PROTOCOL # PS-1701 0314 5529-SACT

PROTOCOL TITLE:	A Multi-Center, Evaluator Blinded, Randomized Clinical Study to Evaluate the Efficacy and Tolerance of Two Acne Treatment Regimens on Subjects with Mild to Moderate Acne Vulgaris
PROTOCOL IDENTIFICATION:	PS-1701 0314 5529-SACT
DATE & VERSION:	06 March 2017, Final Version 1.0
SPONSOR:	JOHNSON & JOHNSON Consumer Inc. [redacted]
STUDY SITES:	Academic Dermatology Associates (Site 1001) [redacted] Albuquerque, NM 87106 USA [redacted] Thomas J. Stephens and Associates, Inc. (Site 1002) [redacted] Richardson, TX 75081 USA [redacted]
PRINCIPAL INVESTIGATORS (PIs):	Alicia Bucko, D.O. Academic Dermatology Associates Lily Jiang, Ph.D. Thomas J. Stephens and Associates, Inc.

[redacted]

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

VERSION TRACKING

VERSION	DATE	STATE	REASON FOR CHANGE	DESCRIPTION OF CHANGE
1.0	06 March 2017	Issued	New	N/A

SYNOPSIS

PROTOCOL IDENTIFICATION	PS-1701 0314 5529-SACT
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PRINCIPAL INVESTIGATORS (PIs)	Alicia Bucko, D.O. Academic Dermatology Associates Lily Jiang, Ph.D. Thomas J. Stephens and Associates, Inc.
STUDY SITES	Academic Dermatology Associates (Site 1001) [redacted] Albuquerque, NM 87106 USA Thomas J. Stephens and Associates, Inc. (Site 1002) [redacted] Richardson, TX 75081 USA
OBJECTIVE	To evaluate and compare the efficacy and tolerance of two different acne treatment regimens (a cleanser used with a currently marketed red and blue light acne light therapy mask alone vs. the cleanser used with the same mask in conjunction with a light therapy topical gel-cream) in subjects with mild to moderate acne over a 12-week period.
STUDY DESIGN	Multi-center, 2-cell, full-face, randomized, evaluator-blind
STUDY POPULATION	• Males (up to 50%) and females, 12 to 40 years old • Mild to moderate acne vulgaris on the face (10-100 non-inflammatory lesions, 10-50 inflammatory lesions; no cysts; up to 2 nodules; Investigator Global Acne [IGA] assessment score of 2-3.5 using the Modified Cook's Scale)
SAMPLE SIZE	A sufficient number of subjects will be screened to enroll up to 136 subjects to finish with at least 90 subjects (targeting 45 subjects per cell).
INVESTIGATIONAL PRODUCTS (IP)	**Regimen/Cell 1:** 1) AM & PM Cleanser, [redacted] 2) PM Mask Treatment, [redacted] 3) Replacement Mask Activators, [redacted] **Regimen/Cell 2:** 1) AM & PM Cleanser, [redacted] 2) PM Gel-Cream, [redacted] 3) PM Mask Treatment, [redacted] 4) Replacement Mask Activators, [redacted]

DOSE AND MODE OF APPLICATION	Subjects will be randomly assigned to use one of the two IP regimens for 12 weeks. Each subject will be instructed to wash his/her face twice daily (morning and evening) with the AM & PM Cleanser. In the evening after washing, subjects assigned to Regimen 1 will use the PM Mask Treatment for 10 minutes, while subjects assigned to Regimen 2 will apply the PM Gel-Cream full-face and let it dry prior to using the PM Mask Treatment for 10 minutes (mask treatment should begin within 15 minutes after PM Gel-Cream application).
STUDY DURATION	The study will consist of 6 visits over 12 weeks. Visit 1 (Week 0) will consist of Screening/Baseline and Post-1st Product Usage time points. The Post-1st Product Usage time point should occur within 20 minutes after the initial product usage. Subsequent visits will occur at Week 1 (Visit 2), Week 2 (Visit 3), Week 4 (Visit 4), Week 8 (Visit 5), and Week 12 (Visit 6). As necessary, Visit 2 may be adjusted ± 1 day and Visits 3-6 may be adjusted ± 3 days. All scheduling windows are versus Visit 1.
METHODOLOGY	• Clinical evaluations of efficacy: facial acne lesion counts (open comedones, closed comedones, total inflammatory lesions, nodules), IGA assessment, overall redness of inflammatory lesions, overall size of inflammatory lesions, [redacted] • [redacted]
SAFETY AND ADVERSE EVENTS	Any Adverse Event (AE) (including Serious Adverse Events [SAEs]) related or unrelated to the IP or study participation must be documented as required (occurrence date, location, outcome, and assessment of causality, severity, and relatedness). SAEs must be reported immediately and relevant supportive documentation must be sent within 24 hours of the site's awareness to the Study Manager or designee. See section 10.3.3. for reporting timelines.

SUCCESS CRITERIA	[redacted]
STATISTICAL METHODS	The primary efficacy variable is the percent change from baseline in Week 12 global face total lesion count, defined as the sum of inflammatory lesions (papules and pustules), open comedones, and closed comedones. For the primary efficacy variable, treatment means and between-treatment differences will be assessed by means of a one-way Analysis of Covariance (ANCOVA) model with treatment, gender, and center as factors and the corresponding baseline score as a covariate. Monadic efficacy for a treatment will be concluded if the respective mean percent change from baseline is significantly different from zero. Non-inferiority will be concluded if monadic efficacy is demonstrated in both treatments and the upper bound of the two-side 95% confidence interval of treatment difference (mask with topical gel-cream minus the mask alone) is less than 15 percentage points. If non-inferiority is demonstrated, the testing will proceed to superiority test. Superiority of the mask with topical gel-cream treatment will be concluded if the upper bound of the two-sided 95% confidence interval of the treatment difference is less than 0. Each comparison will be tested at the 0.05 significance level, two-sided. With the stepwise procedure, the familywise error rate is controlled at the 0.05 level.

LIST OF ABBREVIATIONS

Abbreviation	Definition
[redacted]	[redacted]
AE	Adverse Event
AHA	Alpha Hydroxy Acid
AIDS	Acquired Immunodeficiency Syndrome
ANCOVA	Analysis of Covariance
CRF	Case Report Form
DPR	Designated Physician Representative
EDC	Electronic Data Capture
EIU	Exposure in Utero
FDA	US Food and Drug Administration
[redacted]	[redacted]
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICD	Informed Consent Document
ICH GCP	International Conference on Harmonisation Good Clinical Practice
ID	Identification
IEC	Independent Ethics Committee
IGA	Investigator Global Acne
IP	Investigational Product(s) (i.e. test products)
IRB	Institutional Review Board
ITT	Intent-to-Treat
LED	Light-Emitting Diode
[redacted]	[redacted]
LOCF	Last Observation Carried Forward
OCMS	Office of Consumer Medical Safety
OTC	Over-the-Counter
PI	Principal Investigator
[redacted]	[redacted]
[redacted]	[redacted]
PPOL	Parallel Polarized (imaging modality)
PQC	Product Quality Complaint
[redacted]	[redacted]
SAE	Serious Adverse Event
SMF	Site Master File
SPF	Sun Protection Factor
TEAE	Treatment Emergent Adverse Event
TMF	Trial Master File
[redacted]	[redacted]
UV	Ultraviolet
[redacted]	[redacted]
[redacted]	[redacted]

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1. BACKGROUND

Acne vulgaris is a common chronic skin disease involving blockage and/or inflammation of the pilosebaceous units (hair follicles and their accompanying sebaceous gland). It is a multifactorial disease which results from an interplay of the following four main factors: (1) follicular epidermal hyperproliferation with subsequent plugging of the follicle, (2) excess sebum production, (3) increased proliferation and activity of the commensal bacteria such as *Propionibacterium acnes (P. acnes)*, and (4) inflammation.

Research has shown the benefits of red and blue light therapy in the treatment of mild to moderate acne, with red and blue light shown to target the acne-causing bacteria and have an effect on inflammation reduction.[1,2]

Light-based therapies have been used successfully to treat dermatological conditions since the early 1900s, with various parts of the electromagnetic spectrum (i.e. ultraviolet [UV], visible, near-infrared, etc.) demonstrating different benefits.[3] Light-emitting diodes (LEDs) offer delivery of light to the skin in a gentler manner as compared to light delivered by lasers, primarily due to the lower energy output. It has been reported that LEDs do not deliver enough power to damage tissues and do not have the same risk of accidental eye damage that lasers do. Visible-LED light therapy has been deemed a non-significant risk by the U.S. Food and Drug Administration (FDA) and has been approved for use in humans.[4]

It is well established in the literature[5-10] that visible light penetration into the epidermal and dermal layers of human skin is primarily governed by absorption and scattering events, with the latter being the more impactful of the two.[8] Specifically, it is recognized that scattering in the Mie regime, where the size of the particles is equal to or greater than the wavelength of the incoming radiation, is the major obstacle to penetration. Mie scattering is primarily anisotropic, making both forward and backward scattering possible.[6] This is particularly relevant considering the structural heterogeneity of the epidermal and dermal layers. Both *in vivo* and *in vitro* measurements have shown that scattering in the epidermal layer is due to melanin grains, which normally range from 30 – 400 nm in size, while scattering in the dermis is caused by collagen and its fibrillary suprastructure.[6,11] Also relevant to note is the wavelength dependence of Mie scattering, with longer wavelengths being more penetrative.[7] It follows from the above that visible light penetration into human skin can be increased by reducing Mie scattering. This can be accomplished by temporary hydrogen bonding disruption, which leads to the reversible rearrangement of epidermal and dermal structures that cause scattering. Glycerol (i.e. glycerin), a known optical clearing agent, is hypothesized to generate the level of hydrogen bonding disruption described above, and therefore will be investigated in the present study.[11]

This study will look to evaluate and then compare the acne clearing efficacy and tolerance of two different acne treatment regimens – a cleanser used with a currently marketed red and blue light acne light therapy mask alone vs. the cleanser used with the same mask in conjunction with a light therapy topical gel-cream – to determine the efficacy of these treatments and then to assess if the efficacy of the light therapy mask used with the topical gel-cream treatment is non-inferior to the mask alone in the reduction of lesions in mild to moderate acne. If non-inferiority is demonstrated, the mask with topical gel-cream treatment will be further assessed for its superiority to the mask alone.

2. OBJECTIVE

The objective of this study is to evaluate and compare the efficacy and tolerance of two different acne treatment regimens (a cleanser used with a currently marketed red and blue light acne light therapy mask alone vs. the cleanser used with the same mask in conjunction with a light therapy topical gel-cream) in subjects with mild to moderate acne over a 12-week period.

3. OVERALL STUDY DESIGN AND PLAN DESCRIPTION

This is a multi-center, 2-cell, full-face, randomized, evaluator-blind clinical usage study. Up to 136 subjects will be enrolled to finish with at least 90 subjects (targeting 45 subjects per cell). The target population is 12- to 40-year-old males and females of any skin type who have mild to moderate acne vulgaris on the face. Up to 50% of the enrolled subjects may be male.

Subjects will be randomly assigned to use one of the two acne treatment regimens at home for 12 weeks. Each subject will be instructed to wash his/her face twice daily (morning and evening) with the AM & PM Cleanser. In the evening after washing, subjects assigned to Regimen 1 will use the PM Mask Treatment for 10 minutes, while subjects assigned to Regimen 2 will apply the PM Gel-Cream full-face and let it dry prior to using the PM Mask Treatment for 10 minutes (mask treatment should begin within 15 minutes after PM Gel-Cream application).

Subjects will be assessed at Baseline (Week 0), within 20 minutes after the first product usage, Week 1, Week 2, Week 4, Week 8, and Week 12, according to the Schedule of Events in Table 1 below.

Table 1. Schedule of Events

Time Points/Procedures	Visit 1		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Screening/ Baseline (Week 0)	Post-1st Product Usage[a]	Week 1 (± 1 day)	Week 2 (± 3 days)	Week 4 (± 3 days)	Week 8 (± 3 days)	Week 12 (± 3 days)
Informed consent (and assent, as applicable) with HIPAA disclosure & photograph release	X						
Collect demographics (including Fitzpatrick Skin Type & skin sensitivity), general medical history, & concomitant medications	X						
Interview for compliance			X	X	X	X	X
15-minute acclimation	X		X	X	X	X	X
Acne lesion counts	X[b]			X	X	X	X
Investigator Global Acne (IGA) assessment	X[b]		X	X	X	X	X
Review of eligibility	X						
Subject qualification by medically qualified staff	X						
Enrollment & randomization	X						
Additional investigator efficacy assessments	X		X	X	X	X	X
[redacted]							
[redacted]							
[redacted]							
[redacted]							
(Pre-weighed, as applicable) IP dispensed with subject instructions and daily diary[c]	X *Starter Kit*				X *Replacement kit*	X *Replacement kit*	
Supervised first use of IP per evening instructions	X						
Daily diary reviewed			X	X	X	X	X
IP weighed/checked for use compliance (as applicable)			X	X	X	X	X
IP and daily diary collected					X *Used Activator*	X *Used Activator*	X
Collect/record adverse events (AEs) and changes in health/medications	X *AEs only*	X *AEs only*	X	X	X	X	X
Subject disposition							X[d]

[a]Post-1st Product Usage time point should occur within 20 minutes after the initial product usage.
[b]Part of eligibility review.
[c]Additional IP and diary units may be dispensed as needed/previous units collected.
[d]Subject disposition will be recorded at final study visit or at the time of subject discontinuation from the study. If a subject discontinues prior to this visit, every effort will be made to complete these procedures (if the subject agrees).

4. STUDY DURATION

The study will consist of 6 visits over 12 weeks. Visit 1 (Week 0) will consist of Screening/Baseline and Post-1st Product Usage time points. The Post-1st Product Usage time point should occur within 20 minutes after the initial product usage. Subsequent visits will occur at Week 1 (Visit 2), Week 2 (Visit 3), Week 4 (Visit 4), Week 8 (Visit 5), and Week 12 (Visit 6).

As necessary, Visit 2 may be adjusted ± 1 day and Visits 3-6 may be adjusted ± 3 days. All scheduling windows are versus Visit 1.

If a subject misses a scheduled visit but notifies the study site, he/she will be allowed to re-schedule the missed visit if it is within the scheduling window as specified above. If it is outside the scheduling window, the Study Manager should be notified to determine if the visit should be rescheduled outside the scheduling window. Study staff will need to assess subject compliance with IP usage to ensure the missed/altered visit did not result in lack of compliance. A lack of compliance will be documented as a deviation and the Sponsor should be notified.

5. SUBJECT SELECTION AND ENROLLMENT

The study can fulfill its objective only if the required number of appropriate subjects are enrolled. The 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 PI or, if the PI does not have a medical background, a medically qualified designee (M.D./D.O.) at Visit 1 in order to determine subject eligibility.

Prior to any review of personal data, the Informed Consent Document (and Assent, as applicable) should be signed.

5.1. INFORMED CONSENT

The Informed Consent Document (ICD) will be read by the subject and explained to the subject by the PI or designee. For subjects below the age of consent (i.e. 12-17 years old), the subject's legally acceptable representative will review the ICD and the subject will be given an IRB-approved Assent Form in place of the ICD. The PI or designee must ensure that each study subject (and his/her legally acceptable representative, as applicable) is fully informed about the nature and objectives of the study and possible risks associated with participation (to the extent compatible with their understanding). After understanding and agreeing, the subject (and his/her legally acceptable representative, as applicable) will express his/her consent (or assent, as applicable) to the subject's participation in the study by signing the ICD (or Assent Form, as applicable).

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

One copy of the signed ICD (and Assent Form, as applicable) must be given to the subject (and his/her legally acceptable representative, as applicable); the subject (and his/her legally acceptable representative, as applicable) will remain free to withdraw this consent (or assent, as applicable) at any time without any negative consequence to the subject.

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

5.2. STUDY POPULATION

5.2.1. Inclusion Criteria

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

a) Subject (and/or his/her legally acceptable representative, as applicable) has read, understood, signed, dated, and received a copy of the Photograph Release and Informed Consent Document (including HIPAA disclosure) after the nature of the study has been fully explained. The legally acceptable representative's consent and the subject's assent must be secured for subjects under the age of 18 years (i.e. 12 – 17 years of age).

b) Male or female (up to 50% of subjects may be male).

c) 12 to 40 years old.

d) Has 10-100 total non-inflammatory lesions (open comedones plus closed comedones), 10-50 total inflammatory lesions, no cysts, and up to 2 nodules (if deemed appropriate by the PI or designee) on the face (see section 7.1.2.4.1).

e) Has mild to moderate acne vulgaris on the face, as defined by an IGA assessment score of 2, 2.5, 3, or 3.5 using the Modified Cook's Scale (see section 7.1.2.4.2).

f) Able to read, write, speak, and understand English.

g) In generally good health as determined by the PI or designee, based on medical history reported by the subject.

h) Males and females of reproductive potential must agree to practice a medically acceptable form of birth control during the study and for 30 days after study completion. Females must have used such birth control for at least 3 months prior to Visit 1. 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 spermicide: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.
   - Intrauterine device or intrauterine system.
   - 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.

A female is not considered of reproductive potential if she is post-menopausal (i.e. amenorrheic [not menstruating] for at least 12 months prior to study start).

i) Intends to complete the study and is willing and able to fulfill the subject responsibilities (see section 5.3).

5.2.2. Exclusion Criteria

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

a) Has very sensitive skin or known allergies or sensitivities to skincare products, toiletries or their components, or ingredients contained in the IPs (Appendix XIV).

b) Has a known light or photosensitivity disorder, or is currently using medication that may cause sensitivity of the skin to light, as determined by the PI or designee based on subject report.

c) Has severe acne or acne conglobata.

d) Has a pre-existing or dormant facial dermatologic condition (e.g., psoriasis, rosacea, rashes, many and/or severe excoriations, etc.) that could interfere with the evaluations, confound study results, or increase health risk to the subject, as determined by the PI or designee.

e) Has a history of immunosuppression/immune deficiency disorders (including HIV infection or AIDS) or is currently using immunosuppressive medications (e.g., azathioprine, belimumab, cyclophosphamide, Enbrel®, Imuran®, Humira®, mycophenolate mofetil, methotrexate, prednisone, Remicade®, Stelara®, etc.) and/or radiation (based on subject report).

f) Is currently using, planning to use during the study (other than the IPs), or has used any of the following in the specified time range (based on subject report):

Any of the following on the face: • Light therapy • OTC topical medications/products (including anti-acne or antibacterial agents, topical anti-inflammatories, topical retinoids, etc.). Sunscreens (SPF) are acceptable.	2 weeks prior to Visit 1
Natural or prescription testosterone blocker (e.g. saw palmetto, black cohosh, chaste tree, chasteberry, spironolactone, drospirenone, progestins). Oral contraceptives are acceptable.	Currently at Visit 1
Prescription (oral or topically applied on the face) antibiotics, inhaled steroids (except	1 month prior to Visit 1

those prescribed for allergies), or hormones (pre- or post-menopausal hormone-replacement therapy; insulin, etc.), or other medications that could make skin more sensitive or have an effect on the skin, as determined by the PI or designee. Oral contraceptives are acceptable.	
Prescription medication for acne (e.g. doxycycline, minocycline, clindamycin, sulfamethoxazole and trimethoprim [Bactrim], tetracycline, erythromycin, azithromycin, or Vibramycin®)	1 month prior to Visit 1
Topical prescription retinoids (e.g. Retin-A®, Retin-A Micro®, Renova®, Adapalene, Tazarotene, Avita®, Tazorac®, Avage®, Differin®), azelaic acid, benzoyl peroxide, dapsone, sodium sulfacetamide, Epiduo®, or other similar prescription drug on the face	1 month prior to Visit 1
Accutane or other oral retinoid	6 months prior to Visit 1

g) Female who (to the best of her knowledge) is pregnant, lactating, or planning to become pregnant during the study or within 30 days of study completion. (*Subject must document her response in ICD/Assent Form).*

h) Male whose female partner is (to the best of his/her knowledge) pregnant or planning to become pregnant during the study or within 30 days of study completion. (*Subject must document his response in ICD/Assent Form).*

i) Has a surgery and/or invasive medical procedure planned during the study.

j) Has observable suntan, scars, nevi, tattoo, excessive hair (including beard, mustache, or goatee), or other dermal conditions on the face that that could interfere with study evaluations or confound study results, as determined by the PI or designee.

k) Concurrently participating in any other clinical study or has participated in another clinical study within 4 weeks prior to study start (Visit 1).

l) Has a medical history of a disease/condition, a concurrent illness, or any other condition/situation that could interfere with study evaluations, confound study results, or increase health risk to the subject, as determined by the PI or designee.

m) Is related to those persons involved directly or indirectly with the conduct of this study (i.e., Sponsor, PI, Sub-I, study coordinators, other site personnel, and the immediate families of each).

5.3. SUBJECT RESPONSIBILITIES

The subject responsibilities are as follows:

- Use the provided AM & PM Cleanser twice daily (morning and evening) to wash your full face for the duration of the study.
- *Regimen 1 subjects only*: Every evening for the duration of the study: after washing and drying your face, use the PM Mask Treatment for 10 minutes.
- *Regimen 2 subjects only*: Every evening for the duration of the study: after washing and drying your face, apply the provided PM Gel-Cream full-face and let it dry prior to using the PM Mask Treatment for 10 minutes (mask treatment should begin within 15 minutes after PM Gel-Cream application).
- Use only the assigned products and your regular, non-medicated (other than SPF, which is acceptable) facial products that you have used for at least one month and that have been recorded/approved by the study staff at Visit 1 (see section 5.4).
- Do not use any other light-based devices or receive any professional or aesthetic facial spa procedures during the study.
- Do not shave or use any hair removal method on your face within the 24 hours prior to a study visit.
- Do not start using any new personal care products (e.g. makeup, lotions, etc.) or change your currently used brands during the study.
- On the day of study visits: remove all leave-on facial products (including eye makeup) and wash with the provided facial cleanser 30 minutes to 2 hours prior to the visit and then do not apply any leave-on facial products until the visit is completed. Note: if you do not follow these directions, you will be asked to remove your makeup/products and wash your face with the provided cleanser on-site and then wait 30 minutes before evaluations are performed.
- Avoid excessive sun/UV exposure (including tanning beds) for the duration of the study.
- Attend all scheduled visits.
- Do not begin any other clinical study during the current study.
- Report any side effects, changes in health/medication, pregnancies, issues, or questions to the study staff.
- Bring your study products to all visits. Products must be returned at the final study visit. Failure to return your products may result in forfeiture of compensation.

See section 6 regarding detailed product usage instructions.

5.4. CONCURRENT PRODUCTS

During the study, subjects may not use any products on their face other than the assigned IPs and the subject's regular facial products that have been recorded and approved by study staff at Visit 1.

To be approved, the subject's regular facial products (moisturizers, eye makeup removers, color cosmetics, etc.):

- must be recorded by the study staff at Visit 1.
- must have been used for at least one month prior to study start.
- must be non-medicated [other than SPF] and not contain benzoyl peroxide, salicylic acid, alpha hydroxy acids (AHAs), vitamins A (retinol) or C (ascorbic acid) or their analogs or derivatives. The presence of SPF in products is acceptable.
- cannot include cleansers, scrubs, cleansing products, masks, makeup removers/wipes (except to remove eye makeup only), or light-based devices.
- must be maintained over the course of the study. Intermittent recreational sunscreen usage (minimum SPF 30 recommended for face) is allowed if sun exposure is unavoidable.

A subject should not shave or use any hair removal method on his/her face within the 24 hours prior to a study visit. Subjects should not receive any professional or aesthetic facial spa procedures during the study.

For the rest of the body, subjects should not start using any new personal care products (e.g. cleanser, treatments) or change their currently used brands during the study.

5.5. CONCURRENT MEDICATION

If a subject is taking any medication during the course of the study or within 1 month prior to the study, it must be recorded on the Concomitant Medication Form. Minimum information required is the name of the medication.

If this medication is linked to the treatment of a study/IP-related AE, the dose and duration of the treatment should be specified.

Medications/therapies excluded are indicated in the Subject Exclusion criteria; the use of any excluded medications/therapies during the study will result in discontinuation of the subject.

5.6. SCREENING FAILURE

All individuals who signed the ICD/Assent Form and withdraw their participation or fail to meet all of the screening criteria during the initial evaluation will be considered a "screening failure." Data for screen failures will not be considered in the final report.

An individual who is screen-failed but may qualify at a later time may be re-screened at the PI's discretion, but the individual should be treated as a new candidate (i.e. new subject ID, new ICD, etc.). Any individual who screen fails and has an AE will not be re-screened.

6. INVESTIGATIONAL PRODUCTS (IPs)

6.1. IDENTITY OF IPs

The following IPs will be supplied by the Sponsor:

Product Identity (As Labeled)	[redacted]	Regulatory Classification & Marketing Status	Included in Regimen 1?	Included in Regimen 2?
AM & PM Cleanser[a]	[redacted]	Cosmetic – Marketed	✓	✓
PM Gel-Cream	[redacted]	Device – Non-Marketed	---	✓
PM Mask Treatment[b]	[redacted]	Device – Marketed	✓	✓
Replacement Mask Activator	[redacted]	Device – Marketed	✓	✓

[a]A few additional units of the cleanser will be provided for on-site usage prior to acclimation, as needed.
[b][redacted] A Replacement Mask Activator will be supplied to subjects at Baseline (Visit 1), Week 4 (Visit 4), and Week 8 (Visit 5).

The non-marketed IP will be manufactured by the Sponsor or its agents under GMP conditions; the marketed IPs will be commercially sourced. A Letter of Non-Significant Risk will be provided to the PIs for use of the non-marketed device in this study, and the commercial package inserts will be provided to the PIs as reference safety information for the marketed devices. The ingredient list for each of the formulated products is provided in Appendix XIV.

6.2. PACKAGING AND LABELING

The marketed cosmetic product will be used in its original commercial packaging over-labeled under GMP conditions. The marketed devices will be transferred to blinded packaging and the commercial package inserts (containing claims and consumer call center information) will be removed; brand markings on the devices themselves will be over-labeled under GMP conditions.

The study label affixed to each IP unit or packaging may contain (but is not limited to) fields for the following information:

- Protocol Number
- Product Identity (see table in section 6.1)
- Randomization Number (as applicable)
- Directions
- Warnings
- Study Site Identification
- Net Contents or Net Weight
- Site Emergency Contact Information
- Storage Information
- Unit # or Kit # (as applicable)

[redacted]

[redacted]

[redacted]

Units of the AM & PM Cleanser will also be available for on-site usage prior to acclimation, as needed. Additional PM Mask Treatment units will also be available should a subject need a replacement.

6.3. STORAGE AND ACCOUNTABILITY

The PI or designee must ensure that deliveries of IPs from the Sponsor are correctly received by a responsible person and that the products are stored in a secure area under recommended storage conditions. The products for this study will be secured in a locked room or cabinet that is only accessible to site personnel and kept at 20-25°C (68-77°F) with relative humidity up to 60%. Temperature and relative humidity should be recorded at least daily on business days (an alarm should be utilized to signal if conditions go out of range). The PI or designee must maintain adequate records documenting the receipt, use, loss, or other disposition of the products on the Product Accountability Log or equivalent.

At the end of the study, all IP units (used and/or unused) must be returned to the Sponsor [redacted]

6.4. 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. This does not include effectiveness, preference, or performance measures, which will be reviewed in aggregate at appropriate intervals. 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 listed in Appendix XV.

In addition, PQC information must be included on the Product Accountability Log 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.

When enrolling subjects into this study, it is the site's responsibility to instruct subjects not to use the product if they have a concern related to the product, labeling, or package integrity and to immediately report it to the study site.

6.5. RANDOMIZATION

Subjects who sign the ICD (or Assent Form, as applicable) will be sequentially assigned a Subject ID. The Subject ID will begin with the four-digit center ID (Academic Dermatology Associates: "1001"; Thomas J. Stephens and Associates, Inc.: "1002") followed by a unique four-digit subject identifier assigned in ascending order and beginning with "1001," resulting in an eight-digit Subject ID (e.g. "10011001," "10011002," etc.). Once a Subject ID has been assigned to a subject, it cannot be reassigned to another subject.

Upon enrollment in the study, each subject will be assigned a unique randomization number, which will determine the treatment assignment for each subject according to a randomization schedule. The randomization scheme will be devised by the Sponsor's Quantitative Sciences Department. For subjects with a score of 2.0 or 2.5 on the IGA assessment, the site will assign randomization numbers in ascending sequential order within the site, i.e. starting with the lowest available number. For subjects with a score of 3.0 or 3.5 on the IGA assessment, the site will assign randomization numbers in descending sequential order, i.e. starting with the highest available number. Once a randomization number has been assigned to a subject, it cannot be reassigned to another subject.

6.6. BLINDING

The randomization numbers will be incorporated into the product labeling and the regimen-specific products will be packaged in opaque kits, as described in section 6.2.

This study will be evaluator-blinded, so the PI/evaluators will not know which treatment cell each subject is in. Personnel dispensing the IPs, supervising IP use, and/or administering/databasing Part B of the Subject Questionnaire will not participate in the evaluation of subjects in order to minimize potential bias. IPs will be kept separate from the site personnel involved in assessing or evaluating the subjects, and subjects will be instructed not to discuss their assigned IPs with the evaluators.

The randomization schedule will be used by the Sponsor to generate randomization number-specific single disclosure envelopes. In the event that the PI or medically qualified designee believes an un-blinding is necessary and circumstances allow, the PI or designee will contact the Study Manager who will consult with the Designated Physician Representative (DPR) to determine whether a code break is needed. If there is a medical emergency and the PI or medically qualified designee deems it necessary to urgently know which IP the subject is using for the subject's proper medical care, then the PI or designee may break the treatment code immediately by opening the provided randomization number-specific disclosure envelope for that subject. 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. Upon completion of the study, all disclosure envelopes will be returned to the Sponsor.

Blinding should only be broken for serious, unexpected, and related adverse events, and only for the subject in question, or when required by local regulatory authorities.

6.7. APPLICATION/USE OF THE IPs & SUBJECT COMPLIANCE

Subjects will be randomly assigned to use one of the two treatment regimens for 12 weeks (see sections 6.1 and 6.5). As described in section 6.2, they will receive a starter kit of the assigned regimen at Visit 1, and a replacement kit will be dispensed at Visit 4 and Visit 5.

The regimen-specific instructions (Appendix VI or VII) and subject-directed device package inserts (Appendix VIII, IX, and/or X) will be included in the corresponding subject kits.

Regimen/Cell 1: Each subject will be instructed to wash his/her face twice daily (morning and evening) with the AM & PM Cleanser. In the evening after washing, subjects will use the PM Mask Treatment for 10 minutes. See the detailed subject instructions in Appendix VI.

Regimen/Cell 2: Each subject will be instructed to wash his/her face twice daily (morning and evening) with the AM & PM Cleanser. In the evening after washing, subjects will apply the PM Gel-Cream full-face and let it dry prior to using the PM Mask Treatment for 10 minutes (mask treatment should begin within 15 minutes after PM Gel-Cream application). See the detailed subject instructions in Appendix VII.

IP weights/review, daily diary, and subject interview will be used to assess subject compliance. All units of the PM Gel-Cream should be weighed (with weight recorded) prior to dispensing and at each subsequent visit through collection. The AM & PM Cleanser will not be weighed but should be visually assessed for usage compliance. Each Activator supplied to the subjects (as part of the starter or replacement kits) should be reviewed by study staff for usage compliance [redacted]

The diary and Activator must indicate at least 90% compliance (i.e. 3 usage misses in 30 days is allowed); anything less than that will be documented as a compliance deviation and the subject will be re-instructed on proper product usage or be dropped from the study at the PI's or designee's discretion after consultation with the Sponsor.

Subjects are expected to use at least 5 grams of the PM Gel-Cream per week; anything less than that will be documented as a compliance deviation. Subjects should be re-instructed on proper product usage or dropped from the study at the PI's or designee's discretion after consultation with the Sponsor.

7. INVESTIGATIONAL PLAN

7.1. STUDY PROCEDURES AND EVALUATION SCHEDULE

7.1.1. Pre-Study

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

7.1.2. Visit 1

Selected candidates will report to the test facility. On the day of the study visit, candidate subjects should remove all leave-on facial products and arrive at the visit with a clean face. Note: if a candidate subject arrives with facial products on, he/she may remove the facial products and wash his/her face with a non-medicated cleanser on-site and then wait 30 minutes before screening evaluations are performed. This will not be recorded as a deviation. They will take part in the following procedures:

7.1.2.1. Informed Consent

Informed consent (and assent, as applicable) will be obtained as described in section 5.1. The ICD will include a Health Insurance Portability and Accountability Act (HIPAA) disclosure. Subjects (and their legally acceptable representatives, as applicable) will also review and sign a Photograph Release. Subjects who sign the ICD (or Assent Form, as applicable) will be sequentially assigned a Subject ID (see section 6.5).

7.1.2.2. Acclimation

Subjects will acclimate to conditions in the facility for at least 15 minutes before clinical evaluations of eligibility are conducted.

7.1.2.3. Medical History, Concomitant Medications, and Review of Eligibility

The demographics (including Fitzpatrick Skin Type [Appendix I] and skin sensitivity [Appendix II]), medical history, and concomitant medications of each candidate subject will be collected and reviewed (this interview may occur during the acclimation period).

All of the eligibility requirements of the study will also be reviewed to assess each candidate subject's eligibility. As part of this review, the Expert Grader will conduct a visual examination of the subject's face and conduct the applicable clinical evaluations (see sections 7.1.2.4.1 and 7.1.2.4.2) after the acclimation period is completed in order to determine if the individual meets the eligibility requirements. In addition, the PI or designee will record each subject's regular facial products and review them for continued use during the study (see section 5.4).

The PI or, if the PI does not have a medical background, a medically qualified designee (M.D./D.O.) will review the above information (medical history, concomitant medications, and eligibility review) to confirm the eligibility of each subject prior to their enrollment in the study.

Upon enrollment, each subject will be assigned a randomization number (see section 6.5).

7.1.2.4. Clinical Evaluations of Efficacy [redacted]

7.1.2.4.1. Acne Lesion Counts

Each subject will have their open comedones, closed comedones, total inflammatory lesions (papules and pustules counted together in a combined "total inflammatory lesions" count), and nodules (defined

as greater than or equal to 5mm in size) counted by the Expert Grader and individually recorded for the total face. The total face consists of the forehead, left and right checks, and the chin (including the area above the upper lip).

Note: For enrollment (see Inclusion Criterion d), an individual must have 10-100 total non-inflammatory lesions (open comedones plus closed comedones), 10-50 total inflammatory lesions, no cysts, and up to 2 nodules (if deemed appropriate by the PI or designee) on the face.

7.1.2.4.2. Investigator Global Acne (IGA) Assessment

The Expert Grader will assign each subject an IGA assessment score using the grading scale in Appendix III. Intermediate (i.e. half-point) grades will be used to permit for finer distinctions in the skin condition.

Note: For enrollment (see Inclusion Criterion e), an individual must have an IGA assessment score of 2, 2.5, 3, or 3.5.

7.1.2.4.3. Additional Investigator Efficacy Assessments

The Expert Grader will assess each subject's facial skin for the additional efficacy parameters shown below using the grading scales in Appendix IV. Intermediate (i.e. half-point) grades will be used to permit for finer distinctions in the skin condition.

- Overall Redness of Inflammatory Lesions
- Overall Size of Inflammatory Lesions

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.1.2.7. IP Dispensing and First Use

Each subject will receive a starter kit of the randomly assigned IP regimen (see section 6), along with a daily diary for the subject to record his/her product usage. The site designee will review the IP usage instructions with the subjects prior to their first use of the regimen on-site. The first use will follow the evening instructions regardless of the time of the visit (this will not be considered a deviation). Subjects attending a visit in the morning should wash their face again in the evening but not use the PM Mask Treatment or PM Gel-Cream again that first evening.

[redacted]

[redacted]

7.1.2.9. Adverse Event Collection

Individuals that have signed the ICD/Assent Form will be questioned and assessed for AEs before leaving the facility.

7.1.3. Visit 2 (Week 1), Visit 3 (Week 2), Visit 4 (Week 4), Visit 5 (Week 8), & Visit 6 (Week 12)

On the day of each study visit, subjects should remove all leave-on facial products (including eye makeup) and wash with the provided facial cleanser 30 minutes to 2 hours prior to the visit and then not apply any leave-on facial products until the visit is completed. Note: if a subject does not follow these directions, he/she will be asked to remove his/her facial products and wash his/her face with the provided cleanser on-site and then wait 30 minutes before evaluations are performed (Note: this will not be considered a deviation).

At each visit:

- Subjects will be interviewed for compliance with study instructions. This may occur during the acclimation period.
- Subjects will acclimate to conditions in the test facility for at least 15 minutes before the evaluations are conducted.
- *Visit 2*: The IGA assessment, additional investigator efficacy assessments, [redacted] will be repeated as described in sections 7.1.2.4.2 to 7.1.2.4.4.
- *Visit 3, Visit 4, Visit 5, and Visit 6*: All of the clinical evaluations of efficacy [redacted] will be repeated as described in section 7.1.2.4.
- [redacted]
- A trained site designee will review each subject's daily diary and weigh/review the IPs (as applicable) to assess subject compliance (see section 6.7).
- *Visit 4 and Visit 5*: A replacement kit of IPs will be dispensed. The used Activators will be collected and retained by study staff.
- *Visit 6 only*: the daily diary and IP will be collected and retained by study staff.
- Subjects will be questioned and assessed for AEs and any changes in their health or concomitant medications.

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted] skin within the given ROI normalized by the total number of pixels within the redness mask.

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

7.3. SUBJECT COMPLETION/WITHDRAWAL

7.3.1. 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 on the Screening and Enrollment Log (or equivalent) as well as in the Electronic Data Capture (EDC) system on the Subject Disposition page.

7.3.2. Subject Withdrawal

When an individual who has signed the ICD (or Assent, as applicable) is not enrolled in the study or withdraws/is withdrawn prior to completing the study, the reason is to be documented on the Screening and Enrollment Log (or equivalent) and (only for randomized subjects plus screen failed subjects with a reported AE) in the EDC system on the Subject Disposition page. The subject disposition should also be summarized 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
- Withdrawal by subject
- Non-compliance with study treatment (including non-compliance with product use/study directions)

- Lack of efficacy
- Protocol deviation/violation (other than non-compliance)
- Death (must be reported in accordance with the reporting requirements defined in the SAE section)
- Other AE/SAE (must be reported in accordance with the reporting requirements defined in the AE/SAE section)
- Pregnancy (must be reported in accordance with the reporting requirements defined in the Exposure in Utero section)
- Study terminated by Sponsor
- Lost to follow-up
- Other

Subjects may withdraw from the study 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, at least 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 study 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.

In case of early subject withdrawal, subjects may be replaced based upon overall enrollment numbers and with the approval of the Sponsor.

8. STATISTICAL ANALYSIS METHODS

The Sponsor's Quantitative Sciences Department will be responsible for the data management and statistical analyses of this trial, [redacted]

Demographic and baseline characteristics will be summarized by treatment. For continuous variables, descriptive summary will include number of subjects, mean, standard deviation, median, minimum and maximum values. For categorical variables, descriptive summary will include the number and percentage of subjects in each response category.

8.1. Statistical Analysis Population

Tolerance and efficacy data will be evaluated for all intent-to-treat (ITT) subjects who used the IP and had baseline and at least one post-baseline data point. Adverse events will be summarized for all subjects who signed the ICD (or Assent Form, as applicable), differentiating Treatment Emergent Adverse Events (see section 10.3.2.1).

8.2. Efficacy Analysis

For each efficacy variable, summary statistics will be provided by treatment group at each time point. For continuous variables, descriptive summaries will include number of subjects, mean, standard deviation, median, minimum and maximum values. Distributions of categorical variables will be summarized by presenting the number and percent of subjects in each response category.

8.2.1. Analysis of Primary Variable

The primary efficacy variable is the percent change from baseline in global face total lesion count at Week 12. The total lesion count is the sum of inflammatory lesions (papules and pustules), open comedones, and closed comedones.

The following comparisons will be performed:

1. Mask alone treatment Week 12 vs. baseline
2. Mask with topical gel-cream treatment Week 12 vs. baseline
3. Mask with topical gel-cream treatment vs. mask alone treatment for non-inferiority
4. Mask with topical gel-cream treatment vs. mask alone treatment for superiority

To evaluate the efficacy of the mask alone treatment and the mask with topical gel-cream treatment, statistical comparisons for the primary variable will be based on a stepwise procedure starting with comparisons #1 and #2, which evaluate the monadic efficacy of mask alone treatment and the mask with topical gel-cream treatment, respectively. If both comparisons are significant, testing will proceed to comparison #3 to evaluate the non-inferiority of the mask with topical gel-cream treatment to the mask alone treatment; otherwise, comparison #3 will be exploratory. The difference between treatment groups will be computed as the mask with topical gel-cream treatment minus the mask alone treatment, and non-inferiority will be concluded if the upper bound of the two-side 95% confidence interval is less than 15 percentage points. If the mask with topical gel-cream treatment is demonstrated to be non-inferior to the mask alone treatment, then testing will proceed to comparison #4; otherwise, comparison #4 will be exploratory.

Comparison #4 will evaluate the superiority of the mask with topical gel-cream treatment versus the mask alone treatment. Superiority will be concluded if the upper bound of the two-sided 95% confidence interval of the treatment difference is less than 0.

Each comparison will be tested at the 0.05 significance level, two-sided. With the stepwise procedure, the familywise error rate is controlled at the 0.05 level.

For the primary efficacy variable, treatment means and between-treatment differences will be assessed by means of an Analysis of Covariance (ANCOVA) model with treatment, gender, and center as factors and the corresponding baseline score as a covariate.

If the global face total lesion count is missing at Week 12 for more than 5% of the subjects, the missing value will be imputed by using the last observation carried forward (LOCF) method.

8.2.2. Analysis of Secondary Variables

The secondary efficacy variables are:

a) The percent change from baseline in global face total lesion count:
   - Mean across all post-baseline visits (Week 2, Week 4, Week 8, and Week 12)
   - Mean of Week 2 and Week 4
   - Mean of Week 4 and Week 8
   - Mean of Week 8 and Week 12
   - Week 2, Week 4, and Week 8 analyzed separately

b) Acne lesion counts at Week 2, Week 4, Week 8, and Week 12. Each of the following lesions will be analyzed for the total global face:
   - Open comedones
   - Closed comedones
   - Inflammatory acne lesions (papules and pustules are counted together)
   - Non-inflammatory acne lesions (sum of open comedones and closed comedones)
   - Total lesion counts (sum of inflammatory and non-inflammatory acne lesions counts)

c) IGA assessment using Modified Cook's Scale at Week 1, Week 2, Week 4, Week 8, and Week 12.

d) Additional investigator efficacy assessment at Week 1, Week 2, Week 4, Week 8, and Week 12:
   - Overall redness of inflammatory lesions
   - Overall size of inflammatory lesions

For these variables, summary statistics will be summarized by visit and treatment. The mean change from baseline within group and the corresponding 95% confidence interval will be calculated for each variable by treatment and time point. Treatment means and between-treatment differences in change from baseline will be assessed by means of an Analysis of Covariance (ANCOVA) model with treatment, gender, and center as factors and the corresponding baseline score as a covariate. The two-sided 95% confidence interval of the between-treatment difference will be constructed to provide information regarding the extent of the difference between two groups. Percent change from baseline in acne lesion counts will be analyzed using the same methods as for the primary endpoint.

8.2.3. Analysis of Tertiary Variables

[redacted]

8.3. [redacted] Safety Analysis

[redacted]

The safety analysis will be based on all randomized subjects who use IP. The number and percentage of subjects experiencing AEs during the clinical study will be presented by MedDRA System Organ Class, preferred term, and treatment. A listing of adverse events will be provided for all subjects who signed the ICD (or Assent Form, as applicable), differentiating Treatment Emergent Adverse Events.

8.4. Sample Size Determination

Between the two sites, a sufficient number of subjects will be screened to enroll up to 136 subjects to finish with at least 90 subjects (targeting 45 subjects per cell). The total sample size of 90 (45 per treatment cell) completed subjects provides 87% power to demonstrate non-inferiority of the mask with topical gel-cream treatment vs. the mask alone treatment with respect to percent change in total lesion count, based on a one-sided test at the 0.025 significance level and a non-inferiority margin of 15 percentage points. This power calculation assumes that the standard deviation is 30, and that the population mean for the mask with topical gel-cream treatment is better by 5 percentage points than that for the mask alone treatment.

If in fact the mask with topical gel-cream treatment is more efficacious than the mask alone treatment, this sample size provides 65% power to detect a difference of 15 percentage points between two treatments using a two-sided test at the 0.05 significance level, based on the superiority test. A standard deviation of 30 is assumed.

9. SUCCESS CRITERIA

[redacted]

10. MANAGEMENT OF INTERCURRENT EVENTS

10.1. AMENDMENTS TO THE PROTOCOL

Neither the PI/Site nor Sponsor will modify this protocol without obtaining the concurrence of the other. The modification will be confirmed in writing.

Amendments must be approved by the Sponsor and IRB/IEC 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 or designee must notify the IRB and the Sponsor in writing within 3 working days after the implementation.

10.2. PROTOCOL DEVIATIONS

Protocol deviations should be avoided whenever possible. When a protocol deviation occurs, it must be captured on a Deviation Log and on the individual subject source documentation and CRF, as applicable.

The PI or designee will also contact the Study Manager (see Contact Information in Appendix XV). 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.

10.3. ADVERSE EVENT REPORTING

10.3.1. 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.

If a screen-failed subject reports an AE, only the safety data (Demography, Subject Disposition, and Adverse Event) will be entered in the EDC system.

10.3.2. Definitions

10.3.2.1. 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 designee) 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 Events

All IPs have the potential to cause some skin reactions, including erythema, scaling/peeling, edema, burning/stinging, tightness/dryness, itching, or rash.

Any signs or symptoms of irritation are considered a clinical endpoint and may or may not be coded as adverse events based on the PI's or trained designee's assessment. Irrespective of whether the sign(s) or symptom(s) is (are) coded as an adverse event, the signs or symptoms must be documented on the clinical evaluation source documentation. If any of these irritation parameters appear to be exacerbated, more than normally associated with use of these types of products, the event will be recorded as an AE. This can only be determined by the PI or trained designee. 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)

A TEAE is defined as any event not present prior to the initiation of the IP. Note that AEs will be summarized for all subjects who signed the ICD (or Assent Form, as applicable), differentiating TEAEs.

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

10.3.2.2. Serious Adverse Event (SAE)

An AE (untoward medical occurrence) will be considered an SAE if it meets either of the following definitions:

Definition 1:

The event 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).

Definition 2:

- the event involves subject contact with a device AND
- the event results in:
    - death
    - serious injury, which means an injury or illness that:
        - is life-threatening (immediate risk of death)
        - results in permanent impairment of a body function or permanent damage to a body structure, or
        - necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure (*permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage*).
    - Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
    - Congenital anomaly/birth defect
    - Any suspected transmission of any infectious agent via a product (medically significant).

10.3.2.3. 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 (M.D./D.O.). 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.

10.3.2.4. 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 (M.D./D.O.) 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).

10.3.3. 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 within 30 calendar days after completion of the study will only be reported to the Sponsor if they are serious (SAEs). 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 or designee beyond the timeframe 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 since their last appointment). For each AE reported by the subject or observed by the study team, the study team member should notify the PI 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 paper AE form. 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 designee (MD/DO), must record or confirm on the source document their opinion concerning the seriousness, severity, and relationship of the AE to the study. All measures required for adverse event management must be recorded in the source document and reported according to Sponsor instructions.

These events must be entered into the EDC system within 3 business days of the site's awareness.

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

If an **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 XV 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 or designee is obligated to pursue and provide information to the Sponsor in accordance with the timeframes for reporting specified above. In addition, the PI or designee 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 paper 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.

10.3.4. Monitoring and Resolution of Adverse Events

10.3.4.1. 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 paper source documents and entered into the EDC system.

10.3.4.2. Serious AEs (SAEs)

The PI or, if the PI does not have a medical background, the medically qualified designee (M.D./D.O.) will monitor SAEs until resolution or until one of the conditions in 10.3.4.3 is met. The information will be captured in the source document and entered into the EDC system. The PI/designee will also document follow-up information on an updated SAE form, which will be reviewed by the PI or medically qualified designee and sent to the Study Manager or designee. The Study Manager or designee will forward the document(s) to the DPR, the Study Director or designee, and to OCMS per local procedures.

10.3.4.3. 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

SAEs 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).

10.4. EXPOSURE IN UTERO

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

- A woman is exposed to the IP at any time between her last menses prior to conception through the delivery of the baby.
- There is a possibility of intrauterine exposure to the product via semen from the male partner who is using the IP at the time of conception, thereby possibly exposing the fetus to the product.

If any study subject or a subject's partner becomes or is found to be pregnant during the study or within 30 days of the subject's participation, the PI or designee 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 or designee will follow the pregnancy until completion or until pregnancy termination (i.e., induced abortion) and then notify the Sponsor of the outcome. The PI or designee 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 or designee 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 (or designee) assesses as possibly related to in utero exposure to the IP.

11. ETHICAL CONSIDERATIONS

The privacy information such as the ICD/Assent Form and health related questionnaire of the subjects will be kept confidential during the study and clearly separated from the Trial Master File (TMF).

11.1. 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 XV.

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, as 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 has 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 or designee must notify the IRB/IEC and the Sponsor in writing within 3 working days after the implementation.

12. 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 and must collect only relevant data required by this protocol. All documentation should be completed using good documentation and data integrity practices.

[redacted]

EDC pages should be completed for each randomized subject. The completed pages of the EDC system are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor.

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

The Sponsor or its designee will have responsibility for verifying for accuracy of the data entered into the EDC system against the source documents.

All data entered in the EDC system will be sent to the Sponsor's Quantitative Sciences Department for statistical analysis. All final data recorded in the EDC system will be retained in the TMF and the SMF.

The 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 Sponsor obligations under this project for 2 years from the time the final report is issued.

Before the 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.

13. STUDY MONITORING, QUALITY CONTROL AND QUALITY ASSURANCE

The study will be monitored (in accordance with a study- or site-specific Monitoring Plan) by the Sponsor, or its designee. A Monitoring Plan and 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. The visits 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 monitors may review source documents to confirm that the data recorded is complete and accurate.

The PI and institution will allow the Sponsor's monitors 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 XV).

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(s) and their relevant personnel are available during monitoring and possible audits or inspections and that sufficient time is devoted to the process.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this clinical trial may occur because of a change in opinion of the IRB/IEC, IP or study safety problems, 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 the Sponsor, all trial materials must be collected, all study documents/EDC completed to the greatest extent possible, and termination reported to the IRB/IEC.

15. FINAL REPORT

The final report will be prepared by Thomas J. Stephens and Associates, Inc. and will include (but is not limited to) the following information: [redacted]

16. 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 site during the recruitment and admission will be handled confidentially.

17. PUBLICATION

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

18. REFERENCES

1) Ashkenazi, H., et al. (2003). Eradication of *Propionibacterium acnes* by its endogenic porphyrins after illumination with high intensity blue light. *FEMS Immunology and Medical Microbiology*, 35, 17-24.

2) Kjeldstad, B. (1984). Photoinactivation of *Propionibacterium acnes* by near-ultraviolet light. *Z Naturforsch*, 39, 329-335.

3) Roelandts, R. (2005). A new light on Niels Finsen, a century after his Nobel Prize. *Photodermatol Photoimmunol Photomed*, 21, 115-117.

4) Barolet, D. (2008). Light-emitting diodes (LEDs) in dermatology. *Semin Cutan Med Surg*, 27, 227-238.

5) Salomatina, E., et al. (2006). Optical properties of normal and cancerous human skin in the visible and near-infrared spectral range. *J Biomed Opt*, 11(6).

6) Bashkatov, A.N., et al. (2000). Optical properties of melanin in the skin and skin-like phantoms. *Proc. of SPIE*, 4162, 219-226.

7) Bashkatov, A.N. et al. (2005). Optical properties of human skin, subcutaneous and mucous tissues in the wavelength range from 400 to 2000 nm. *J Phys D: Appl Phys,* 38, 2543-2555.

8) Jacques, S.L. (2013). Optical properties of biological tissues: a review. *Phys Med Biol,* 58, R37-R61.

9) Lamouche, G., et al. (2012). Review of tissue simulating phantoms with controllable optical, mechanical and structural properties for use in optical coherence tomography. *Biomed Opt Express,* 3(6), 1381-1398.

10) Pogue, B.W., & Patterson, M.S. (2006). Review of tissue simulating phantoms for optical spectroscopy, imaging and dosiometry. *J Biomed Opt*, 11(4).

11) Hirshburg J., et al. (2007). Correlation between collagen solubility and skin optical clearing using sugars. *Lasers in Surg and Med*, 39, 140-144.

12) Wiegand, B., Luedtke, K., Rapp, SR. Acne Profile. Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933-7003, assignee. Patent US 2006/0008484 A1. 12 Jan. 2006. Print.

20. 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, I agree to make no additions and/or changes without the consent of the Sponsor, except when necessary to protect the safety of the subjects.

I will 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. I will discuss this material with them to ensure that they are fully informed regarding the protocol and conduct of this study.

Signature and Date:

Alicia Bucko, D.O.
Principal Investigator
Academic Dermatology Associates

[redacted]

Lily Jiang, Ph.D.
Principal Investigator
Thomas J. Stephens and Associates, Inc.

21. APPENDICES

Appendix I. Fitzpatrick Skin Type Classification

The skin classification is based on the subject-reported, unprotected skin response to the first 30 to 45 minutes of sun exposure after a winter season without sun exposure. The categories of skin types are as follows:

Skin Type	Characteristics
I	White; very fair; red or blonde hair; blue eyes; freckles; Always burns easily; never tans
II	White; fair; red or blonde hair; blue, hazel, or green eyes; Always burns easily; tans minimally
III	Cream white; fair with any eye or hair color; very common; Burns moderately; tans gradually
IV	Brown; typical Mediterranean white skin; Burns minimally; always tans well
V	Dark brown; mid-eastern skin types, black hair, olive skin; Rarely burns; tans profusely
VI	Black; black hair, black eyes, black skin; Never burns; deeply pigmented

Appendix II. Skin Sensitivity

Subjects will rate their self-perceived skin sensitivity as per the scale below:

Do you consider you skin to be sensitive:

- None of the time
- Some of the time
- Most of the time
- All of the time

This is for demographic information collection purposes only and is not considered an evaluation endpoint.

Appendix III. Investigator Global Acne (IGA) Assessment

The following scale (Modified Cook's Scale) will be used for the IGA assessment. Half points may be used:

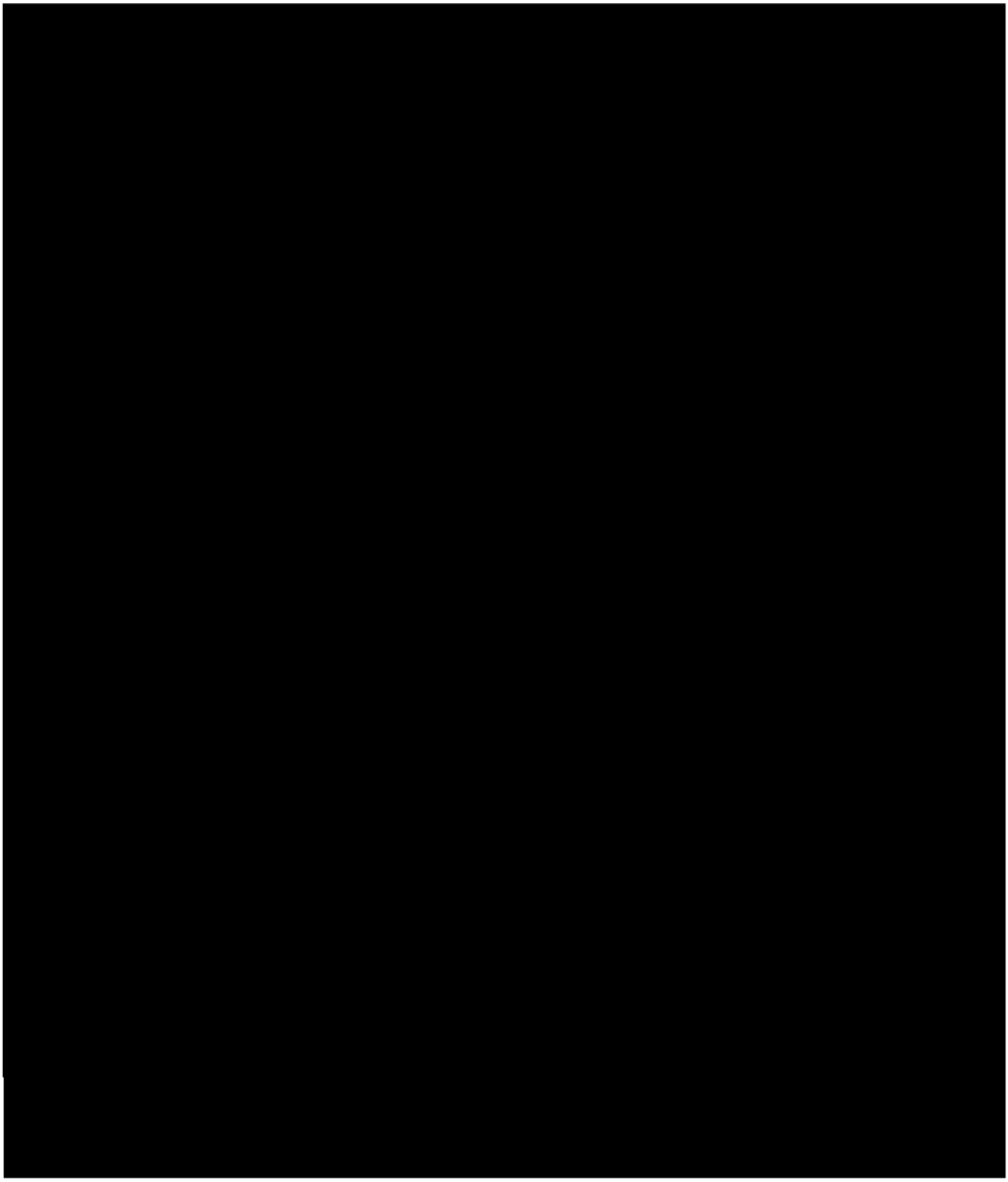
0	Clear	Residual hyperpigmentation and erythema may be present.
1	Almost Clear	A few scattered comedones and a few (less than five) small papules.
2	Mild	Easily recognizable; less than half the face is involved. Many comedones and many papules and pustules.
3	Moderate	More than half of the face is involved. Numerous comedones, papules, and pustules.
4	Severe	Entire face is involved. Covered with comedones, numerous papules and pustules, and few nodules and cysts.
5	Very Severe	Highly inflammatory acne covering the face; with nodules and cysts present.

Appendix IV. Additional Investigator Efficacy Assessments

The following scale will be used for the additional investigator efficacy assessments. Half points may be used:

Parameter	Scale								
	0 = None	1-3 = Mild			4-6 = Moderate			7-9 = Severe	
Overall Redness of Inflammatory Lesions	0 = no redness associated with the inflammatory lesions	1	2	3	4	5	6	7	8	9 = overall, inflammatory lesions exhibit severe degree of redness
Overall Size of Inflammatory Lesions	0 = no longer visible	1	2	3	4	5	6	7	8	9 = overall size is very large
[redacted]										

[redacted]



Appendix VI. Subject Instructions – Regimen 1

Subject Instructions
Study # PS-1701 0314 5529-SACT

You have been provided with an **AM & PM Cleanser** and a **PM Mask Treatment**. Please use them as follows:

- Wash your face twice daily (morning and evening) with the **AM & PM Cleanser**. In the evening after washing, use the **PM Mask Treatment** for 10 minutes. See the detailed directions below.

In the morning:

1. Wash your face with the **AM & PM Cleanser**:
   Wet your face. Pump cleanser into your hands, add water, and work into a lather. Massage your face gently and rinse thoroughly. Pat dry.

In the evening:

1. Wash your face with the **AM & PM Cleanser**:
   Wet your face. Pump cleanser into your hands, add water, and work into a lather. Massage your face gently and rinse thoroughly. Pat dry.

2. Use the **PM Mask Treatment**. See insert for detailed instructions, warnings, etc.

[redacted]

Continued on Back

Other Instructions:

- Use only the assigned products and your regular, non-medicated (other than SPF, which is acceptable) facial products that you have used for at least one month and that have been recorded/approved by the study staff at Visit 1.
- Do not use any other light-based devices or receive any professional or aesthetic facial spa procedures during the study.
- Do not shave or use any hair removal method on your face within the 24 hours prior to a study visit.
- Do not start using any new personal care products (e.g. makeup, lotions, etc.) or change your currently used brands during the study.
- On the day of study visits: remove all leave-on facial products (including eye makeup) and wash with the provided facial cleanser 30 minutes to 2 hours prior to the visit and then do not apply any leave-on facial products until the visit is completed. Note: if you do not follow these directions, you will be asked to remove your makeup/products and wash your face with the provided cleanser on-site and then wait 30 minutes before evaluations are performed.
- Avoid excessive sun/UV exposure (including tanning beds) for the duration of the study.
- Attend all scheduled visits.
- Do not begin any other clinical study during the current study.
- Report any side effects, changes in health/medication, pregnancies, issues, or questions to the study staff.
- Bring your study products to all visits. Products must be returned at the final study visit. Failure to return your products may result in forfeiture of compensation.

Appendix VII. Subject Instructions – Regimen 2

Subject Instructions
Study # PS-1701 0314 5529-SACT

You have been provided with an **AM & PM Cleanser**, a **PM Gel-Cream**, and a **PM Mask Treatment.** Please use them as follows:

- Wash your face twice daily (morning and evening) with the **AM & PM Cleanser.** In the evening after washing, apply the **PM Gel-Cream** full-face and let it dry prior to using the **PM Mask Treatment** for 10 minutes (mask treatment should begin within 15 minutes after PM Gel-Cream application). See the detailed directions below.

In the morning:

1. Wash your face with the **AM & PM Cleanser**:
   Wet your face. Pump cleanser into your hands, add water, and work into a lather. Massage your face gently and rinse thoroughly. Pat dry.

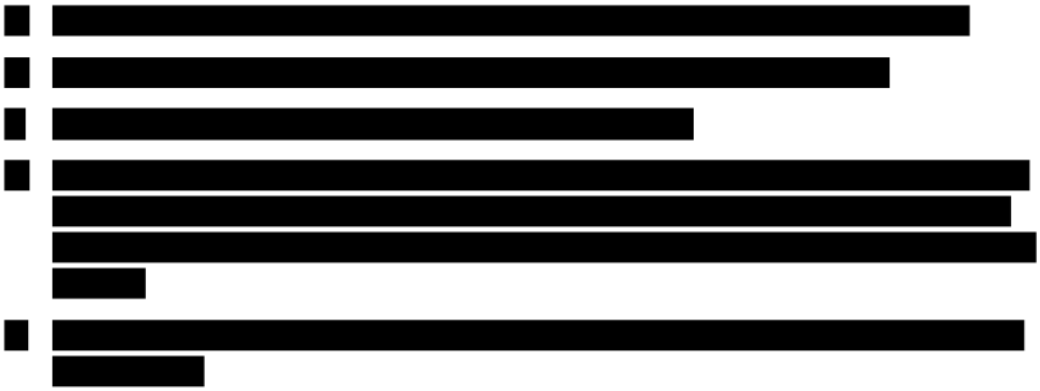
In the evening:

1. Wash your face with the **AM & PM Cleanser**:
   Wet your face. Pump cleanser into your hands, add water, and work into a lather. Massage your face gently and rinse thoroughly. Pat dry.

2. Apply the **PM Gel-Cream** on your full-face:

[redacted] *Apply an even layer to your full face, including your forehead, nose, cheeks, and chin. Rub in the product until fully absorbed.* [redacted]

3. After the PM Gel-Cream is fully dry, use the **PM Mask Treatment** (mask treatment should begin within 15 minutes after PM Gel-Cream application). See insert for detailed instructions, warnings, etc.

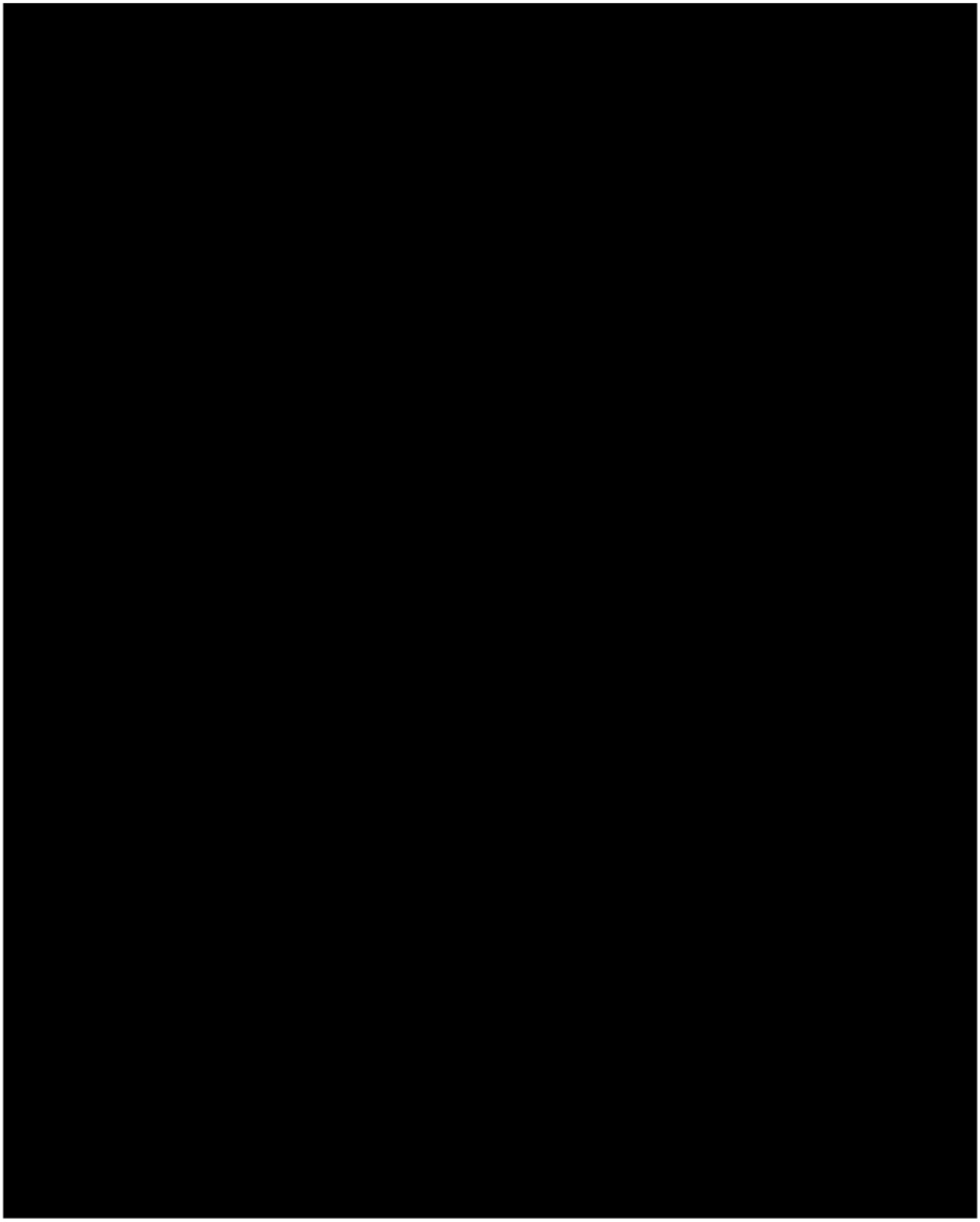


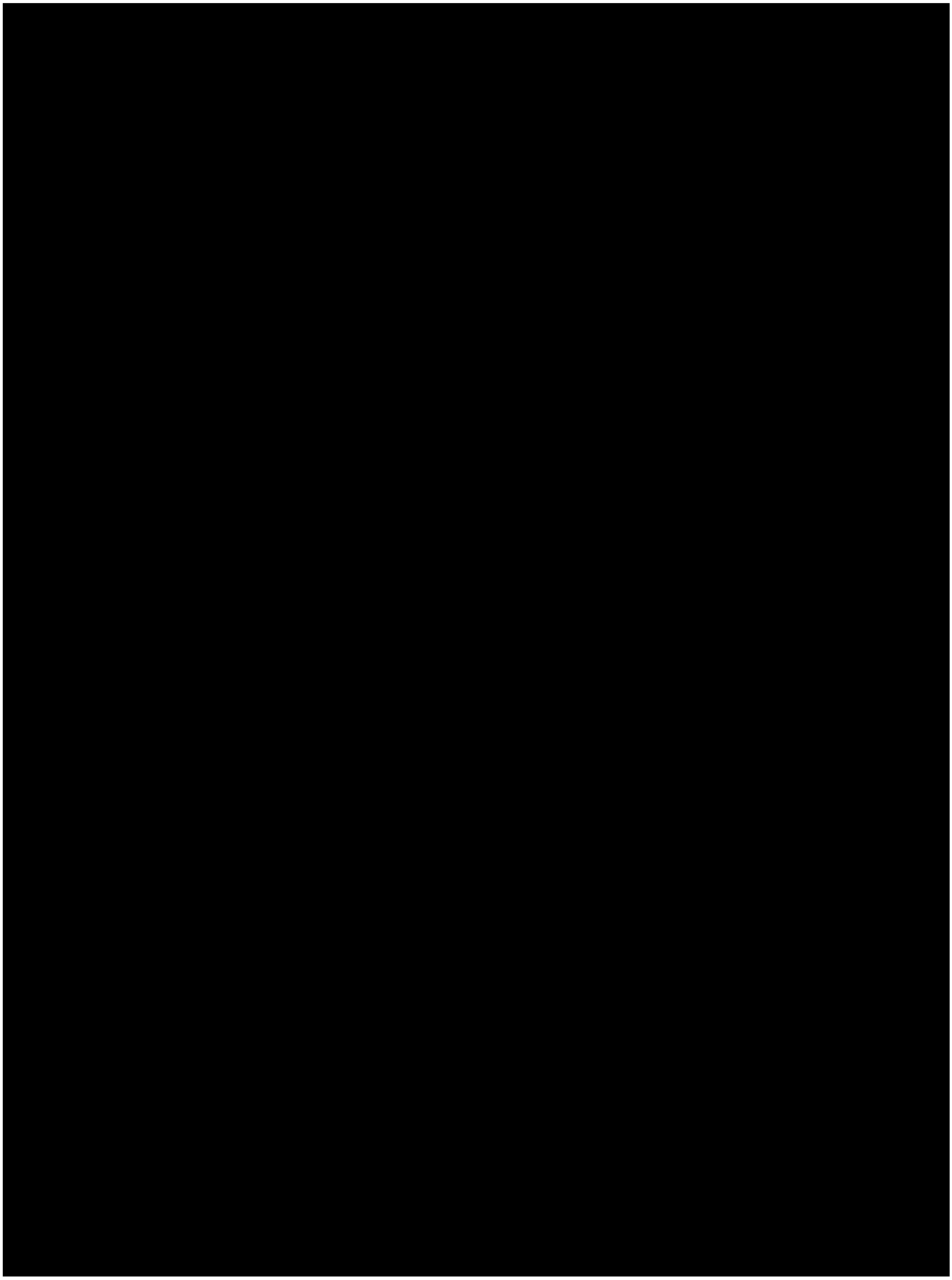
Other Instructions:

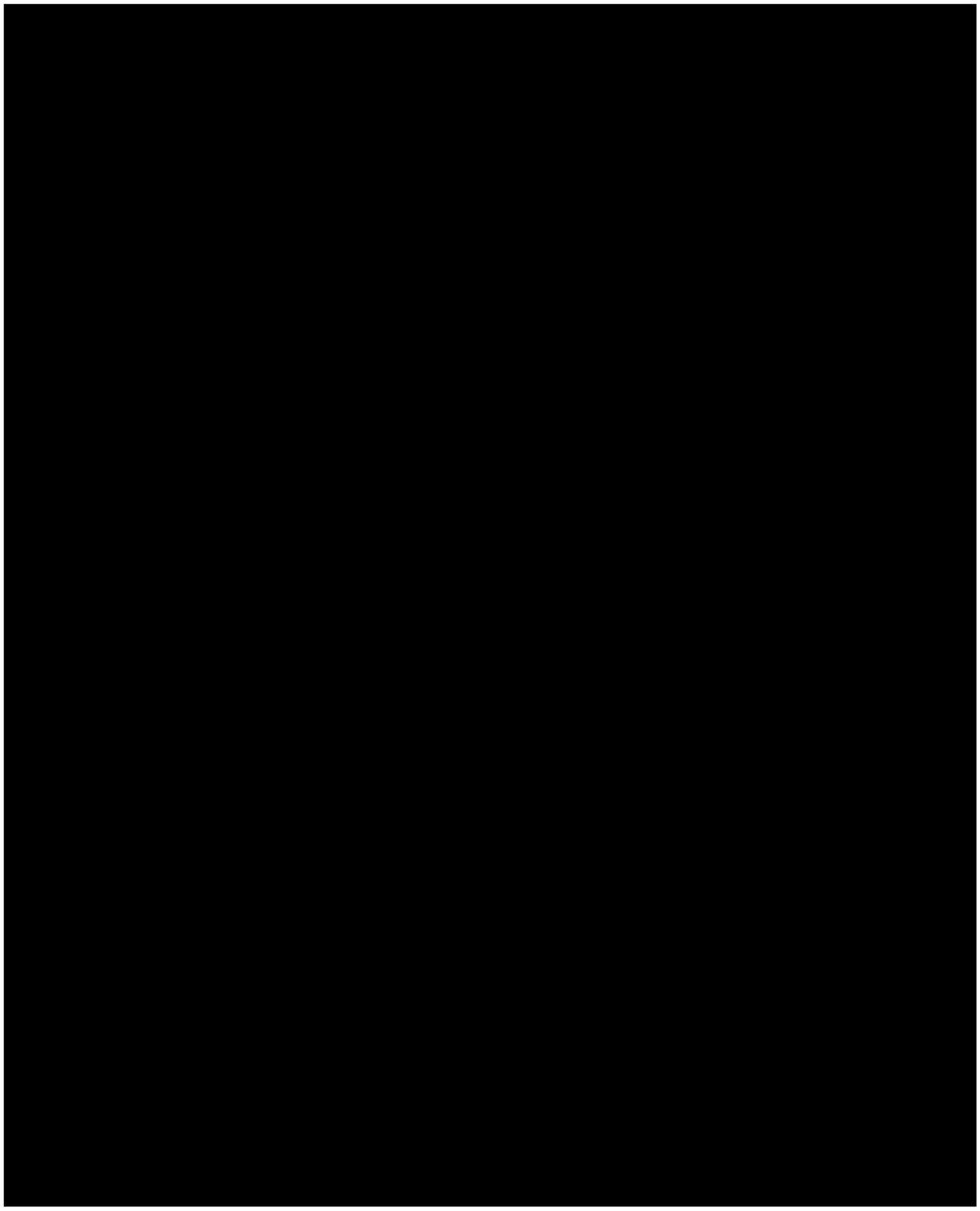
- Use only the assigned products and your regular, non-medicated (other than SPF, which is acceptable) facial products that you have used for at least one month and that have been recorded/approved by the study staff at Visit 1.
- Do not use any other light-based devices or receive any professional or aesthetic facial spa procedures during the study.
- Do not shave or use any hair removal method on your face within the 24 hours prior to a study visit.
- Do not start using any new personal care products (e.g. makeup, lotions, etc.) or change your currently used brands during the study.
- On the day of study visits: remove all leave-on facial products (including eye makeup) and wash with the provided facial cleanser 30 minutes to 2 hours prior to the visit and then do not apply any leave-on facial products until the visit is completed. Note: if you do not follow these directions, you will be asked to remove your makeup/products and wash your face with the provided cleanser on-site and then wait 30 minutes before evaluations are performed.
- Avoid excessive sun/UV exposure (including tanning beds) for the duration of the study.
- Attend all scheduled visits.
- Do not begin any other clinical study during the current study.
- Report any side effects, changes in health/medication, pregnancies, issues, or questions to the study staff.
- Bring your study products to all visits. Products must be returned at the final study visit. Failure to return your products may result in forfeiture of compensation.

Appendix VIII. PM Mask Treatment Package Insert

PM Mask Treatment Package Insert

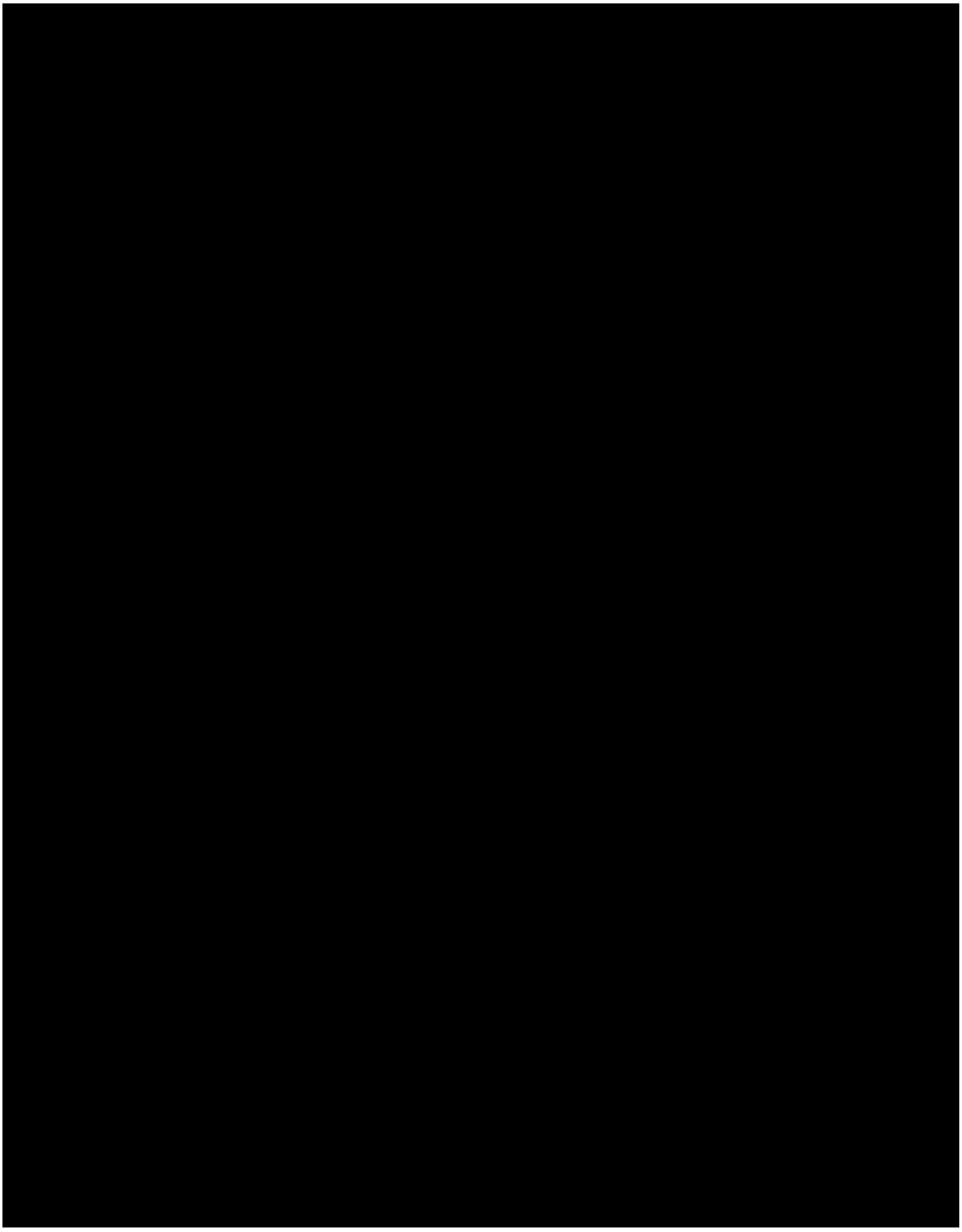


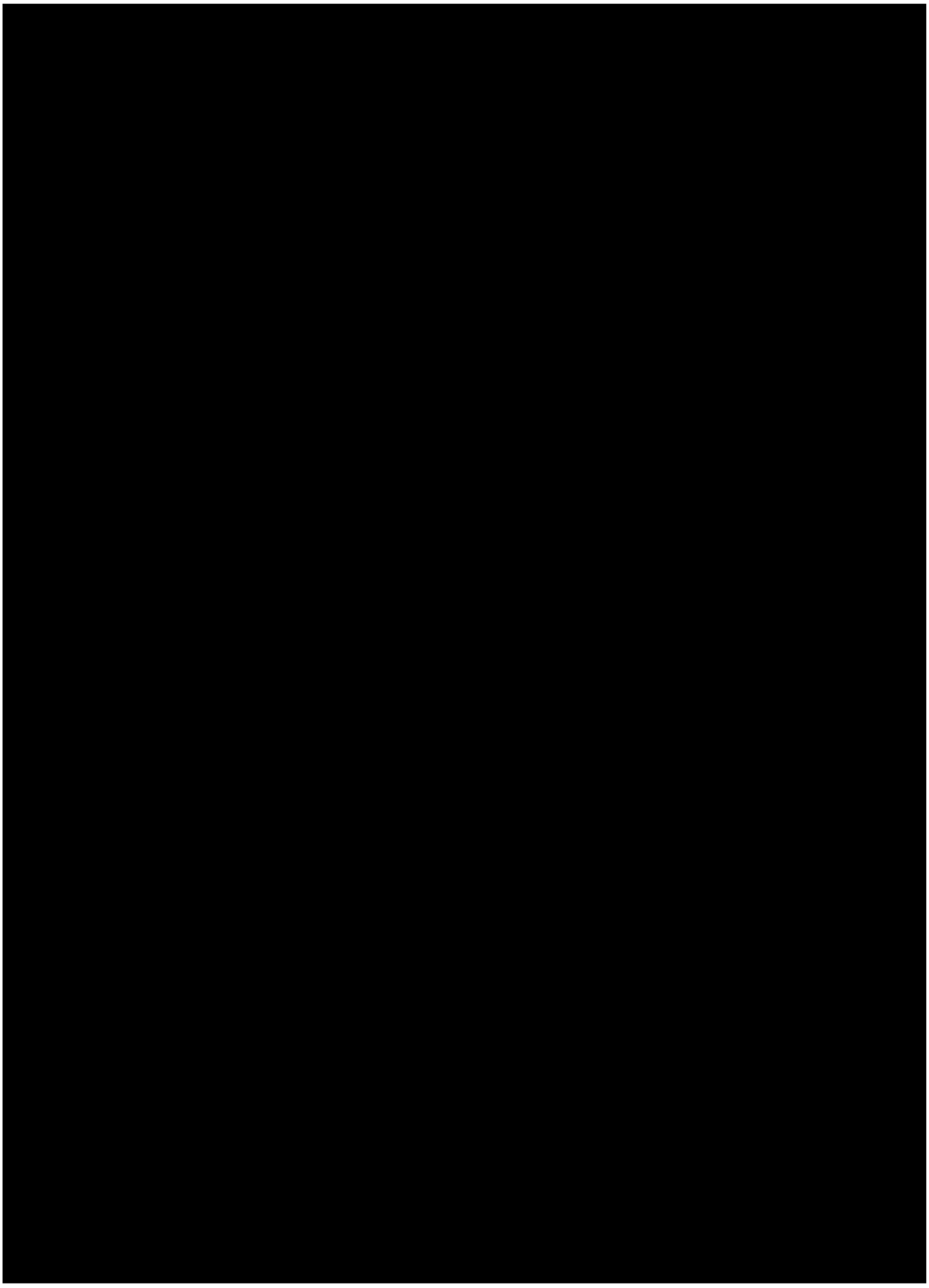


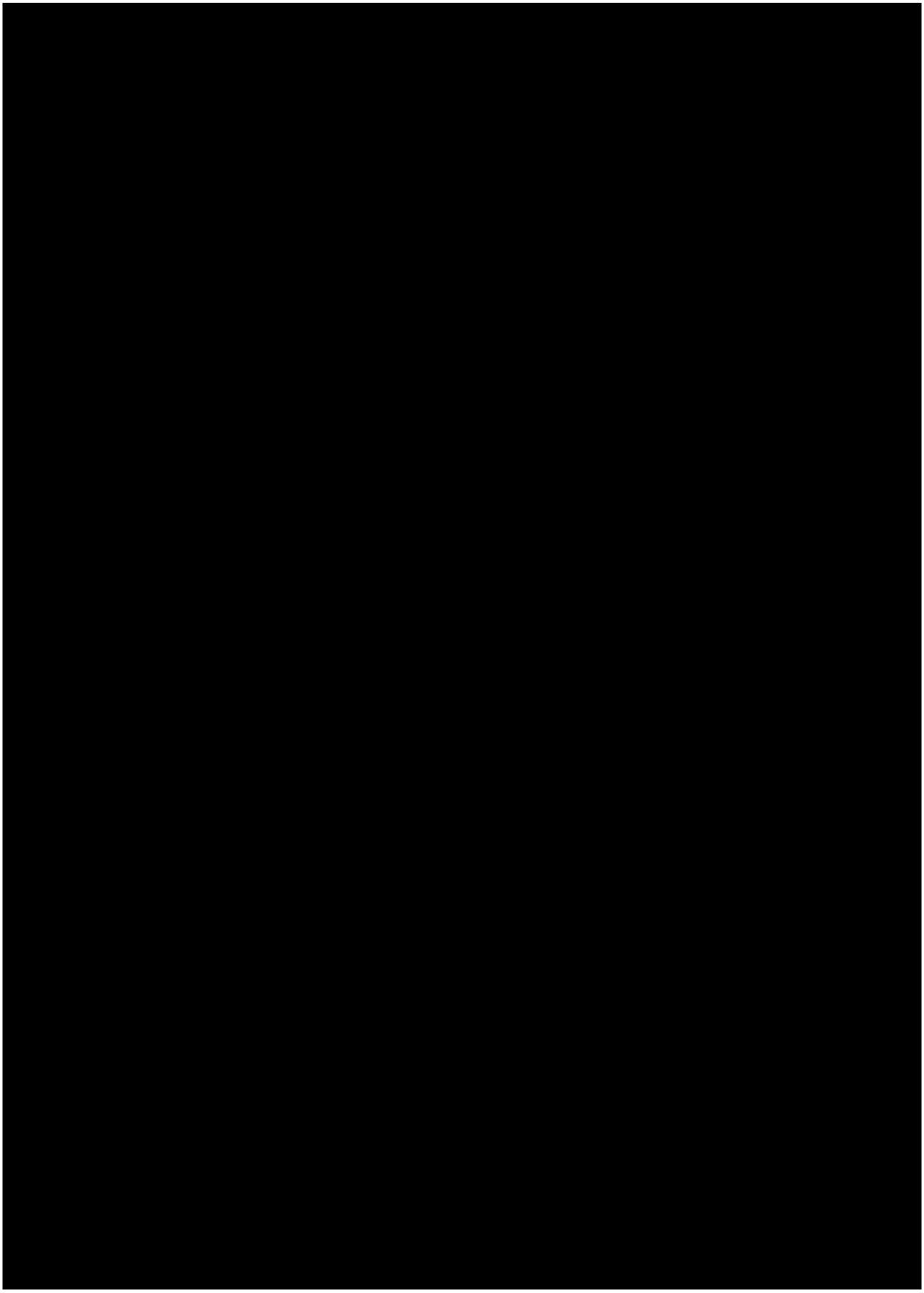


Appendix IX. PM Gel-Cream & PM Mask Treatment Package Insert

PM Gel-Cream & PM Mask Treatment Package Insert

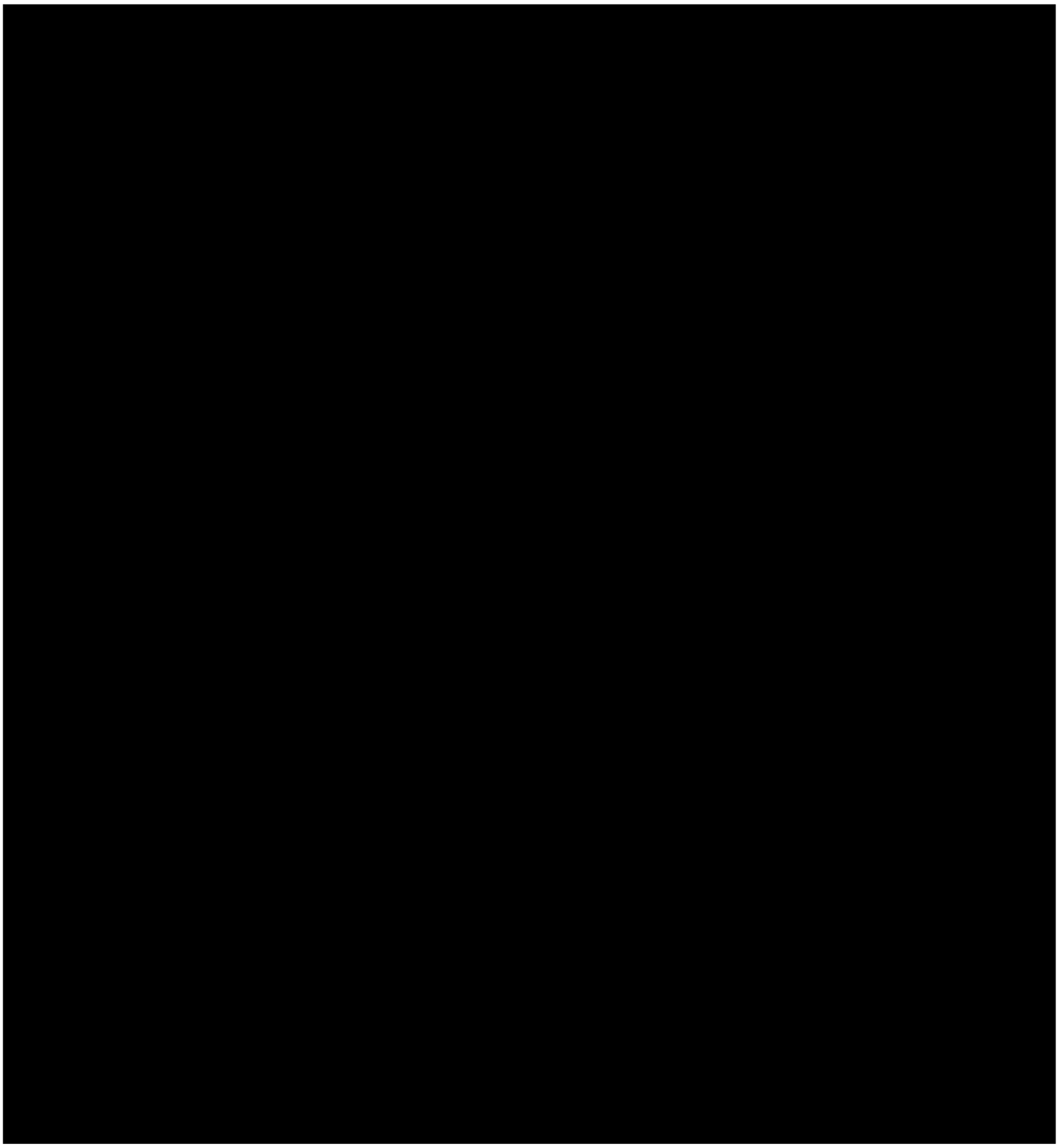


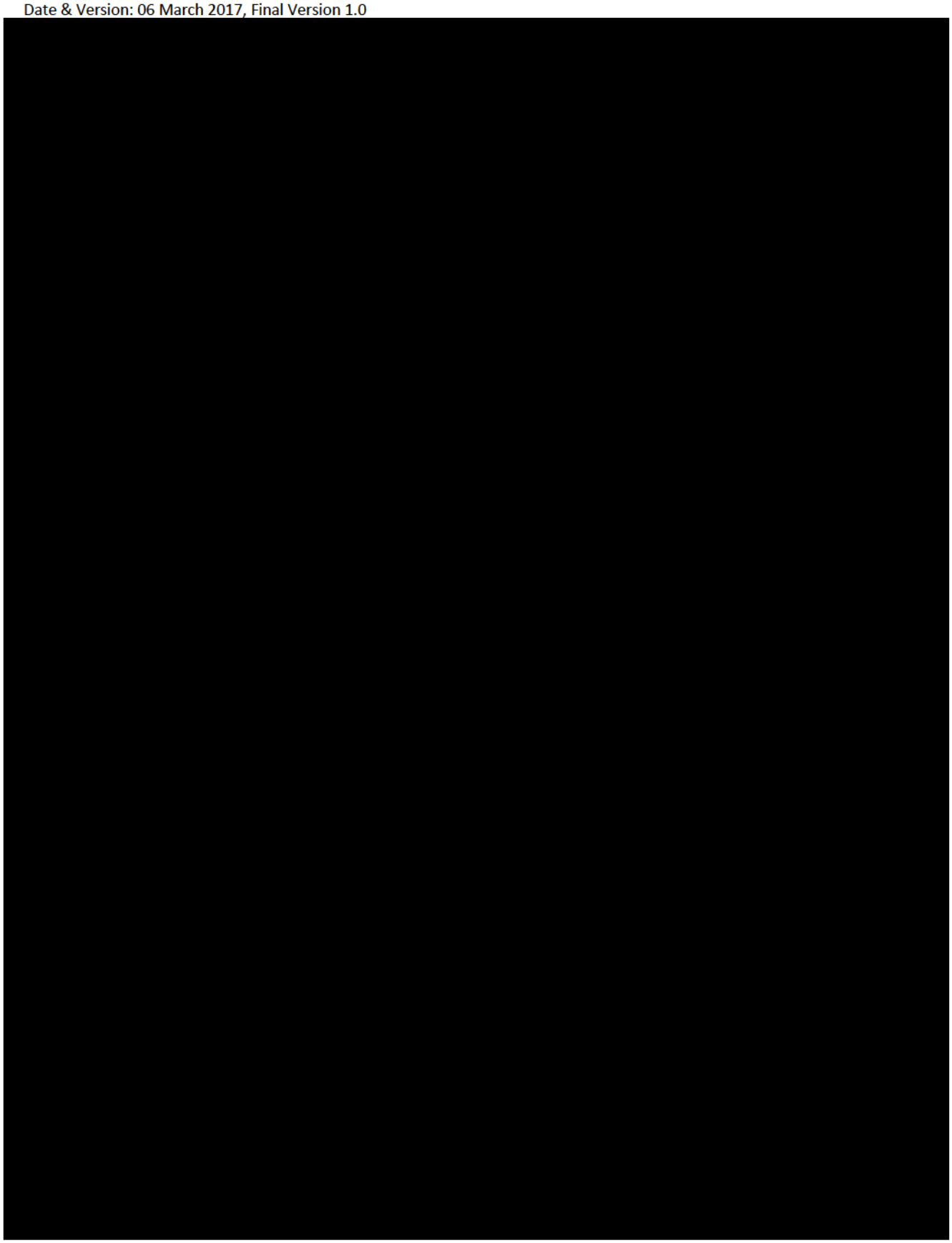


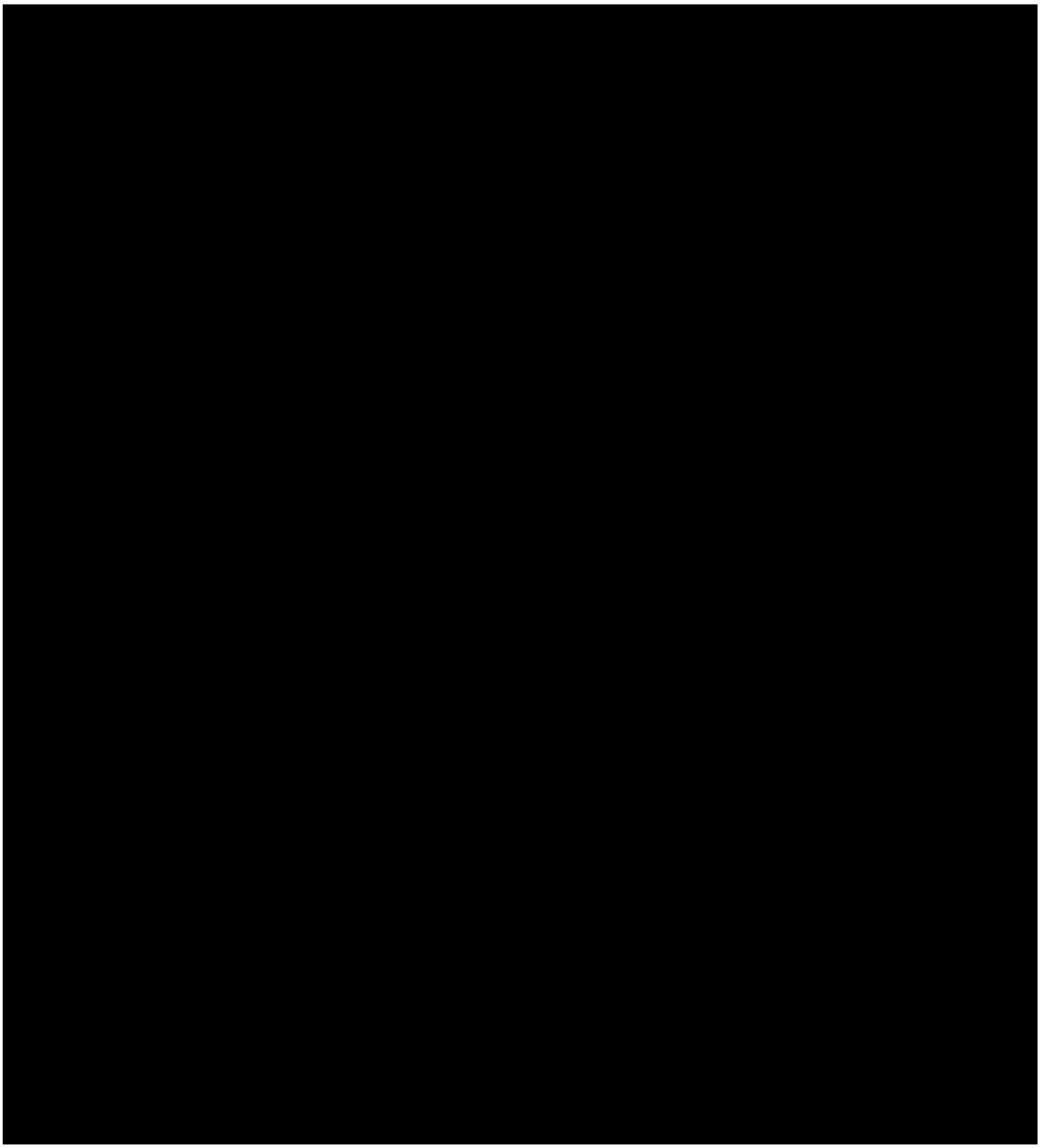


Appendix X. Replacement Mask Activator Package Insert

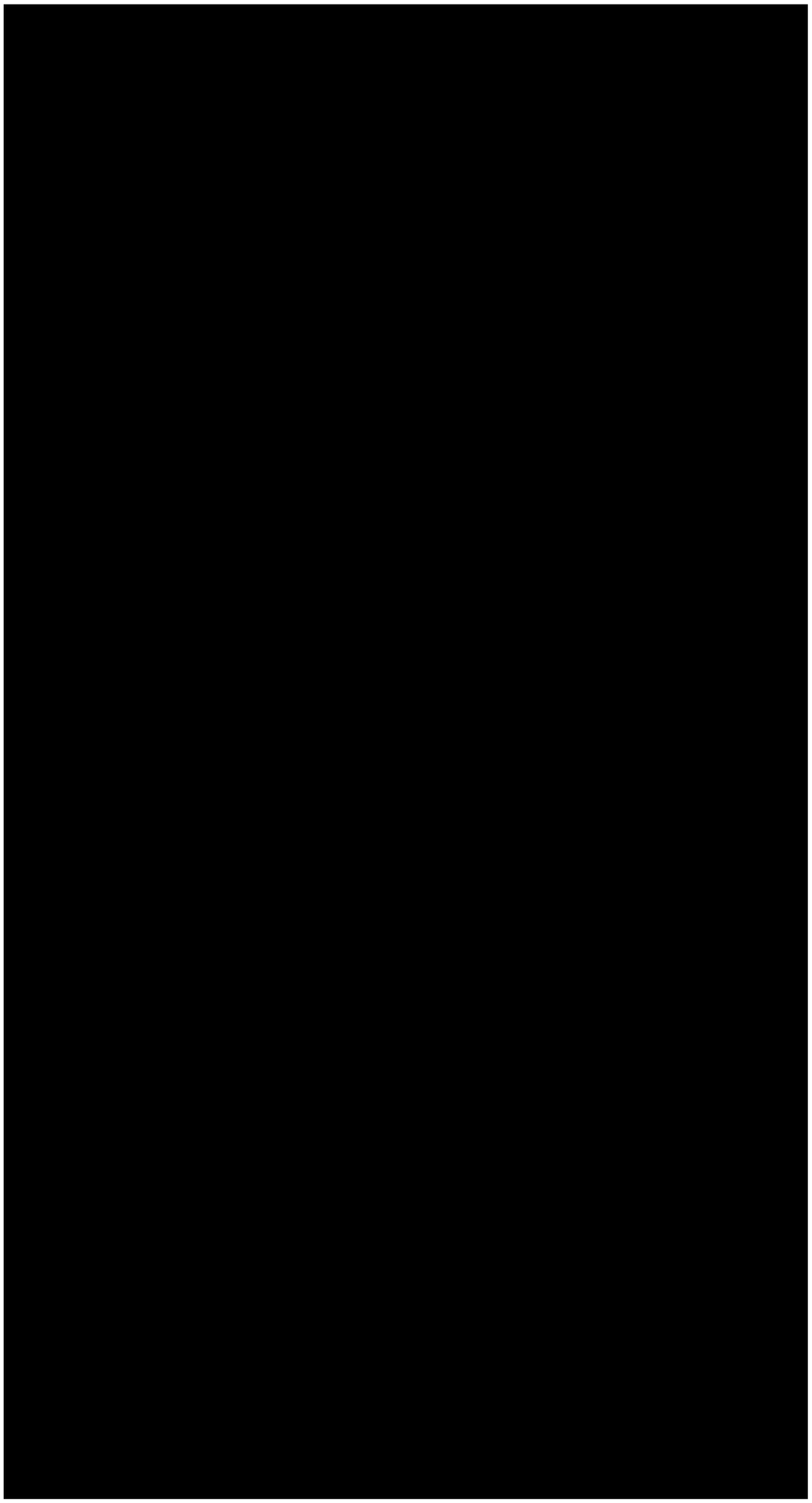
Replacement Mask Activator Package Insert







Appendix XIV. Ingredient Lists



Appendix XV. Contact Information