THERAPEUTICS INC.
The Dermatology CRO

STATISTICAL ANALYSIS PLAN
VERSION: 1.0

DATE: 15Aug2019

SPONSOR:	Naked Biome, Inc.
PROTOCOL NUMBER:	NB01-P1BMA
TI PROJECT NUMBER:	227-10851-101
PROTOCOL 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
PROTOCOL DATE:	Version 3.0, July 15, 2019
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SAP APPROVAL

The following individuals approve version 1.0 of the SAP dated 15Aug2019. All changes to this version of the SAP must have written approval and require an amendment.

The **Project Statistician** is signing below to confirm he/she has developed the SAP to provide a comprehensive description of the methods of data analyses for the clinical study.

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Emma Taylor, MD / Naked Biome Co-Founder & CEO

ABBREVIATIONS

Acne-QoL	Acne Quality of Life
AE	Adverse Event
BPO	Benzoyl Peroxide
CBC	Complete Blood Count
CMH	Cochran-Mantel-Haenzsel
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
IGA	Investigator's Global Assessment
LSR	Local Skin Reaction
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MMRM	Mixed effect Model Repeated Measures
NB01	*P. acnes* microbiome transplant
PP	Per-Protocol
PT	Preferred Term
QD	Once Daily Dose
SAP	Statistical Analysis Plan
SOC	System Organ Class
TI	Therapeutics, Inc.
UPT	Urine Pregnancy Test
VEH	Vehicle
WOBCP	Women of Childbearing Potential

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1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned statistical analyses to be performed for data from Protocol NB01-P1BMA, "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".

This SAP was created using Clinical Protocol NB01-P1BMA, Version 3.0, dated 15Jul2019, and the Electronic Case Report Forms (eCRF) Version 1.0, dated 09Nov2018.

2. PURPOSE OF THE ANALYSES

The purpose of this SAP is to outline the planned analyses to be completed to support the Clinical Study Report (CSR) for Protocol NB01-P1BMA. Any post-hoc or unplanned analyses not identified in this SAP will be clearly identified in the CSR.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

The objectives of this study are:
Primary:

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

Exploratory:

1. To define engraftment duration of NB01.
2. To evaluate preliminary clinical efficacy based on acne lesion counts, 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.

3.2 Exploratory Engraftment Endpoints

Skin Engraftment Assay

- Change and percent change from Screening at EOT in Cas 5/PanBac, deoR/PanBac, and Transposase2/PanBac

Follicular Engraftment Assay

- Change and percent change from Screening at EOT in Cas 5/PanBac, deoR/PanBac, and Transposase2/PanBac
- Proportion of subjects with "success" at EOT where "success" is defined as a Follicular Biore sample with evidence of live NB01

3.3 Exploratory Efficacy Endpoints

The efficacy endpoints are:

- Change in IGA score and the proportions of subjects with (a) at least one-point improvement and (b) at least two-point improvement in IGA score relative to Screening at each follow-up visit.
- Change and percent change from Screening at each follow-up visit in total, inflammatory and non-inflammatory lesion counts.
- Change and percent change from Screening to follow-up in each of the four Acne QoL domain scores and total score.

Exploratory sebum endpoint:

- Change and percent change from Screening to follow-up in sebum production in a subpopulation from sites 02 and 03.

3.4 Primary Safety Endpoints

The safety endpoints are:

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

4. 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. Subject randomization will be stratified by sex and age (18-25 years old / 26-40 years old). Subjects will be randomized at a 2:1 ratio to NB01 (10^5CFU/cm^2) or Vehicle (VEH) which are to be applied at approximately the same time each evening for 11 weeks.

The visit schedule and procedures to be conducted at each visit are presented in the table below.

Table 1: Schedule of Events

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	
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).

5. DEFINITIONS

- Study Day: The study day is the day of study relative to the first dose date and is calculated by follow-up visit date – first dose date + 1. For a subject who was randomized but not treated, the randomization date will be used.

- "Treatment success" for follicular engraftment assay: A post-Screening Follicular Biore sample having evidence of live NB01.

6. CLINICAL EVALUATIONS

6.1 Investigator's Global Assessment

The Investigator's Global Assessment (IGA) is an assessment of the overall severity of acne at the time of the clinic visit and is scored at each visit using the five-point scale specified in Table 2.

Table 2: Investigator's Global Assessment Scores

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.

6.2 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 at each visit. Counts of nodules and cysts will be reported separately and are not to be included in the inflammatory or non-inflammatory lesion counts.

6.3 Acne-specific Quality of Life Questionnaire

The Acne Quality of Life (Acne-QoL) questionnaire will be administered at each visit to assess the subject's subjective assessment of improvement of acne. The Acne-QoL consists of 19 questions:

1. In the past WEEK, how unattractive did you feel because of your facial acne?
2. In the past WEEK, how embarrassed did you feel because of your facial acne?
3. In the past WEEK, how self-conscious (uneasy about oneself) did you feel about your facial acne?
4. In the past WEEK, how upset were you about having facial acne?

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?
6. In the past WEEK, how dissatisfied with your self-appearance did you feel because of your facial acne?
7. In the past WEEK, how concerned or worried were you about not looking your best because of your facial acne?
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?
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?
10. In the past WEEK, how much was your self-confidence (sure of yourself) negatively affected because of your facial acne?
11. In the past WEEK, how concerned or worried were you about meeting new people because of your facial acne?
12. In the past WEEK, how concerned or worried were you about going out in public because of your facial acne?
13. In the past WEEK, how much was socializing with people a problem for you because of your facial acne?
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?
15. In the past WEEK, how many bumps did you have on your face?
16. In the past WEEK, how many bumps full of pus did you have on your face?
17. In the past WEEK, how much scabbing from your facial acne did you have?
18. In the past WEEK, how concerned or worried were you about scarring from your facial acne?
19. In the past WEEK, how oily was your facial skin?

The responses to all of the questions except 15 – 17 are: 0-extremely, 1-very much, 2-quite a bit, 3-a good bit, 4-somewhat, 5-a little bit and 6-not at all.

The responses to questions 15 – 17 are: 0-extensive, 1-a whole lot, 2-a lot, 3-a moderate amount, 4-some, 5-very few and 6-none.

The 19 questions are organized into four domains (self-perception, role-social, role-emotional, acne symptoms). The domain scores are calculated by summing all of the scores within the domain where higher scores reflect improved QoL.

The questions included in each domain are as follows:

- Self-perception: 1, 2, 3, 6, and 10
- Role – social:11, 12, 13, and 14
- Role – emotional: 4, 5, 7, 8, and 9
- Acne symptoms: 15, 16, 17, 18, and 19

6.4 Engraftment Samples

Follicular engraftment sampling will be completed via use of Biore® Strips applied across the bridge of the nose extending to either cheek at Visits 1/Screening and Visit 5/EOT. Results will be reported as both a genotype assessment and as absence or presence of live NB01. Skin surface engraftment sampling will be completed via cheek swab at each visit. Three genotypes (deoR, Cas5, Transposase2) will be assessed and reported as the percentage of total bacteria count (PanBac) for both the follicular and skin surface engraftment samples.

6.5 Sebum Production

Sebum production ($\mu g/cm^2$) is measured at the mid-glabellar region of the forehead using a Sebumeter at each visit at sites 02 and 03.

7. SAFETY EVALUATIONS

7.1 Adverse Events

All reported or observed adverse events (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 unless they are related to a study-specific procedure. AEs will be assessed from the time of consent.

7.2 Local Skin Reactions

Local skin reactions (LSRs) will be assessed at each visit using a four-point ordinal scale: 0-absent, 1-mild (slight, barely perceptible), 2-moderate (distinct presence) and 3-severe (marked, intense). The investigator will assess erythema, edema, erosion/ulceration, scaling/dryness, and scabbing/crusting in the treatment area. Subjects will assess itching and pain in the treatment area. LSRs that require medical intervention, withholding or discontinuation of study drug application, or extend 2 cm beyond the treatment area will be documented as AEs.

In addition to the clinic visit assessments, subjects will maintain a daily diary to assess each of the seven LSR parameters. The subjects are to record the greatest severity of each LSR experienced during the previous 7 days (weekly score for Weeks 1 through 16).

7.3 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.

7.4 Vital Signs

Vital signs including blood pressure, heart rate, and temperature will be measured at Screening/Baseline and Visit 5/EOT.

7.5 Pregnancy Test

A urine pregnancy test (UPT) will be performed at Screening/Baseline and Visit 5/EOT for women of childbearing potential (WOCBP).

7.6 Complete Blood Count

The complete blood count (CBC) will be assessed locally at Screening and Visit 5/EOT and must include Differential.

8. STATISTICAL METHODS

8.1 General Considerations

All statistical processing will be performed using SAS® version 9.4. 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.

In general, all tables will be supported by relevant listing (by-subject). Figures may be created to aid in the interpretation of results.

The by visit data analyses will be summarized and analyzed using the visit window for modified intent-to-treat (mITT) and per-protocol (PP) populations based on target day as shown in Table 3.

Table 3: Analyses Windows for mITT and PP Populations

Visit	Target Day	mITT Window	PP Window
Visit 1 / Screening	-28 to -1	-28 to -1	-28 to -1
Visit 2 / Baseline	1	1	1
Visit 3 / Week 2	8	2 – 21	6 – 10
Visit 4 / Week 7	43	22 – 61	36 – 50
Visit 5 / Week 12 / EOT	80	> 61	71– 90

If there is more than one measurement within a visit after windowing is applied, the one closest to the target day will be used in the analysis by visit. If a study visit is outside of the window in PP analyses, it will be treated as missing data.

8.2 Analysis Populations

8.2.1 Safety Population

The Safety population will include all randomized subjects who received and applied study drug. Subjects will have their first application of test article applied in the clinic by the PI (or sub-I-designee) during their Baseline Visit on Day 1. Subjects will be included in a treatment group based on the treatment they received (even if not the treatment group to which they were randomized). If a subject administered more than one type of test article during the trial, then the subject will be included in the treatment group to which they were randomized.

8.2.2 Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population will include all randomized subjects who were dispensed the study drug and have at least one post-baseline assessment. Subjects will be included in the treatment group to which they were randomized, regardless of the treatment received.

8.2.3 Per-Protocol Population

The per-protocol (PP) population will include a subset of the mITT population who completed the study without significant protocol deviations (as will be determined prior to unblinding the randomization) and met the criteria as specified below. Subjects will be included in the treatment group based on the treatment received.

- Meets all inclusion criteria and does not meetexclusion criteria #1-11 and #13-22.
- Has not taken or applied any interfering concomitant medications/therapies.
- Completed Visit 5/EOT procedures on Days 71 to 90 with the visit occurring 1 to 10 days after the final application of test article.
- Applied at least 80% of the expected doses with no other evidence of material dosing non-compliance.

8.3 Final Analyses and Reporting

An initial data freeze will occur once all subjects have completed the treatment period and all subject data through Visit 5/EOT has been monitored. Analysis populations will be identified and the Project Statistician will be unblinded in order to produce key summary tables that will be provided to the Sponsor. Final database lock will occur after all subjects have completed the study assessment period (or discontinued early) and all subject data has been monitored. The EOS visit captures safety (AE and LSR) data only.

Further exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc or unplanned analyses performed and not described in this SAP will be clearly identified in the CSR.

8.4 Sample Size

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

8.5 Randomization and Blinding

Subject randomization will be stratified by sex and age (18-25 years old / 26-40 years old). Subjects will be randomized at a 2:1 ratio to NB01 (10^5CFU/cm^2) or Vehicle which are to be applied at approximately the same time each evening for 11 weeks.

8.6 Subject Disposition

The number and percent of subjects who were enrolled in the study, in each analysis population, who completed the study, who withdrew from the study and their reasons for discontinuation will be tabulated by treatment group.

Protocol deviations will be provided in a listing and summarized by deviation type by treatment group and overall for the mITT population. Subjects who are excluded from the PP population will be identified in this listing.

Subjects who are screen failures with their reason for screen failure will be provided in a listing. The frequency distribution of the reasons for screen failure will be tabulated.

8.7 Screening and Baseline Assessments

8.7.1 Demographics

Demographic and baseline characteristics including age, sex, ethnicity, and race will be summarized by treatment group for the mITT, PP and Safety populations. Demographic data for screen failures will be summarized separately.

If a subject has more than one self-reported race, then he/she will be summarized in "multiple" category.

8.7.2 Medical History

Medical history will be presented in a subject listing.

8.7.3 Physical Examination

Abnormal findings noted during the Screening and Baseline examinations will be captured in the Medical History and not presented separately.

8.7.4 Vital Signs

Descriptive statistics will be provided by treatment group and overall for systolic and diastolic blood pressure, heart rate, and temperature for the Safety population.

8.7.5 Baseline Clinical Evaluations

Screening and Baseline IGA scores will be tabulated and descriptive statistics will be for the acne lesion counts, QoL domain scores, sebum production, and the skin surface engraftment parameter Cas5/PanBac ratio will be provided by treatment group and overall for the mITT and PP populations. Results of the follicular engraftment sample at Screening will also be presented as the proportion of subjects with live NB01 by treatment group and overall.

8.7.6 Baseline Local Skin Reactions

Frequency distributions of the Screening and Baseline local skin reaction severity scores will be presented by treatment group and overall for the Safety population.

8.8 Dosing Compliance

Subjects who consent to participate in the study are to apply 5% topical BPO gel QD for 5 to 7 days prior to randomization at the Baseline visit (Day 1). The number of days of BPO dosing and the number of doses applied during the screening period will be tabulated by treatment group and overall for the mITT and PP populations. The proportion of subjects compliant with BPO dosing will also be tabulated where compliance is defined as at least 5 days of BPO application during the week prior to Day 1 with the last BPO application occurring 24-48 hours prior to Day 1 and no BPO application within approximately 24 hours of the Day 1 visit.

Descriptive statistics will be used to summarize for each treatment group 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 for the mITT and PP populations. The protocol specifies that a subject will dose each evening for 11 weeks for a total of 77 doses. Visit 5/EOT is expected to occur 3 to 7 days after the last dose is applied, therefore, the final dose should be applied between Study Days 73 to 77, inclusive. Accordingly, the percent of expected doses applied by a subject will use 75 doses as the denominator. 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.

8.9 Exploratory Engraftment Evaluation

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

8.9.1 Skin Engraftment

For the endpoint of skin engraftment, the change and percent change in Cas5/PanBac, deoR/PanBac, and Transposase2/PanBac ratio from Screening at each follow-up visit, will be summarized with descriptive statistics at each visit. NB01 and VEH will be compared at Visit 5/EOT wtih respect to change or percent change values using Mixed effect Model Repeated Measures (MMRM).

The MMRM model used for the analysis of continuous variables will include treatment, visit, treatment by visit, and investigator site as fixed effects, the Screening value as a covariate, and subject as a random effect. The MMRM analyses will be based on observed data. The p-value for the hypothesis of no treatment difference at Visit 5/EOT will be reported. The MMRM analysis will use an unstructured covariance type. The Kenward-Roger method will be used to estimate denominator degrees of freedom.

8.9.2 Follicular Engraftment

Multiple samples were obtained at Screening and Visit 5/EOT visits for a subject. The mean of each parameter, Cas5/PanBac, deoR/PanBac, and Transposase2/PanBac ratio, will be determined for each visit and serve as the observation for that visit. The change and percent change in Cas5/PanBac, deoR/PanBac, and Transposase2/PanBac ratio from Screening at Visit 5/EOT will be summarized with descriptive statistics. NB01 and VEH will be compared at Visit 5/EOT using MMRM.

The treatment groups will also be compared with respect to the proportions of subjects with "success" at Visit 5/EOT using the Cochran-Mantel-Haenszel (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. If any one of the samples at a given visit has live NBO1, the success outcome is "yes" for that visit.

8.10 Exploratory Sebum Evaluation

8.10.1 Sebum Production

For the endpoint of sebum production, the observed, change and percent change from Screening values at each follow-up visit will be summarized with descriptive statistics. NB01 and VEH will be compared at Visit 5/EOT using MMRM.

Sebum production data will not be available for all subjects. One site, Dr. Bhatia (Site 4), did not have a Sebumeter, therefore, sebum production was not assessed for any subject. Site 3, Dr. Moore, 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 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 change and percent change from Screening.

8.11 Exploratory Efficacy Evaluation

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

8.11.1 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 one-point improvement and (b) at least 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.

8.11.2 Acne Lesion Counts

For the endpoint of Acne Lesion Counts, the change and percent change from Screening at each follow-up visit in total, inflammatory and non-inflammatory lesions, NB01 and VEH will be compared at Visit 5/EOT using MMRM. Descriptive statistics will be provided for the observed and the change and percent change from Screening at each visit.

8.11.3 Acne QoL

For the endpoint of Acne-QoL, the change and percent change from Screening at each follow-up visit for the four domain scores separately and total, NB01 and VEH will be compared at Visit 5/EOT using MMRM. Descriptive statistics will be provided for the observed and the change and percent change from Screening at each visit.

8.11.4 Statistical / Analytical Issues

8.11.4.1 Handling of Dropouts or Missing Data

The primary method of handling missing data will be the MMRM method without explicit imputations for missing data. Since IGA is analyzed based on a "success" criteria (one- or two-point improvement in score), subjects with a missing IGA score will be considered a "failure" in the analysis for the mITT population. Analyses in the PP population will use observed data only.

8.11.4.2 Interim Analyses

No interim analyses are planned.

8.11.4.3 Multicenter Studies

Data will be pooled from the three study centers for statistical analysis. The justification for pooling is made on a clinical basis based on the following. Each center will conduct the clinical

study under a common protocol. Consistency in study execution at each center will be emphasized. The sponsor will provide monitoring of study center compliance. The results for efficacy endpoints will be presented across the three sites by treatment groups for a descriptive evaluation of treatment by site interaction.

8.11.4.4 Multiple Comparisons / Multiplicity

No multiplicity adjustment is planned in this study.

8.11.4.5 Examination of Subgroups

Subgroup analysis for IGA, lesion counts, and sebum production will be performed based on the following subgroups at Visit 5/EOT only:

- Sex: male | female
- Age: 18-25 years | 26-40 years
- Follicular engraftment success: yes | no

8.12 Safety Evaluation

All safety analyses will be performed on the Safety population.

8.12.1 Extent of Exposure

The study drug is supplied as single-use cotton pads. 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).

8.12.2 Adverse Events

All AEs reported during the study will be listed, documenting course, severity, Common Terminology Criteria for Adverse Events (CTCAE) grade, 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. For all AE summaries, if a subject has more than one AE within a preferred term, the subject is counted once in that preferred term. If a subject has more than one AE within a system organ class, the subject is similarly counted once in that system organ class.

The number and percentage of unique subjects reporting each treatment-emergent AE will be summarized by SOC and preferred term. The number and percent of unique subjects reporting each treatment-emergent AE will also be summarized by SOC, preferred term, and maximum severity (mild, moderate, severe) and closest relationship to study drug (not related, unlikely, possibly, probably, definitely).

Dose limiting toxicities, if any, will be summarized by SOC, PT and treatment group.

Serious AEs, if any, will be summarized by SOC, PT and treatment group.

For any partial date, the general rules for imputation are:

- If only day is missing, then the 1st day of the month will be used.
- If only year is present, then 01Jan will be used.

If the imputed date is for an AE start date and is in the same year and month as the first dose date but before the first dose date, then the first dose date will be used, or if the imputed AE start date is after the AE end date, then the AE end date will be used. If the imputed date is for an AE start date and is in the same year and month as, but after the last dose date + 30 days, then the last dose date + 30 days will be used.

If the imputed date is for an AE end date and is after the death date, the date of death will be used, or if the imputed AE end date is before the AE start date, the AE start date will be used.

8.12.3 Local Skin Reactions

The frequency of the individual LSRs (Investigator assessed: erythema, edema, erosion/ulceration, scaling/dryness, and scabbing/crusting; Subject reported: itching and pain) will be tabulated by severity and treatment group at each visit. In addition, the change from Screening at Visit 5/EOT will be dichotomized to no change/improved versus worsened and will be tabulated by treatment group. 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.

8.12.4 Physical Examination

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

8.12.5 Vital Signs

Descriptive statistics of vital signs (temperature, blood pressure, and heart rate) will be provided by treatment group for Screening, Baseline and Visit 5/EOT, as well as, change from Screenng at Visit 5/EOT.

8.12.6 Pregnancy Test

Results from UPTs will be provided in a listing.

8.12.7 Complete Blood Count

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.

8.12.8 Concomitant Medications and Concurrent Therapies/Procedures

Information on concomitant medications administered during the study and concurrent procedures performed during the study will be collected. Prior medications are medications with a stop date prior to the first dose of study treatment.

Concomitant medications will be summarized for the Safety population using the World Health Organization drug dictionary drug class (ATC3) and preferred name, overall, and by treatment group. All medication data will be listed.

Concurrent procedures will be will be listed.

Unknown start dates and end dates will be imputed based on the rules provided for AE.

9. CHANGES TO PROTOCOL

The protocol version 2 specified that the endpoints of absolute and percent change at follow-up visits would be relative to the Baseline values; this has been changed to be relative to the Screening values in the SAP and protocol version 3.

The protocol version 2.0 specified EOS as the timepoint for the analysis of the engraftment parameters. The final samples are taken at Visit 5/EOT, therefore, EOS was replaced with Visit 5/EOT in the SAP and protocol version 3.

All endpoints of absolute change have been changed to observed change since the parameter values may differ from Screening values in a positive or negative direction.

The protocol specified the analysis of continuous variables as ANCOVA with and without Last Observation Carried Forward imputation. The analysis method was changed to MMRM as it is preferred over LOCF imputation.