PROTOCOL # GATT CO-161115154122-SACT

PROTOCOL TITLE	Human Comedogenicity Test
PROTOCOL IDENTIFICATION :	CO-161115154122-SACT
DATE & VERSION :	10 February 2017, Final Version (1.0)
SPONSOR :	[redacted]
STUDY SITE :	[redacted]
PRINCIPAL INVESTIGATOR (PI):	Michael J. Babcock, MD, FAAD
STUDY MANAGER:	[redacted]
STUDY DIRECTOR:	[redacted]
DEPARTMENT HEAD:	[redacted]
DESIGNATED PHYSICIAN REPRESENTATIVE (DPR):	[redacted]

This study will be performed in compliance with International Conference on Harmonization Guidelines for Good Clinical Practice (E6).

VERSION TRACKING

VERSION	DATE	STATE	REASON FOR CHANGE	DESCRIPTION OF CHANGE
1.0	10FEB2017	FINAL	New	N/A

SYNOPSIS

PROTOCOL IDENTIFICATION	CO-161115154122-SACT
PROTOCOL TITLE	Human Comedogenicity Test
PRINCIPAL INVESTIGATOR	Michael J. Babcock, MD, FAAD
STUDY SITE	[redacted]
OBJECTIVE	To determine the potential of a test material to induce comedones.
STUDY DESIGN	A single center, evaluator blinded, randomized study to test the potential of comedogenicity of test products. The backs of volunteers with a propensity to comedone formation are patched with the test material three times a week for a four-week period. At the last visit, a follicular biopsy is performed on each site of each subject, Microcomedones on the slides are counted and the product categorized as to comedogenic potential."
STUDY POPULATION	Males and Females aged 18-45 years old who meet the eligibility criteria of the study.
SAMPLE SIZE	Enroll up to 18 volunteers satisfying the inclusion and exclusion criteria. 15 subjects completing the study is sufficient.
INVESTIGATIONAL STUDY MATERIALS	Test Material (TM) information will be provided in protocol addendum for each test panel.
DOSE AND MODE OF APPLICATION	Test materials and Negative Control will be applied with occlusive or semi-occlusive patches. The patch type may be changed if irritation develops. Occlusive patches consist of a non-woven cotton pad (e.g., Webril®) covered by Blenderm tape and held securely to skin on all sides with a porous, hypoallergenic tape (e.g., Micropore®). Semi-occlusive patches consist of a non-woven cotton pad (e.g., Webril®) covered and held securely to skin on all sides with a porous, hypoallergenic tape (e.g., Micropore®). Patches are placed on the back no closer than 2 cm apart. The cotton pads used for the patches

	are approximately 4 cm^2 in area, and are dosed with a quantity of test material as follows (unless otherwise instructed by the Sponsor): Liquids and fragrances approximately 100 µl; Creams, lotions, petroleum, etc. approximately 100 µl; Paper or other solid materials will cover the pad area.
STUDY DURATION	The study will consist of approximately 13 visits: Visit 1 (Screening/Baseline), Visit 2 through 12: Patching and Grading, Make-up visit, and Visit 13 (Grading and Follicular Biopsy collection visit)
METHODOLOGY	Skin sites on the back in the interscapular region will be utilized as application sites. The test material(s) and negative control will be assigned to specific sites for each subject be assigned to specific site for each subject according to a randomization scheme and will be applied repetitively under occlusive/semi-occlusive patches for a period of 28 days.
SAFETY AND ADVERSE EVENTS	Any Adverse Event (AE) (including Serious Adverse Events (SAE) related or unrelated to the test material(s) or study participation must be documented as required (occurrence date, site, outcome, and assessment of causality, severity, and relatedness). SAEs must be reported immediately and relevant supportive documentation must be sent to the Study Manager or designee within 24 hours of the site becoming aware of the event. See section 10.3.3. for reporting timelines.

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
CRF	Case Report Form
EDC	Electronic Data Capture
ICH GCP	International Conference on Harmonisation Good Clinical Practice
ICD	Informed Consent Document
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
PI	Principal Investigator
PP	Per-Protocol
PQC	Product Quality Complaint
SI	Sub-Investigator
SAE	Serious Adverse Event
TEAE	Treatment Emergent Adverse Event

TABLE OF CONTENTS

1 BACKGROUND

The human comedogenicity test has been shown to be a predictive method for assessing the comedogenic potential of products intended for use on skin.

2 RATIONALE

This human comedogenicity test panel(s) is being conducted on product(s) making the claim of "non-comedogenic".

3 OBJECTIVE(S)

The objective of this protocol is to evaluate the comedogenic potential of the test material(s) using the back of human volunteers.

4 OVERALL STUDY DESIGN AND PLAN DESCRIPTION

A single center, evaluator blinded, randomized, four-week clinical test panel(s). This human comedogenicity test panel(s) is being conducted in order to assess the comedogenic potential of the test material(s) and determine if the test material(s) induce microcomedones under repetitive patch test conditions. The target population for each test panel is adult men and women (age 18 through 45 years), who are acne-prone and have large pores on the back and/or a history of acne vulgaris on the face or back. Subjects will be patched on the upper back with test material dosed patches and an undosed occlusive patch (negative control) every Monday, Wednesday, and Friday for 4 consecutive weeks. Each test site will be graded for irritation after each patch removal. After 12 full patching sessions, a follicular biopsy will be collected from the test material and control sites, and graded for microcomedones.

Protocol Activity:	**Visit 1 Screening/Baseline**	**Visit 2- Visit 12 (Conducted Monday Wednesday, and Friday for 4 consecutive weeks) ****	**Make-up visit* (if needed)**	**Visit 13**
Informed consent with HIPAA disclosure	X			
Collect demographics, general medical history & concomitant medications	X			
Review of potential test sites (upper back) by PI (or designee)	X			
Eligibility review and subject qualification by PI (or medically qualified designee)	X			
Interview for compliance		X	X	X
Remove TM, control, and negative control dosed patches from test sites		X	X	X
Clinical NACDG grading of test sites by PI or designee		X	X	X
Test sites marked (to be remarked as needed)	X	X	X	
Test sites wiped with distilled or deionized water and air dried	X			
Randomization of TM, control, and negative control on test sites	X			
Apply TM, control, and negative control dosed patches on test sites	X	X	X	
Dispense study visit calendar to subject	X			
Review study instructions with subject	X			
Collect follicular biopsy from each test site				X
Collect/record AEs and changes in health/medications	X	X	X	X
Subject disposition				X

* Denoted activity will only occur if subject missed one of the scheduled visits from visits 2 to 12 and requires a make-up visit

** See Study Duration in section 5

5 STUDY DURATION

Each test panel will consist of 13 subject visits: Screening/Baseline (Visit 1) will be completed on either a Monday, Wednesday or Friday, and Visit 2 will be completed 48-72 hours post Visit 1. Visits 3-13 will occur 48-72 hours post each subsequent visit, i.e., Monday, Wednesday, and Friday for four consecutive weeks.

As necessary, a subject may complete a make-up patching visit. Make-up visit will be conducted 48-72 hours post Visit 12. Subject will return to site for Visit 13 for the collection of Follicular Biopsies.

Visit 13 will be conducted 48-72 hours post Visit 12 or post make-up visit if applicable.

Note: 72-hour exposure time is only applicable for visits conducted on Friday and/or to allow for site closed days.

6 SUBJECT SELECTION AND ENROLLMENT

Each study panel can fulfill its objective only if appropriate and required number of subjects is enrolled. The following eligibility criteria are designed to select subjects for whom protocol procedures are considered appropriate. All relevant medical and non-medical conditions should be taken into consideration, in addition to the inclusion/exclusion criteria below, when deciding if a particular individual is suitable for this protocol. The inclusion and exclusion criteria will be reviewed for each subject and confirmed by the Principal Investigator (PI) or a medically qualified individual (MD/DO) at Visit 1 in order to determine subject eligibility for the relevant test panel.

Prior to any review of personal data, Informed Consent documents should be signed.

6.1 INFORMED CONSENT

The Informed Consent Document (ICD), will be read by the subject or explained to the subject by the PI or designee. The PI or designee must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation. After understanding and agreeing, the subject will express his/her consent to the subject's participation in the study by signing the ICD.

No subject will be evaluated without a signed ICD, which should be kept by the PI as part of the Site Master File. The ICDs of subjects who are not enrolled in the study will also be part of the Site Master File.

One copy of the signed ICD must be given to the subject; the subject will remain free to withdraw this consent at any moment without any negative consequence to the subject.

The ICD must be approved by the Sponsor and the IRB must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

In addition to the ICD, an IRB approved Supplemental Consent form may be completed if the subject has indicated that they have previously had eczema and would like to participate in the study. See exclusion criterion VIII.

6.2 STUDY POPULATION

Individuals must meet all of the following eligibility criteria for enrollment into the study.

6.2.1 Inclusion Criteria

Individuals must meet all of the following inclusion criteria for enrollment into the study:

I. Male or female.
II. 18 to 45 years old.
III. Individuals that are willing to provide written informed consent and are able to read, speak, write, and understand English.
IV. Individuals who are acne-prone with large pores on the back, or individuals who have a history of acne vulgaris on the face or back.
V. Individuals who have had at least a 2-week rest period since participation in any previous clinical studies involving patch applications on the back.
VI. Individuals who are willing to avoid direct sun exposure on the back and use of tanning beds for the duration of the study.
VII. Generally, in good health based on medical history reported by the subject.
VIII. Have generally healthy skin condition appropriate for study assessments
IX. Available for the entire study duration.
X. Individuals who are willing to keep patch sites as dry as possible and refrain from swimming or soaking in a hot tub for the duration of the study (no showering/bathing restrictions).
XI. Willing to cooperate and follow instructions.
XII. Female subjects, not of child-bearing potential, must meet at least one of the following criteria:
- Had a hysterectomy and/or bilateral oophorectomy,
- Be post-menopausal (amenorrhea for at least 1 year),
- Had a Tubal Ligation,
- Surgical sterilization (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy);

XIII. Female subjects, of child-bearing potential, must agree to practice a medically acceptable form of birth control during the study and 30 days after study completion. Females must have used such birth control for at least 3 months prior to study start;
XIV. Medically acceptable forms of birth control that may be used by the subject and/or his/her partner include:
- Established use of hormonal methods of contraception (oral, injected, implanted, patch or vaginal ring).
- Barrier methods of contraception **with or without** spermicide: condom or occlusive cap (diaphragm or cervical/vault caps),
- Intrauterine device (IUD) or intrauterine system (IUS),
- Surgical sterilization (e.g., in a monogamous relationship with male partner with vasectomy that has been confirmed effective by sperm count check, tubal occlusion, hysterectomy, bilateral salpingectomy).
- Abstinence from heterosexual intercourse: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception;

6.2.2 Exclusion Criteria

Subjects with any of the hereafter criteria must be excluded from the study:

I. Individuals with known allergies or sensitivities to common topical skincare products, including adhesives and/or cyanoacrylate (super glue) or ingredients to the test materials for a specific test panel.
II. Deprived from liberty by a judiciary or administrative decision.
III. Having undergone organ excision (kidney, lung, spleen, and liver), an organ transplant, or a skull concussion with extended loss of consciousness within the last 5 years or with present symptoms and/or side effects.
IV. Individuals with self-reported UNCONTROLLED metabolic conditions, such as diabetes, hypertension, hyper/hypothyroidism, hypercholesterolemia, etc.
V. Individuals with CONTROLLED health conditions may be excluded from the study at the discretion of the PI or designee:
    - Subjects with conditions that do not affect the skin, such as hypertension and hypercholesterolemia, could be enrolled when their health condition is managed through diet, medication, etc.
    - Subjects with conditions, which might affect the skin, such as hyper/hypothyroidism, diabetes must be excluded, regardless whether their health condition is controlled or not.
VI. Subjects who are taking medication for chronic conditions (e.g., insulin, antihistamines, steroidal and non-steroidal anti-inflammatory drugs, antibiotics, etc…) – exception could be made for hypercholesterolemia as per point IV.
VII. Individuals with adult asthma and/or epilepsy.
VIII. Skin diseases on tested sites (e.g., psoriasis, eczema, erythema, edema, scars, wounds, melanomas, etc.), which may influence the outcome of the study;
    a. Supplemental Consent
    During the eligibility screening, individuals who indicate that they have previously had eczema will be advised of the Koebner phenomenon, which refers to the appearance of these conditions either at the patch site or unrelated sites. If the individual chooses to participate in the study, 2 copies of a supplemental consent form will be signed by the subject (1 for the study files and 1 will be given to the subject).

IX. Subjects who are self-reported to be pregnant, lactating or planning to become pregnant; females of child-bearing potential who are unwilling or unable to use an acceptable method of contraception during the study.
X. Male subjects who have a pregnant partner.
XI. Male subjects whose partner is planning to become pregnant during the study period or is unwilling or unable to use an acceptable method of contraception.
XII. Simultaneous participation in any other type of clinical study.
XIII. An individual who has any condition which in the PI's judgment makes the candidate an inappropriate subject for study participation.
XIV. Subjects who are related to those persons involved directly or indirectly with the conduct of this study (i.e., PI, sub-investigators, study coordinators, other site personnel, employees of the Sponsor subsidiaries, contractors of the Sponsor, and the families of each).
XV. Individuals with a condition or situation which, in the PI's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study.
XVI. Individual viewed by the PI as not being able to complete the study.

XVII. Subjects who are planning to use any new personal care products (e.g. makeup) or are planning to change existing brands during the study

6.3 CONCURRENT PRODUCTS

During the study, subjects will be permitted to follow their normal bathing routine. They will not be permitted to apply any topical product to the patch sites during the span of this study. Subjects should not start using any new personal care products (e.g. makeup, cleanser) or change their currently used brands during the study.

6.4 CONCURRENT MEDICATION

If a subject is taking any medication during the course of the study or within 2 weeks prior to the study, it must be recorded on the Concomitant Medication Form or equivalent. The minimum information required is the name of the medication. If this medication is linked to the treatment of an IP-related AE, dose and duration of the treatment should be specified. Medications excluded are indicated in the Subject Exclusion criteria*;* the use of any excluded medications during the study will result in discontinuation of the subject.

6.5 SCREENING FAILURE

All individuals who signed ICD and withdraw their participation or fail to meet all of the screening criteria during the initial evaluation will be considered a "screening failure." These subjects will be replaced (note: screening numbers will not be reused) and their data will not be considered in the final report.

7 SAMPLE SIZE DETERMINATION

A sufficient number of subjects will be screened to enroll as many as 18 qualified subjects to ensure completion of 15 subjects per test panel.

8 INVESTIGATIONAL STUDY MATERIALS

8.1 IDENTITY OF INVESTIGATIONAL STUDY MATERIALS

The test material(s) will be manufactured and packaged by the Sponsor. The ingredient list and Safety Attestation letter for each product will be provided to the PI for review and submission to the IRB. The ingredient list and Safety Attestation letters will be filed in the Site Master File for the test panels.

Formula numbers of the test material(s) will be provided via the protocol addendum form prior to the conduct of each study.

A label will be affixed to each test material. The label may contain (but is not limited to) fields for the following information:

- Reference Number
- Type of test material
- Directions
- Net Contents or Net Weight
- Formula number
- Storage Information
- "**For Investigational Use Only**"

8.2 RANDOMIZATION

Upon qualification and enrollment, each subject will be sequentially issued a subject number starting with "001". Once a subject number has been assigned to a subject, it cannot be reassigned to another subject. The subject numbers will be used to randomly assign the test material(s) and control to the specific test sites for each subject according to a randomization scheme created by the site.

The site will create the randomization scheme for each test panel prior to the initiation of the test panel.

8.3 BLINDING PROCEDURE

This study will be evaluator-blinded, so the PI or delegated evaluator conducting the NACDG grading evaluations will not know the placement of the TM and control patched test sites. The PI or delegated evaluator should not participate in product(s)/patch application and should not have access to the randomization.

In the event that the PI/evaluator believes an un-blinding is necessary and circumstances allow, the PI/designee will contact the Study Manager who will consult with the DPR to determine whether unblinding is needed. If it is determined that the blind should be broken, the PI/evaluator will contact the designated site representative to obtain information about the individual subject's randomization. The time, date, and reason for the un-blinding should be noted in the subject's source document and documentation should be provided to the Sponsor.

If there is a medical emergency and the PI/evaluator deems it necessary to know the randomization urgently for the subject's proper medical care, then the PI/evaluator may break the blind immediately by contacting the designated site representative. The PI/designee should promptly document and explain to the Study Manager any premature un-blinding.

The PI/evaluator may assist with data entry/review/analysis after individual subjects complete all test procedures. This will not be documented as premature un-blinding.

8.4 STUDY MATERIAL STORAGE AND ACCOUNTABILITY

The PI or designee must ensure that deliveries of test material(s) from the Sponsor are correctly received by a responsible person and that the test material(s) is stored in a secure area under recommended storage conditions. The test material(s) will be secured in a locked room or cabinet that is only accessible to authorized site personnel and kept at 59 - 86°F (15 -30°C). Temperature should be recorded at least daily. The PI must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product on the Investigational Product Accountability/Dispensing Log or site equivalent

At the end of the study, investigational test material(s) (used and/or unused) may be destroyed by the site following its Standard Operating Procedure (SOP) and in compliance with applicable regulations, institutional policy, and any special instructions provided by the Sponsor, or they may be returned to the Sponsor depending on the product classification.

When product is destroyed on-site, the destruction must be properly documented and documentation provided to the Study Manager and/or designee.

In case of return to Sponsor, all containers must be returned to [redacted].

8.5 PRODUCT QUALITY COMPLAINTS

A Product Quality Complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, or safety of a product, including its labeling, delivery system or packaging integrity. It also includes device malfunctions. Any PQC discovered during the initial inventory should follow the instructions provided on the receipt letter; no PQC form should be filed for issues identified when opening or unpacking a shipment. Subsequently, any observation of a PQC requires immediate notification to the Study Manager via a completed PQC form and telephone call. The PI or designee should complete, sign, and forward a copy of the PQC form to the Study Manager.

In addition, PQC information must be included on the Investigational Product accountability and reconciliation Form or equivalent in the comments field. The Study Manager listed can assist you or answer questions related to this process. To aid in the initial conversation and understanding of a PQC, the site staff may be asked to photograph the issue and send it to the Study Manager.

8.6 APPLICATION OF THE INVESTIGATIONAL PRODUCT

Test materials will be applied using occlusive or semi-occlusive patches. The patch type may be changed during the study if irritation develops. Occlusive patches consist of a non-woven cotton pad (e.g., Webril®) covered by Blenderm tape and held securely to skin on all sides with a porous, hypoallergenic tape (e.g., Micropore®). Semi-occlusive patches consist of a non-woven cotton pad (e.g., Webril®) covered and held securely to skin on all sides with a porous, hypoallergenic tape (e.g, Micropore®). Open patches consist of a non-woven cotton pad (e.g., Webril®) held to the skin on 2 opposing sides by a strip of hypoallergenic tape (e.g., Micropore®). The pad is open on 2 sides like a Band-Aid ®.

Patches will be placed on the upper back, to the right and left of the spine. Patches will not be applied closer than 2 centimeters (cm) to each other. The cotton pads used for the patches are approximately 4 cm^2 in area, and will be dosed with a quantity of test material as follows (unless otherwise instructed by the Sponsor):

- Liquids and fragrances approximately 100 microliters (µL)
- Creams, lotions, petroleum, etc. approximately 100 µL
- Paper, powder or other solid materials a sufficient amount to cover the pad area

Patches will be applied starting at the lower edge of the patch and pressing from below to let air escape. The patch will be secured by gently rubbing the tape (especially the corners) to ensure good adherence.

9 INVESTIGATIONAL PLAN

9.1 STUDY PROCEDURES AND EVALUATION SCHEDULE

Pre-Study:

Candidate subjects will be recruited using IRB-approved materials. Interested candidates will be scheduled for Visit 1.

Screening/Baseline: Visit 1

Interested candidates will report to the site and take part in the following procedures:

1. Prospective candidates will be sequentially assigned a 2-digit screening number preceded by "S" (e.g. S01).
2. Subjects will be given an IRB-approved ICD and IRB-approved Supplemental Consent form (when applicable) to read and sign. They will have all of their study related questions answered by the Investigator or designated staff, and if they agree, they will sign 2 copies of the ICD and Supplemental Consent form (when applicable). They will retain 1 copy, and 1 will be kept in the study file.
3. Subjects will complete a health and eligibility questionnaire and a medical and medication history questionnaire.
4. Potential test sites (upper back) will be examined by the Investigator or designee for qualification criteria.
5. The screened subjects that meet all eligibility requirements will be enrolled into the study and assigned a subject number as describe in the "Randomization" section.
6. A delegated clinician will delineate up to six test sites on the subject's upper back, to the right and left of the spine, using an indelible marker. Each test site will be a 4 cm^2 and no closed than 2 cm^2 from each other. The test sites may be re-delineated at subsequent visits as needed
7. The test sites will be wiped with distilled or deionized water and allowed to air dry prior to patching.
8. The test material dosed patches and an undosed negative control patch will be applied to each subject's upper back according to the predetermined randomization.
9. Subjects will be provided with a calendar of study visits and study instructions. Subjects will be reminded of sun exposure/tanning and swimming/hot tub restrictions. Subjects will also be instructed to reinforce the edges of the patch with a bandage tape in the event that the tape applied in the clinic does not adhere.

Interim Visits: Visit 2 – Visit 12

Visit 2 will be completed 48-72 hours post Visit 1. Visits 3-12 will occur 48-72 hours post each subsequent visit, i.e., Monday, Wednesday, and Friday for four consecutive weeks. Subjects will report to the site at their scheduled visit time and will participate in the following procedures at each interim visit:

1. The PI or designee will interview the subjects to collect and record any AEs or changes to health/concomitant medications that may have occurred since the previous visit. Subjects will also be interviewed for compliance with study directions. Refer to Adverse Event Reporting section.
2. Patches applied during the prior visit will be removed by clinic personnel.
3. Each test site will be evaluated for irritation/reactions by the delegated evaluator.
4. Test sites may be re-delineated as needed, as described in Visit 1.

5. New test material dosed patches and an undosed negative control patch will be applied to the same test sites as described for Visit 1.

Make-up Visit

As necessary, a subject may complete a make-up patching visit. Make-up will be conducted 48-72 hours post Visit 12. Subject will return to site for Visit 13 for the collection of Follicular Biopsies. Subjects will report to the site at their scheduled visit time and will participate in the following procedures:

1. The PI or designee will interview the subjects to collect and record any AEs or changes to health/concomitant medications that may have occurred since the previous visit. Subjects will also be interviewed for compliance with study directions. Refer to Adverse Event Reporting section.
2. Patches applied during the prior visit will be removed by clinic personnel.
3. Each test site will be evaluated for irritation/reactions by the delegated evaluator.
4. Test sites may be re-delineated as needed, as described in Visit 1.
5. New test material dosed patches and an undosed negative control patch will be applied to the same test sites as described for Visit 1.

Visit 13:

Visit 13 will be conducted 48-72 hours post Visit 12. Subjects will report to the site at their scheduled visit time and will participate in the following procedures

1. The PI or designee will interview the subjects to collect and record any AEs or changes to health/concomitant medications that may have occurred since the previous visit. Subjects will also be interviewed for compliance with study directions. Refer to Adverse Event Reporting section.
2. Patches applied during the prior visit will be removed by clinic personnel.
3. Each test site will be evaluated for irritation/reactions by the delegated evaluator.
4. A delegated clinician will collect follicular biopsies from each test site as described below in the *Study Instrument*(s) section.
5. The PI or designee will interview the subjects to collect and assess any AEs or changes to health.
6. After all assessments are completed, subjects will leave site.

Note: 72-hour exposure time is only applicable for visits conducted on Friday and/or to allow for site closed days.

Site Irritation / Reaction Grading

At visits 2 through 13 (and makeup visit if applicable), the designated test sites will be graded for irritation/reactions using the North American Contact Dermatitis Group (NACDG) grading scale. Sites will be adequately illuminated using lighting provided by a 60-watt incandescent blue day light bulb.

NACDG Grading Scale

0 No reaction
+0.5 Macular erythema
+1 Indurated erythema
+2 Erythema, infiltration and vesicles
+3 Bullous reaction or ulcer

If irritation develops as indicated by the NACDG score, the patch type may be changed or patch applications may be skipped for specific sites. Skipping a patch application should be documented as a protocol deviation. This may also have an impact on the follicular biopsy process at the final study visit. Any changes made to the patch type, application schedule, or biopsy procedures will be documented in the appropriate source documents.

9.2 STUDY INSTRUMENT(S)

Follicular Biopsies:

Follicular biopsies will be collected from each patch site at Visit 13 or make-up visit for each subject. The following procedures will be followed for follicular biopsy collection:

- The test sites will be gently cleansed with warm soapy, water and patted dry.
- A glass slide containing a drop of cyanoacrylate glue will be held against each site until it has dried.
- The slide will then be removed slowly, so as to extract follicles and their contents.
- The specimen slides will be stored in labeled slide boxes until graded.
- The specimens collected using the cyanoacrylate follicular biopsy technique will be evaluated by a trained grader using a stereomicroscope (magnification ratio of 0.8). Hyperkeratotic follicles (microcomedones) will appear as cylindrical horny impactions surrounding extracted vellus hairs.

Specimens will be graded using a 5-point global assessment scale as follows:

0 None (0%, No microcomedones)
0.5 Slight (1-24% Smallish horny masses)
1 Mild (25-49% Smallish horny masses)
2 Moderate (50-74% Moderately sized horny masses)
3 Severe (75-100% Larger globoid microcomedones)

The results from the microcomedone grading of the follicular biopsies will be recorded using the Stephens Electronic Data Capture (EDC) system, if available, which documents the identity of the evaluator/technician as well as the time and date of all entries, or all corrected entries. Subject data can also be provided by Stephens at the Sponsor's request. Paper grading forms will be completed if EDC is unavailable. Any test site with a NACDG grading score of 2 or greater may not receive a follicular biopsy, which will be noted in the appropriate source documents.

9.3 SUBJECT COMPLETION/WITHDRAWAL

9.3.1 Subject Completion

Subjects are considered to have completed the study when all study procedures have been completed as designated by the protocol. Completion should be noted in the source documents and Screening and Enrollment log.

9.3.2 Subject Withdrawal

When an individual who has signed the ICD is not enrolled in the study or withdraws/is withdrawn prior to completing the study, the reason is to be documented in the source documents, Screening and Enrollment log, and in the final study report. Reasons for subject withdrawal may include:

- Screen Failure (e.g. fails to meet inclusion/exclusion criteria, chooses not to enroll, etc.)
- Participant is determined to be ineligible after enrollment
- Subject's choice to withdraw
- Investigator terminated (e.g. noncompliance, etc.)
- Adverse Event / SAE (must be reported in accordance with the reporting requirements defined in the Adverse Event Reporting Section.
- Lost to follow-up
- Other

Subjects may withdraw from the trial at any time at their request, or they may be withdrawn at any time at the discretion of the Sponsor, PI, or designee for safety, behavioral, or administrative reasons. If a subject does not return for a scheduled visit, 3 documented attempts will be made to contact the subject in order to establish the reason for withdrawal, and the outcome will be documented. The PI or designee should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events.

Should a subject withdraw from the trial and also withdraw consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The PI and staff may retain and continue to use any data collected before such withdrawal of consent.

Additional subjects may be enrolled in a test panel to compensate for early subject withdrawal

10 STATISTICAL ANALYSIS PLAN.

The per-protocol (PP) population will be the primary population for comedogenicity analyses. The PP population will include all subjects who received treatment and completed the study in general accordance with the protocol. Only the data of completing subjects will be analyzed. Subjects may be removed from the analysis in the case of an AE, SAE, non-compliance, or Investigator discretion. The reason for any subjects excluded from the analyses will be documented in a note to file and included in the study report.

Demographic data and baseline characteristics will be summarized for all subjects who are enrolled in the study. For continuous variables, descriptive statistics including number of subjects (N), mean, median, standard deviation (SD), minimum (MIN) and maximum (MAX) values will be presented. For categorical variables, the frequency and percentage of each category will be provided.

A descriptive statistical summary will be provided for the global assessments of microcomedone data from biopsies for the test material and control sites. The descriptive statistical summary includes the number of observations (N), mean, median, standard deviation (SD), minimum (MIN), and maximum

(MAX).

In addition, microcomedone scores will be analyzed using a mixed-effects model, where the test Material/negative control is a fixed effect and the subject is a random effect. Each test product will be compared to the negative control within the model frame. A test material will be considered positive for comedogenicity if it has a mean microcomedone value of 1.0 or greater, and is statistically greater than the mean microcomedone value for the negative control site.

All statistical tests will be 2-sided at significance level alpha=0.05. P-values will be reported to 3 decimal places (0.000). No multiple testing corrections will be considered in the study. Statistical analyses are performed using SAS software version 9.30 or later series (SAS Statistical Institute). The results will be sent to the Sponsor along the raw data in a Microsoft Excel document at the completion of the study.

A test material is considered negative for comedogenicity as long as it satisfies 1 of the following 2 conditions: the microcomedone mean score is less than 1.0 and/or the mean score is not greater than the control with p-value < 0.05.

11 MANAGEMENT OF INTERCURRENT EVENTS

11.1 AMENDMENTS TO THE PROTOCOL

Neither the PI nor Sponsor will modify this protocol without obtaining the concurrence of the other. The party initiating a modification will confirm it in writing. Amendments must be approved by the Sponsor and IRB prior to implementation.

Note that submission of administrative change/non-substantial amendments to regulatory authorities and/or IRB/IECs for approval prior to study implementation is determined after consultation with the local regulatory representative and/or IRB/IEC policy and may vary by country/region.

The only circumstance in which an amendment may be initiated prior to IRB approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the PI must notify the IRB and the Sponsor in writing within 3 working days after the implementation.

11.2 PROTOCOL DEVIATIONS

Protocol deviations should be avoided whenever possible. When a protocol deviation occurs, it must be captured on a Deviation Log.

The PI or designee will also contact the Study Manager, Contact with the Study Manager will be made as soon as possible in order to discuss the situation and agree on an appropriate action. If it is determined that the subject safety/well-being was affected, the IRB/IEC, if any, will also be notified. The final report will describe the deviation from the protocol and the circumstances requiring it.

11.3 ADVERSE EVENT REPORTING

11.3.1 Introduction

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the Sponsor, and are mandated by regulatory

agencies worldwide. The Sponsor has established procedures in conformity with regulatory requirements to ensure appropriate reporting of safety information.

11.3.2 Definitions

11.3.2.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical study subject temporally associated with the clinical investigation, whether or not the event has a causal relationship to the subject's participation in the trial. It is therefore any unfavorable and unintended sign (including an abnormal finding), symptom, or disease that occurs during the trial. This can include any occurrence that is new in onset, an aggravation of severity/frequency of a baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Examples of AEs include but are not limited to:

Abnormal test findings,
Clinically important symptoms and signs,
Changes in physical examination findings,
Hypersensitivity, and
Progression/worsening of underlying disease.

Any change in existing medical condition (Medical History) would be considered an AE and recorded appropriately.

Additionally, they may include the signs or symptoms resulting from:

Investigational product overdose,
Investigational product withdrawal,
Investigational product abuse,
Investigational product misuse,
Investigational product interactions,
Medication errors,
Investigational product dependency,
Exposure *in utero*, and
Study related procedure.

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

Test result is associated with accompanying symptoms, and/or
Test result requires additional diagnostic testing or medical/surgical intervention, and/or
Test result leads to a discontinuation from the study, significant additional concomitant treatment, or other therapy, and/or
Test result is considered to be an adverse event by the PI or the Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Expected AE

All investigational products have the potential to cause some uncomfortable effects or other reactions. Signs and symptoms of erythema, edema, scaling/dryness, itching, burning, stinging, and tingling are

considered clinical endpoints if they are mild in nature and should not be reported as AE. These conditions may or may not resolve over time. Symptoms that are persistent and moderate to severe in nature, or that involve elevation (e.g. edema, papules, vesicles, spreading) will be considered adverse events (AEs). The Investigator or designee will have the final authorization to determine if a reaction will be considered an AE.

If a subject is discontinued due to worsening of a sign or symptom (including worsening of the signs and or symptoms recorded as part of the evaluations), then it should be recorded as an AE.

Treatment Emergent AE (TEAE)

TEAE is defined as any event not present prior to the initiation of the IPs. Note that AEs will be summarized for all subjects who signed the ICD, differentiating TEAEs.

AEs are considered serious and require expedited reporting if they meet the definition of a **Serious Adverse Event** (see part below).

11.3.2.2 Serious Adverse Event (SAE)

An SAE is an AE (untoward medical occurrence) that fulfills at least one of the following criteria:

- results in death;
- is life-threatening (immediate risk of death);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- is a suspected transmission of any infectious agent via a medicinal product (medically significant) and should be reported as an SAE in the category "*Other medically important conditions*";
- results in a congenital anomaly/birth defect;
- is another medically significant event (i.e. a medically significant condition that may jeopardize the subject or require medical or surgical intervention to prevent any of the previously listed outcomes). Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations other than those listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an Emergency Room or at home, blood dyscrasia, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse, or malignancy).

11.3.2.3 Severity

The severity of all AEs must be evaluated by the PI or, if the PI does not have a medical background, by a medically qualified individual (MD/DO). The severity classifications are:

- **Severe** – Extreme distress, causing significant impairment of functioning or incapacitation; interferes significantly with subject's usual function; prevents normal everyday activities.
- **Moderate** – Sufficient discomfort is present to cause interference to some extent with subject's usual function or normal everyday activity.
- **Mild** – Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with subject's usual function or normal everyday activities.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

11.3.2.4 Causality Assessment

An AE (serious or non-serious) is considered "study-related" if the causality assessment is possible, probable, or very likely. The PI or, if the PI does not have a medical background, a medically qualified individual (MD/DO) determines the causality by using the following definitions:

- **Not related** – an AE that is not related to the participation in the study.
- **Doubtful** – an AE for which an alternate explanation is more likely (e.g. concomitant drug), or the relationship in time suggests that a causal relationship is unlikely.
- **Possible** – an AE that might be a result of participation in the study. An alternative explanation is inconclusive and the relationship in time is reasonable so a causal relationship cannot be excluded.
- **Probable** – an AE that might be a result of participation in the study. The relationship in time is suggestive (e.g. confirmed by the challenge). An alternative explanation is less likely.
- **Very Likely** – an AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation. The relationship in time is very suggestive (e.g. confirmed by dechallenge and rechallenge).

11.3.3 Procedures for Reporting Adverse Events

All AEs will be reported from the time a signed and dated ICD is obtained until completion of the subject's last study procedure or visit (or termination if the subject terminates early from the study for any reason).

AEs that occur between end of study and 30 calendar days after completion of the study will only be reported to the Sponsor if they are serious. SAEs are reportable beyond this period if the event is considered study-related. The Sponsor will evaluate any safety information that is spontaneously reported by the PI beyond the time frame specified in the protocol.

Subjects are encouraged to report AEs spontaneously and in response to questioning during the visit (e.g. if they have had any side effects/issues or changes in their health). For each AE reported by the subject or observed by the study team, the study team member should notify the PI, Study Physician, or designee, who will collect information about the event.

All AEs, regardless of seriousness, severity, or presumed relationship to study procedures, must be recorded using medical terminology on the Sponsor provided AE form and then entered into the Electronic Data Capture (EDC), Medidata Rave AE Universal Database. These events must then be entered into the Medidata Rave AE Universal Database within 5 business days of the site's awareness. The DPR review of AEs/SAEs in Medidata Rave AE Universal Database will be conducted within 5 business days of each entry into Medidata Rave AE Universal Database in order to escalate any potential safety signal to the Department Head.

Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). The PI or, if the PI does not have a medical background, a medically qualified individual (MD/DO) designee, must record or confirm their opinion concerning the

seriousness, severity, and relationship of the AE to the study. All measures required for AE management must be recorded and reported according to Sponsor instructions.

The PI or designee must also report AEs to the appropriate IRB unless otherwise required and documented by the IRB.

If a **SAE** occurs, in addition to the above reporting procedures, the Site will **immediately** notify the Study Manager and Study Director by telephone or encrypted e-mail (see Appendix III for Contact Information)

Subsequent to a telephone or encrypted e-mail report of an SAE, a Clinical Trial SAE Report Form (provided to the study site at the initiation of the study) must be completed by the investigational staff with as much information as possible (however at a minimum, the subject identification number, name of investigational product [if applicable], SAE description, investigator's assessment of causality, and name of site personnel reporting event are required), signed by the PI (or the medically qualified designee), and securely transmitted to the Study Manager and Study Director **within 24 hours** of becoming aware of the event.

This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports.

In the rare event that the Investigator's site does not become aware of the occurrence of a SAE immediately (e.g., if an outpatient study subject initially seeks treatment elsewhere), the Investigator's site is to report the event immediately after learning of it as described and document the time of the study site's first awareness of the SAE.

The Study Manager or designee will notify the DPR within 1 calendar day of SAE information receipt. The DPR will request more information as necessary. The Study Manager or designee will send an e-mail appropriate document to Sponsor's OCMS group per local procedures within the following timelines:

- fatal/life-threatening reports: within 2 calendar days from regulatory clock start date
- other SAEs and pregnancy exposure reports: within 3 calendar days from regulatory clock start date

For all SAEs, the PI is obligated to pursue and provide information to the Sponsor in accordance with the timeframes for reporting specified above. In addition, the PI may be requested by the Sponsor to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the AE Form. In general, this will include a description of the SAE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses, must be provided.

In the case of a subject death, a summary of available autopsy findings (if available) and death certificate should be collected if permission is obtained from the subject's family.

For a hospitalization, a copy of the hospital discharge summary should be requested. If obtained, these documents (with subject's personal identifiers redacted) should be securely submitted as soon as possible to the Sponsor or its designated representative.

11.3.4 Monitoring and Resolution of Adverse Events

11.3.4.1 Non-Serious AEs

All study-related AEs will be followed until resolution, until a stable clinical endpoint is reached, or at least 30 days post-study withdrawal/completion. This information will be captured in the source document and entered into Medidata Rave AE Universal Database.

11.3.4.2 Serious AEs (SAEs)

The PI or, if the PI does not have a medical background, the medically qualified designee (MD/DO) will monitor SAEs until resolution or until one of the conditions in 11.3.4.3 is met. The information will be captured in the source document and entered into Medidata Rave AE Universal Database. The PI/designee will also document follow-up information on an updated Clinical Trial SAE form, which will be reviewed by the PI or medically qualified individual designee and sent securely to the Study Manager or designee. The Study Manager or designee will forward the document(s) to the DPR and Study Director or designee, and to OCMS per local procedures.

11.3.4.3 Resolution

The PI will be required to assess the outcome of each AE as one of the following:

Resolved;
Not Resolved;
Fatal;
Resolved with sequelae;
Resolving;
Unknown.

Serious AEs that have not been resolved by the end of the study, or that have not been resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

the event resolves
the event stabilizes
the event returns to baseline, if a baseline value is available
the event can be attributed to factors unrelated to study conduct
when it becomes unlikely that any additional information can be obtained (subject or healthcare practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

11.3.5 Exposure In Utero

For investigational products within clinical studies, an exposure *in utero* (EIU) occurs if:

- A woman is exposed to the investigational product at any time between her last menses prior to conception through the delivery of the baby.

If any study subject becomes or is found to be pregnant during the study subject's participation, the PI must report the pregnancy to the Sponsor on a Pregnancy Notification Form (to be provided by the Sponsor when applicable). Initial notification via telephone to the Sponsor's study team contact must occur immediately upon the Investigator site's awareness of the pregnancy. The Pregnancy Notification Form must then be sent to the Sponsor within 24 hours of the site's awareness. The

information submitted should include the anticipated date of delivery (see below for information to document termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all EIU reports. The PI will follow the pregnancy until completion or until pregnancy termination (i.e., induced abortion) and then notify the Sponsor of the outcome. The PI will provide this information as a follow-up to the initial Drug Exposure During Pregnancy Collection Form A and/or End of Pregnancy Collection Form B (provided by the Sponsor when applicable). The reason(s) for an induced abortion should be specified. An EIU report is not created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, a SAE case is created with the event of ectopic pregnancy.

The PI should follow the procedures for reporting SAEs if the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth, or neonatal death]). In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth (i.e., no minimum follow-up period of a presumably normal infant is required before an End of Pregnancy Collection Form B can be completed). The "normality" of an aborted fetus can be assessed by gross visual inspection, unless pre-abortion test findings are suggestive of a congenital anomaly.

Additional pregnancy outcomes that are classified as SAEs and should be reported as such include:

"Spontaneous abortion" includes miscarriage and missed abortion;
All neonatal deaths that occur within 1 month of birth, without regard to causality;
Any infant death after 1 month that the PI assesses as possibly related to in utero exposure to the investigational product.

12 ETHICAL CONSIDERATIONS

The privacy information such as the ICD and health related questionnaire of the subjects will be kept confidential during the study and clearly separated from the TMF.

12.1 STUDY SUBMISSION TO INSTITUTIONAL REVIEW BOARD/ INDEPENDENT ETHICS COMMITTEE OR HEALTH AUTHORITIES

This study (protocol, ICD, recruiting material [advertisements, phone script, etc.], and all addenda) will be reviewed and approved by an Institutional Review Board/Independent Ethics Committee (IRB/IEC) contacted by the Study Site.

Details of the IRB/IEC for this study are in Appendix I.

It is the responsibility of the PI to have approval of the study protocol, protocol amendments, ICD(s), and other relevant documents, e.g., advertisements, if applicable from the IRB/IEC.

The study will not be activated, subjects will not be recruited, consented, or receive test materials until such time as the IRB/IEC as approved the required documentation. In addition, the IRB/IEC will review the study before any significant change in the protocol is initiated. After each review, the IRB/IEC's approval letter will be forwarded to the Sponsor.

All correspondence with IRB/IEC should be retained in the SMF. Copies of IRB/IEC approvals should be forwarded to the Sponsor and will be filed in the TMF.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the PI must notify the IRB/IEC and the Sponsor in writing within 3 working days after the implementation.

13 DATA HANDLING AND RECORD KEEPING

All subject source documents are the site's subject records and are to be maintained at the trial site. These source documents must be attributable, legible, contemporaneous, original, and accurate. All documentation should be completed using good documentation practices. Study data will be captured as shown in the table below.

	Stephens EDC Only	Excel Spreadsheet	Medidata Rave
Expert Grader Assessment, demography and Screening and Enrollment Log	X		
AE(s)			X
IP Accountability		X	

It is the Investigator's responsibility to ensure completion and to review and approve all information captured in Medidata. The subject's data in the Medidata must be electronically signed by the PI. These signatures serve to attest that the information contained in the Medidata is true. At all times, the PI has final personal responsibility for the accuracy and authenticity of all clinical data entered in the Medidata system. In Medidata, "Signature" should be understood to refer to electronic signature.

The study site shall maintain and archive records of all source documentation generated by the activity (including emails, questionnaires, and reports) and personnel training records relating to the Sponsor obligations under this project for 2 years from the time the final report is issued.

Before the study site destroys any of the above safety records, it will notify the Sponsor of its intention to do so, affording the Sponsor the opportunity to retain such records if it so wishes.

If it becomes necessary for the Sponsor or a Regulatory Authority to review any documentation relating to the study, the PI must permit access to such records.

If the PI relocates, retires, or for any reason withdraws from the study, the Sponsor must be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to Sponsor. The investigator must obtain Sponsor's written permission before disposing of any records, even if retention requirements have been met. The Sponsor must be notified in writing of the name and address of the new custodian prior to re-assignment/transfer.

14 STUDY MONITORING, QUALITY CONTROL AND QUALITY ASSURANCE

The study will be monitored (in accordance with the study or site specific monitoring plan) by the Sponsor. Frequent communications (via telephone or e-mail) will be utilized to provide Sponsor oversight and to assist in resolving any difficulties encountered while the study is in progress. An on-site visit may occur during the trial or shortly after study completion to ensure that the investigation is/was conducted according to the protocol and that ICH GCP is/was being followed. The monitor(s) may review

source documents to confirm that the data recorded is complete and accurate. The PI and institution will allow the Sponsor's monitor(s) or its designee and appropriate regulatory authorities direct access to source documents to perform this verification. If there are any issues noted, the PI will be notified.

Any contact concerning this study should be made with the Study Manager or the Study Director (see Appendix I).

The study site may be subject to review by the IRB/IEC, and/or to quality assurance audits performed by the Sponsor, and/or to inspection by appropriate regulatory authorities.

It is important that the PI and his/her relevant personnel are available during monitoring and possible audits or inspections and that sufficient time is devoted to the process.

15 SPONSOR DISCONTINUATION CRITERIA

Premature termination of this clinical trial may occur because of a change in opinion of the IRB/IEC, investigational product or study safety or at the discretion of the Sponsor. If a trial is prematurely terminated or discontinued, the Sponsor will promptly notify the PI. After notification, the PI or designated staff must contact all participating subjects within 10 business days (phone, voicemail, or certified letter), as applicable. As directed by Sponsor, all trial materials must be collected, all CRFs completed to the greatest extent possible, and termination reported to the IRB/IEC.

16 FINAL REPORT

The draft report will be submitted to the Sponsor for review and changes and may be made to the draft report at the Sponsor's request. Upon Sponsor's/study team's approval, the report will be finalized and forwarded to the Sponsor.

The final report will include (but is not limited to) the following information: study design and protocol, subject population demographics statistical methods used, results, description of adverse events (if any), discussions, and conclusions.

17 CONFIDENTIALITY

All the information, data and results of the study will be confidential. Every person having access to these data will be informed of this confidentiality.

Medical information concerning the subjects obtained by the investigator during the recruitment and admission will be handled confidentially.

18 PUBLICATION

The publication agreement, if any, between the Sponsor and the site is detailed in the clinical trial agreement.

19 BIBLIOGRAPHIC REFERENCES

1. Mills OH, Berger RS, Stephens TJ, Drake K, Fisher L. Assessing acnegenic and acne aggravating potential. American Academy of Dermatology, 46th Annual Meeting, 1987;108.

2. Mills OH, Kligman AM. A human model for assessing comedogenic substances. *Arch. Dermatol*. 1982;118(11):903-5.

3. Mills OH, Kligman AM. The follicular biopsy. *Dermatologica*. 1983;167(2):57-63.

20 PROTOCOL SIGNATURES PAGE

[redacted]
Study Manager

[redacted]

[redacted]
Study Director

[redacted]

[redacted]
Designated Physician Representative

[redacted]

[redacted]
Department Head

[redacted]

21 PRINCIPAL INVESTIGATOR RESPONSIBILITY STATEMENT

I have read and understood this study protocol, attached appendices, and any amendments and/or supplements thereto. I agree to conduct the study in compliance with the protocol agreed to by the Sponsor and in accordance with U.S. FDA regulations, applicable local regulations, and International Conference on Harmonisation Guidelines for Good Clinical Practice (ICH GCP) as outlined herein. Furthermore, Iagree to make no additions and/or changes without the consent of the Sponsor, except when necessary to protect the safety of the subjects.

Iwill provide copies of the final approved protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. Iwill discuss this material with them to ensure that they are fully informed regarding the protocol and conduct of this study.

Signature and Date:

[redacted]

Principal Investigator

[redacted]

Appendix I. Protocol Amendment

Date Written: MM/DD/2017

Protocol Section(s) Affected:8 **Protocol Appendix 1**

Summary: The product chart will be as follows:

Test Product	Formula #/Batch #	Dilution	Patch Type

.

Reason for Ammendment:
Sponsor Request

[redacted]

[redacted]

Appendix II. Contact Information

SPONSOR:

- Study Manager:
  [redacted]
- Study Director:
  [redacted]
- Department Head:
  [redacted]
- Study Monitor:
  [redacted]

STUDY SITE:

[redacted]

- Principal Investigator: [redacted]

IRB:

- Investigational Review Board (IRB):
  [redacted]