CLINICAL STUDY PROTOCOL

Study Title:	A Multicenter, Randomized, Double-Blind, Vehicle-Controlled Phase 1B Study of the Safety, Short-Term Engraftment and Action of NB01 in Adults with Moderate Acne	
Sponsor:	Naked Biome, Inc.	
IND Number:	17552	
EudraCT Number:	Not Applicable	
NCT Number:	NCT03709654	
Indication:	Acne Vulgaris	
Protocol ID:	NB01-P1BMA	
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PROTOCOL SYNOPSIS

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Study Title:	A Multicenter, Randomized, Double-Blind, Vehicle-Controlled Phase 1B Study of the Safety, Short-Term Engraftment and Action of NB01 in Adults with Moderate Acne
IND Number:	17552
EudraCT Number:	Not Applicable
Clinical Trials.gov Identifier:	NCT03709654
Study Centers Planned:	Approximately three study centers in the US.
Objectives:	The objectives of this study are as follows: 1. Primary **1.** To determine the safety and tolerability of a multiple application of topical Propionibacterium acnes (*P. acnes*) microbiome transplant ("NB01"). 2. Exploratory **1.** To define engraftment duration of NB01. **2.** To evaluate preliminary clinical efficacy using Acne Lesion Counts (total, inflammatory, and non-inflammatory), Investigator Global Assessment (IGA) and subjective improvement on acne based on subject reported outcomes (Acne QoL Questionnaire). **3.** To evaluate treatment effects, based sebum production in a subpopulation from sites 02 and 03.
Study Design:	Multicenter, Randomized, Double-Blind, Vehicle-Controlled, Phase 1B Study
No. of Subjects:	36
Target Population:	Adult Male and Female Subjects with Moderate Facial Acne Vulgaris

Duration of Subject Participation:	Subject participation will be approximately four months. Study duration will be approximately one year.
Diagnosis and Main Eligibility Criteria:	**Inclusion Criteria** 1. Subject has provided written informed consent. 2. Subject is male or non-pregnant female, 18-40 years of age, inclusive at Screening. 3. Subject has a clinical diagnosis of moderate facial acne vulgaris defined as Grade 3 on the IGA (see Appendix 3, IGA Grading). 4. Subject meets all of the following: • A minimum of 20 but not more than 50 facial inflammatory lesions (papules plus pustules), including nasal lesions, and no more than 1 facial nodular lesion (<5 mm) • No cystic lesions • A minimum of 20 but not more than 125 facial noninflammatory lesions (open and closed comedones), including nasal lesions 5. Female subject with non-cyclical acne. 6. Women of childbearing potential (WOCBP) willing to use adequate contraception (e.g., total abstinence, intrauterine device [IUD], barrier method with spermicide, surgical sterilization or surgically sterilized partner, Depo-Provera®, Nexplanon®, or NuvaRing®) for the duration of the Screening Period and during study participation. All oral contraceptive and hormonal implants will need to have been initiated and on a stable dose for at least 3 months prior to the screening period. WOCBP are defined as any female who has experienced menarche and who is NOT permanently sterile (hysterectomy, status-post 6 month or more, a bilateral tubal ligation or bilateral oophorectomy) or postmenopausal; postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause. 7. Male subjects willing to use an acceptable method of contraception (e.g., total abstinence, barrier methods with spermicide) during study participation. 8. Subject has the ability to personally apply benzoyl peroxide (BPO) and study drug, as per protocol.

Exclusion Criteria

1. Subject has active bacterial, viral, or fungal skin infections.
2. Subject has used any of the following topical anti-acne preparations or procedures on the face:
    - Topical anti-acne treatments including, but not limited to, over-the-counter (OTC) acne cleansers or treatments, BPO (other than the BPO required during Screening), antibiotics, azelaic acid, dapsone, sulfa based products, corticosteroids, and salicylic acid within two weeks of Screening;
    - Topical retinoids (e.g., prescription tazarotene, adapalene, and tretinoin including OTC adapalene) within four weeks of Screening;
    - Light treatments, microdermabrasion, or chemical peels within eight weeks of Screening;
    - Other topical therapy, which may materially affect the subject's acne, in the opinion of the Principal Investigator (PI).
3. Subject has used any of the following systemic anti-acne medications:
    - Corticosteroids (including intramuscular, intra-articular and intralesional injections) within four weeks of Screening. Inhaled, intranasal, or ocular corticosteroids are allowed if use is stable (stable use is defined as dose and frequency unchanged for at least four weeks prior to Screening);
    - Antibiotics or other systemic anti-acne medications within four weeks of Screening, with the exception of five days or less of antibiotic therapy during this period, but not within one week of Screening;
    - Androgen receptor blockers (i.e., spironolactone or flutamide) within eight weeks of Screening; with the exception of five days or less of spironolactone therapy during this period, but not within one week of Screening;
    - Retinoid therapy (e.g., isotretinoin) within six months of Screening;
    - Vitamin A supplements (greater than 10,000 units per day) within six months of Screening;

- Other systemic therapy, which may materially affect the subject's acne, in the opinion of the PI.

4. Subject has received any light-based therapies including photodynamic therapy (PDT), blue light, red light lasers, artificial tanning devices within four weeks of Screening, and is planning to be exposed to excessive sunlight during the study period;
5. Subject has active nodulocystic acne or acne conglobate, acne fulminans, or other forms of acne (e.g., acne mechanica).
6. Subject has any skin diseases with compromised skin barrier function (e.g. atopic dermatitis, etc.) such as noticeable breaks or cracks in the skin on the face, including severely excoriated skin or skin with open or weeping wounds suggestive of an active infection or increased susceptibility to infection in the treatment area (i.e., face).
7. Subject has facial hair, scarring or other clinical conditions in the treatment area that could interfere with study assessments, in the PI's opinion.
8. Subject has active clinically significant periodontal disease in the opinion of the PI, or ongoing procedures (e.g., gum grafting).
9. Subject has history/current ocular infections/surgeries within six months of enrollment at Baseline (Day 1), with the exception of any history of cataracts.
10. Subject has a history of septic joints/endocarditis.
11. Subject has sensitivity to or difficulty tolerating any ingredients in the study drug including glycerin, polyethylene glycol.
12. Subject demonstrates non-compliance with BPO pre-treatment during the Screening period. Non-compliance is defined as BPO application for less than 5 days the week prior to Day 1, failure to apply BPO 24-48 hours prior to Day 1, and BPO application within approximately 24 hours of the Day 1 visit.
13. Subject is currently participating in an investigational drug, device, or biologic study or has used an investigational drug, biologic or device treatment within 30 days prior to first application of the study drug.

14. Subjects with prosthetic heart valves, pacemakers, intravascular catheters, or other foreign or prosthetic devices/implantable devices/hardware.
15. Subject has a history of chronic human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) infections.
16. Subject has a history of malignancy (with the exception of non-melanoma skin cancer).
17. Subject is immunosuppressed (such as resulting from transplantation, immunosuppressive therapy, active HIV infection/acquired immune deficiency syndrome [AIDS], neutropenia).
18. Subject had a major surgical procedure, open biopsy, or significant traumatic injury within 14 days of initiating study drug (unless the wound has healed), or anticipation of the need for major surgery during the study.
19. Subject has a medical or psychiatric condition and/or history of drug or alcohol abuse that, in the opinion of the PI, makes the subject inappropriate for study inclusion.
20. Subjects with close contacts (e.g., spouses, children, or members in the same household) that have severe skin barrier defects or are immunocompromised.
21. Subject is unable or unwilling to comply with study protocol procedures.
22. Female subject is pregnant or lactating or is planning to become pregnant and/or breast feed within the duration of study participation.

Study Procedures/ Frequency:	Subjects will complete the following clinical site visits during the study: Screening, Day 1/Baseline, Week 2, Week 7, Week 12 End of Treatment (EOT), and Week 16/End of Study (EOS). The following procedures will be completed at all study visits, unless otherwise indicated: • Review of medical history (Screening only) • Limited physical examination (Screening, Day 1, and Week 12/EOT only) • Vital signs, which include blood pressure, heart rate, and temperature (Screening, Day 1, and Week 12/EOT only) • Local complete blood count (CBC) (Screening and Week 12/EOT only)

	• Local urine pregnancy test (Screening, Day 1, and Week 12/EOT only)
	• Twice daily facial washing
	• BPO pre-treatment of at least 5, but no more than 7, consecutive days (Screening). Should a subject require a modified Screening period schedule, BPO may be applied for more than 7 days with prior approval of the Sponsor Medical Monitor.
	• Subject Diary completion for pre-treatment period BPO and facial washing (Screening)
	• Subject Diary completion for study drug application (Day 1 through Week 12/EOT), facial washing (Day 1 through Week 12/EOT), and LSRs (Day 1 through Week 16/EOS)
	• Assessment of adverse events (AEs) and local skin reactions (LSRs)
	• Review of concomitant medications
	• IGA (Day 1 through Week 12/EOT)
	• Acne lesion counts, including inflammatory and non-inflammatory lesion counts (Day 1 through Week 12/EOT)
	• Optional photography (Day 1 through Week 12/EOT)
	• Sebum production measurements (Day 1 through Week 12/EOT)
	• Acne Quality of Life (QoL) questionnaire (Day 1 through Week 12/EOT)
	• Obtain facial samples for TaqMan® engraftment assay
	  ○ Cheek Swab, skin surface (Day 1 through Week 12/EOT)
	  ○ Biore® Strip, follicular (Screening, and Week 12/EOT only)
	• Study drug application (Day 1 through end of Week 11*)
	
	*Subjects must complete application of study drug at least 3 days prior to, but no more than 7 days from, the Week 12 visit.
	
	See Appendix 2 for additional details in the Schedule of Events table.

Test Product, Dose, and Mode of Administration:	NB01 is a topical live biologic. The active pharmaceutical ingredient consists of a single strain of health-associated *P. acnes* bacterium in a cryopreservative (glycerol), water and phosphate buffered saline (PBS). Vehicle-control consists of glycerol, water and PBS. Both NB01 and vehicle-control are delivered topically in single-dosed vacuum-sealed pads.
Study Measurements:	The following assessments will be completed for each subject according to the Schedule of Events (see Appendix 2).

Dosing Compliance: Measures of study drug compliance will include the duration (days) of treatment (defined as last dose date – first dose date +1), the total number of applications (determined from the doses reported in the Subject Diary), and the percent of expected doses applied. Subjects who apply at least 80% of the expected total number of applications and have no other evidence of material dosing non-compliance will be considered to be compliant with study drug dosing.

Primary Safety:

Adverse Events

All reported or observed AEs will be recorded. At each visit, subjects will also be questioned specifically about the status of any ongoing AEs. Untoward events that occur prior to the first dose of study drug will be captured in the medical history section of the electronic case report form (eCRF) unless they are related to a study-specific procedure. Optional photographs may be obtained for areas outside of the face, as clinically indicated for the classification and management of AEs.

Local Skin Reactions

At each visit, LSRs will be assessed. Erythema, edema, erosion/ulceration, scaling/dryness, and scabbing/crusting in the treatment area will be assessed by the PI and itching and pain in the treatment area will be assessed by the subject using a 4-point ordinal scale where 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), and 3=severe (marked, intense). Only LSRs that require medical intervention (e.g., prescription medication), require withholding or discontinuation of the application of the study drug, or extend 2 cm beyond the treatment area will be documented as AEs. Any LSRs that are not listed above will be recorded as an AE.

LSRs will also be assessed by subjects weekly during the Screening Period, Treatment Period, and Follow-up Period using a subject diary to assess redness, swelling, erosions/ulceration, scaling/dryness, scabbing/crusting, itching and pain by the same 4-point scale used during clinic visits. Subjects will be asked to report the greatest severity of each LSR experienced during the previous 7 days.

Limited Physical Examination

The limited physical examination will include examination of the face, chest, arms, and back (i.e., relevant acne regions). Abnormalities at Screening/Baseline will be recorded as medical history. Any new or worsening abnormalities at Visit 5/EOT will be recorded as AEs.

Vital Signs

	Vital signs including blood pressure, heart rate, and temperature will be measured at Screening/Baseline and Visit 5/EOT. Assessments will be made after the subject has rested in a seated position for at least five minutes. Complete Blood Count CBC will be assessed locally at Screening and Visit 5/EOT and must include Differential. Urine Pregnancy Test (UPT) A UPT will be performed at Screening/Baseline and Visit 5/EOT for WOCBP.
Exploratory Engraftment:	Engraftment Assay Follicular engraftment sampling will be completed via use of Biore® Strips applied across the bridge of the nose extending to either cheek. Skin surface engraftment sampling will be completed via cheek swab.
Exploratory Efficacy:	Investigator's Global Assessment (IGA) Overall severity of acne will be assessed using a five-point scale where 0=Clear, 1=Almost Clear, 2=Mild, 3=Moderate, and 4=Severe. This is a static morphological scale that refers to a point in time and not a comparison to Baseline (see Appendix 3). Acne Lesion Counts The number of total lesions, inflammatory lesions (papules and pustules), and non-inflammatory lesions (open and closed comedones) on the face (including those present on the nose) will be counted. Counts of nodules and cysts will be reported separately and are not to be included in the inflammatory or non-inflammatory lesion counts. Acne Quality of Life (QoL) Questionnaire At each visit, subjects will be asked to complete the Acne QoL Questionnaire to assess subjective improvement of acne (see Appendix 5).
Exploratory Sebum:	Sebum Production At each visit, sebum levels will be assessed for any changes from Screening, Baseline to Weeks 2, 7, and 12 at sites 02 and 03. Sebum production data will not be available for all subjects. Site 04 did not have a Sebumeter, therefore, sebum production was not assessed for any subject. Site 03 received a Sebumeter after having started enrollment of subjects. Some of the site's subjects will not have any sebum data while others may have only partial data with the Screening values missing. Subjects without any sebum data will be excluded from the summaries and analyses. Subjects with partial

	data will be included in the summaries for observed values where data is available, but will be excluded from summaries and analyses for absolute change and percent change from Screening.
Study Endpoints:	
Primary Safety:	• Incidence (severity and causality) of any local and systemic AEs. • Number of subjects with presence (and severity) of each LSR and each time point. • Changes from Screening/Baseline in physical examination findings at Visit 5/EOT. • Changes from Screening/Baseline in vital signs at Visit 5/EOT. Changes from Screening in local CBC at Visit 5/EOT.
Exploratory Engraftment:	• For skin engraftment assay, absolute and percent change from Screening to follow-ups in Cas5/PanBac and for follicular engraftment assay, the proportion of subjects with "success" at EOT where "success" is defined as a Follicular Biore® with "yes" outcome for presence of live NB01.
Exploratory Efficacy:	• Absolute change in IGA score from Screening at each follow up visit. Percentage of subjects with (a) at least a one-point change in IGA score and (b) percentage of subjects with at least a two-point change in IGA score from Screening at each follow-up visit. • Absolute and percent change from Screening at each follow-up visit in total, inflammatory, and non-inflammatory lesions. • Absolute and percent change from Screening to follow-up in each of the four Acne QoL domain scores.
Exploratory Sebum:	• Absolute and percent change from Screening to follow-up in sebum production in a subpopulation from sites 02 and 03.
Sample Size Calculations:	No formal sample size calculations were performed for this study given it is an initial proof of concept study.
Statistical Methods:	All statistical processing will be performed using SAS®. Summary tables (descriptive statistics and/or frequency tables) will be provided for screening and/or baseline variables, efficacy variables, and safety variables. Summaries will be provided for each treatment group. In general, continuous variables will be summarized by descriptive statistics including sample size, mean, Standard

	Deviation (SD), median, minimum, and maximum. Categorical variables will be summarized by frequency and percentage. The Safety population will include all randomized subjects who received and applied study drug. The intent-to-treat (ITT) population will include all randomized subjects who were dispensed the study drug. The Per-Protocol (PP) population will include a subset of the ITT population who completed the study without significant protocol deviations (as will be determined prior to unblinding the randomization).
Dosing Compliance:	Descriptive statistics will be used to summarize for each treatment group the duration of treatment (defined as last dose date – first dose date +1), the total number of applications (determined from the doses reported in the Subject Diary), and the percent of expected doses applied for the ITT and PP populations. Subjects who apply at least 80% of the expected total number of applications and have no other evidence of material dosing non-compliance will be considered to be compliant with study drug dosing.
Primary Safety:	All safety analyses will be performed on the Safety population. <u>Extent of Exposure</u> Descriptive statistics will be used to summarize the extent of exposure in the Safety population. The total amount of study drug used by each subject will be calculated based on the number of days the study drug was applied (according to the subject's diary entries). <u>Physical Examinations</u> Findings from the physical exam will be recorded in medical history (from assessment at Visit 1/Screening) or as AEs (from assessment at Visit 5/EOT). <u>Vital Signs</u> Descriptive statistics of vital signs (temperature, blood pressure, and heart rate) will be provided by treatment group. <u>Clinical Laboratory Tests</u> Local CBC tests will be evaluated for any material changes during the study period. All laboratory data will be listed and reported in the units received by the laboratory. Shift tables by analyte and by out-of-range flag will be presented. <u>Local Skin Reactions</u> The frequency of the individual LSRs (PI: erythema, edema, erosion/ulceration, scaling/dryness, and scabbing/crusting; Subject:

itching and pain) will be tabulated by severity and treatment group at each visit. The frequency of the individual LSRs recorded by subjects in weekly diaries (redness, swelling, erosion/ulceration, scaling/dryness, and scabbing/crusting, itching, and pain) will be tabulated by severity and treatment group for each study week.

Adverse Events
All AEs reported during the study will be listed, documenting course, severity, PI assessment of the relationship to the study drug, and outcome. Verbatim terms on the eCRFs will be linked to preferred terms (PTs) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) mapping system. The PTs and SOC will then be tabulated. All reported AEs will be summarized by the number of subjects reporting AEs, SOC, PT, severity, and relationship to study drug by treatment group.

Urine Pregnancy Tests (UPT)
Results from UPTs will be provided in a listing.

Exploratory Engraftment:

The engraftment assay analyses will be conducted on the ITT and PP populations.

For endpoint of Engraftment Assay of the Cas5/PanBac, the absolute and percent change from Screening at each follow-up visit, the comparison between NB01 and vehicle-control will be analyzed using ANCOVA with the dependent variable being absolute or percent change values and the factor treatment and the Screening value as a covariate in the model, with and without LOCF imputation.

For the endpoint of Follicular Biore®, treatment groups will be compared with respect to the proportions of subjects with "success" at EOT Week 12 using the CMH test with and without stratification on study center, where "success" is defined as a Follicular Biore® with "yes" outcome based on recovery of live NB01.

Exploratory Efficacy:

The efficacy analyses will be conducted on the ITT and PP populations.

Investigator's Global Assessment
The observed and change from Screening scores at each follow-up visit will be tabulated. For the endpoint of IGA, the treatment groups will be compared with respect to the proportions of subjects with (a) at least a one-point improvement and (b) at least a two-point improvement in IGA score relative to Screening at each

	follow-up visit using the CMH test with and without stratification on study center. Acne Lesion Counts For the endpoint of Acne Lesion Counts, absolute and percent change from Screening at each follow-up visit in total, inflammatory, and non-inflammatory lesions, the comparison between NB01 and vehicle-control will be analyzed using Analysis of Covariance (ANCOVA) model with the factor treatment and the Screening counts as a covariate in the model, with and without Last Observation Carried Forward (LOCF) imputation. Acne Quality of Life For endpoint of Acne-QoL, the absolute and percent change from Screening at each follow-up visit on four domains separately and total, the comparison between NB01 and vehicle-control will be analyzed using ANCOVA model with the factor treatment and the Screening score as a covariate in the model, with and without LOCF imputation.
Exploratory Sebum:	Sebum Production For endpoint of sebum production, the absolute and percent change from Screening at each follow-up visit, the comparison between NB01 and vehicle-control will be analyzed using ANCOVA model with the factor treatment and the Screening value as a covariate in the model, with and without LOCF imputation.

This study will be conducted in accordance with the guidelines of Good Clinical Practice including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
AIDS	acquired immune deficiency syndrome
ANCOVA	Analysis of Covariance
BID	Twice Daily
BPO	5.0% Benzoyl Peroxide
CAMP	Christie, Atkins, and Munch-Peterson
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
CoNS	coagulase-negative Staphylococcus
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
deoR	Deoxyribose operon repressor
DLT	Dose Limiting Toxicity
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IGA	Investigator Global Assessment
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine device
LOCF	Last Observation Carried Forward
LSR	Local Skin Reaction
MedDRA	Medical Dictionary for Regulatory Activities
NB01	*P. acnes* microbiome transplant
OTC	Over-the-Counter
P. acnes	Propionibacterium acnes
pIMPLE	*P. acnes* plasmid
PBS	Phosphate Buffered Saline
PDT	Photodynamic Therapy
PI	Principal Investigator
PP	Per-Protocol

PT	Preferred Term
QD	Once Daily
QoL	Quality of Life
SAE	Serious Adverse Event
S. aureus	Staphylococcus aureus
SD	Standard Deviation
SOC	System Organ Class
UPT	Urine Pregnancy Test
US	United States
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

1. INTRODUCTION

1.1. Background

Naked Biome hypothesizes that eliminating resident disease-associated bacterial strains and replacing them with a health-associated *Propionibacterium acnes* (*P. acnes*) transplant may help to improve, mitigate, treat, or prevent acne flares. In a Phase I single application study of NB01 conducted by the Sponsor, all 10 subjects completed the study without any drug-related adverse events (AEs).

Genotypic and phenotypic work performed by the Sponsor has identified candidate strains sourced from healthy subjects that match all our criteria for health as defined by the literature. Genotypically, the Sponsor's candidate strain is a *P. acnes* ribotype 2, deoR+ (Johnson et al. 2016), lipase type II+ (Tomida et al. 2013) which contains a complete CRISPR system (Johnson et al. 2016), does not contain the pIMPLE plasmid (Kasimatis et al. 2013), and has no identifiable genomic evidence of antibiotic resistance. Phenotypically, the candidate strain produces low levels of porphyrin, comparable to other healthy associated ribotype 2's in the literature and is sensitive to all five antibiotics tested internally (Clindamycin, Doxycycline, Erythromycin, Minocycline, Tetracycline as was measured with Etest [bioMérieux]).

Additional safety assessments were performed by CHR-Hansen, Naked Biome's GMP manufacturer, who confirmed that no genomic antibiotic resistance genes were present and that the candidate strain was sensitive to 13 out of 14 tested antibiotics, resistant only to metronidazole which *P. acnes* has known natural resistance to and was additionally non-hemolytic and non-cytotoxic.

Outside of known association of *P. acnes* with acne vulgaris, below is an accrued list of rare opportunistic infections associated with *P. acnes*. *P. acnes* has been observed in other infections such as implant-associated, soft tissue, periodontal, periocular, cardiovascular system, and deep-organ tissues infections, and may also have a role in relation to pulmonary infection as the bacteria can be isolated from lungs and lymph nodes. Routes of infection are often from the subject's own commensal flora (normal skin or oral tract) (Kwon and Suh 2016). The expanded multi-locus sequence typing scheme based on 7 housekeeping genes and 2 putative virulence genes developed by McDowell et al gives a good resolution and revealed strains which seem to have an increased capacity to cause infections and others that are rarer or found mainly among healthy individuals (McDowell et al. 2012, McDowell et al. 2013).

Strain HP4G1 has a deoR repressor gene just upstream of the porphyrin operon suggesting a mechanism for reduced porphyrin synthesis and thus may not be associated with acne vulgaris. Further, the strain has a PAp60/PAmce allele combination found in non-invasive *P. acnes* strains and lacks 2 of 4 genes involved in iron uptake, which is of importance for growth in the human body at conditions with low iron access. Notably, regarding CAMP factors 1-4, which are expected to be involved in pathogenicity and are involved in co-hemolysin with *Staphylococcus aureus* (*S. aureus*), HP4G1 had a mutation in the CAMP 2

gene leading to an extension of the gene as the stop codon was interrupted. This variant has not been observed before and as CAMP factor 2 is described as having properties for co-hemolysin and exotoxin, this may lower the pathogenic potential of the strain. Moreover, the strains belong to the CC72 clonal complex which, compared to CC5, contains strains less commonly isolated from healthy humans or individuals with infections. HP4G1 was found to be a ST100-like type not previously reported and most likely has a non-functional CAMP2 gene due to a mutation in the stop codon. Therefore, HP4G1 is most likely less virulent than *P. acnes* in general with a low risk of causing infections.

Porphyrin is a known inflammatory metabolite involved in the pathogenesis of acne. Porphyrin is produced by the *P. acnes* bacterium and is a photosensitizing agent. Dermatologists routinely use blue and red-light therapies to selectively target *P. acnes*-produced coproporphyrin III and protoporphyrin IX, respectively, thereby eliminating *P. acnes* and improving disease. As stated above, HP4G1 has a repressor of porphyrin production, called deoR. *In vivo*, the HP4G1 strain produces less porphyrin than acne-associated strains that lack the deoR repressor operon. Despite that, the HP4G1 strain is a low porphyrin producer; the fact that it is applied in significant quantities (10^5 CFU/cm^2) could lead to a temporary increase in porphyrin upon application. This hypothetical increase could be photosensitizing to subjects, as such, photosensitivity has been included as a theoretical side effect of HP4G1 application.

The Sponsor intends to address the risk of these opportunistic infections through the selection of genotypic and phenotypic characteristics most associated with health and with the implementation of appropriate exclusion criteria to eliminate subjects that may have increased risk of a *P. acnes* infection.

P. acnes is most specific to facial pilosebaceous region which is the natural niche for *P. acnes*, and therefore the best region for application to appropriate the sensitivity and therapeutic impact of a topical *P. acnes* transplant (McGinley et al. 1980).

1.2. Investigational Medicinal Product Name

1.2.1. General Information

For further information on NB01, refer to the current investigator's brochure (IB) for NB01.

1.2.2. Preclinical Pharmacology and Toxicology

There is no animal *in vivo* data to date on the safety or clinical efficacy of a topical live *P. acnes* microbiome transplant. There are no well substantiated animal models for inflammatory acne and Naked Biome is investigating human-specific bacteria. Therefore, *in vivo* animal clinical and toxicology studies will not yield clinically relevant results that would be applicable for human use. Animal clinical and toxicology studies are not relevant or useful when using human-specific bacteria absent well-substantiated animal models for inflammatory acne for pre-human efficacy testing (Mirshahpanah and Maibach 2007). The best, most relevant, and only useful model to test NB01 is first in humans

(Mirshahpanah P, Howard Maibach 2007; Achermann et al. 2014). Additional literature on previous human studies for probiotics and acne are referenced (Baquerizo et al. 2014; Wei et al. 2016; Thiboutot et al. 2009).

1.2.3. Clinical Studies of NB01

The first clinical study of NB01, NB01-P1BSA, is a Phase Ib single-center open-label dose-escalation study using a single dose application with monitoring over 28 days on 10 subjects at two different concentrations (lower bound (10^4 CFU/cm^2) and upper bound (10^5 CFU/cm^2)). This study is ongoing, however, in meeting the safety criteria of this initial study, Naked Biome plans to expand the IND research to a Phase Ib multi-dosed study under this protocol. All subjects will have been pre-treated with a daily 5.0% BPO gel (Perrigo 5% Benzoyl Peroxide Aqueous Gel) to decrease their resident microbiome bacterial load in preparation for transplantation and successful repopulation with a healthy microbiome.

1.3. Rationale for This Study

Acne vulgaris is a multifactorial disease affecting 85% of the global population over a lifetime and 40-50 million people in the US currently. It impacts individuals over a large timespan ranging from 13-40 years and has a large psychosocial impact on an individual's self-esteem. The majority of those afflicted (50%-75%) are now resistant to conventional antibiotic therapy (Walsh et al. 2016). Acne is caused by overgrowth of *P. acnes*, impaction of hair follicles, excessive sebum production and hormonal dysregulation. Current standard of care includes treatment with 5.0% BPO, retinoids, and antibiotics. However, there are significant side effects of the above medications, limiting subject compliance and leading to suboptimal long-term efficacy. The heavy dependence on long treatment courses of antibiotics combined with antibiotic resistance rising upwards of 50%-75%, is resulting in treatment failures and contributing to overall global antibiotic resistance. There has been little innovation in acne therapy in the past several decades and a significant current need to develop antibiotic alternatives.

Current therapeutic options include:

- Topical antibiotics-erythromycin/clindamycin
- Oral Antibiotics-tetracycline, doxycycline, minocycline
- Topical 5.0% BPO products
- Topical retinoids
- Oral Retinoids
- Topical acids-salicylic acid, glycolic acid
- Peels
- Blue and red-light therapies
- Dapsone (Aczone®)
- Azelaic acid (Finacea®)

Recent literature from the Human Microbiome Project has shown there are unique microbial signatures specific to healthy and acne disease states (Fitz-Gibbon et al. 2013; Tomida et al.

2013). Subsequent literature discovered a repressor in the porphyrin pathway in health-associated strains resulting in significantly lower porphyrin production (Johnson et al. 2016). Porphyrin is a known inflammatory mediator in acne pathogenesis (Kang et al. 2015). Porphyrin levels inversely correlate with therapeutic improvement in acne (Richter et al. 2016). Additional papers have highlighted other virulent factors such as the pIMPLE plasmid that may be associated with acne pathogenesis and were found to be more common in disease-associated strains (Kasimatis et al. 2013).

From this data, the Sponsor believes that by eliminating resident disease-associated bacterial strains and replacing them with a health-associated *P. acnes* transplant, there is the potential to improve, mitigate, treat, or prevent acne flares. Naked Biome is currently testing this in an initial Phase I study evaluating the safety, tolerability, and clinical impact that a single dose application of NB01 has on adult subjects with moderate acne. Naked Biome aims to test this further in multiple dosing with NB01 on subjects under this protocol.

1.4. Risk/Benefit Assessment for the Study

The risks of this study are that the applied study drug may contribute to worsening of disease and/or subjects may experience side effects including but not limited to unlikely opportunistic infections, irritation, dryness, or redness. The benefits are that individual subjects may have improvement of their disease. Overall benefits to society include development of novel therapeutics for the treatment of acne.

1.5. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice, and all applicable regulatory requirements.

2. OBJECTIVES

The objectives of this study are:

1. Primary: To determine the safety and tolerability of a multiple application of topical *P. acnes* microbiome transplant ("NB01").

2. Exploratory:

    1. To define engraftment duration of NB01.

    2. To evaluate preliminary clinical efficacy using Acne Lesion Counts (total, inflammatory, and non-inflammatory), IGA, and subjective improvement of acne based on subject reported outcomes (Acne QoL Questionnaire).

    3. To evaluate treatment effects, based on sebum production in a subpopulation from sites 02 and 03.

3. STUDY DESIGN

3.1. Study Measurements

3.1.1. Dosing Compliance

Measures of study drug compliance will include the duration (days) of treatment (defined as last dose date – first dose date +1), the total number of applications (determined from the doses reported in the Subject Diary), and the percent of expected doses applied. Subjects who apply at least 80% of the expected total number of applications and have no other evidence of material dosing non-compliance will be considered to be compliant with study drug dosing.

3.1.2. Primary Safety

Adverse Events
All reported or observed AEs will be recorded. At each visit, subjects will also be questioned specifically about the status of any ongoing AEs. Untoward events that occur prior to the first dose of study drug will be captured in the medical history section of the electronic case report form (eCRF) unless they are related to a study-specific procedure.

Local Skin Reactions
At each visit, LSRs will be assessed. Erythema, edema, erosion/ulceration, scaling/dryness, and scabbing/crusting in the treatment area will be assessed by the PI and itching and pain in the treatment area will be assessed by the subject using a 4-point ordinal scale where 0=absent, 1=mild (slight, barely perceptible), 2=moderate (distinct presence), and 3=severe (marked, intense). Only LSRs that require medical intervention (e.g., prescription medication), require withholding or discontinuation of the application of the study drug, or extend 2 cm beyond the treatment area will be documented as AEs. Any LSRs that are not listed above will be recorded as an AE.

LSRs will also be assessed by subjects weekly during the Screening, Treatment and Follow-up periods using a subject diary to assess redness, swelling, erosion/ulceration, scaling/dryness, scabbing/crusting, itching and pain by the same 4-point scale used during clinic visits. Subjects will be asked to record the greatest severity of each LSR experienced during the previous 7 days.

Limited Physical Examination
The limited physical examination will include examination of the face, chest, arms, and back (i.e., relevant acne regions) Abnormalities at Screening/Baseline will be recorded as medical history. Any new or worsening abnormalities at Visit 5/EOT will be recorded as AEs.

Vital Signs
Vital signs including blood pressure, heart rate, and temperature will be measured at Screening/Baseline and Visit 5/EOT. Assessments will be made after the subject has rested in a seated position for at least five minutes.

Complete Blood Count
CBC will be assessed locally at Screening and Visit 5/EOT and must include Differential.

Urine Pregnancy Test
A UPT will be performed at Screening/Baseline and Visit 5/EOT for WOCBP.

3.1.3. Exploratory Engraftment

Engraftment Assay
Follicular engraftment sampling will be completed via use of Biore® Strips applied across the bridge of the nose extending to either cheek. Skin surface engraftment sampling will be completed via cheek swab.

3.1.4. Exploratory Efficacy

Investigator's Global Assessment
Overall severity of acne will be assessed using a five-point scale where 0=Clear, 1=Almost Clear, 2=Mild, 3=Moderate, and 4=Severe. This is a static morphological scale that refers to a point in time and not a comparison to Baseline (see Appendix 3).

Acne Lesion Counts
The number of total lesions, inflammatory lesions (papules and pustules), and non-inflammatory lesions (open and closed comedones) on the face (including those present on the nose) will be counted. Counts of nodules and cysts will be reported separately and are not to be included in the inflammatory or non-inflammatory lesion counts.

Acne Quality of Life (QoL) Questionnaire
At each visit, subjects will be asked to complete the Acne QoL Questionnaire to assess subjective improvement of acne (see Appendix 5).

3.1.5. Exploratory Sebum

At each visit, sebum levels will be assessed for any changes from Screening/Baseline to Weeks 2, 7, and 12.

3.2. Endpoints

3.2.1. Pimary Safety Endpoints

The safety endpoints of this study are:

- Incidence (severity and causality) of any local and systemic AEs.
- Number of subjects with presence (and severity) of each LSR and each time point.
- Changes from Screening/Baseline in physical examination findings at Visit 5/EOT.

- Changes from Screening/Baseline in vital signs at Visit 5/EOT.
- Changes from Screening in local CBC at Visit 5/EOT.

3.2.2. Exploratory Engraftment Endpoint

The engraftment endpoint for this study is:

- For skin engraftment assay, absolute and percent change from Screening to follow-ups in Cas5/PanBac and for follicular engraftment assay, the proportion of subjects with "success" at EOT where "success" is defined as a Follicular Biore® sample with "yes" outcome based on recovery of live NB01.

3.2.3. Exploratory Efficacy Endpoints

The efficacy endpoints of this study are:

- Absolute change from Screening at each follow-up visit in IGA score. Percentage of subjects with (a) at least a one-point change in IGA score and (b) percentage of subjects with at least a two-point change in IGA score from Screening at each follow-up visit.
- Absolute and percent change from Screening at each follow-up visit in total, inflammatory, and non-inflammatory lesions.
- Absolute and percent change from Screening to follow-up in Acne QoL.

3.2.4. Exploratory Endpoint

The exploratory endpoint of this study is:

- Absolute and percent change from Screening to follow-up in sebum production.

3.3. Study Design

This is a multicenter, randomized, double-blind, vehicle-controlled Phase 1B study of daily doses of topically-delivered NB01 or vehicle-control in subjects with moderate, non-cyclical facial acne.

Subjects who consent to participate in the study will initiate Screening procedures, during which they will be pre-treated with 5% topical BPO gel once daily (QD) for 5 to 7 days before randomizing into the study. Subjects with modified screening period schedules may be able to apply BPO for more than 7 days; however, this must be pre-approved by the Sponsor's Medical Monitor.

Thirty six subjects were randomized into the study to receive high-dose NB01 (10^5 CFU/cm^2) or vehicle-control.

Subjects will be stratified according to these variables:

- Sex (male/female)

- Age (18-25 years old/26-40 years old)

The study will comprise of subjects with moderate facial acne who will be randomized to one of two treatment arms, either vehicle-control or high-dose NB01.

The study arms consist of vehicle-control control and daily high-dose (10^5CFU/cm^2) NB01, with subjects enrolled at a 2:1 ratio (treatment arm to vehicle-control arm). The PI may employ a dose reduction strategy with approval from the Sponsor's Medical Monitor to reduce/modify dosing based on individual subject's tolerability. Such changes, however, shall not be made without the written approval of the Medical Monitor, see Section 7.4.

Subjects will remain on study through 11 weeks of study treatment.

3.4. Study Treatments

On Day 1, the first study drug dose will be PI-applied approximately 24 hours after the subject has completed their final BPO dose. After Day 1, subjects will continue to apply study drug to the whole face at approximately the same time every evening, for 11 weeks. Subjects will hold all at-home facial washing, shaving, and/or product application on study visit clinic days; once pre-wash procedures have been completed at the study visit, subjects may wash their face at the study clinic.

3.5. Duration of Treatment

Subject participation in the study will be approximately 4 months.

• Screening Period: 1-14 days which includes BPO Pre-Treatment Period: 5 days (up to 7 days)

• On-Study Treatment Period: 11 weeks of daily study drug treatment.

• Follow-Up Period: 4 weeks.

The overall study is expected to last approximately one year

3.6. End of Study

Subjects who complete all study visits through Week 12/Visit 5 will follow up via a telephone visit at Week 16/Visit 6 in order to complete safety follow-up. Subjects who discontinue early (before Week 12) should still have the EOT procedures performed in order to terminate the subject's participation in the study. If the subject will not return to the clinic, efforts to contact the subject must be documented and the subject will be considered lost to follow-up.

3.7. Biomarker Testing

3.7.1. Biomarker Samples to Address the Study Objectives

The following biological specimens may be collected in this study and will be used to evaluate the association of exploratory biomarkers with study drug response, including engraftment, efficacy and/or AEs and to increase knowledge and understanding of the biology of acne or related diseases, and/or the validation of a companion diagnostic for acne. The specific analyses may include but will not be limited to the following biomarkers and assays: cheek swab and Biore® strip TaqMan® and microbial sequencing laboratory analysis. Because biomarker science is a rapidly evolving area of investigation, and AEs in particular are difficult to predict, it is not possible to specify prospectively all tests that will be done on the specimens provided. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon the growing state of art knowledge. Any future testing must be approved by local authorities, as applicable, according to specific local regulations.

3.7.2. Biomarker Samples for Optional Future Research

In addition to the study-specific informed consent to be signed by each subject participating in the study, a separate, specific signature will be required to document a subject's agreement to allow the use of the remainder of their already collected microbial biomarker specimens for optional future research, once approved by local authorities, as applicable, according to specific local regulations.

The specimens collected for optional future research will be used to increase our knowledge and understanding of the biology of the study disease and related diseases and to study the association of biomarkers with disease pathogenesis, progression and/or treatment outcomes, including efficacy, AEs, and the processes of drug absorption and disposition. These specimens may be used also to develop biomarker or diagnostic assays and establish the performance characteristics of these assays. The collection and analysis of optional future research specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

4.2. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study.

1. Subject has provided written informed consent.

2. Subject is male or non-pregnant female, 18-40 years of age, inclusive at Screening.

3. Subject has a clinical diagnosis of moderate facial acne vulgaris defined as Grade 3 on the IGA (see Appendix 3, IGA Grading).

4. Subject meets all of the following:
   - A minimum of 20 but not more than 50 facial inflammatory lesions (papules plus pustules), including nasal lesions, and no more than 1 facial nodular lesion (<5 mm)
   - No cystic lesions
   - A minimum of 20 but not more than 125 facial noninflammatory lesions (open and closed comedones), including nasal lesions

5. Female subject with non-cyclical acne.

6. WOCBP willing to use adequate contraception (e.g., total abstinence, IUD, barrier method with spermicide, surgical sterilization or surgically sterilized partner, Depo-Provera®, Nexplanon®, or NuvaRing® for the duration of the Screening Period and during study participation. All oral contraceptive and hormonal implants will need to have been initiated and on a stable dose for at least 3 months prior to the Screening Period. WOCBP are defined as any female who has experienced menarche and who is NOT permanently sterile (hysterectomy, status-post 6 month or more a bilateral tubal ligation or bilateral oophorectomy) or postmenopausal; postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause.

7. Male subjects willing to use an acceptable method of contraception (e.g., total abstinence, barrier methods with spermicide) during study participation.

8. Subject has the ability to personally apply BPO and study drug, as per protocol.

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not eligible for participation in this study.

1. Subject has active bacterial, viral, or fungal skin infections.

2. Subject has used any of the following topical anti-acne preparations or procedures on the face:

    - Topical anti-acne treatments including, but not limited to, OTC acne cleansers or treatments, BPO (other than the BPO pre-treatment required during Screening), antibiotics, azelaic acid, dapsone, sulfa based products, corticosteroids, and salicylic acid, within two weeks of Screening;

    - Topical retinoids (e.g., prescription tazarotene, adapalene, and tretinoin, including OTC adapalene) within four weeks of Screening;

    - Light treatments, microdermabrasion, or chemical peels within eight weeks of Screening;

    - Other topical therapy, which may materially affect the subject's acne, in the opinion of the PI.

3. Subject has used any of the following systemic anti-acne medications:

    - Corticosteroids (including intramuscular, intraarticular and intralesional injections) within four weeks of Screening. Inhaled, intranasal, or ocular corticosteroids are allowed if use is stable (stable use is defined as dose and frequency unchanged for at least four weeks prior to Screening);

    - Antibiotics or other systemic anti-acne medications within four weeks of Screening, with the exception of five days or less of antibiotic therapy during this period, but not within one week of Screening;

    - Androgen receptor blockers (i.e., spironolactone or flutamide) within eight weeks of Screening, with the exception of five days or less of spironolactone therapy during this period, but not within one week of Screening;

    - Retinoid therapy (e.g., isotretinoin) within six months of Screening;

    - Vitamin A supplements (greater than 10,000 units per day) within six months of Screening;

    - Other systemic therapy, which may materially affect the subject's acne, in the opinion of the PI.

4. Subject has received any light-based therapies including PDT, blue light, red light lasers, artificial tanning devices within four weeks of Screening and is planning to be exposed to excessive sunlight during the study period.

5. Subject has active nodulocystic acne or acne conglobate, acne fulminans, or other forms of acne (e.g., acne mechanica).

6. Subject has any skin diseases with compromised skin barrier function (e.g. atopic dermatitis, etc.), such as noticeable breaks or cracks in the skin on the face, including severely excoriated skin or skin with open or weeping wounds suggestive of an active infection or increased susceptibility to infection in the treatment area (i.e., face).

7. Subject has facial hair, scarring or other clinical conditions in the treatment area that could interfere with study assessments, in the opinion of the PI.

8. Subject has active clinically significant periodontal disease in the opinion of the PI, or ongoing procedures (e.g., gum grafting).

9. Subject has history/current ocular infections/surgeries within six months of enrollment, with the exception of any history of cataracts.

10. Subject has a history of septic joints/endocarditis.

11. Subject has sensitivity to or difficulty tolerating any ingredients in the study drug, including glycerin, polyethylene glycol.

12. Subject demonstrates non-compliance with BPO pre-treatment during the Screening period. Non-compliance is defined as BPO application for less than 5 days the week prior to Day 1, failure to apply BPO 24-48 hours prior to Day 1, and BPO application within approximately 24 hours of the Day 1 visit.

13. Subject is currently participating in an investigational drug, device, or biologic study or has used an investigational drug, biologic or device treatment within 30 days prior to first application of the study drug.

14. Subjects with prosthetic heart valves, pacemakers, intravascular catheters, or other foreign or prosthetic devices/implantable devices/hardware.

15. Subject has a history of chronic HIV, HCV, or HBV infections.

16. Subject has a history of malignancy (with the exception of non-melanoma skin cancer).

17. Subject is immunosuppressed (such as resulting from transplantation, immunosuppressive therapy, active HIV infection/ AIDS, neutropenia).

18. Subject had a major surgical procedure, open biopsy, or significant traumatic injury within 14 days of initiating study drug (unless the wound has healed), or anticipation of the need for major surgery during the study.

19. Subject has a medical or psychiatric condition and/or history of drug or alcohol abuse that, in the opinion of the PI, makes the subject inappropriate for study inclusion.

20. Subjects with close contacts (e.g., spouses, children, or members in the same household) that have severe barrier defects or are immunocompromised.

21. Subject is unable or unwilling to comply with study protocol procedures.

22. Female subject is pregnant or lactating or is planning to become pregnant and/or breast feed within the duration of study participation.

5. STUDY DRUG PRODUCT

5.1. Randomization, Blinding and Treatment Codes

5.1.1. Procedure for Subject Randomization

Subjects will be randomized to one of the two Treatment Groups on a 2:1 basis (NB01 or vehicle-control) using a central randomization scheme. Randomization will be stratified by sex (male/female) and age (18-25 years old/26-40 years old).

Subjects will be randomized on Day 1 after the subject has arrived at the site and eligibility has been confirmed. To randomize a subject the PI or designee will call the contract research organization (CRO) and provide the required subject information. The CRO will have a designated unblinded staff member available to assign a study drug kit number to the subject, which contains the treatment specified by the randomization schedule. A subject randomization form documenting study drug kit number assignment will be provided to the site by the CRO.

5.1.2. Procedures for Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the PI may obtain treatment assignment by opening the unblinding envelope for the subject kit. Sponsor recommends but does not require that the PI contact the Medical Monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine subject emergency medical care. The rationale for unblinding must be clearly explained in source documentation and on the CRF/eCRF, along with the date on which the treatment assignment was obtained. The PI is requested to contact the Medical Monitor promptly in case of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical study and therefore, if a subject's treatment assignment is disclosed to the PI, the subject will have study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

Sponsor may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions.

5.2. Description and Handling of Study Drug

5.2.1. Formulation

"Study drug" for this study refers to the blinded NB01 or vehicle-control that will be administered to the study subjects as described in the procedures in Section 6.

NB01 Formulation:

- Live culture of a single strain of *P. acnes*
- Purified water
- Glycerol
- Phosphate buffered saline

Vehicle-control Formulation:

- Purified water
- Glycerol
- Phosphate buffered saline

All excipients are generally regarded as safe and present in concentrations found on the FDA Inactive Ingredient Guide https://www.fda.gov/drugs/informationondrugs/ucm113978.htm.

5.2.2. Packaging and Labeling

NB01 and vehicle-control will be packaged, labeled, and supplied in a blinded fashion for this study. The clinical study formulation comes as a clear solution dispensed using individual vacuum-sealed cotton pads.

The packaging for NB01 and vehicle-control will be identical and supplied frozen to the PI by the Sponsor in single aliquot dosages delivered as a clear, topical solution in a cotton applicator pad packaged in a vacuum-sealed plastic pouch. A sample image of the study drug and label are as follows:

5.2.3. Storage and Handling

At clinical site: Study drug will be stored at the clinical site in a -80° Celsius lab freezer before application to study subjects at Day 1, with the exception that Site 04 will maintain drug at -70° Celsius. A range of ± 10 degree Celsius is acceptable for storage. Please contact the Sponsor in the event of temperature departure from that range. Subjects will be provided with study drug at their study visit, with adequate supply to apply until their subsequent visit.

At home: Subjects will take the study drug home from the site in temperature-conserving travel-packs containing ice packs to maintain temperature until their arrival at home, at which time the entire travel-pack (with two different types of freezer blocks) will be stored in the subject's residential freezer.

Study drug should be removed from the freezer 5 minutes prior to application to allow it to thaw to room temperature. The study drug must be used within 5 to 30 minutes of removal from freezer storage. If for any reason application is not able to occur at the planned time within 30 minutes, the site/subject will be instructed to dispose of the study drug in a standard waste receptacle at either the clinical site or at the subject's home. The instructions for application glove and study drug pad disposal are discussed in Section 5.3.

5.3. Application of Study Drug

Administerers of study drug should wash their hands and wear non-powdered nitrile gloves for application.

At clinic: Subjects will wash their face with Cetaphil® right before in-office application on Day 1. Subject's dose will be administered by the PI (or sub-investigator designee) at the Day 1 visit after swab samples have been procured.

At home: From Day 2 and thereafter, subjects will apply study drug every evening after their Cetaphil® wash. Subjects will be instructed to stop study drug application 3-7 days before Visit 5.

Used study drug pads, shrink-wrap packaging (bags) and application gloves will be discarded in a standard waste receptacle at either the clinical site or at the subject's home. Once the study drug has been applied, the administerer will dispose of the used pad and bag by pinching the pad and bag together with the gloved hand and, using the ungloved hand, peel off the glove inside-out thereby containing the pad and bag within the glove. The subject will discard the glove (with pad and bag contained inside) in a standard waste receptacle and wash hands thoroughly with soap and water.

5.4. Prior and Concomitant Medications & Therapies

Current medications and any medications taken within 30 days prior to the start of the study (Baseline) will be recorded as prior/concomitant medications with the dose and corresponding indication. The medications to be recorded include prescription, OTC medications, and all vitamins, minerals, and dietary supplements being taken by the subject. All concomitant medications will be coded with the current version of the WHO Drug Dictionary.

Any changes in concomitant medications and/or procedures/therapies during the study must be recorded. The reason for any changes in concomitant medications and/or procedures/therapies should be reported and should reflect either a baseline medical condition documented in the medical history or in conjunction with an AE.

5.4.1. Prohibited Medications or Therapies

Subjects are excluded from the study if taking any other acne medication:

- Topical anti-acne treatments including, but not limited to, OTC acne cleansers or treatments, BPO (other than the BPO pre-treatment required during Screening), antibiotics, azelaic acid, dapsone, sulfa based products, corticosteroids, and salicylic acid
- Topical retinoids (e.g., prescription tazarotene, adapalene, and tretinoin, including OTC adapalene)

BPO use is only allowed once subjects have been consented to participate in the study and only as part of the Screening period. Subjects are to wait until the end of the study before initiating any other therapy or investigational agent for the treatment of acne.

5.4.2. Allowed Medications or Therapies

Contraception for WOCBP is required per Inclusion Criterion #6 (see Section 4.2). Vitamins and mineral supplements are permitted at dosages considered by the PI as reasonable for maintaining good health and will be recorded in the eCRFs.

Therapies (medication and non-medication therapies) not restricted by the protocol may be used during the study for the treatment or prevention of disease or to maintain good health.

Non-prohibited chronic therapies being used at Screening/Baseline may be continued but must be recorded.

Reasonable use of OTC medications such as acetaminophen or acetylsalicylic acid for relief of headache, muscle ache, etc. is allowed during the study and must be recorded.

5.4.3. Use of Other Moisturizers, Sunscreens and Makeup

Once subjects have completed the evening Cetaphil® wash, they are prohibited from using moisturizers, sunscreens (including moisturizers containing sunscreens), face makeup or other facial products, until the morning Cetaphil® wash throughout the study treatment period.

The PI (or designee) will review the subject's current topical facial product use during the Screening Period to ensure they do not contain prohibited medications such as benzoyl peroxide, retinol, salicylic acid, or glycolic acid. The site will let the subjects know which of their products are acceptable for use during the trial.

Once use of topical facial products (e.g. moisturizers, sunscreens, face make-up) has been approved by the PI (or designee), subjects may continue using them after completion of the Day 1 Visit, during the daytime hours only (after the morning Cetaphil® wash and before the evening Cetaphil® wash).

Subjects will be instructed to contact the PI or study staff for approval prior to the use of any new facial products. Site staff will query the subjects regarding use of topical facial products at each study visit.

5.4.4. Use of Other Cleansers

The use of cleansers, other than the study-provided Cetaphil®, is prohibited throughout the subject's participation in the study, from the Screening Visit through the Week 16/EOS visit.

5.4.5. Facial Shaving

Shaving of the face is allowed during the study, with these exceptions:

- Subjects may not shave in the morning prior to study clinic visits
- Subjects are not to shave in the evening after the application of study drug.

5.5. Accountability for NB01

The PI is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgement of receipt of each shipment of study drug (quantity and condition). All unused study drug dispensed to subjects must be returned to the site at the following clinic visit for accountability and compliance assessments.

NB01/vehicle-control study drug accountability records will be provided to each study site to:

- Record the date and quantity of study drug kits received from the Sponsor
- Record the date, subject number, subject initials, the study drug kit dispensed
- Record the date, quantity of any unused study drug returned

5.6. Study Drug Product Return or Disposal

Unused study drug packages may be returned to the Sponsor by the site, upon Sponsor request, after the completion of the study. Details on the return process are provided in the Study Reference Manual for this trial.

5.7. Study Drug Product Complaints

The Sponsor collects product complaints on study drugs and drug delivery systems used in clinical studies to ensure the safety of study subjects, monitor quality, and facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by the Sponsor or its designee will be reported to the Sponsor. All product complaints associated with other study material will be reported directly to the respective manufacturer.

The PI or his/her designee is responsible for reporting a complete description of the product complaint via email or other written communication to the Sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be reported to Sponsor.

If the PI is asked to return the product for investigation, he/she will return a copy of the product complaint communication with the product.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows.

The PI must document any deviation from protocol procedures and notify the Sponsor or CRO.

6.1. Subject Enrollment and Treatment Assignment

Subjects will be assigned a subject number once written informed consent has been obtained. Subjects who qualify for the study will be enrolled at Visit 2 when they are randomized to a treatment assignment.

6.1.1. Subject Re-Screening

Subjects who screen fail may be considered for enrollment at a later date, with prior Sponsor approval, but must re-consent and repeat necessary screening procedures.

6.1.2. Subject Replacement

If a subject is discontinued from the study for any reason other than a dose-limiting toxicity (DLT; see Section 7.2.1) prior to the completion of Week 2/Visit 3, that subject will be replaced.

6.2. Pretreatment Assessments

6.2.1. Screening Visit – Visit 1

Subjects will be screened (Day -14 to Day -1) before randomization to determine eligibility for participation in the study. The following will be performed and documented at the Screening Visit:

- Obtain a signed, written informed consent.
- Review inclusion/exclusion criteria and confirm subject eligibility.
- Record medical history.
- Record prior and/or concomitant medications, topical facial products and procedures/therapies.
- Have subject complete washout from any prohibited medications, if necessary.
- Limited physical examination.
- Vital signs.
- UPT.
- Local CBC.
- Pre-Treatment with BPO of at least 5, but no more than 7, consecutive days (Screening)
- Dispense Subject Diary (for completion of at-home Cetaphil® BID washes and BPO QD application).

- Sebum levels, measured at the mid-glabellar region of the forehead using a Sebumeter SM – 815 (COURAGE + KHAZAKA electronic GmbH, Köln, Germany).
- Assess AEs.
- Assess LSRs.
- IGA.
- Acne Lesion Counts (total, inflammatory, and non-inflammatory lesion counts).
- Quality of life assessment (Acne QoL Questionnaire).
- Optional facial photography.
- Cheek swab skin engraftment sample.
- Face wash with Cetaphil®.
- Biore® strip follicular engraftment sample.
- Schedule the Visit 2/Baseline visit.

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic after screening for randomization into the study on Day 1.

From the time of obtaining informed consent through the first administration of study drug, record all serious adverse events (SAEs), as well as any AEs related to protocol-mandated procedures on the AE eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history CRF/eCRF. See Section 7 (Adverse Event Reporting and Toxicity Management) for additional details.

6.2.2. Baseline Assessments – Visit 2 (Day 1)

The following will be performed and documented at the Day 1 visit:
- Reconfirm inclusion/exclusion criteria and subject eligibility.
- Review of Screening Subject Diary.
- Limited physical examination.
- Vital signs.
- UPT.
- Sebum levels, measured at the mid-glabellar region of the forehead using a Sebumeter SM – 815 (COURAGE + KHAZAKA electronic GmbH, Köln, Germany).
- Assess AEs.
- Assess LSRs.
- Review concomitant medications, topical facial products and procedures/therapies.
- IGA.
- Acne Lesion Counts (total, inflammatory, and non-inflammatory lesion counts).
- Quality of life assessment (Acne QoL Questionnaire).
- Optional facial photography.
- Cheek swab skin engraftment sample.
- Randomize the subject (see Section 5.1.1).
- PI or designee shall apply the first dose of study drug and review application instructions with the subject.

- Dispense Subject Diary (for documentation of at-home Cetaphil® BID washes and evening study drug application).
- Dispense Study Drug and gloves, reminding the subject that study drug is to be stored in the freezer
- Schedule the next visit.

6.2.3. Treatment Assessments - Visit 3 (Week 2/Day 8), Visit 4 (Week 7/Day 43) and Visit 5 (Week 12/End of Treatment/Day 80)

The following will be performed and documented at each visit during the treatment phase:

- Collect, review, and dispense Subject Diary. NOTE: In review of the Subject Diary, the PI should question the subject to gauge understanding of application instructions, and re-instruct, at each visit except Visit 5, EOS.
- Sebum levels, measured at the mid-glabellar region of the forehead using a Sebumeter SM – 815 (COURAGE + KHAZAKA electronic GmbH, Köln, Germany).
- Assess AEs.
- Assess LSRs.
- Review concomitant medications, topical facial products and procedures/therapies.
- Limited physical examination **(Visit 5/EOT only)**.
- Vital signs **(Visit 5/EOT only)**.
- UPT **(Visit 5/EOT only)**.
- Local CBC **(Visit 5/EOT only)**.
- IGA.
- Acne Lesion Counts (total, inflammatory, and non-inflammatory lesion counts).
- Quality of life assessment (Acne QoL Questionnaire).
- Optional facial photography.
- Cheek swab skin engraftment sample.
- Face wash with Cetaphil® **(only at Visit 5/EOT prior to Biore® strip sampling)**.
- Biore® strip follicular engraftment sample **(Visit 5/EOT only)**.
- Dispense Study Drug (**only at Visit 3 and Visit 4**).
- Schedule the next visit.

6.2.4. Follow-up Assessment – Visit 6 (Week 16/End of Study/Day 106)

The following will be performed and documented during a telephone follow-up call with the subject:

- Assess AEs and LSRs. If the subject reports any worsening ongoing AEs or material new AEs, especially those that may potentially be related to the study drug, the subject will be scheduled for an office visit if, in the opinion of the PI, a clinical evaluation is warranted (e.g., a significant safety concern).
- Counsel the subject regarding the need for post study follow up with their primary care physician for any ongoing medical needs if indicated.
- Review concomitant medications, topical facial products and procedures/therapies.

6.2.5. Unscheduled Visit

The following will be performed and documented at unscheduled visits:

- Review Subject Diary. NOTE: In review of the Subject Diary, the PI should question the subject to gauge understanding of application instructions, and re-instruct, as needed.
- Sebum levels, measured at the mid-glabellar region of the forehead using a Sebumeter SM – 815 (COURAGE + KHAZAKA electronic GmbH, Köln, Germany).
- Assess AEs.
- Assess LSRs.
- Review concomitant medications, topical facial products and procedures/therapies.
- Limited physical examination.
- Vital signs.
- UPT.
- Local CBC.
- IGA.
- Acne Lesion Counts (total, inflammatory, and non-inflammatory lesion counts).
- Quality of life assessment (Acne QoL Questionnaire).
- Optional facial photography.
- Cheek swab skin engraftment sample.
- Biore® strip follicular engraftment sample.
- Confirm next scheduled visit.

6.3. Assessments for Premature Discontinuation from Study

If a subject discontinues the study prior to Week 12/Visit 5 (for example, as a result of an AE), every attempt should be made to schedule the subject to complete EOT visit procedures (see Section 10.2, Subject Discontinuation).

7. ADVERSE EVENT REPORTING AND TOXICITY MANAGEMENT

7.1. Adverse Event Definitions

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE (also referred to as an adverse experience) can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (e.g., off-label use, use in combination with any drug) and from any route of administration, formulation, or dose, including an overdose.

A **suspected adverse reaction** is any AE for which there is a reasonable possibility that the drug caused the event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE.

An **adverse reaction** is any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug. For the purposes of prescription drug labeling, the term adverse reaction means an undesirable effect, reasonably associated with the use of a drug that may occur as part of its pharmacological action or may be unpredictable in its occurrence.

An AE does not include the following:

Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.

Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen.

Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).

Overdose without clinical sequelae.

Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed; or, if an IB is not required or

available, the event is considered “unexpected” if it is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

Timely and complete reporting of all AEs assists the Sponsor and/or their designee in identifying any untoward medical occurrence, thereby allowing:

1) protection of the safety of study subjects;
2) a greater understanding of the overall safety profile of the study drug;
3) recognition of dose-related study drug toxicity;
4) appropriate modification of study protocols;
5) improvements in study design or procedures; and
6) adherence to worldwide regulatory requirements.

7.2. Adverse Event Details

AEs may be either spontaneously reported or elicited during questioning and examination of a subject. All AEs must be recorded on the AE CRF. If known, the PI should report the diagnosis of the underlying illness or disorder, rather than its individual symptoms. Subjects experiencing AEs that cause interruption or discontinuation of study drug or those experiencing AEs that are present at the end of their participation in the study should receive follow-up as appropriate. AEs should be followed to resolution or stabilization (if possible) and, if they become serious, reported as SAEs. If possible, the outcome of any AEs that caused permanent discontinuation or that were present at the end of the study, especially those considered by the PI to be related to the study drug, should be reported.

Information on the medical condition of subjects should begin following the subject’s written informed consent to participate in the study and a medical history should be taken at screening. During any wash out and baseline periods, any changes in the health of subjects should be recorded as changes in medical history unless an event occurred as a result of a study-related procedure and is unanticipated; in such cases, the event should be recorded as an AE and reported to the Institutional Review Board (IRB) as an “unanticipated problem” in accordance with local procedures. Other changes in subject health information becomes AE data when the subject begins dosing with the study drug; therefore, AE data should be collected from the date of the first dose of study drug until the date of the final study visit. These data are considered treatment-emergent AEs.

The PI will instruct the subject to report any AEs that may occur during the study. At each visit, the PI should ask the subject, in non-directive fashion, about any change in the subject’s overall

health status since the previous visit. Optional photographs may be obtained for areas outside of the face, as clinically indicated for the classification and management of AEs.

The PI will assign a CTCAE grade to all AEs (CTCAE Version 5.0, Appendix 4). The severity of each AE, as judged by the PI, will be recorded on the appropriate AE CRF and will be graded according to the following scale:

> **Mild** - The AE is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
>
> **Moderate** - The AE is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research participant.
>
> **Severe** - The AE interrupts usual activities of daily living or significantly affects clinical status or may require intensive therapeutic intervention.

The PI must determine the relationship of the AE to the study drug according to the following categories:

> **Definitely related** - An event that follows a reasonable temporal sequence from administration of the study drug; that follows a known or expected response pattern to the study drug; and that is confirmed by improvement on stopping or reducing the dosage, and reappearance of the event on repeated exposure (re-challenge).
>
> **Probably related** - An event that follows a reasonable temporal sequence from administration of the study drug; that follows a known or expected response pattern to the study drug; and that is confirmed by improvement on stopping or reducing the dosage of the study drug; and that is unlikely to have been caused by concurrent/underlying illness or other drugs, procedures, or other causes.
>
> **Possibly related** - An event that follows a reasonable temporal sequence from administration of the study drug; that follows a known or expected response pattern to the study drug; but may have been caused by concurrent/underlying illness, other drug, procedure, or other causes.
>
> **Unlikely related** - An event that does not follow a reasonable temporal sequence from administration of the study drug; that does not follow a known or expected response pattern to the study drug, or most likely was caused by concurrent/underlying illness, other drug, procedure, or other causes, because of their known effects.
>
> **Not Related** - An event almost certainly caused by concurrent/underlying illness, other drug, procedure, or other causes.

The PI should categorize the outcome of the AE according to the following categories:

Fatal - Termination of life as a result of an AE.

Not Recovered/Not Resolved - AE has not improved or the subject has not recuperated.

Recovered/Resolved - AE has improved or the subject has recuperated.

Recovered/Resolved with Sequelae - subject recuperated but retained the pathological conditions resulting from the prior disease or injury.

Recovering/Resolving - AE is improving or the subject is recuperating.

Unknown - Not known, not observed, not recorded or subject refused.

7.2.1. Dose Limiting Toxicity and Stopping Rules

The Medical Monitor will consider DLT when reviewing the safety data and making recommendations for discontinuing a subject from the study per Section 10.2. A DLT is defined as a new onset systemic Grade 2 or higher (CTCAE Version 5.0, Appendix 4) AE for which there is no clear alternative explanation of the cause of the AE. In the event a subject is enrolled in the study with a baseline medical condition that would not exclude the subject from entering the study, but meets the classification criteria for a systemic Grade 2 (or higher) or non-systemic (local) Grade 3 (or higher) event, a worsening of the baseline condition during the study that results in an increase in one grade above their Baseline grade shall warrant assessment as a potential DLT.

Non-systemic (local) AEs Grade 3 or higher for which there is no clear alternative explanation of the cause of the AE will also be considered DLTs. Any subject who experiences a DLT, as described above, must discontinue treatment and be scheduled for a final visit. Any DLTs that are Grade 2 or greater systemic AEs must be reported by the PI immediately. If three or more subjects experience DLTs in the study, enrollment in the study will be halted, and a safety review will occur using an independent medical reviewer who will have access to the subject's treatment allocation. This review shall be completed promptly within 10 business days. Subjects who are active in the study will be instructed to withhold study drug applications during the safety review period. If all of the subjects experiencing DLTs (i.e. three or more) are found to be subjects receiving the active NB01 study drug, the independent medical reviewer will provide a written recommendation to the Sponsor to continue the study, discontinue the study or modify the study protocol. The Sponsor is responsible for promptly reviewing the independent medical reviewer's recommendations, accepting or rejecting these recommendations, and determining whether amendments to the protocol or changes in study conduct will be required. The Sponsor will provide the final written decision regarding the study status. In the event this is not the case, the independent medical reviewer will notify the Sponsor and Medical Monitor of how many subject's DLTs were in subjects receiving vehicle (e.g. Y subjects). In the event Y new subjects experience DLTs, the independent medical reviewer review process outlined above will be repeated. This process will be repeated throughout the entire study until the study is complete or

the stopping rule has been met. In the event that a total of three (3) or more subjects experience DLTs related to NB01 study drug, the study will be discontinued.

If an SAE occurs during the study and is determined by the Sponsor to be at least possibly related to the study drug, enrollment of new subjects and dosing of active subjects will be halted. A safety review will occur using an independent medical reviewer who will have access to the subject's treatment allocation. This review shall be completed promptly within 5 business days. The independent medical reviewer will provide a written recommendation to the Sponsor to continue the study, discontinue the study or modify the study protocol. The Sponsor is responsible for promptly reviewing the independent medical reviewer's recommendations, accepting or rejecting these recommendations, and determining whether amendments to the protocol or changes in study conduct will be required. The Sponsor will provide the final written decision regarding the study status. A summary of the event should also be reported to FDA as part of an IND Safety Report in accordance with Section 7.2.2. FDA should also be notified within 48 hours of the final decision and provided an IND Safety Follow-up Report as necessary (if new information was collected since the initial Safety Report).

7.2.2. Serious Adverse Events

An event that is serious must be recorded on the CRF/eCRF and requires expeditious handling to comply with regulatory requirements.

An AE or suspected adverse reaction is considered "serious" if, in the opinion of either the PI or Sponsor, it results in any of the following outcomes:

- Death; the event must be the cause of death for the SAE to meet this serious criterion.
- Life-threatening event; an event in which the subject was at risk of death at the time of the event and not an event that hypothetically might have caused death if it had been more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization (for ≥24 hours).
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect.
- Important medical events; a medical event(s) that may not result in death, be life-threatening, or require hospitalization but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events NOT considered to be SAEs are:

- Hospitalizations for the treatment, which was elective or pre-planned, of a pre-existing condition that did not worsen; and

- Treatment on an emergency, outpatient basis, for an event not fulfilling any of the definitions of "serious" given above and not resulting in hospital admission.

AEs classified as "serious" by either the PI or the Sponsor require expeditious handling and reporting to the Sponsor or designee to comply with regulatory requirements. **All SAEs, whether related or unrelated to study drug, must be immediately reported by telephone to the Medical Monitor listed on the first page of the protocol. In the event that he/she is unavailable, contact the back-up Medical Monitor listed in the study reference manual.** Written notification of all SAEs should be sent to the Trial Manager by email or confirmed facsimile transmission. These include those SAEs listed in the protocol or IB and must include an assessment of whether there is a reasonable possibility that the study drug caused the event.

Any suspected adverse reactions that are serious and unexpected represent especially important safety information that must be reported more rapidly to Health Authorities; therefore, it is important that the PI submit any information requested by the Sponsor or designee as soon as it becomes available.

If only limited information is initially available, follow-up reports are required. Should the PI become aware of an SAE (regardless of its relationship to study drug) that occurs within 30 days after stopping the study drug, the SAE must be reported in accordance with procedures specified in this protocol. In the event of death, if an autopsy is performed, a copy of the report should be sent to the Sponsor or designee, if available.

As required, the Sponsor or designee will notify participating PIs of all suspected adverse reactions that are serious and unexpected. This notification will be in the form of an IND safety report of potential serious risks as soon as possible but no later than 15 calendar days after the Sponsor determines that the information is "reportable" according to the criteria listed in 21 CFR Section 312.32. These are:

i) Serious and unexpected suspected adverse reactions;
ii) Findings from other studies including epidemiological studies, pooled analyses, or other clinical studies that suggest a significant risk in humans exposed to the study drugs;
iii) Findings from animal or in vitro tests that suggest a significant risk to humans exposed to the study drugs, or reports of significant organ toxicity at or near the expected human exposure; and
iv) Clinically important increases in the rate of occurrence of serious suspected adverse reactions.

Upon receiving such notices, the PI must review and retain the notice with the IB and promptly submit a copy of this information to the responsible IRB according to local regulations. The PI and IRB will determine if the informed consent requires revision. The PI should also comply with the IRB procedures for reporting any other safety information. Where required, submission of safety updates by the PI to Health Authorities should be handled according to local regulations.

The Sponsor or designee may be required to report certain SAEs to regulatory authorities (e.g., United States FDA) within seven calendar days of being notified about the event; therefore, it is important that PIs submit any information requested by the Sponsor or designee as soon as it becomes available.

7.2.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

The PI will evaluate clinical laboratory results, physical exam findings and vital signs to determine if any findings are clinically significant. Any clinically significant results that represent and new or worsening change from Baseline should be recorded as an AE.

7.3. Pregnancy

Male subjects who are not surgically sterile, and are sexually active with a female partner must agree to use an effective method of birth control from the first administration of the study drug until 30 days after the last study drug application. Female subjects who are WOCBP, and are sexually active with a male partner must agree to use an effective method of birth control from the first administration of the study drug until 30 days after the last study drug application. Protocol Section 4.2, Inclusion Criteria #6, provides definitions of sterility and methods of acceptable birth control.

Prior to study enrollment, subjects must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) during the study and for 30 days after she has completed her last test article application. If a subject or investigator suspects that a subject may be pregnant at any time during the study, the test article must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive or apply further test article.

If following initiation of study treatment, it is subsequently discovered that a subject was pregnant or may have been pregnant at the time of test article exposure, the investigator must immediately notify the Medical Monitor of this event and record the pregnancy on the appropriate pregnancy surveillance form. The form will be sent to the Sponsor or designee. The investigator must notify the IRB of any pregnancy associated with the study treatment and keep careful source documentation of the event, including abortion (accidental, therapeutic, or spontaneous) and birth of offspring. Offspring should be followed for a minimum of eight weeks and any congenital anomaly/birth defect in a child born to a subject or a male subject's sexual partner that was exposed to the study drug should be documented on the pregnancy surveillance form as appropriate.

During the study, all male subjects should be instructed to contact the PI immediately if they suspect that their sexual partner might be pregnant (e.g., female sexual partner has missed or late menstrual period).

7.4. Toxicity Management

A dose mitigation strategy will be employed whereby, with Medical Monitor approval, the dose may be reduced/modified according to the individual subject's tolerance. Typical modification may include short drug holiday periods off therapy, every other day dosing, etc. Such changes however shall not be made without the written approval of the Medical Monitor.

8. STATISTICAL CONSIDERATIONS

8.1. Sample Size

No formal sample size calculations were performed for this study given it is an initial proof of concept study.

8.2. Analysis Populations

8.2.1. Safety Population

The Safety population will include all randomized subjects who received and applied study drug.

8.2.2. Intent-to-Treat Population

The ITT population will include all randomized subjects who were dispensed the study drug.

8.2.3. Per-Protocol Population

The PP population will include a subset of the ITT population who completed the study without significant protocol deviations (as will be determined prior to unblinding the randomization).

8.3. Endpoints

8.3.1. Primary Safety Endpoints

- Incidence (severity and causality) of any local and systemic AEs.
- Number of subjects with presence (and severity) of each LSR and each time point.
- Changes from Screening/Baseline in physical examination findings at Visit 5/EOT.
- Changes from Screening/Baseline in vital signs at Visit 5/EOT.
- Changes from Screening in local CBC at Visit 5/EOT.

8.3.2. Exploratory Engraftment Endpoint

- For skin engraftment assay, absolute and percent change from Screening to follow-ups in Cas5/PanBac and for follicular engraftment assay, the proportion of subjects with "success" at EOT where "success" is defined as a Follicular Biore® with "yes" outcome based on recovery of live NB01.

8.3.3. Exploratory Efficacy Endpoints

- Absolute change from Screening at each follow-up visit in IGA score.
- Absolute and percent change from Screening at each follow-up visit in total, inflammatory, and non-inflammatory lesions.

- Absolute and percent change from Screening to follow-up in Acne QoL.

8.3.4. Exploratory Sebum Endpoint

- Absolute and percent change from Screening to follow-up in sebum production.

8.4. Statistical Methods

All statistical processing will be performed using SAS®. Summary tables (descriptive statistics and/or frequency tables) will be provided for screening and/or baseline variables, efficacy variables, and safety variables. Summaries will be provided for each treatment group. In general, continuous variables will be summarized by descriptive statistics including sample size, mean, SD, median, minimum, and maximum. Categorical variables will be summarized by frequency and percentage.

8.4.1. Dosing Compliance

Descriptive statistics will be used to summarize for each treatment group the duration of treatment (defined as last dose date – first dose date +1), the total number of applications (determined from the doses reported in the Subject Diary), and the percent of expected doses applied for the ITT and PP populations. Subjects who apply at least 80% of the expected total number of applications and have no other evidence of material dosing non-compliance will be considered to be compliant with study drug dosing.

8.4.2. Pimary Safety Analyses

All safety analyses will be performed on the Safety population.

Extent of Exposure
Descriptive statistics will be used to summarize the extent of exposure in the Safety population. The total amount of study drug used by each subject will be calculated based on the number of days the study drug was applied (according to the subject's diary entries).

Physical Examinations
Findings from the physical exam will be recorded in medical history (from assessment at Visit 1/Screening) or as AEs (from assessment at Visit 5/EOT.

Vital Signs
Descriptive statistics of vital signs (temperature, blood pressure, and heart rate) will be provided by treatment group.

Clinical Laboratory Tests
Local CBC tests will be evaluated for any material changes during the study period. All laboratory data will be listed and reported in the units received by the laboratory. Shift tables by analyte and by out of range flag will be presented.

Local Skin Reactions
The frequency of the individual LSRs (PI: erythema, edema, erosion/ulceration, scaling/dryness, and scabbing/crusting; Subject: itching and pain) will be tabulated by severity and treatment group at each visit. The frequency of the individual LSRs recorded by subjects in weekly diaries (redness, swelling, erosion/ulceration, scaling/dryness, and scabbing/crusting, itching, and pain) will be tabulated by severity and treatment group for each study week.

Adverse Events
All AEs reported during the study will be listed, documenting course, severity, PI assessment of the relationship to the study drug, and outcome. Verbatim terms on the eCRFs will be linked to preferred terms (PTs) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) mapping system. The PTs and SOC will then be tabulated. All reported AEs will be summarized by the number of subjects reporting AEs, SOC, PT, severity, and relationship to study drug by treatment group.

Urine Pregnancy Tests
Results from UPTs will be provided in a listing.

8.4.3. Exploratory Engraftment Analyses

The engraftment analyses will be conducted on the ITT and PP populations.

Engraftment Assay
For endpoint of Engraftment Assay of Cas5/PanBac, the absolute and percent change from Screening at each follow-up visit, the comparison between NB01 and vehicle-control will be analyzed using ANCOVA model with the dependent variable being absolute or percent change values and the factor treatment and the Screening value as a covariate in the model, with and without LOCF imputation.

For endpoint of Follicular Biore®, the treatment groups will be compared with respect to the proportions of subjects with “success” at Week 12 using the CMH test with and without stratification on study center, where “success” is defined as a Follicular Biore® with “yes” outcome based on the recovery of live NB01.

8.4.4. Exploratory Efficacy Analyses

The efficacy analyses will be conducted on the ITT and PP populations.

Investigator’s Global Assessment
The observed and change from Screening scores at each follow-up visit will be tabulated. For endpoint of IGA, the treatment groups will be compared with respect to the proportions of subjects with (a) at least a one-point improvement and (b) at least a two-point improvement in IGA score relative to Screening at each follow-up visit using the CMH test with and without stratification on study center.

Acne Lesion Counts

For endpoint of Acne Lesion Counts, the absolute and percent change from Screening at each follow-up visit in total, inflammatory, and non-inflammatory lesions, the comparison between NB01 and vehicle-control will be analyzed using Analysis of Covariance (ANCOVA) model with the factor treatment and the Screening counts as a covariate in the model, with and without Last Observation Carried Forward (LOCF) imputation.

Acne Quality of Life

For endpoint of Acne-QoL, the absolute and percent change from Screening at each follow-up visit on four domains separately and total, the comparison between NB01 and vehicle-control will be analyzed using ANCOVA model with the factor treatment and the Screening score as a covariate in the model, with and without LOCF imputation.

8.5. Exploratory Sebum Analyses

Sebum Production

For endpoint of sebum production, the absolute and percent change from Screening at each follow-up visit, the comparison between NB01 and vehicle-control will be analyzed using ANCOVA model with the factor treatment and the Screening value as a covariate in the model, with and without LOCF imputation.

8.6. Interim Analyses

No interim analyses are planned for this study.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

This study will be conducted in compliance with the principles of the Declaration of Helsinki, with the current Good Clinical Practice guidelines and with other applicable regulations. The PI and all study staff will conduct the study in compliance with this protocol. The protocol, informed consent documents, recruitment advertisements, and any amendments to these items will have IRB approval prior to study initiation. Voluntary informed consent will be given by every subject prior to the initiation of any study-related procedures. The rights, safety and well-being of the study subjects are the most important considerations and prevail over the interests of science and society. All personnel involved in the conduct of this study must be qualified by education, training, and experience to perform their assigned responsibilities. Contact information for each site and any clinical laboratories used in the study will be maintained up to date in a separate reference document.

9.1.2. Institutional Review Board Review and Approval

Before study initiation, the PI must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to the subject. The PI should also provide the IRB with a copy of the product labeling, information to be provided to the subject and any updates. The PI will submit documentation of the IRB approval to the Sponsor.

The IRB approved consent form must include all elements required by FDA, state, and local regulations, and may include appropriate additional elements.

9.1.3. Informed Consent

The PI/designee will explain the study to each potential subject and the subject must indicate voluntary consent by signing and dating the approved informed consent form. The PI must provide the subject with a copy of the consent form, in a language the subject understands.

The PI will maintain documentation that informed consent was obtained prior to the initiation of any study-specific procedures.

9.1.4. Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access.

The study Sponsor, and its representatives, may review optional photographs taken during the study, but will not have access to other personal identifying information during review of these photographs. In order to protect subject privacy, a rectangular bar will be placed over subjects' eyes in the photographs, to help de-identify any photo(s) to be used in any of the publication or presentation materials described in Section 9.2.3. Additionally, any features that could be used to identify subjects, such as a scars or tattoos, will also be covered in the photographs. Clinical information will not otherwise be released (with the exception of de-identified data described in Section 9.2.3) without the written permission of the subject, except as necessary for monitoring by TI or the Sponsor, the FDA or other regulatory authority, or the IRB.

The PI and all employees and coworkers involved with this study shall not disclose or use for any purpose other than performance of the study, any data, records, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from TI or the Sponsor must be obtained for the disclosure of any said confidential information to other parties.

9.1.5. Study Files and Retention of Records

The PI must maintain all study records (including study drug disposition, informed consents, CRFs, source documents, correspondence, regulatory documents, contracts, etc.) for the maximum period required by the Sponsor or the institution where the study is conducted, whichever is longer. Study drug Accountability Logs and original Label Pages (if applicable) must be kept with study records at the site.

The PI must contact the Sponsor prior to destroying any records associated with this study.

If the PI withdraws from the study, the records shall be transferred to a mutually agreed upon designee. Written notification of such a transfer must be given to the Sponsor.

9.1.6. Case Report Forms

This study utilizes eCRFs; validated 21 CFR Part 11 compliant electronic data capture (EDC) software will be used to collect data. All requested information must be entered on the eCRFs in the areas provided in a timely manner. When changes or corrections are made in the eCRF, the EDC system will maintain a complete audit trail of the person making the changes, the date and time of the change, and the reason for the change. Only individuals who have completed EDC training and are listed on the Delegation of Responsibilities Log with responsibility for eCRF completion will be provided usernames and passwords in order to access the system and make entries on the eCRF.

The PI or physician sub-investigator must electronically sign and date each subject's eCRF. Individuals who will be providing electronic signatures must first submit documentation with a handwritten signature acknowledging that their electronic signature is a legally binding equivalent to their handwritten signature.

9.1.7. Inspections

Representatives from TI and/or the Sponsor or a third party selected by the Sponsor may conduct a quality assurance audit of this study. During the audit, the PI must provide the auditor with direct access to all relevant documents and discuss any findings with the auditor.

In the event of an inspection by the FDA or other regulatory authorities, the PI must give the inspector direct access to relevant documents and to discuss any findings with the inspector. The PI must notify TI in the event of an FDA site audit.

9.1.8. Protocol Compliance

The IRB approved protocol must be followed except in the case of a change that is intended to eliminate an immediate risk to subjects. All protocol deviations must be documented.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

The Sponsor will prepare all protocol revisions. All protocol amendments must receive IRB approval prior to implementation. All administrative letters must be submitted to the IRB for their information. Copies of all correspondence with the IRB regarding this study must be sent to TI.

New or altered consent forms required by the IRB due to a protocol change must be signed by all subjects currently enrolled in the study and must be used for any subsequent subject enrollment.

9.2.2. Access to Information for Monitoring, Auditing or Inspections

Representatives of the Sponsor and the Sponsor's CRO must be allowed to visit all study sites, to review study records, and to directly compare them with source documents (including, but not limited to patient and hospital records), to discuss the study conduct with the PI and study staff, and to verify that the PI, study staff, and facilities remain acceptable for the conduct of the study.

Representatives of government regulatory authorities may also evaluate the study records, source documents, PI, study staff, and facilities.

The PI should immediately notify the Sponsor of any audits of this study by any regulatory agency and must promptly provide copies of any audit reports.

9.2.3. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency. Naked Biome will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content

of Clinical Study Reports (ICH E3). NOTE: An abbreviated report may be prepared in certain cases.

The trial Sponsor may use de-identified data (including de-identified photographs) obtained during the study in scientific journals or magazines and as part of other presentations for corporate, research, medical, scientific, or educational purposes.

PIs in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

1. The results of the study in their entirety have been publicly disclosed by or with the consent of Naked Biome in an abstract, manuscript, or presentation form or the study has been completed at the study site for at least two years.
2. The PI will submit to Naked Biome any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.
3. No such communication, presentation, or publication will include Naked Biome's confidential information.
4. The PI will comply with Naked Biome's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days to obtain patent protection if deemed necessary.

10. END OF STUDY CRITERIA

At the end of each subject's participation in the study, the PI will complete an End of Study form for all completed and discontinued subjects.

10.1. Completion of the Study

Each subject who completes all study visits, as specified in this protocol will have completed the study.

10.2. Subject Discontinuation

A subject may be withdrawn from the study prior to completion for any of the following reasons:

- Adverse event
- Death
- Lost to follow-up
- Subject non-compliance
- PI decision
- Pregnancy
- Progressive disease
- Significant protocol deviation
- Study terminated by Sponsor
- Withdrawal of consent by subject*

*If the subject decides to withdraw from the study due to an AE it should be classified as withdrawal due to an AE.

If a subject withdraws prior to the Week 12 visit, every attempt should be made to complete final study procedures prior to discharge from the study. If a subject withdraws prematurely during the treatment period for any reason, the Week 12/EOT procedures will be completed. When a subject is withdrawn from the study for a treatment-related AE (i.e., possibly, probably or definitely related as defined in Section 7.2), when possible, the subject should be followed until resolution of the AE.

10.3. Study Termination

The study may be terminated by the PI or the Sponsor. If, in the opinion of the PI, clinical observations made during the study suggest that it may be unwise to continue, he or she may stop the study. A study termination by the PI will be reported to the Sponsor.

In addition, a written statement fully documenting the reasons for this action will be submitted to the Sponsor by the PI within five working days.

In the event that the Sponsor chooses to discontinue or terminate the study, appropriate notification will be given to the PI and an orderly discontinuation of all subjects per Section 10.2 will occur.

11. REFERENCES

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APPENDICES

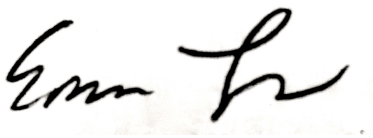
APPENDIX 1. SPONSOR-INVESTIGATOR SIGNATURE PAGE

NAKED BIOME, INC.

STUDY ACKNOWLEDGEMENT

This protocol has been approved by Naked Biome, Inc. The following signature documents this approval.

Emma Taylor



Name (Printed) | Signature

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Naked Biome, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed) | Signature

Date | Site Number

Appendix 2. Schedule of Events Table

STUDY PERIOD ►	**Pre-Treatment**	**Treatment**					**Follow-Up**
STUDY VISIT (± visit window)►	**Visit 1 Screening**	**Visit 2[b] Baseline**	**Visit 3** (±2 days)	**Visit 4** (±7 days)	**Visit 5[p] End of Treatment** (+3 to +7 days)	**Unscheduled Visit[s]** (n/a)	**Visit 6 (End of Study)[x]** (±3 days)
PROCEDURE▼TREATMENT DAY►	**Day -14 to -1**	**Day 1**	**Day 8 (Week 2)**	**Day 43 (Week 7)**	**Day 80 (Week 12/EOT)**	**n/a**	**Day 106 (Week 16/EOS[t])**
Eligibility Criteria Review[a]	X	X					
Informed Consent Process	X						
Limited Physical Examination[c]	X	X			X	X	
Medical History Review	X						
Concomitant Medication Review	X	X	X	X	X	X	
Adverse Event Assessment	X[d]	X[e]	X	X	X	X	X
Vital Signs[f]	X	X			X	X	
Laboratory Assessment – CBC[g]	X				X	X	
Urine Pregnancy Test[h]	X	X			X	X	
BPO Pre-Treatment	X[i]						
Subject Diary[j] & Compliance Review	X[u]	X[u, v, w]	X[u, v, w]	X[u, v, w]	X[u, v, w]		X[v, w]
Twice Daily Facial Washing[l]	X[k]	X[k, m]	X[k]	X[k]	X[k]		
Randomization		X					
Quality of Life Questionnaire	X	X	X	X	X	X	
Sebum production[y]	X	X	X	X	X	X	

STUDY PERIOD ►	Pre-Treatment	Treatment					Follow-Up
STUDY VISIT (± visit window)►	**Visit 1 Screening**	**Visit 2[b] Baseline**	**Visit 3** (±2 days)	**Visit 4** (±7 days)	**Visit 5[p] End of Treatment** (+3 to +7 days)	**Unscheduled Visit[s]** (n/a)	**Visit 6 (End of Study)[x]** (±3 days)
PROCEDURE ▼TREATMENT DAY►	**Day -14 to -1**	**Day 1**	**Day 8 (Week 2)**	**Day 43 (Week 7)**	**Day 80 (Week 12/EOT)**	**n/a**	**Day 106 (Week 16/EOS[t])**
Facial Photography (optional)	X	X	X	X	X	X	
Engraftment Sampling – follicular[0]	X[n]				X[q]	X	
Engraftment Sampling - skin surface	X[n]	X	X	X	X	X	
Investigator Global Assessment (IGA)	X	X	X	X	X	X	
Acne Lesion Counts	X	X	X	X	X	X	
Dispense Study Drug to Subjects		X	X	X			
Local Skin Reactions	X	X	X	X	X	X	X
Study Drug Application[r]		X[b, m]	X	X			

Abbreviations: BPO = Benzoyl Peroxide; CBC = Complete Blood Counts; EOS = End of Study

Footnotes:

a Includes confirmation of contraception use for the duration of Screening prior to first application and through study participation.
b Day 1 procedures must be completed prior to the application of study drug. Day 1 study drug is applied by the PI or sub-investigator designee at the site.
c Limited physical examination of face, chest, arms, back (relevant acne regions).
d Adverse Events are assessed from the time of consent.
e Subjects will remain at the clinic for at least 30 minutes after the initial (Day 1) study drug application to be assessed for AEs.
f Blood pressure, heart rate, temperature.
g CBC is assessed locally and must include Differential.
h Urine dipstick test assessed locally.

i All screening visit procedures will be completed prior to initiating BPO pre-treatment. BPO gel should be applied for at least 5 days, in the AM immediately after the AM Cetaphil® wash. Final BPO pre-treatment should be approximately 24 hours prior to application of study drug.
j Study subjects will note date and time of each BPO pre-treatment and Cetaphil® wash for the Screening period, and date and time for each Cetaphil® wash and study drug application during the study treatment period.
k Subjects must not wash, shave, apply make-up or other products to their face, and subjects must hold their application of study drug, on clinic visit days.
l Subjects will wash their face with Cetaphil® cleanser twice daily beginning at the Screening visit throughout the Week 12/EOT visit. No other face wash products may be used during the Subject's participation in the study.
m Subjects will wash with Cetaphil® at the clinic after all other Day 1 procedures have been completed and immediately prior to study drug application by the PI.
n Screening samples are obtained prior to initiation of BPO pre-treatment.
o Follicular engraftment sampling is completed via use of Biore® Strips applied across the bridge of the nose extending to either cheek.
p The Week 12/EOT visit will take place between 3 to 7 days following the Subject's final study drug application. The PI should inquire regarding the subjects understanding of and compliance with study drug application procedures and re-instruct, as necessary.
q Week 12/EOT follicular engraftment sampling will be obtained after facial washing via Biore® strip at the clinic and should be completed 3 to 7 days following the last study drug application.
r Study drug is applied by the PI (or sub-I designee) on Day 1; study drug is applied by the Subject daily thereafter in the evenings.
s Study procedures are completed as is clinically indicated for vital signs, physical exam, urine pregnancy, and CBC for unscheduled study visits.
t EOT procedures should be completed at the Week 12 visit. Should the subject discontinue the study prior to Week 12 (Visit 5), the EOT procedures should be scheduled and completed as soon as possible.
u Dispense Subject Diary to the subject.
v Review the Subject Diary to calculate study drug compliance.
w Collect the Subject Diary from the subject.
x The Week 16 telephone visit is to determine the outcome of on any AEs or LSRs that were ongoing at the Week 12 Visit and to determine if any new AEs or LSRs occurred during the follow-up period. The Week 16 visit will become a clinic visit if the subject reports any new AEs, especially those (in the opinion of the PI) that may be potentially be related to the study (e.g., a significant safety concern).
y Measured at the mid-glabellar region of the forehead using a Sebumeter SM – 815 (COURAGE + KHAZAKA electronic GmbH, Köln, Germany).

Appendix 3. Investigator's Global Assessment (IGA)

Investigator's Global Assessment		
Score	**Definition**	**Guideline**
0	Clear	Absence of active disease with no inflammatory or non-inflammatory lesions.
1	Almost Clear	Few non-inflammatory lesions are present; few inflammatory lesions may be present.
2	Mild	Some non-inflammatory lesions and some inflammatory lesions (papules/pustules only; no nodular lesions) are present.
3	Moderate	Many non-inflammatory lesions and many inflammatory lesions are present, but no more than one nodular lesion.
4	Severe	Significant degree of inflammatory disease; inflammatory lesions are a predominant feature, with a few nodular lesions present; non-inflammatory lesions may be present.

Appendix 4. Common Terminology Criteria for Adverse Events (CTCAE) V. 5.0

For the current CTCAE Criteria for use in evaluating Dose Limiting Toxicities for this trial, please refer to:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Appendix 5. Acne Specific Quality of Life (QoL) Questionnaire

(Please check one box for each question)

1. In the past WEEK, how unattractive did you feel because of your facial acne?
   extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

2. In the past WEEK, how embarrassed did you feel because of your facial acne?
   extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

3. In the past WEEK, how self-conscious (uneasy about oneself) did you feel about your facial acne?
   extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

4. In the past WEEK, how upset were you about having facial acne?
   extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

5. In the past WEEK, how annoyed did you feel at having to spend time every day cleaning and treating your face because of your facial acne?
   extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

6. In the past WEEK, how dissatisfied with your self-appearance did you feel because of your facial acne?
   extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

7. In the past WEEK, how concerned or worried were you about not looking your best because of your facial acne?
   extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

8. In the past WEEK, how concerned or worried were you that your acne medication/products were working fast enough in clearing up the acne on your face?
   extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

9. In the past WEEK, how bothered did you feel about the need to always have medication or cover-up available for the acne on your face?
   extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

10. In the past WEEK, how much was your self-confidence (sure of yourself) negatively affected because of your facial acne?
    extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

11. In the past WEEK, how concerned or worried were you about meeting new people because of your facial acne?
    extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

12. In the past WEEK, how concerned or worried were you about going out in public because of your facial acne?
    extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

13. In the past WEEK, how much was socializing with people a problem for you because of your facial acne?
    extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

14. In the past WEEK, how much was interacting with the opposite sex (or same sex if gay or lesbian) a problem for you because of your facial acne?
    extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

15. In the past WEEK, how many bumps did you have on your face?
    Extensive ☐ A whole lot ☐ A lot ☐ A moderate amount ☐ Some ☐ Very Few ☐ None ☐

16. In the past WEEK, how many bumps full of pus did you have on your face?
    Extensive ☐ A whole lot ☐ A lot ☐ A moderate amount ☐ Some ☐ Very Few ☐ None ☐

17. In the past WEEK, how much scabbing from your facial acne did you have?
    Extensive ☐ A whole lot ☐ A lot ☐ A moderate amount ☐ Some ☐ Very Few ☐ None ☐

18. In the past WEEK, how concerned or worried were you about scarring from your facial acne?
    extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

19. In the past WEEK, how oily was your facial skin?
    extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐