in the traditional sense, but rather a dysbiosis characterized by decreased overall diversity of organisms and a high abundance of *S. aureus*. It has been hypothesized that in subjects without AD, the commensal bacteria in the microbiome contribute to host defense by producing metabolites that can control the abundance of *S. aureus*. The dysbiosis seen in AD may be functionally important because of a loss of these protective strains as well as the AD patient's deficiency in host produced antimicrobial peptides. Several different bacterial species on healthy human skin produce anti–*S. aureus* activity and bacteria with this activity were far less frequent on the skin of AD patients. The application of antimicrobial Coagulase Negative Staphylococci (CoNS) strains to animal or human skin greatly reduced *S. aureus* abundance. Together, these observations show that specific bacteria within the human skin microbiome defend against an overabundance of *S. aureus* (Nakatsuji et al. 2017; Williams and Gallo 2017).

Application of [redacted] to the skin of amphibians has been shown to treat and prevent the acquisition of a lethal cutaneous fungal infection. (Harris et al. 2009). The exact mechanism by which [redacted] inhibits the growth of bacteria, fungi and other microorganisms is not yet known. It is known that [redacted] produces some metabolites that have antimicrobial activity. These compounds are [redacted].

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 at a dose of 10^9 CFUs/ml (US9738870B2 2017). In addition, a coagulase-negative *Staphylococcus* strain at a dose of 10^7CFUs/ml (Williams and Gallo 2017) has been used in atopic dermatitis patients, and a strain of *P. acne* has been applied to the face of acne patients at a dose of 10^8CFUs/ml (Naked_Biome:NCT03450369 2018). In addition, the sponsor has completed clinical trials with DBI001 in patients with AD (DBI-CSR-203) and T. pedis (DBI-CSR-201, DBI-CSR-204) .

The Sponsor believes that it is possible that the application of DBI-001 to the skin of patients with AD will decrease the abundance of *S. aureus* resulting in an improvement in the signs and symptoms of AD. This therapeutic approach would have the potential to decrease the use of oral and topical antibiotics.

The purpose of the current protocol is to investigate the effect of [redacted] on the signs and symptoms of AD. In addition, the safety, tolerability and efficacy of daily application of [redacted] to the skin of AD subjects will be evaluated as will the effect of [redacted] on the abundance of *S. aureus*.

1.2 Rationale

In-vitro [redacted] has been shown to significantly inhibit the growth of *S. aureus* (DR005 2019) most frequently associated with AD. 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. (Harris et al. 2009). In a previous small pilot clinical trial, a single application of DBI001 was well tolerated and resulted in the reduction in the abundance of *S. aureus* and improvement in the signs and symptoms of AD, most noticeable pruritis (DBI-CSR-203). In a clinical trial of subjects with T. pedis 28 daily applications of DBI001 to the entire foot was well tolerated, decreased the abundance of T. rubrum, and improved the signs and symptoms of T. pedis. (DBI-CSR-201, DBI-CSR-204) Based on these observations, topical application of the probiotic [redacted] has the potential to be a novel approach to the treatment of AD.

POTENTIAL RISKS AND BENEFITS

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 AD, impetigo, folliculitis, or cellulitis. It is possible that [redacted] could be an opportunistic pathogen in severely immune compromised subjects. PBS solution will be used to collect samples and it could cause a local irritant reaction [redacted]

As detailed in the Investigator's Brochure, if worsening of the AD, impetigo, or folliculitis or cellulitis were to occur, [redacted] is susceptible to commonly used topical and oral antimicrobials and antibiotics.

Potential Benefits

It is possible that daily applications of [redacted] could result in improvement in the subject's AD. Such a treatment also has the potential to decrease the use of oral and topical antibiotics.

3. STUDY OBJECTIVES AND PURPOSE

The purpose of the study is to evaluate the effect of 27 daily applications of DBI-001 on the signs and symptoms of active AD, and the safety and tolerability of DBI-001 in subjects with active AD. Secondly, to see the effect of this treatment on the abundance of *S. aureus*. Thirdly to evaluate the presence or persistence of [redacted] and the impact on the overall microbiome following once daily application of DBI-001 for 4 weeks.

STUDY DESIGN AND ENDPOINTS

Description of the Study Design

This is a randomized, observer blinded, Aqueous Gel-controlled, once daily application for 27 days within-subject, bilateral comparison trial examining the effect of DBI-001 Gel vs. Aqueous Gel. Approximately 20 subjects will be enrolled. Women of childbearing potential will be tested for pregnancy with urine pregnancy test. Women who are pregnant or who have a positive pregnancy test will be excluded from the study. At each investigative site there will be two types of investigators: treating investigators and evaluating or observing investigators. The treating investigator(s), or delegate(s), will apply the treatments and be unblinded to treatment assignment.

The observing or evaluating investigator(s) will be blinded to treatment assignment and perform all clinical evaluations.

Subjects meeting the inclusion/exclusion criteria will be enrolled into the study. Each subject's comparable anatomically symmetrical, bilateral treatment sites will be randomly assigned to be treated with either DBI-001 or the Aqueous Gel control. Treatments will be applied in the clinic by a treating investigator, or designee. On weekdays at home, the subjects, or LAR, will apply under the supervision (by telemed) of a treating investigator, or delegate(s), and unsupervised (no telemed visit) on weekends. Clinical evaluations will be made by a blinded-to-treatment evaluating investigator who will grade the severity of signs and symptoms of AD (erythema, pruritus, exudation, excoriation and lichenification) to calculate the ADSI score and local tolerability, which will also include assessment of the severity of pain, burning, or stinging as reported by subjects. Samples for microbiology will be tested by qPCR for the presence and abundance of [redacted] and *S. aureus*, 16s and/or whole genome sequencing will be used to characterize the entire microbiome. [redacted]

After Screening, study visits will occur at Day 1 Baseline (may be combined with Screening), Days 7 (±2), 14 (±2), 21 (±2), 28 (±2), 35 (±4), and 42 (±4). At each study visit, the following procedures will be conducted: clinical assessment of the severity of the signs and symptoms of AD (erythema, pruritus, exudation, excoriation and lichenification) and the severity of local tolerability (pain, burning, or stinging) as reported by subjects in addition to erythema, pruritus, exudation, excoriation, and lichenification. [redacted]. Subjects will be instructed on test site restrictions related to avoiding activities for 12 hours prior to clinic visits and 12 hours after test article application that might affect the quantity of quality samples collected, impact the signs and symptoms of AD, or remove test articles from the treatment sites. Images of both treated sites will be taken at all visits except Screening. Subjects will be queried for adverse events during their follow up visits.

Study Endpoints

4.2.1 Primary Endpoint

The hypothesis of this trial related to clinical effect is that 4 weeks of daily dosing with DBI-001 will improve the signs and symptoms of AD in comparison of sites treated with DBI-001 DP or Aqueous Gel on the following:

- Change from baseline in ADSI score at days 7 (±2), 14 (±2), 21 (±2), 28 (±2), 35 (±4), and 42 (±4).
- Change from baseline in individual signs and symptoms of AD (components of ADSI score) at days 7 (±2), 14 (±2), 21 (±2), 28 (±2) 35 (±4), and 42 (±2).

4.2.2 Secondary Endpoints

In the *S. aureus* MITT population, comparison of sites treated with DBI-001 or Aqueous Gel on the following microbial metrics:

- Change from baseline in abundance of *S. aureus* based on molecular diagnostic qPCR and CFU counts on samples obtained from treatment sites at days 7, 14, 21, 28, 35, and 42.
- Abundance of [redacted] based on qPCR and CFU counts.
- Changes in the abundance and diversity of the microbiome as determined by 16s and/or whole genome sequencing.
- The proportion of subjects with a greater decrease in ADSI for the DBI-001-treated site than the Aqueous Gel-treated site.
- Change from baseline in signs and symptoms of local tolerability (pruritus, erythema, exudation, excoriation, and lichenification as well as pain, burning, or stinging) for the DBI-001-treated lesion and the Aqueous Gel-treated lesion.

INVESTIGATIONAL PRODUCT (IP)

Investigational Product and Aqueous Gel (Test Articles)

Test articles	Doses per Subject
1mL vial contains DBI-001 Gel with 10^7-10^9 CFU / mL of [redacted] *or* **Aqueous Gel**	27 doses (once daily for 4 weeks)

ELIGIBILTY CRITERIA

Inclusion Criteria

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

1. Ability to understand, agree to, and sign the study Informed Consent. If the subject is unable to provide consent for him/herself, the subject's legally authorized representative may provide written consent.

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 or Female Subjects of any race 12-65 years of age.

4. Physician diagnosed clinically stable AD according to the criteria of Hanifin and Rajka with comparable anatomically symmetrical, bilateral target lesions (Hanifin and Rajka 1980). Each lesion must have an Atopic Dermatitis Severity Index (ADSI) score of ≥ 6. It will be in the

opinion of the Investigator based on subject's medical history whether the lesions are clinically stable.

5. Female subjects of child-bearing potential must use at least one method of birth control that results in a low failure rate (i.e., less than 3 % per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence or vasectomized partner for the duration of study participation.

6. Technical ability and willingness to self-apply, or LAR to apply, test articles during telemed visits with the study staff.

7. Willingness to discontinue use of systemic AD treatments and topical treatments to the target areas for the duration of the study unless specifically permitted by the Investigator.

8. Willingness to comply with test site restriction for 12 hours prior to all office visits including the Baseline visit and for 12 hours after each treatment application. These treatment site restrictions include:

a. No washing of test sites with any cleansers or soaps. Water passing over the areas during showering is acceptable.
b. No rubbing the test sites with a washcloth, towel, luffas. Pat dry after showering is acceptable.
c. No recreational activities in chlorinated or chemically treated water such as swimming pools, hot tubs, and spas.
d. No tight or form fitting clothing covering the treatment areas.
e. No sunbathing or use of suntan parlors or tanning beds.
f. If participating in physical activities resulting in heavy perspiration only pat dry test site areas with towel if needed.
g. Any activity that in the opinion of the investigator might alter the quality of the samples collected or risk removal of the test article.

9. Willingness to undergo the following washout periods:

a. Washout of 2 weeks prior to the Baseline visit for topical treatments used on the two treatment target sites, including but not limited to: antibacterial products, anti-inflammatories (e.g., corticosteroids, tacrolimus, Pimecrolimus). Other than the two treatment sites, topical medications may be used before/during the duration of the study. Subjects will be provided 1% hydrocortisone for treating non-target areas during the trial.

b. Washout of 4 weeks prior to the Baseline visit for systemic treatments for AD, including but not limited to corticosteroids (oral or intramuscular injections), systemic immunomodulators or immunosuppressors (e.g., methotrexate, cyclosporine, hydroxychloroquine), antibiotics (oral or injected, if required to treat a medical condition short duration of oral antibiotics (≤10 days) are permitted after randomization)
c. Washout of 2 weeks prior to the Baseline visit for bleach baths.
d. Washout of 2 weeks prior to the Baseline visit for phototherapy.

10. No history of allergy to at least two of the following classes of antibiotics:

Cephalosporins, Quinolones, Tetracyclinea, Aminoglycosides Macrolides, Carbapenems and Lipopeptides.

11. Willingness to allow digital photos of treatment areas to be taken and stored.

Exclusion Criteria

The following are the exclusion criteria that will exclude subjects from enrolling into the trial:

1. Women who are pregnant, planning a pregnancy, breastfeeding or have a positive pregnancy test at screening.

2. Any dermatological conditions that could interfere with clinical evaluations or any disease state or physical condition which might expose the subject to an unacceptable risk by study participation.

3. Any underlying disease(s) or other dermatological conditions that require the use of exclusionary topical or systemic therapy.

4. Spontaneously improving or rapidly deteriorating dermatitis anywhere on the body.

5. Netherton's syndrome or other genetic dermatoses that result in defective epidermal barrier function.

6. Treatment of any type of cancer within the last 6 months other than cutaneous basal cell carcinoma.

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

8. Subjects who are known to be allergic to any of the test product(s) or any components in the test product(s) or have a history of hypersensitivity or allergic reactions to any of the study preparations as described in the Investigator's Brochure.

9. AIDS or AIDS related complex by medical history.

10. Known or suspected immune suppressive medications or diseases or any condition that in the opinion of the investigator would increase the subject's susceptibility to opportunistic infections.

11. Treatment with systemic immune modulating or anti-inflammatory biologics agents within 16 weeks of Baseline Visit.

12. Poorly controlled diabetes mellitus Type I or II by medical history.

13. Peripheral vascular disease based on medical history.

14. Any subject not able to meet the study attendance and telemed visit requirements.

15. Participants with a history of psychiatric disease or history of alcohol or drug abuse that would interfere with the ability to comply with the study protocol.

16. 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.

Recruitment and Retention

Subjects will be recruited from the Investigator's clinical dermatology practice. Subjects may also be recruited through the use of recruitment material(s) approved by the study IRB or Ethics Committee.

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 documented accordingly. Subjects may be replaced at the discretion of the Investigator and/or 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

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

The sponsor (Medical Director/Chief Medical Officer) will halt the study for a review of the safety data if there are safety concerns noted for any reason and if one or more subjects experience two AE's assessed as a Grade 3 (severe) or higher, of the same type that is considered possibly, probably or definitely related to the IP.

Study Visits

The study will be conducted with a Screening visit, Day 1 / Baseline visit, Study Day visits 7, 14, 21, 28 and two follow-up visits on Days 35 and 42.

If reported violations of treatment site restrictions occurred prior to the visit at Screening, Day 1 / Baseline, Day 7, 14 or 21, details of the violation should be recorded in the CRF and the evaluations and sampling completed as scheduled.

If reported violations of treatment site restrictions occurred less than 24 hours prior to the visit at Day 28, 35, or 42, details of the violation should be recorded in the CRF and evaluations can be completed, but an additional visit 24-48 hours after the violation should be scheduled for sample collections. However, if reported violations of treatment site restrictions occurred more than 24 hours prior to the visit at Day 28, 35, or 42, details of the violation should be recorded in the CRF and the evaluations and sampling completed as scheduled.

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 evaluations.

(-14 Day to Day 0) Screening visit:

1. Informed consent.
2. Record demographics.
3. Review of Inclusion/Exclusion Criteria.
4. Women of childbearing potential will be tested for pregnancy with a urine pregnancy test.
5. Medical history.
6. Concomitant medication.
7. Record adverse event, if any.
8. Clinical assessment of signs and symptoms of AD Calculate ADSI score of both potential treatment sites.
9. Schedule baseline visit

Screening and Day 1 / Baseline visit can be on the same day.

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

6.5.2 All Other Visits

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

The Screening and Day 1/Baseline visit can be combined for subjects meeting *all* eligibility requirements and only if *all* Screening and Day 1/Baseline tests and tasks can be completed on the same day.

Day 1/Baseline visit:

1. Confirm compliance with treatment site restrictions.
2. Record any changes in concomitant medications.
3. Record adverse event, if any.
4. Blinded evaluating investigator complete clinical assessment of severity of signs and symptoms of AD prior to application of test article.
5. Calculate ADSI score of both potential treatment sites if the Screening visit was on an earlier date. At Baseline, if ADSI eligibility criterion is no longer met, the subject is to be withdrawn from the study prior to sample collection and test article application.
6. Digital images of both treatment sites.
7. Collect PBS swabs from both treatment sites.
8. Collect samples [redacted] from both treatment sites.
9. Unblinded treating investigator, or designee, to train subjects and/or LAR on method for self- or LAR to apply with a training vial.
10. Unblinded treating investigator, or designee, apply test articles after all evaluations and sampling have been completed.
11. Blinded evaluating investigator complete clinical assessment of local tolerability (severity pain, burning, or stinging in addition to pruritus, erythema, exudation, excoriation, and lichenification) 30-minutes after application of test articles to both treatment sites.
12. Review treatment site restrictions.
13. Review procedures for telemed visits.
14. Dispense 1% hydrocortisone ointment as needed.
15. Schedule appointment for Day 7 clinic visit and telemed visits.

Detailed instructions for sample collection, storage, and shipping are in the Collection Sampling, Storage, Shipping Procedure (CSSSP) provided separately. If violations of treatment site restrictions prior to the visit are reported details of the violation should be recorded in the CRF and the visit should be completed including evaluations and sampling.

Day 7 (±2)

1. Confirm compliance with treatment site restrictions.
2. Record any changes in concomitant medications.
3. Record adverse event, if any.
4. Blinded evaluating investigator complete clinical assessment of severity of signs and symptoms of AD.
5. Blinded evaluating investigator complete clinical assessment of local tolerability (severity pain, burning, or stinging in addition to pruritus, erythema, exudation, excoriation, and lichenification).
6. Calculate ADSI score of both potential treatment sites.
7. Digital images of both treatment sites.
8. Collect PBS swabs from both treatment sites.
9. Unblinded treating investigator, or designee, apply test articles after all evaluations and sampling have been completed.
10. Collect used and unused returned test articles.
11. Dispense test articles for home treatment.
12. Review treatment site restrictions.
13. Dispense 1% hydrocortisone ointment as needed.
14. Schedule appointment for Day 14 clinic visit and telemed visits.

Detailed instructions for sample collection, storage, and shipping are in CSSSP provided separately. If violations of treatment site restrictions prior to the visit is reported details of the violation should be recorded in the CRF and the visit should be completed including evaluations and sampling.

Day 14 (±2)

1. Women of childbearing potential will be tested for pregnancy with a urine pregnancy test.
2. Confirm compliance with treatment site restrictions.
3. Record any changes in concomitant medications.
4. Record adverse event, if any.
5. Blinded evaluating investigator complete clinical assessment of severity of signs and symptoms of AD.
6. Blinded evaluating investigator complete clinical assessment of local tolerability (severity pain, burning, or stinging in addition to pruritus, erythema, exudation, excoriation, and lichenification).
7. Calculate ADSI score of both potential treatment sites.
8. Digital images of both treatment sites.

9. Collect PBS swabs from both treatment sites.
10. Unblinded treating investigator, or designee, apply test articles after all evaluations and sampling have been completed.
11. Collect used and unused returned test articles.
12. Dispense test articles for home treatment.
13. Review treatment site restrictions.
14. Dispense 1% hydrocortisone ointment as needed.
15. Schedule appointment for Day 21 clinic visit and telemede visits.

Detailed instructions for sample collection, storage, and shipping are in the CSSSP provided separately**.** If violations of treatment site restrictions prior to the visit is reported details of the violation should be recorded in the CRF and the visit should be completed including evaluations and sampling

Day 21 (±2)

1. Confirm compliance with treatment site restrictions.
2. Record any changes in concomitant medications.
3. Record adverse event, if any.
4. Blinded evaluating investigator complete clinical assessment of severity of signs and symptoms of AD.
5. Blinded evaluating investigator complete clinical assessment of local tolerability (severity pain, burning, or stinging in addition to pruritus, erythema, exudation, excoriation, and lichenification).
6. Calculate ADSI score of both potential treatment sites.
7. Digital images of both treatment sites.
8. Collect PBS swabs from both treatment sites.
9. Unblinded treating investigator, or designee, apply test articles after all evaluations and sampling have been completed.
10. Collect used and unused returned test articles.
11. Dispense test articles for home treatment.
12. Review treatment site restrictions.
13. Dispense 1% hydrocortisone ointment as needed.
14. Schedule appointment for Day 21 clinic visit and telemed visits.

Detailed instructions for sample collection, storage, and shipping are in the CSSSP provided separately. If violations of treatment site restrictions prior to the visit is reported details of the violation should be recorded in the CRF and the visit should be completed including evaluations and sampling.

Day 28 (±2) Follow up visit (no treatment)

1. Confirm compliance with treatment site restrictions
2. Record any changes in concomitant medications.
3. Record adverse event, if any.
4. Blinded evaluating investigator complete clinical assessment of severity of signs and symptoms of AD.
5. Blinded evaluating investigator complete clinical assessment of local tolerability (severity pain, burning, or stinging in addition to pruritus, erythema, exudation, excoriation, and lichenification).
6. Calculate ADSI score of both potential treatment sites.
7. Digital images of both treatment sites
8. Collect PBS swabs from both treatment sites
9. Collect samples [redacted] from both treatment sites
10. Review treatment site restrictions with subject
11. Dispense 1% hydrocortisone ointment as needed
12. Schedule appointment for Day 35 clinic visit

Detailed instructions for sample collection, storage, and shipping are in the CSSSP provided separately.

If reported violations of treatment site restrictions occurred more than 24 hours prior to the Day 28 visit, details of the violation should be recorded in the CRF and the evaluations and sampling completed as scheduled.

If reported violations of treatment site restrictions occurred less than 24 hours prior to the Day 28 visit, details of the violation should be recorded in the CRF the evaluations can be completed, but an additional visit 24-48 hours after the violation should be scheduled for sample collections.

Day 35 (±4) Follow up visits (no treatment)

1. Confirm compliance with treatment site restrictions.
2. Record any changes in concomitant medications.
3. Record adverse event, if any.
4. Blinded evaluating investigator complete clinical assessment of severity of signs and symptoms of AD.
5. Blinded evaluating investigator complete clinical assessment of local tolerability (severity pain, burning, or stinging in addition to pruritus, erythema, exudation, excoriation, and lichenification).
6. Calculate ADSI score of both potential treatment sites.
7. Digital images of both treatment sites.
8. Collect PBS swabs from both treatment sites.
9. Review treatment site restrictions.

10. Dispense 1% hydrocortisone ointment as needed.
11. Schedule appointment for Day 42.

Detailed instructions for sample collection, storage, and shipping are in the CSSSP provided separately.

If reported violations of treatment site restrictions occurred more than 24 hours prior to the Day 35 visit, details of the violation should be recorded in the CRF and the evaluations and sampling completed as scheduled.

If reported violations of treatment site restrictions occurred less than 24 hours prior to the Day 35 visit, details of the violation should be recorded in the CRF the evaluations can be completed, but an additional visit 24-48 hours after the violation should be scheduled for sample collections.

Day 42 (±4) Follow up visits (no treatment)

1. Women of childbearing potential will be tested for pregnancy with a urine pregnancy test.
2. Confirm compliance with treatment site restrictions
3. Record any changes in concomitant medications.
4. Record adverse event, if any.
5. Blinded evaluating investigator complete clinical assessment of severity of signs and symptoms of AD.
6. Blinded evaluating investigator complete clinical assessment of local tolerability (severity pain, burning, or stinging in additional to in addition to pruritus, erythema, exudation, excoriation, and lichenification).
7. Calculate ADSI score of both potential treatment sites.
8. Digital images of both treatment sites
9. Collect PBS swabs from both treatment sites
10. Dispense 1% hydrocortisone ointment as needed

Detailed instructions for sample collection, storage, and shipping are in the CSSSP provided separately.

If reported violations of treatment site restrictions reported occurred more than 24 hours prior to the Day 42 visit, details of the violation should be recorded in the CRF and the evaluations and sampling completed as scheduled.

If reported violations of treatment site restrictions occurred less than 24 hours prior to the Day 42 visit, details of the violation should be recorded in the CRF the evaluations can be completed, but an additional visit 24-48 hours after the violation should be scheduled for sample collections.

Study Specific Procedures

Clinical Evaluations:

All primary endpoint assessments must be done by an observing evaluating investigator who is a board-certified dermatologist. Investigators who are not board-certified dermatologists may perform the role of an observing, evaluating investigator at the Sponsor's discretion.

6.6.1 Grading of signs and symptoms of AD using ADSI

Both targeted treatment areas will be evaluated using the ADSI. The ADSI score represents the sum of the individual severity scores on none, mild, moderate, or severe for the following component signs and symptoms: erythema, pruritus, exudation, excoriation and lichenification. The investigators will only be required to calculate the ADSI at the Screening and Baseline visits to confirm that the subjects meet the inclusion criteria for disease severity. The ADSI for subsequent visits will be calculated during data analysis. The same observer-blinded investigator should perform the ADSI grading for each subject for the duration of a subject's participation in the study.

The same signs and symptoms of AD are also commonly use to evaluate application site - reactions to topical product and serves a secondary role in characterizing tolerability. The sponsor will consider improvement in the ADSI and the individual signs and symptoms of AD an indicator of either a favorable therapeutic effect or the demonstration of the natural variation of AD over time. If the signs and symptoms increase in severity, the sponsor will consider this an indication of an application site reaction and/or the natural variation in AD over time. To further characterize local tolerability, subject self-reporting of pain, burning, or stinging will also be recorded. Each component is measured using the following scale:

Erythema score: (redness presents specifically in the target lesion)

0=none	No redness
1=mild	Mildly detectable erythema; pink
2=moderate	Dull red; clearly distinguishable
3=severe	Deep, dark red; marked and extensive

Exudation score: (oozing or crusting of the target lesion)

0=none	No oozing or crusting
1=mild	Minor or faint signs of oozing
2=moderate	Definite oozing or crusting present
3=severe	Marked and extensive oozing or crusting present

Excoriation score: (evidence of scratching in the target lesion)

0=none	No evidence of excoriation
1=mild	Slight excoriation present

2=moderate	Definite excoriation present
3=severe	Marked, deep, or extensive excoriation present

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

Lichenification score: (epidermal thickening of the target lesion)

0=none	No epidermal thickening
1=mild	Minor epidermal thickening
2=moderate	Definite epidermal thickening; accentuated skin lines
3=severe	Marked epidermal thickening; deeply accentuated skin lines

To calculate the ADSI score, the component scores are added together.

6.6.2 Local Tolerability

Tolerability will be evaluated based on calculating the scores for pruritus, erythema, exudation, excoriation, lichenification and the additional symptoms of pain, burning, or stinging using the following scale:

Pain, Burning, or Stinging: 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, or stinging
1	Mild	Slight pain, burning or stinging sensation; not really bothersome
2	Moderate	Definite pain, burning or stinging that is somewhat bothersome
3	Severe	Significant pain, burning, or stinging sensation that causes definite discomfort and may interrupt daily activities and/or sleep.

6.6.3 Sample Collection

Samples for microbiologic [redacted] testing will be obtained separately from both treatment targeted sites as detailed in Table 2 below. Details of sample collection, storge, and shipment can be found in the CSSSP.

Table 2. Microbiological [redacted] Samples.

Visit	Sample	Test
Screening	None	
Day 1 (Baseline - Prior to Application)	1 Swab and 12 tape sample [redacted]	qPCR Bacterial Culture S. aureus CFU [redacted]
Day 7	1 Swab from each treatment site	qPCR Bacterial Culture S. aureus CFU
Day 14	1 Swab from each treatment site	qPCR Bacterial Culture S. aureus CFU
Day 21	1 Swab from each treatment site	qPCR Bacterial Culture S. aureus CFU
Day 28	1 Swab and 12 tape sample [redacted]	qPCR Bacterial Culture S. aureus CFU [redacted]
Day 35	1 Swab from each treatment site	qPCR Bacterial Culture S. aureus CFU
Day 42	1 Swab from each treatment site	qPCR Bacterial Culture S. aureus CFU

If the atopic dermatitis has cleared completely in a treatment site, the investigator is to use clinical judgment, anatomical landmarks and previously captured digital images to identify the specific location to be sampled.

Test Article Administration

All subjects will have approximately 27 applications of the assigned test articles applied to each treatment site by unblinded study personnel at the Day 1/Baseline, Day 7, Day 14 and Day 21 visits. Doses between visits will be applied by the subjects, or LAR, under the supervision of an unblinded treating investigator, or designee, during telemed visits on weekdays and unsupervised on weekends. Details of test article preparation are in the Pharmacy Instruction Manual, provided

separately. Approximately 0.1 ml of assigned test article will be applied to each treatment site (each site is approximately 100 cm^2). The product is to be air dried.

If technical or other logistical issues prevent a telemed connection (i.e., a weekday telemed is missed for any reason) the subject is to apply test articles unsupervised.

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. Subjects will be supplied with 1% Hydrocortisone Ointment to treat areas of A remote from the designated treatment sites.

Randomization

Each enrolled subject will be randomized to a test article kit number containing two different vials of test articles for each scheduled application. Each kit will contain vials labelled with "Right" or "Left", indicating the treatment side to apply onto. Treatment compliance will be monitored by recording all missed doses in source documentation and the CRF.

DATA ANALYSIS AND STATISTICAL CONSIDERATION.

General Statistical Considerations

All statistical processing will be performed using Statistical Analysis System (SAS®) unless otherwise stated. No interim analyses are planned. Except where noted, all statistical tests will be two-sided and will be performed at the 0.05 level of significance. P-values will be provided primarily for exploratory purposes.

Descriptive statistics will be used to provide an overview of the efficacy and safety results. For categorical parameters, the number and percentage of subjects in each category will be presented. For continuous parameters, descriptive statistics will include the number of subjects, mean, and standard deviation, median, minimum, and maximum. Appropriate inferential statistics will be used for the primary and secondary efficacy variables in an exploratory manner.

Linear interpolation of efficacy variables will be performed using observed data that precedes and follows the off-schedule visit, if present. The last observation will be carried forward if all the data subsequent to the off-schedule value is missing.

No adjustments will be made for multiplicity.

The number of subjects in each analysis set will be summarized. Reasons for study withdrawal will be summarized using frequencies and percentages by treatment group.

Reported AEs, medical history terms and prior and concomitant procedures and therapies will be classified on the basis of the f Medical Dictionary for Regulatory Activities (MedDRA) terminology. Prior and concomitant medications will be classified on the basis of the World Health Organization Drug Dictionary (WHO-DDE) terminology.

A statistical analysis plan (SAP), describing all statistical analyses will be provided as a separate document. The SAP will be finalized prior to unblinding of the study treatments.

Analysis of Efficacy Data for Objectives

7.2.1 Primary Efficacy:

The primary analysis will compare the differences from baseline in ADSI score between DBI-001 and Aqueous Gel will be done using a two-sided Wilcoxon sign rank test at each of Days 7, 14, 21, 28 ,35 and 42.

The proportion of subjects with a greater decrease in ADSI for the DBI-001-treated lesion than the Aqueous Gel-treated lesion will be summarized descriptively for Days 7, 14, 21, 28, 35, and 42.

Comparison of differences at Day 28 between DBI-001 and Aqueous Gel of abundance of [redacted] on lesioned skin will be done using a two-sided Wilcoxon sign rank test.

Comparison of differences at Day 28 between DBI-001 and Aqueous Gel of abundance and diversity of the microbiome based on DNA sequencing will be done using a two-sided Wilcoxon sign rank test.

Comparisons at Days 7, 14, 21, 35, and 42 will also be done. Additionally, a repeated measures model will be used to compare DBI-001 to Aqueous Gel for the secondary endpoints. P-values will be provided for descriptive purposes.

7.2.2 Secondary Efficacy:

The secondary analysis of the S. aureus MITT population will compare the differences at Day 28 between DBI-001 DP and Aqueous Gel in abundance of *S. aureus* based on qPCR using a 2-sided Wilcoxon sign rank test, alpha = 0.05, with a null hypothesis of median difference equal to zero.

Comparisons at Days 7, 14, 21, and 35 will also be done. Additionally, a repeated measures model will be used to compare DBI-001 DP to Aqueous Gel for the secondary endpoints. P-values will be provided for descriptive purposes.

7.2.3 Exploratory Efficacy:

Comparison in changes in the overall microbiome as defined by whole genome sequencing of samples obtained prior to, during, and after treatment.

Comparison of change from baseline in individual signs and symptoms of AD (components of ADSI score) between DBI-001 DP and Aqueous Gel will be done using a two-sided sign test at each of Days 7, 14, 21, 28, 35, and 42.

Additionally, a repeated measures model will be used to compare DBI-001 DP to Aqueous Gel for the above exploratory endpoints.

7.3 Analysis of Safety Data for Objectives

7.3.1 Local Tolerability

Signs and symptoms of local tolerability pruritus, erythema, exudation, excoriation, lichenification as well as pain, burning, or stinging) will be summarized with changes from baseline.

7.3.2 Adverse Events

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, seriousness, action taken regarding the investigational product, corrective treatment, outcome, and Investigator's assessment of causality. All reported treatment-emergent AEs (TEAEs), defined as any AE with an onset on or after the date of first investigational product application, will be summarized by treatment group, the number of subjects reporting TEAEs, system organ class, preferred term, severity, and relationship to investigational product. When summarizing TEAEs by severity or relationship to investigational product, each subject will be counted only once within a system organ class or a preferred term using the event with the greatest severity or causality, respectively, within each category. All reported serious adverse events (SAEs) will be summarized by treatment group, the number of subjects reporting SAEs, system organ class, preferred term, severity, and relationship to investigational product.

All information pertaining to AEs noted during the study will be listed by subject and will include a verbatim description of the event as reported by the Investigator, as well as the preferred term, system organ class, start date, stop date (if stopped), seriousness, severity, action taken regarding

the investigational product, corrective treatment, outcome and relationship to the investigational product. In addition, a listing of subjects who prematurely discontinue from the study due to AEs will be provided as well as a listing of subjects who reported an SAE.

7.4 Analysis Populations

All subjects who are randomized and dispensed investigational product will be included in the Intent-to-Treat analysis set. All subjects who are randomized, receive at least one (1) confirmed dose of investigational product, and have at least one (1) post-baseline safety assessment will be included in the Safety analysis set.

7.5 Sample Size Determination

Sample size is based on clinical judgement and deemed adequate to successfully demonstrate these goals.

4. ASSESSMENT OF SAFETY

8.1 Safety Evaluations and Criteria

As detailed in sections 5.6.1 and 5.6.2, local tolerability will be evaluated by recording the severity of the signs of AD as well as subjective symptoms of pain, burning, or stinging on treated areas involved with AD. In addition, adverse events will be documented.

8.2 Adverse Event

An AE refers to any untoward medical occurrence in a subject administered a pharmaceutical product, whether or not considered investigational product related. 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 investigational product, whether or not it is considered to be investigational product related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of investigational product (treatment-emergent).

8.3 Serious Adverse Event

A serious adverse event (or adverse reaction, or suspected adverse reaction) refers to 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 event 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).
- Results in inpatient hospitalization or prolongation of an existing hospitalization.
- Results in persistent or significant incapacity, or disability, or substantial disruption of the ability to perform normal life functions.
- Is a congenital anomaly or 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 treatment in an emergency room, a physician's office or clinic, 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 an SAE.

8.4 Unexpected Adverse Event

An AE (or a suspected adverse reaction) is deemed unexpected if itis not reported in the Investigator's Brochure (IB), is not listed at the specificity or severity that has been observed or is not consistent with the risk information described in the general investigational plan or elsewhere in the current IND studies.

8.5 Relationship of Adverse Events to Investigational Product

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

1. **Unrelated**: No relationship between the experience and the administration of investigational product; related to other etiologies such as concomitant medications or subject's clinical state.
2. **Probably not related**: The current state of knowledge indicates that a relationship is unlikely.
3. **Possibly related**: A reaction that follows a plausible temporal sequence from administration of the investigational product and follows a known response pattern to the suspected investigational product. The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject.
4. **Probably related**: A reaction that follows a plausible temporal sequence from administration of the investigational product and follows a known response pattern to the suspected

investigational 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 related**: A reaction that follows a plausible temporal sequence from administration of the investigational product and follows a known response pattern to the suspected investigational product and can be confirmed with a positive re-challenge test or supporting laboratory data.

8.6. Intensity: Classification of Intensity of Adverse Event.

The following classifications should be used when evaluating the intensity of AE's and SAE's:

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
5. Death

PROCEDURES FOR ADVERSE EVENT RECORDING AND REPORTING

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), investigational site personnel must immediately contact the Medical Monitor.

Medical Monitor Contact	
Name:	[redacted] MD, MS, MPH (primary)
Telephone:	[redacted]
[redacted]	[redacted]
Name:	[redacted] (secondary)
Telephone:	[redacted]
[redacted]	[redacted]

Other Required Safety Assessments

A clinically significant worsening from Baseline of any abnormal study assessment 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.

SPECIAL REQUIREMENTS AND PROCEDURES

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, CRFs, source documents 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.

Audits and Inspections

The Investigators and clinical sites will permit study related monitoring, audits, IRB/IEC review, and regulatory inspections as requested by the regulatory authorities, 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.

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.

Confidentiality

To maintain subject privacy, all eCRFs, study samples, investigational product 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.

Subject Rights

Study subjects can withdraw their consent to have their clinical samples stored even after the sample has been shipped to the sponsor laboratory. A study subject should contact the Investigator or the Investigator's designee and ask for his/her sample to be withdrawn from the storage 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.

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.

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 product administrations; recording the subject's data on the source documents and CRFs; documenting the presence or absence of AEs following sample collection and investigational product applications and following the reporting requirements of any SAEs to the Sponsor and IRB/IEC.

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.

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.

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.

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.

DATA HANDLING AND RETENTION OF RECORDS

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 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.

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.

REFERENCES

Asakura, H., M. Tachibana, M. Taguchi, T. Hiroi, H. Kurazono, S.I. Makino, F. Kasuga, and S. Igimi. 2016. 'Seasonal and Growth-Dependent Dynamics of Bacterial Community in Radish Sprouts', *Journal of Food Safety*, 36: 392-401.

Blazewicz, I., M. Jaskiewicz, M. Bauer, L. Piechowicz, R. J. Nowicki, W. Kamysz, and W. Baranska-Rybak. 2017. 'Decolonization of Staphylococcus aureus in patients with atopic dermatitis: a reason for increasing resistance to antibiotics?', *Postepy Dermatol Alergol*, 34: 553-60.

DBI-CSR-201 (2021), Open label, single-dose, dose escalating evaluation of the safety and tolerability of DBI-001 in patients with Tinea pedis. DermBiont Clinical Study Report DBI-201.

DBI-CSR-204 (2021), Double-Blind, Randomized, Placebo Controlled Trial of the Safety and Efficacy of DBI-001, Gel in Patients with Interdigital Tinea pedis. DermBiont Clinical Study Report DBI-204.

DBI-CSR-203 (2021), A Randomized, Observer-Blinded, Vehicle Controlled, Single Dose, Dose Escalating, Single Application within-patient, Bilateral Comparison to Study the Safety and Antimicrobial Efficacy of DBI-001 Gel Vs. Vehicle Gel in Adults with Atopic Dermatitis. DermBiont Clinical Study Report DBI-203.

DR001, DermBiont Report. 2019. 'Sourcing and bioprospecting of [redacted] strains', *DermBiont Report*, DR001.

DR002, DermBiont Report. 2019. 'Prevalence and genetic diversity of [redacted] strains', *DermBiont Report*, DR002.

DR003, DermBiont Report. 2019. '*In vitro* assays of [redacted] *rubrum*_2019.02.12.00', *DermBiont Report*, DR003.

DR005, DermBiont Report. 2019. 'F107 and F108 fermentor runs of [redacted] in progress stability and activity tests_2019.02.21.00', *DermBiont Report*, DR005.

George Kerry, R., J. K. Patra, S. Gouda, Y. Park, H. S. Shin, and G. Das. 2018. 'Benefaction of probiotics for human health: A review', *J Food Drug Anal*, 26: 927-39.

Hanifin, J. M., and G. Rajka. 1980. 'Diagnostic Features of Atopic-Dermatitis', *Acta Dermato-Venereologica*, 60: 44-47.

Harris, R. N., R. M. Brucker, J. B. Walke, M. H. Becker, C. R. Schwantes, D. C. Flaherty, B. A. Lam, D. C. Woodhams, C. J. Briggs, V. T. Vredenburg, and K. P. Minbiole. 2009. 'Skin microbes on frogs prevent morbidity and mortality caused by a lethal skin fungus', *ISME J*, 3: 818-24.

Hepburn, L., D. J. Hijnen, B. R. Sellman, T. Mustelin, M. A. Sleeman, R. D. May, and I. Strickland. 2017. 'The complex biology and contribution of Staphylococcus aureus in atopic dermatitis, current and future therapies', *Br J Dermatol*, 177: 63-71.

Nakatsuji, T., T. H. Chen, S. Narala, K. A. Chun, A. M. Two, T. Yun, F. Shafiq, P. F. Kotol, A. Bouslimani, A. V. Melnik, H. Latif, J. N. Kim, A. Lockhart, K. Artis, G. David, P. Taylor, J. Streib, P. C. Dorrestein, A. Grier, S. R. Gill, K. Zengler, T. R. Hata, D. Y. Leung, and R. L. Gallo. 2017. 'Antimicrobials from human skin commensal bacteria protect against Staphylococcus aureus and are deficient in atopic dermatitis', *Sci Transl Med*, 9: eaah4680.

Naked_Biome:NCT03450369. 2018. 'A study of the safety, engraftment, and action of NB01 in adults with moderate acne', Accessed 28 October 2019. https://www.clinicaltrials.gov/ct2/show/NCT03450369.

US9738870B2, Aobiome. 2017. "Ammonia oxidizing bacteria for treatment of acne." In.

U.S. Department of HHS, FDA CDER, CBER, CDRH. 2021. 'Sponsor Reponsibilities - Safety Reporting Requirements and Safety Assessment for IND and BA, BE Studies: Guidance for Industry', Accessed 18 November 2021. https://www.fda.gov/media/150356/download

Van Leent, E. J., M. Graber, M. Thurston, A. Wagenaar, P. I. Spuls, and J. D. Bos. 1998. 'Effectiveness of the ascomycin macrolactam SDZ ASM 981 in the topical treatment of atopic dermatitis', *Arch Dermatol*, 134: 805-9.

Williams, M. R., and R. L. Gallo. 2017. 'Evidence that Human Skin Microbiome Dysbiosis Promotes Atopic Dermatitis', *J Invest Dermatol*, 137: 2460-61.