9/23/2015

University of Pennsylvania

Protocol title: The Cutaneous Microbiota of Psoriasis: Lesional Variation and a Phase IV, Interventional Study of its Response to Phototherapy.

Short title: Psoriasis Microbiome and Phototherapy

Protocol number: 821876

NCT number: NCT02552316

THE CUTANEOUS MICROBIOTA OF PSORIASIS: LESIONAL VARIATION AND A PHASE IV, INTERVENTIONAL STUDY OF ITS RESPONSE TO PHOTOTHERAPY

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Study Product/Intervention: Narrow-band UVB phototherapy

Protocol Number: 821876

Study Reference Number: WI195087 (Award Number)

IND Number: N/A

Initial version: 1/23/15
Amended 03/10/2015
Amended 04/06/2015
Amended 07/22/2015
Amended 09/23/2015

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List of Abbreviations

AE	Adverse event
BSA	Body surface area
CRF	Case report form
EC	Ethics committee
HDAC	Histone deacetylase
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human immunodeficiency virus
IL	Interleukin
MED	Minimal erythemal dose
NB-UVB	Narrow-band ultraviolet B
PASI	Psoriasis Area and Severity Index
Penn IRB	Institutional Review Board of the University of Pennsylvania
PGA	Physician Global Assessment
PHI	Protected health information
SAE	Serious adverse event
SD	Standard deviation
Th1	T helper cell type 1
Th17	T helper cell type 17
UVA	Ultraviolet A

Study Summary

Title	The Cutaneous Microbiota of Psoriasis: Lesional Variation and a Phase IV, Interventional Study of its Response to Phototherapy
Short Title	Psoriasis Microbiome and Phototherapy
Protocol Number	To be assigned.
Phase	Phase 4
Methodology	Interventional
Study Duration	9 weeks
Study Center(s)	University of Pennsylvania
Objectives	The primary objectives of this study are to: i. Characterize the bacterial microbiota within psoriatic plaques compared with unaffected skin in patients with plaque psoriasis. ii. Determine the effect of narrow-band ultraviolet B phototherapy on the cutaneous bacterial microbiota of lesional and non-lesional skin among patients with plaque psoriasis.
Number of Subjects	34
Diagnosis and Main Inclusion Criteria	Males and females 18 years of age and older with plaque psoriasis. Subjects must be candidates for phototherapy.
Study Product, Dose, Route, Regimen	Narrow-band UVB Phototherapy three times weekly
Duration of administration	8 weeks
Reference therapy	N/A
Statistical Methodology	Descriptive statistics, specific measures of bacterial diversity and load.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Psoriasis is a common chronic inflammatory disease of the skin that affects 2-4% of the population.[1] We have demonstrated that psoriasis, especially if more severe, is an independent risk factor for major adverse cardiovascular events,[2-4] diabetes, impaired reverse cholesterol transport,[5] chronic kidney disease,[6] and mortality culminating in 5 years of life lost.[7,8] The pathogenesis of psoriasis remains incompletely understood and is suggested to be multifactorial with contributions from altered genetics,[9,10] immune dysfunction characterized by type 1 helper (Th1) T cell- and Th17-mediated inflammation,[11] and environmental/lifestyle risk factors such as obesity[12,13] and smoking.[14-17] Microbial triggers of psoriasis have also been hypothesized based on clinical observations of new-onset or exacerbations of psoriasis being associated with infections such as poorly controlled HIV[18] and streptococcal pharyngitis.[19] In small clinical studies, *Staphylococcus aureus*[20] and *Streptococcus pyogenes*,[21] in particular, have been suggested to contribute to the initiation and progression of psoriasis. Though, only recently with the advent of modern DNA sequencing techniques has it become possible to evaluate the microbiota of psoriasis on a larger scale and in a high-throughput manner. Preliminary results from three relatively small cross-sectional studies of the cutaneous bacterial microbiota in psoriasis patients of varying disease severity and therapy history suggest major alterations in the diversity and composition of the psoriasis microbiota compared to that of unaffected skin and normal skin of patients without psoriasis.[22-24] Specific results from studies have been mixed, though, with identification of increased abundance of Streptococcus in psoriatic lesions compared to unaffected skin, for example, in one study[23] but not in another.[22] Thus, it is still unclear which alterations in the cutaneous microbiota are associated with psoriasis and if the differences are causative or a consequence of psoriasis. Other studies suggest that there are not only important differences between lesional and unaffected skin in psoriasis patients but that the inflammatory infiltrate[25,26] and expression of proteins involved in angiogenesis[27] and epidermal proliferation and differentiation[28-30] differ within lesions at the advancing, metabolically active edge versus the center of a psoriatic plaque compared to unaffected skin. To our knowledge, there have been no studies to determine if the cutaneous microbiota are similarly differentially altered within and surrounding psoriatic plaques. As psoriatic plaques often enlarge in a circumferential manner, identification of changes in the cutaneous microbiota within psoriatic lesions and in the adjacent versus distant unaffected skin may provide important insights into the mechanisms underlying the initiation and/or progression of psoriasis.

The effects of psoriasis therapies on the cutaneous microbiota are also not well known. Narrow-band ultraviolet B (NB-UVB) phototherapy is a well-established, effective, and relatively safe, skin-directed treatment indicated for moderate-to-severe psoriasis and other chronic inflammatory skin disorders. The therapeutic effects of NB-UVB phototherapy are generally attributed to its immunosuppressive and anti-proliferative effects on the skin.[31] Phototherapy has also been suggested to have antimicrobial effects.[32,33] However, the exact therapeutic mechanisms of phototherapy in psoriasis and its impact on normal skin continue to be poorly understood. Importantly, to our knowledge, the effect of phototherapy on the cutaneous microbiota of psoriatic plaques and unaffected skin has not been previously studied. Understanding the impact of UVB phototherapy on the cutaneous microbiota has broad

implications including the potential identification of novel microbial therapeutic targets for psoriasis and other chronic skin conditions that are also treated with phototherapy as well as identification of the microbial effects of chronic UV exposure on normal skin in the general population which could ultimately have systemic consequences that extend beyond the skin.

1.2 Investigational Agent

1.2.1 Narrow-Band Ultraviolet B Phototherapy (NB-UVB)

NB-UVB phototherapy utilizes fluorescent tubes that emit UVB with peak wavelengths of 311-312 nm for the treatment of psoriasis. It has also been shown to be effective at treating atopic dermatitis, vitiligo, mycosis fungoides, and other photodermatoses.[34]

1.3 Preclinical Data

1.3.1 NB-UVB – Pharmacodynamics and Toxicology

UVB interferes with the synthesis of proteins and nucleic acids, which leads to a decreased proliferation of epidermal keratinocytes. Acute changes after UVB exposure include the formation of pyrimidine dimmers and DNA damage, membrane lipid peroxidation, and induction of cytoplasmic transcriptional factors. Subacute changes include alteration of antigen-presenting cells and modification of intracellular and intercellular signaling mechanisms.[35,36] UVB not only reduces keratinocyte proliferation, it produces local immunosuppression by reducing the number of Langerhans cells and T cells, impairing antigen presentation, and altering cytokines secretion in macrophages.[36,37] Suppression of the Th17 and IFN signaling pathways and modulation of epidermal differentiation genes were also shown with clinically effective UVB phototherapy.[38]

Phototoxic effects of NB-UVB have been studied in murine models, which suggested that narrow-band UVB may be 2-3 times more photocarcinogenic than broad-band UVB per minimal erythemal dose (MED).[39,40] However, as NB-UVB is more effective and requires lower MED-equivalent dose than broad-band UVB, its long-term carcinogenic risk may not be enhanced.[36]

1.4 Clinical Data to Date

1.4.1 NB-UVB Phototherapy – Efficacy and Safety

Pharmacokinetic studies do not apply to NB-UVB phototherapy.

NB-UVB phototherapy has become a first-line treatment of psoriasis due to its efficacy and safety. Multiples studies have demonstrated that narrow-band UVB is either superior or equivalent to the efficacy of broad-band UVB in treating psoriasis.[41,42]

The most common side effects of phototherapy are transient erythema, itching, burning, stinging, and tanning of the skin. These risks are generally mild and self-limited. The use of eye protection with goggles is required to decrease the risk of UVB-related cataract formation. Long-term UVB exposure may be associated with an increased risk of genital tumors in men treated without genital shielding; the routine use of shields has been recommended to avoid such an effect. Photoaging, with wrinkling, lentigines, and telangiectasias, may occur as a long-term side effect. Photocarcinogenesis is a potential adverse effect of UVB phototherapy; however, numerous studies have failed to show increased skin cancer risks in patients with psoriasis treated with long term NB-UVB phototherapy.[43]

1.5 Dose Rationale and Risk/Benefits

1.5.1 Dose Rationale

NB-UVB phototherapy with a standard NB-UVB unit (TL-01 fluorescent lamps 311-313 nm) will be administered 3 times a week for 8 weeks. UVB dosing will follow a standard protocol described in Section 5.2 and Appendix A.[44] Initial dosing is determined by MED as estimated by the patient's Fitzpatrick skin type, assessed by the person administering phototherapy. Subsequent dosing will be determined by degree of erythema and burning symptoms (e.g. stinging, pain or itch) based on individual UVB tolerance. Phototherapy dosing may be individualized for certain patients if necessary based on unique patient and center characteristics at request of the PI (Dr. Takeshita). Phototherapy will be continued until the patient receives a total of 24 treatments.

1.5.2 Potential Risks and Benefits

Phototherapy is a well-tolerated, standard of care, first-line treatment for psoriasis with very low risk of serious side effects, particularly with short-term exposure. The potential risks of phototherapy are well defined (see Section 1.4.1) and minimized by careful adherence to FDA prescribing guidance and strict exclusion of subjects with significant contraindications to phototherapy. Subjects will also undergo medical monitoring for any adverse reaction.

In order to monitor for a potential flare of psoriasis during the study (including screening and washout periods), subjects will be evaluated for adverse events at each study visit. Subjects will be removed from the study if they either become unable to tolerate their symptoms or display signs of a potentially serious flare (erythroderma). Safety endpoints are monitored throughout the study treatment duration.

Potential risks from the study assessment procedures are low: skin swabs for microbiome sampling are non-invasive and carry minimal to no risk. Optional skin biopsies for transcription analysis are potentially associated with pain, bleeding, infection, and scarring at the biopsy sites.

Potential benefits for study participation include phototherapy at no cost. Study subjects will be provided with a stipend of $30 per visit involving study Investigator evaluation to offset travel and other indirect costs. Data derived from this study will provide critical information on the cutaneous microbiota of psoriasis and its response to phototherapy. Overall, we expect that the risks of the research study are outweighed by the potential benefits to the participants and others.

2 Study Objectives

Primary objectives

- To characterize the cutaneous bacterial microbiota within psoriatic plaques compared with unaffected skin in patients with plaque psoriasis.
- To determine the effect of NB-UVB phototherapy on the cutaneous bacterial microbiota of lesional and non-lesional skin among patients with plaque psoriasis.

Secondary/exploratory objectives

- To determine the effect of Caucasian vs. African American race on the cutaneous bacterial microbiota of lesional and non-lesional skin in patients with plaque psoriasis.
- To compare the expression level and subcellular localization of histone deacetylase (HDAC) 3 in lesional versus non-lesional skin among patients with plaque psoriasis.

3 Study Design

3.1 General Design

The study is a phase IV, interventional, 9-week clinical trial to investigate the cutaneous microbiota of psoriasis and its response to phototherapy. The subject inclusion and exclusion criteria are shown in Sections 4.1 and 4.2. All 34 subjects will be enrolled at the University of Pennsylvania (Penn).

All study procedures, including therapy washout, will occur only after obtaining signed informed consent. A screening period prior to study treatment initiation will allow for study eligibility assessment and washout of current psoriasis therapies (14 days for topical treatments, UVB phototherapy or Excimer laser; patients on other therapies requiring longer washout periods will be excluded). After the washout period is completed, subjects will receive NB-UVB phototherapy 3 times per week for 8 weeks for up to 24 treatments of each lasting approximately 5-10 minutes. The treatment regimen for NB-UVB phototherapy is described in Section 5.2.

During the screening period, baseline, week 8, and week 9, subjects will be evaluated by investigators. Psoriasis severity will be assessed using the Psoriasis Area and Severity Index (PASI) and the Physician Global Assessment (PGA), both widely accepted measurement tools for psoriasis.[45] Standardized photography of skin lesions to be sampled will be conducted at baseline, week 8, and week 9. Skin sampling for bacterial microbiome analyses will also be performed at baseline before treatment with phototherapy and at weeks 8 and 9 for immediate and delayed sampling, respectively, after treatment with phototherapy (Appendix B). All samples will be labeled with an ID that does not contain identifiable personal information. The date and time of sample collection will be also indicated on a lab transfer sheet. Samples will be processed and stored at University of Pennsylvania.

Additionally, optional skin specimens of lesional +/- non-lesional skin will be obtained from study subjects who specifically provide consent for skin biopsies. Wound care and suture removal instructions will be provided to subjects who undergo skin biopsies (Appendix C). Skin biopsies will be used for both mRNA extraction to determine expression levels of HDAC3 and for histopathologic examination of expression of psoriasis marker genes via immunostaining. Skin biopsy tissue will not be used for research unrelated to HDAC3 and other psoriasis marker gene expression without the express consent of the subject. All samples will be labeled with an ID that does not contain identifiable personal information. The date and time of sample collection will be also indicated on a lab transfer sheet. Samples will be processed and stored at University of Pennsylvania.

The expected duration of this interventional clinical trial for each participant will be 58 to 77 days including an initial screening visit, a washout period of up to 14 days, 8 weeks of outpatient treatment, final assessment and sample collection up to 7 days after last phototherapy dose. Efforts will be made to evaluate all enrolled subjects even if they decide to discontinue treatment.

3.2 Primary Study Endpoints

The primary endpoints to be measured in this study include:

- Differences in microbial diversity and composition within psoriatic lesions compared with non-lesional skin at week 1.

- Change in microbial diversity and composition between weeks 0 and 8 (immediate and delayed samples) for both psoriatic lesions and non-lesional skin.

Microbial diversity and composition will be measured as described in Section 7.2.

3.3 Secondary/Exploratory Study Endpoints

The secondary/exploratory endpoints to be measured in this study include:

- Differences in microbial diversity and composition of psoriatic lesions and non-lesional skin at week 1 between subjects of Caucasian versus African American race.
- Differences in HDAC3 expression and subcellular localization between lesional and non-lesional skin in subjects with plaque psoriasis.
- Safety

3.4 Primary Safety Endpoints

The safety endpoint will be assessed by subject interview (and physical exam if indicated). Subjects will be monitored for any adverse event that may occur during the study treatment period at baseline, week 8, and week 9, including serious adverse events (e.g., serious infection and malignancy). Adverse events per routine clinical care will also be assessed at each phototherapy session. Non-serious adverse events, as defined in Section 8.1, will also be noted. A complete review of systems will also be assessed and physical exam performed during the follow-up visits at weeks 8 and 9. No routine laboratory tests will be monitored.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

1. Males and females 18 years of age and older.
2. Clinical diagnosis of psoriasis for at least 6 months as determined by subject interview of his/her medical history and confirmation of diagnosis through physical examination by Investigator.
3. Stable plaque psoriasis for at least 2 months before Screening and at Baseline (Week 1) as determined by subject interview of his/her medical history.
4. Subject is a candidate for phototherapy.
5. Subject has at least one psoriatic plaque located on either the arms or the legs (excluding intertriginous areas such as the axilla and inguinal folds)
6. Able and willing to give written informed consent and to comply with requirements of this study protocol.

4.2 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. Subject has photosensitizing condition or other contraindication to phototherapy
2. Diagnosis of erythrodermic psoriasis, generalized or localized pustular psoriasis, medication-induced or medication-exacerbated psoriasis, or new onset guttate psoriasis.
3. Cannot discontinue or avoid topical therapies for psoriasis for at least 14 days prior to the Baseline (Week 1) visit and during the study other than on face, underarms, or groin.
4. Cannot discontinue or avoid UVB phototherapy or Excimer laser for at least 14 days prior to the Baseline (Week 1) visit.
5. Subject is receiving therapy for psoriasis that requires a wash out period of more than 14 days (e.g., psoralen-UVA phototherapy, oral systemic therapy, biologic therapy, or other investigational therapy).

6. Other active inflammatory dermatologic conditions (e.g., eczema) or presence of pustular or erythrodermic psoriasis.
7. Any history of acute or chronic bacterial, fungal, or viral infection (including HIV, hepatitis, tuberculosis, or other severe or recurrent infections) within 30 days of baseline sample collection.
8. Subject has used systemic (oral or parenteral) antibiotic, antimycotic, or antiviral within 3 months or topical antibiotic, antimycotic, or antiviral within 14 days of baseline sample collection or requires use of any topical or systemic antibiotic, antimycotic, or antiviral during the study.
9. Consumption of large doses of commercial probiotics (greater than or equal to 10^8 cfu or organisms per day) including tablets, capsules, lozenges, chewing gum or powders in which probiotic is a primary component. Ordinary dietary components such as fermented beverages/milks, yogurts, and foods do not apply.
10. Presence of comorbid medical condition (e.g., HIV, malignancy within past 5 years other than successfully treated basal cell carcinoma, non-metastatic cutaneous squamous cell carcinoma or cervical carcinoma in-situ) that significantly alters the immune system or results in immunosuppression.
11. Subject is taking (within up to 180 days of baseline sample collection) or requires topical or systemic therapy during the study that significantly alters the immune system or results in immunosuppression (e.g., chemotherapy, oral or injectable corticosteroid). Inhaled corticosteroids for stable medical conditions are allowed.
12. Unstable dietary history as defined by major changes in diet within 30 days of baseline or during study, where the subject has or plans to eliminate or significantly increase major food group in the diet.
13. Recent history of substance abuse or psychiatric illness that could preclude compliance with the protocol.
14. History of any substance abuse within 365 days of screening visit.
15. Female subject who is pregnant or breast-feeding or considering becoming pregnant during the study.
16. Major surgery of the gastrointestinal tract, with the exception of cholecystectomy and appendectomy, in the past 5 years. Any major bowel resection at any time.
17. History of active uncontrolled gastrointestinal disorders or diseases including:
    - Inflammatory bowel disease including ulcerative colitis, Crohn's disease, or indeterminate colitis;
    - Irritable bowel syndrome;
    - Persistent, infectious gastroenteritis, colitis, or gastritis, persistent or chronic diarrhea or unknown etiology, *Clostridium difficile* infection (recurrent) or *Helicobacter pylori* infection (untreated).

4.3 Subject Recruitment and Screening

This study is a single center clinical trial with subjects recruited from clinical practices within the University of Pennsylvania Health System. The Principal Investigator has experience with clinical research in psoriasis, and the University of Pennsylvania is a referral center for patients with psoriasis. All 34 subjects will be enrolled at the University of Pennsylvania. All recruitment materials will be submitted to the Institutional Review Board (IRB) of the University of Pennsylvania and receive written approval prior to their use.

Before subjects may be screened for enrollment into this study, full IRB approval of the protocol and consent will be obtained. Subjects will be provided with the approved informed consent form and complete the informed consent process according to FDA regulations and GCP

guidelines prior to any study related procedures. Upon signing consent, subjects will be screened to determine their eligibility for the study (see sections 4.1 and 4.2).

Subjects who meet the inclusion and exclusion criteria will undergo a screening assessment within four weeks of study enrollment. This includes a complete medical history and physical exam; vital signs and weight. Details of the screening procedures can be found in Section 6.2. Subjects who complete all screening visit procedures and meet the inclusion and exclusion criteria will undergo baseline evaluation, undergo skin swab sampling +/- optional skin biopsies, and begin treatment with NB-UVB phototherapy.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to future medical care by the physician or the institution. Any subject who withdraws consent to participate in the study will be removed from further treatment and/or study observation immediately upon the date of request.

Reasons for removal from investigational medication or observation may include:

- Withdrawal of consent
- Administrative decision by investigator
- Ineligibility
- Significant protocol deviation
- Patient noncompliance (e.g., missed visits or doses or other loss to follow-up)
- Disease progression/Treatment failure*
- Significant adverse event, including serious infection

*Disease progression/Treatment failure, identified based on subject report and/or examination of subject's skin at study visits including phototherapy visits, will be defined by development of unstable psoriasis or any potentially serious flare such as erythrodermic or pustular psoriasis.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

If a subject withdraws from the study for any reason, the investigator will make every effort to determine and document the primary reason for withdrawal from the study. The investigator will perform all of the following methods of contact before any subject is considered truly lost to follow-up:

- At least 3 phone calls to the subject
- At least 2 phone calls to the next-of-kin (if possible)
- At least 2 e-mails, text messages, or other form of mobile or electronic communication that may be available to contact the subject
- Certified letter to the subject

5 Study Drug

5.1 Description

Narrow-band UVB phototherapy is administered by 311-312nm TL-01 UVB fluorescent lamps in a phototherapy booth. The study procedure will be administered as a standard phototherapy booth that emits narrow-band UVB phototherapy. Phototherapy will be administered 3 times a week for 8 weeks.

5.2 Treatment Regimen

NB-UVB phototherapy dosing is based on estimated MED and Fitzpatrick skin type using a standardized protocol published by Zanolli and Feldman[44] that is used in routine clinical care at the Penn Dermatology Phototherapy Treatment Center. Subjects with skin types 1-2, 3-4, and 5-6 will respectively receive 300, 500, and 800 mJ/cm^2 as initial doses. Thereafter, dosing will be adjusted at each treatment allowing for increases as a percentage of MED based on patient reaction to the previous treatment. Patients presenting with 1) transient erythema lasting <24 hours following treatment will have 20% dose increase; 2) persistent erythema for 24-48 hours will have the same dose held until the erythema lasts <24 hours; 3) persistent erythema for >48 will receive no treatment on that day and will return to the last lower dose that did not cause persistent erythema. All subjects will have ocular shielding and male subjects will have genital shielding during treatment. On average, 15 to 20 treatments are required for short term clearance of psoriasis.[43] Details of the NB-UVB are found in Appendix A.

5.3 Method for Assigning Subjects to Treatment Groups

Not applicable.

5.4 Preparation and Administration of Study Drug

NB-UVB is administered with a standard TL-01 phototherapy booth emitting UVB with wavelength 311-312nm. All subjects will receive UVB phototherapy for the duration of the study.

5.5 Subject Compliance Monitoring

NB-UVB phototherapy will be administered as described in section 5.2. Compliance with treatment visits and follow-up visits are documented. Non-compliant subjects may be excluded from the final analysis or withdrawn from the study protocol at the discretion of the Investigator.

5.6 Prior and Concomitant Therapy

Study staff will obtain information on the use of all prior (within 180 days of the screening visit) and current medical therapies. A washout period, with no psoriasis therapy permitted for use for up to 14 days depending on current treatment status, is required prior to study treatment randomization. Subjects will be allowed to use low-potency steroids (hydrocortisone up to 2.5% ointment or cream) up to twice daily to the groin, underarms or face and non-prescription shampoos during the study. No other concomitant anti-psoriasis medication (whether topical or systemic) or other phototherapy will be permitted for use during the study treatment period. Subjects who experience worsening of disease requiring additional or alternate psoriasis therapy may be withdrawn from study participation.

Concomitant use of oral or injectable corticosteroids or other immune modulating or immunosuppressive therapies (topical, oral, or injectable) is not permitted. Concomitant use of topical or systemic antibiotic, antimycotic, or antiviral is not permitted. Consumption of large doses of commercial probiotics is not permitted. Subjects will be asked during each study visit to inform study staff and/or investigator of any new concomitant medications or therapies as well as any changes in medications or therapies.

5.7 Packaging

Not applicable.

5.8 Blinding of Study Drug

This is an unblinded study. All study subjects will receive NB-UVB phototherapy.

5.9 Receiving, Storage, Dispensing and Return

Not applicable.

6 Study Procedures

The study procedures for each week are summarized in the Study Flowchart in Appendix D. Subject instructions for preparation for study visits are summarized the Subject Instructions in Appendix E.

6.1 Informed Consent

All Subjects, or legally authorized representatives, must sign an informed consent form for participation in this study prior to screening or performing any screening procedures, including any changes made to medications for the purpose of meeting eligibility criteria**.**

6.2 Screening Phase (Day -14 to Day -1)

- Signed informed consent
- Review of inclusion and exclusion criteria
- Medical and surgical history
- Social history, including alcohol, tobacco, and other recreational drug use
- Review of systems
- Evaluation for presence of psoriatic lesion on arms or legs for sampling
- Review and document medications or therapies and any discontinued medications or therapies in the last 180 days
- Review and document all prior and current psoriasis medications or therapies, including duration of therapy, and if applicable, when and why therapy was discontinued
- Review routine personal hygiene and skin care habits especially relating to frequency of bathing, lotion use, chlorinated pool and/or hot tub use, sauna or steam bath use, and tanning bed use.
- Begin washout period for current psoriasis treatment
    - Topical therapies – 14 days
    - UVB phototherapy or Excimer laser – 14 days

6.3 Treatment Phase (Weeks 1-8)

6.3.1 Day 0/Week 1 (First Visit)

- Review of inclusion and exclusion criteria
- Record demographic information (i.e., sex, date of birth, race/ethnicity, etc.)
- Record height and weight
- Record vital signs, including temperature, pulse, respiratory rate and blood pressure
- Review and update of medical history for any interim events between Screening and Day 0
- Review and update of any changes in medications/therapies between Screening and Day 0
- Review and document medications or therapies and any discontinued medications or therapies in the last 180 days
- Review and document all prior and current psoriasis medications or therapies, including duration of therapy, and if applicable, when and why therapy was discontinued
- Review and evaluation of any adverse events or serious adverse events
- Monitor concomitant psoriasis therapy

- Monitor routine personal hygiene and skin care habits especially relating to frequency of bathing, lotion use, chlorinated pool and/or hot tub use, sauna or steam bath use, and tanning bed use
- Monitor alcohol and tobacco use
- Review of systems
- Vital signs, weight
- Physical exam
- % BSA assessment
- PASI and PGA score
- Photograph(s) of lesions/areas to be sampled
- Skin sampling/swab for microbiome analyses (Appendix B)
- Optional skin biopsies for HDAC3 analyses
- Administer NB-UVB phototherapy (+3 day window)

6.3.2 Phototherapy Week 1 through Week 8

- NB-UVB phototherapy 3 times weekly for 8 weeks
- Review and evaluation of any adverse events or serious adverse events

6.3.3 Week 8 (after final phototherapy dose)/Early Termination Visit

- Review and evaluation of any adverse events or serious adverse events
- Review and document medications or therapies and any discontinued medications or therapies
- Monitor concomitant psoriasis therapy
- Monitor routine personal hygiene and skin care habits especially relating to frequency of bathing, lotion use, chlorinated pool and/or hot tub use, sauna or steam bath use, and tanning bed use
- Monitor alcohol and tobacco use
- Review of systems
- Vital signs, weight
- Physical exam
- % BSA assessment
- PASI and PGA score
- Photograph(s) of lesions/areas to be sampled
- Skin sampling/swab for microbiome analyses (at least 30 minutes after phototherapy dose) (Appendix B)

6.3.4 Week 9 (between 2 to 7 days after final phototherapy dose)/Post-Early Termination Visit

- Review and evaluation of any adverse events or serious adverse events
- Review and document medications or therapies and any discontinued medications or therapies
- Monitor concomitant psoriasis therapy
- Monitor routine personal hygiene and skin care habits especially relating to frequency of bathing, lotion use, chlorinated pool and/or hot tub use, sauna or steam bath use, and tanning bed use
- Monitor alcohol and tobacco use
- Review of systems
- Vital signs, weight

- Physical exam
- % BSA assessment
- PASI and PGA score
- Photograph(s) of lesions/areas to be sampled
- Skin sampling/swab for microbiome analyses (at least 48 hours after final phototherapy dose; ideally 48 to 72 hours after final phototherapy dose) (Appendix B)

7 Statistical Plan

7.1 Sample Size Determination

Sample size calculations are based on previously published estimates of bacterial load, alpha-diversity, and beta-diversity in lesional versus non-lesional skin in psoriasis patients.[22,23] Using a two-sided, 0.0125-level test, a sample size of 30 subjects with at least one sample site will provide 80% power to detect a difference of 2.4% (95% confidence interval [CI] width of 2) in combined bacterial load, 0.24 (95% CI width of 0.2) in alpha-diversity, and 0.012 (95% CI width of 0.01) in beta-diversity. To account for an estimated 10% loss to follow-up, 34 subjects will be recruited.

7.2 Statistical Methods

Stata 13.0 (StataCorp, College Station, TX) will be used for all analyses. All data will be summarized using descriptive statistics (mean, SD, range for continuous variables; frequencies for categorical variables) and graphical techniques (histograms, scatterplots). Tables will be produced describing any missing data patterns due to either withdrawal or other reasons.

Paired-end amplicon sequences will be assembled using PandaSEQ[46] and custom scripts, and processed in QIIME (Quantitative Insights Into Microbial Ecology) open source software package.[47,48] To analyze microbiota, we will apply several metrics to capture multiple dimensions of microbial diversity and composition that may be altered in psoriasis as described below.

1. Alpha-diversity: The diversity present in a given sample will be measured by the Shannon Diversity Index which takes into account the number of species and the evenness of species present in a sample. The number of observed species alone will serve as a measure of richness.
2. *Beta-diversity*: The diversity shared among samples will be measured by the Jaccard index, Bray-Curtis index, and UniFrac metric. The Jaccard index measures shared species amongst samples (“community membership”). The Bray-Curtis index measures shared species and their abundance amongst samples (“community structure”). The UniFrac metric[49] incorporates the unique phylogenetic branch length into a measurement of similarity based on relatedness of colonizing microbiota. The weighted version of the UniFrac metric takes into account abundance of lineages.
3. *Taxonomic composition*: Relative abundance of bacterial taxa present will be determined by classifying 16S rRNA sequences using the Ribosomal Database Project naïve Bayesian classifier[50] and the Greengenes reference database of 16S rRNA sequences.[51]
4. *Bacterial load*: We will use a quantitative real-time PCR assay to amplify the 16S rRNA gene. To calculate bacterial load from real-time PCR data, a standard curve is generated with a well-characterized isolate (i.e., E. coli). The standard curve is then used to convert real-time PCR amplification data to 16S gene copy number, and from gene copy number, the number of bacterial cells in the sample is estimated.

Significance in alpha diversity, taxonomic composition, and bacterial load will be assessed using

the nonparametric Wilcoxon rank-sum test (for pairwise comparisons), Wilcoxon signed-rank test (for matched pairwise comparisons), or Kruskal-Wallis test (for >2 comparisons). Beta-diversity metrics will be visualized by principle coordinates analysis and plots. The significance of the observed clustering will be assessed using the non-parametric Adonis test through permutations. Statistical tests will be adjusted for multiple comparisons as appropriate.

7.3 Subject Population(s) for Analysis

Analyses will be conducted using all subjects for whom microbiome data are collected and available.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e., not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e., possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event
An ***adverse event (AE)*** is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Any adverse event associated with the use of a therapy in humans, whether or not considered therapy related, including the following:

- an adverse event occurring in the course of the administration of the therapy (i.e., narrow-band UVB phototherapy) in professional practice: an adverse event occurring from treatment overdose, whether accidental or intentional;
- an adverse event occurring from therapy abuse/misuse
- an adverse event occurring from therapy withdrawal
- any failure of expected therapeutic action (lack of efficacy)
- therapy error; suspected transmission of any infectious agent via administration of therapy;, unexpected therapeutic or clinical benefit from use of a therapy.

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** **(SAE)** is any adverse experience that results in any of the following outcomes:

- Results in subject death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption in a person's ability to conduct normal activities of daily living)
- Is a congenital anomaly/birth defect.

In addition, an important medical event that may not result in death, be life-threatening, or require/prolong hospitalization may be considered a serious adverse event when, based on appropriate medical judgment, it may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the outcomes listed above.

Examples of such 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.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol (Section 8.3). Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.

- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

8.2 Recording of Adverse Events and Serious Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

Recording should be done in a concise manner using standard, acceptable medical terms.

The adverse event recorded should not be a procedure or a clinical measurement (i.e. a laboratory value or vital sign) but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement.

Preexisting conditions that worsen in severity or frequency during the Study, such as psoriasis severity, will also be recorded (a preexisting condition that does not worsen is not an adverse event).

Further, a procedure or surgery is not an adverse event; rather, the event leading to the procedure or surgery is considered an adverse event. Any event requiring in-patient hospitalization that occurs during the course of a subject's participation in a trial must be reported as an SAE. Hospitalizations that do not meet the criteria for SAE reporting are:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.

- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.
- Surgery or procedure planned prior to entry into the Study for a pre-existing condition that has not worsened.

If a clinical significant worsening from baseline is observed in any laboratory or other test parameter (e.g. electrocardiogram (ECG), angiogram), physical exam finding, or vital sign, a corresponding clinical adverse event should be recorded.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, “hepatitis” and not “elevated liver function tests” should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an adverse event, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the protocol sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- Related to study participation,
- Unexpected, and
- Serious or involve risks to subjects or others
  (see definitions, section 8.1).

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

8.3.1 Investigator Reporting: Notifying the study sponsor

Any study-related unanticipated problem posing risk of harm to subjects or others, and any type of serious adverse event, must be reported to the study sponsor within 24 hours of the event. To report such events, a Serious Adverse Event (SAE) form must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site.

Within the following 48 hours, the investigator must provide further information on the serious adverse event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor

8.3.2 Investigator reporting: notifying the Penn IRB

This section describes the requirements for safety reporting by investigators who are Penn faculty, affiliated with a Penn research site, or otherwise responsible for safety reporting to the Penn IRB. The University of Pennsylvania IRB (Penn IRB) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Penn IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Penn IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

- Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

  Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling.)

  AND

  Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

Reporting Process
Unanticipated problems posing risks to subjects or others as noted above will be reported to the Penn IRB via the HS-ERA online system or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Reporting Deaths: more rapid reporting requirements
Concerning deaths that occur during the course of a research study, the following describes the more rapid reporting requirement of the Penn IRB for specific situations:

- Report the event within 24 hours when the death is unforeseen (unexpected) and indicates participants or others are at increased risk of harm.
- Report the event within 72 hours, for all other deaths, regardless of whether the death is related to study participation.

For reportable deaths, the initial submission to the Penn IRB may be made by contacting the IRB Director or Associate Director. The SAE report can follow via the HS-ERA online system.

Other Reportable events:
For clinical trials, the following events are also reportable to the Penn IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of exposure to the therapeutic device
- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.

- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

8.4 Unblinding Procedures

Not applicable.

8.5 Stopping Rules

Since the study treatment is an FDA-approved treatment for psoriasis, standard of care for NB-UVB phototherapy will be used to ensure primary safety endpoints outlined in Section 3.2. Subjects will be monitored for adverse events and serious adverse events by the Investigator. Subjects who experience adverse events may be removed from study participation at the discretion of the Investigator.

8.6 Safety and Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above at each study visit. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.6.1 Data Monitoring

Study data will be housed in a secure server on an authorized user-access database with extensive, automated data validation rules and other quality assurance features.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If any information is collected directly on the CRF, the CRF will be considered the source document.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10 Study Monitoring, Auditing, and Inspecting

10.1 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, Pfizer, Inc., government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Appendix F for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

This study is financed through a grant from Pfizer, Inc.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the University conflict of interest policy.

12.3 Subject Stipends or Payments

Subjects will be asked to commute to study practices for up to 3 visits per week for study treatment administration and monitoring. Each visit that involves physical examination (Week 1, 8, 9) is estimated to take up to 1 hour. Each phototherapy only visit is estimated to take approximately 30 minutes.

For each study visit, subjects will be reimbursed $30 for study visits that involve evaluation by the study Investigator (Week 1, 8, and 9) to offset travel and other indirect costs for study participation. All monetary amounts will not be paid after each individual visit but instead at the end of study participation. When the subject has reached the end of study participation, after the last study visit, the subject will receive cash payment for the total amount that has been reimbursed for all study visits. If the subject does not complete all study visits the amount received will be pro-rated to reflect the number and type of visits completed. In addition subjects will need to complete a W-9 form which is required by the IRS when study participation will result in a subject receiving more than $600 in a calendar year. This form will be provided for subjects.

13 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study principal investigator. Any investigator involved with this study is obligated to provide the sponsor with all data derived from the study.

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15 Attachments

15.1 Appendix A – Narrow-Band UVB Phototherapy Protocol

15.2 Appendix B – Skin Sampling for Microbiome Analyses

15.3 Appendix C – Skin Biopsy Wound Care Instructions

15.4 Appendix D – Study Flowchart (Screening through Week 9)

15.5 Appendix E – Instructions for Study Subjects: Preparation for Study Visits

15.6 Appendix F – Informed Consent Form