

**NCT02977507**

**Study ID:** SKM16-LYT-MEL

**Title:** Randomized, Double-blinded, Split-face Study comparing the Cosmetic Efficacy and Tolerability of Two Topical Products in Subjects with Moderate Facial Melasma

**Protocol Amendment 1 Date:** 26 Oct 2016

**Randomized, Double-blinded, Split-face Study comparing the  
Cosmetic Efficacy and Tolerability of Two Topical Products  
in Subjects with Moderate Facial Melasma**

**PROTOCOL NUMBER: SKM16-LYT-MEL Amendment 1**

**FUNDING SPONSOR:** SkinMedica Inc., an Allergan Company  
2525 Dupont Drive  
Irvine, CA 92612

**PRINCIPAL INVESTIGATOR:**



**PROTOCOL DATE:** 26/Oct/2016

The study will be conducted according to the protocol and in compliance with International Conference of Harmonisation Good Clinical Practice Guidelines and all other applicable regulatory requirements.

**CONFIDENTIALITY STATEMENT**

THE INFORMATION PROVIDED IN THIS STUDY PROTOCOL IS INTENDED FOR REVIEW BY THE PRINCIPAL INVESTIGATOR, ALL RESEARCH RELATED PERSONNEL, ETHICS COMMITTEE(S) AND HEALTH AUTHORITIES. INFORMATION PROVIDED AND CAPTURED IN THIS PROTOCOL IS STRICTLY CONFIDENTIAL AND WILL ONLY BE DISCLOSED WITH WRITTEN CONSENT FROM THE SPONSORS.



**PROTOCOL SIGNATURE PAGE**

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2525 Dupont Drive  
Irvine, CA 92612

**PRINCIPAL INVESTIGATOR:**

[REDACTED]

**PROTOCOL DATE:** 26/Oct/2016

I, [REDACTED] agree to conduct protocol “**Randomized, Investigator-blinded, Split-face Study comparing the Cosmetic Efficacy and Tolerability of Two Topical Products in Subjects with Moderate Facial Melasma**” in accordance and compliance with International Conference of Harmonisation Good Clinical Practice Guidelines and all applicable regulatory requirements.

**ACCEPTED AND AGREED:**

Principal Investigator Signature:

[REDACTED]

[REDACTED]



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**STUDY SYNOPSIS**

<b>Protocol Number</b>	SKM16-LYT-MEL Amendment 1
<b>Protocol Title</b>	Randomized, Double-blinded, Split-face Study comparing the Cosmetic Efficacy and Tolerability of Two Topical Products in Subjects with Moderate Facial Melasma
<b>Study Duration</b>	3 months (12 Weeks)
<b>Study Population</b>	20 healthy subjects with Fitzpatrick Skin Types III-VI
<b>Objectives</b>	To evaluate and compare the efficacy and tolerability of two topical products in the improvement of facial melasma
<b>Study Design</b>	Single site, investigator-initiated, double-blinded, parallel arm, randomized treatment, split-face, 12-week study comparing the efficacy and tolerability of SkinMedica's cosmetic topical brightener versus generic hydroquinone 4% topical prescription cream. A total of 20 healthy subjects will be enrolled into this study. Subjects will be screened and randomized at Baseline and will return for visits at Weeks 4, 8 and 12. The test products will be applied only to the affected areas (dark patches) twice a day, morning and evening, every day for 12 weeks. Ancillary products will be provided for basic daily skincare regimen use.
<b>Study Products</b>	<ul style="list-style-type: none"> <li>• SkinMedica Facial Cleanser</li> <li>• SkinMedica Rejuvenative Moisturizer</li> <li>• SkinMedica Essential Defense Mineral Shield Broad Spectrum SPF 35 Sunscreen</li> <li>• Test Product A (Lytera 2.0)</li> <li>• Test Product B (4% Hydroquinone Topical Cream)</li> </ul>
<b>Eligibility Criteria</b>	Subjects aged 18+ [REDACTED] with symmetrical moderate facial melasma.

**1.0 BACKGROUND**

Melasma is a common disorder of hyperpigmentation which typically presents as brown or grayish brown macules on the face, including the forehead, malar region, upper lip and chin. Melasma is commonly observed in women with Fitzpatrick skin types III to V (1), especially Asian and Hispanic women, although all skin types can be affected.

Contributing causes of melasma may include ultraviolet irradiation, oral contraceptives, hormone replacement therapy, pregnancy, and thyroid dysfunction (2) however the exact etiology are not yet fully understood.

Many patients find the uneven skin tone appearance caused by melasma to be cosmetically unacceptable. Finding a successful treatment remains challenging and frustrating. Therapies include broad-spectrum sunscreens, hydroquinone, tretinoin, kojic acid, alpha hydroxy acids, salicylic acid, and chemical peels.

The treatment of hyperpigmentation associated with skin aging and melasma is challenging due to the prolonged time to respond and its high relapse rate when therapy is discontinued. Patients are also required to avoid sunlight to improve therapeutic results. Hydroquinone is currently the gold standard for the topical treatment of hyperpigmentation and melasma.

## 2.0 STUDY OBJECTIVE

The objective of this study is to evaluate the efficacy and tolerability of SkinMedica's cosmetic topical brightener versus 4% hydroquinone in the improvement of the appearance of moderate facial melasma over the course of 12 weeks.

## 3.0 STUDY POPULATION

Twenty (20) healthy subjects presenting with symmetrical moderate facial melasma, who meet all inclusion and exclusion criteria will be eligible to participate in this study.

### 3.1 Inclusion Criteria

A subject will be eligible to participate if they meet all of the following inclusion criteria:

1. Female or male aged 18+ years [REDACTED]
2. Individuals with symmetrical (with at least left and right malar region involvement) moderate melasma [REDACTED].
3. Individuals that are willing to provide written informed consent and are able to read, speak, write, and understand English.
4. Individuals willing to sign a photography release.
5. Willing to withhold all facial treatments during the course of the study including botulinum toxin, injectable fillers, microdermabrasion, IPL, peels, facials, waxing, laser treatments and tightening treatments. Threading is allowed but not facial laser hair removal.

6. Willingness to cooperate and participate by following study requirements for the duration of the study and to report any changes in health status or medications, adverse event symptoms, or reactions immediately.
7. Willingness to not begin using any new cosmetic facial make-up during the study. If regular users of cosmetic facial make-up, they must have used the product(s) without any tolerability issues for at least 2 weeks prior to starting the study.
8. Willingness to avoid as much as possible, direct and prolonged sun exposure for the duration of the study (including tanning beds), especially from 10 AM to 2 PM. Subjects are asked to wear protective clothing prior to and during exposure. Any extended sun exposure must be recorded in the source documents.

### **3.2 Exclusion Criteria**

A subject will not be eligible to participate if they meet any of the following exclusion criteria.

1. Individuals diagnosed with known allergies to study provided skin care products.
2. Individuals who are nursing, pregnant, or planning to become pregnant during the study according to subject self-report.
3. Individuals with a history of skin cancer.
4. Individuals having a health condition and/or pre-existing or dormant dermatologic disease on the face (e.g., psoriasis, rosacea, acne, eczema, seborrheic dermatitis, severe excoriations etc.) that the Investigator or designee deems inappropriate for participation or could interfere with the outcome of the study.
5. Individuals with a history of immunosuppression/immune deficiency disorders (including HIV infection or AIDS) or currently using immunosuppressive medications (e.g., azathioprine, belimumab, cyclophosphamide, Enbrel, Imuran, Humira, mycophenolate mofetil, methotrexate, prednisone, Remicade, Stelara.) and/or radiation as determined by study documentation that the Investigator or designee deems inappropriate for participation or could interfere with the outcome of the study.
6. Individuals with an uncontrolled disease such as asthma, diabetes, hypertension, hyperthyroidism, or hypothyroidism. Individuals having multiple health conditions may be excluded from participation even if the conditions are controlled by diet, medication, etc.
7. Individuals with any planned surgeries and/or invasive medical procedures during the course of the study.

8. Individuals who are currently participating in any other facial usage study or have participated in any clinical trial within 4 weeks prior to inclusion into the study.
9. Individuals who have observable suntan, scars, nevi, excessive hair, etc. or other dermal conditions on the face that might influence the test results in the opinion of the Investigator or designee.
10. Individuals who started hormone replacement therapies (HRT) or hormones for birth control less than 3 months prior to study entry or who plan on starting, stopping, or changing doses of HRT or hormones for birth control during the study.
11. Individuals who used any of the following medications or had any of the listed procedures within the listed time frame prior to the study start date:
  - Retin-A®, Retin-A Micro®, Renova®, Avita®, Tazorac®, or Differin® within 3 months
  - Had a light-depth chemical peel or microdermabrasion within 1 month
  - Had a medium-depth chemical peel, medium-depth microdermabrasion, any systemic steroids, non-ablative laser, light and/or radio frequency or fractional laser resurfacing of the face and neck within 3 months
  - Any systemic retinoid (e.g. Soriatane®, Accutane®, Roche Dermatologics) within 12 months
  - Any topical or systemic antibiotics, such as minocycline, or any other known medications that can cause photosensitivity, such as hydrochlorothiazide, lasix, amiodarone, within 1 month
  - Any topical tretinoin product or derivative, imiquimod, 5-fluorouracil, or diclofenac on their face within 3 months
  - Prescription strength skin lightening products (e.g. 4% hydroquinone, tretinoin, AHA, BHA and polyhydroxy acids, 15% or 20% azelaic acid, 4-hydroxyanisole alone or in combination with tretinoin, etc.) within 3 months
  - Any non-prescription cosmetic anti-wrinkle, skin lightening products, or any other product or topical or systemic medication known to affect skin aging or dyschromia (products containing alpha/beta/poly-hydroxy acids, vitamin C, soy, Q-10, hydroquinone; systemic or licorice extract (topically), Tego® Cosmo C250, gigawhite, lemon juice extract (topically), emblica extract, etc.) within 2 weeks
  - Have undergone plastic surgery, Dermabrasion (deep skin peel), a deep chemical peel or ablative laser resurfacing of the face and neck within 12 months
  - Had facial treatment with a botulinum toxin base injectable (Botox), injectable fillers, or a fat transfer within 6 months

## 4.0 METHODS AND MATERIALS

### 4.1 Study Products

SkinMedica Facial Cleanser: Water/Aqua/Eau, Disodium Laureth Sulfosuccinate, Cocamidopropyl Hydroxysultaine, Sodium Lauryl Sulfoacetate, Camellia Oleifera Leaf Extract, Glycerin, Panthenol, Butylene Glycol, Ethylhexylglycerin, PEG-150 Pentaerythrityl Tetrastearate, PEG-6, Caprylic/Capric, Glycerides, Disodium EDTA, Phenoxyethanol, Parfum/Fragrance, Blue 1 (CI 42090), Yellow 10 (CI 47005)

Test Product A (Cosmetic topical serum “Lytera 2.0”): Water/Aqua/Eau, Butylene Glycol, Glycerin, Niacinamide, Polyacrylate-13, Phenylethyl Resorcinol, Tranexamic Acid, Vitis Vinifera (Grape) Flower Cell Extract, Plankton Extract, Tetrapeptide-30, Artemisia Capillaris Flower Extract, Vibrio Alginolyticus Ferment Filtrate, Alteromonas Ferment Extract, Tocopheryl Acetate, Polyisobutene, Polysorbate 20, Caprylic/Capric Triglyceride, Hydroxyacetophenone, Phytic Acid, Diethylhexyl Syringylidenemalonate, Disodium EDTA, Ethylhexylglycerin, Phenoxyethanol

SkinMedica Rejuvenative Moisturizer: Water/Aqua/Eau, Caprylic/Capric Triglyceride, Tocopheryl Acetate, Diglycerin, Isostearyl Behenate, Glyceryl Stearate, PEG-100 Stearate, Tetrahexyldecyl Ascorbate, Butyrospermum Parkii Butter, Panthenol, Phytosterols, Tocopherol, Tocotrienols, Squalene, Oryza Sativa Bran Cera, Aloe Barbadensis Leaf Juice, Algae Extract, Bisabolol, Ginkgo Biloba Leaf Extract, Avena Sativa Kernel Extract, Sodium Hyaluronate, Stearyl Glycyrhethinate, Retinyl Palmitate, Glycerin, Glyceryl Polyacrylate, Dimethicone, Cetyl Alcohol, Cetearyl Alcohol, Cetareth-20, Caprylyl Methicone, Carbomer, Tromethamine, Disodium EDTA, Potassium Sorbate, Phenoxyethanol, Ethylhexylglycerin, Parfum/Fragrance

SkinMedica Essential Defense Mineral Shield Broad Spectrum SPF 35 Sunscreen: Water, Cyclopentasiloxane, Dimethicone, Polyglyceryl-3 Polydimethylsiloxyethyl Dimethicone, Butylene Glycol, Aluminum Hydroxide, Dimethicone/PEG-10/15 Crosspolymer, PEG-9 Polydimethylsiloxyethyl Dimethicone, Sodium Chloride, Caffeine, Camellia oleifera Leaf Extract, Sodium Citrate, Dimethicone/Vinyl Dimethicone Crosspolymer, Triethoxysilylethyl Polydimethylsiloxyethyl Hexyl Dimethicone, Stearic Acid, Ethylhexylglycerin, Phenoxyethanol

Test Product B (4% Hydroquinone Topical Prescription Cream):  
[Ingredients TBD depending on Pharmacy]

#### **4.2 Subject Compliance**

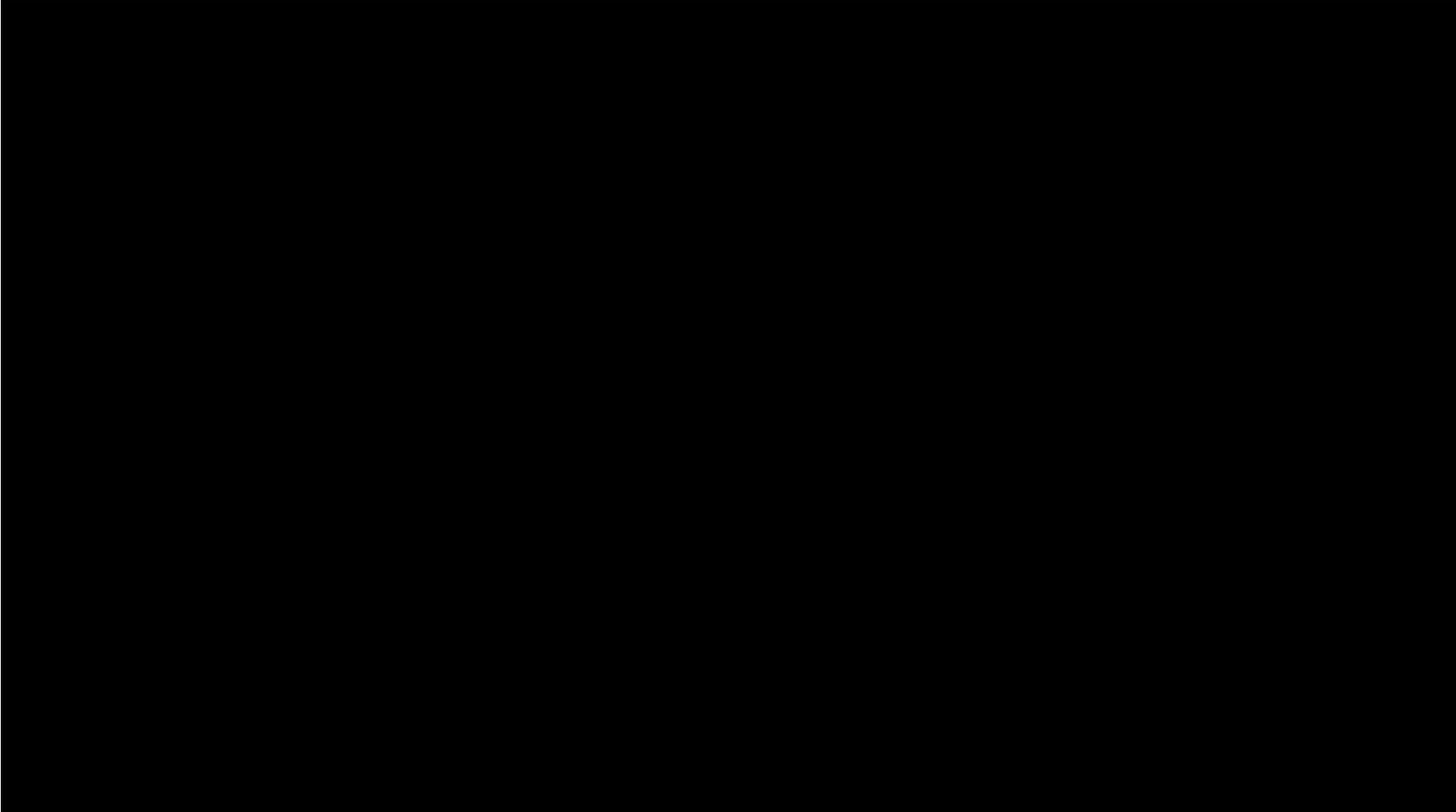
Subject compliance to the study treatment regimen will be verbally assessed; study personnel will ask each subject whether they missed any applications of study treatment since the previous visit and will quantify the subject's response.

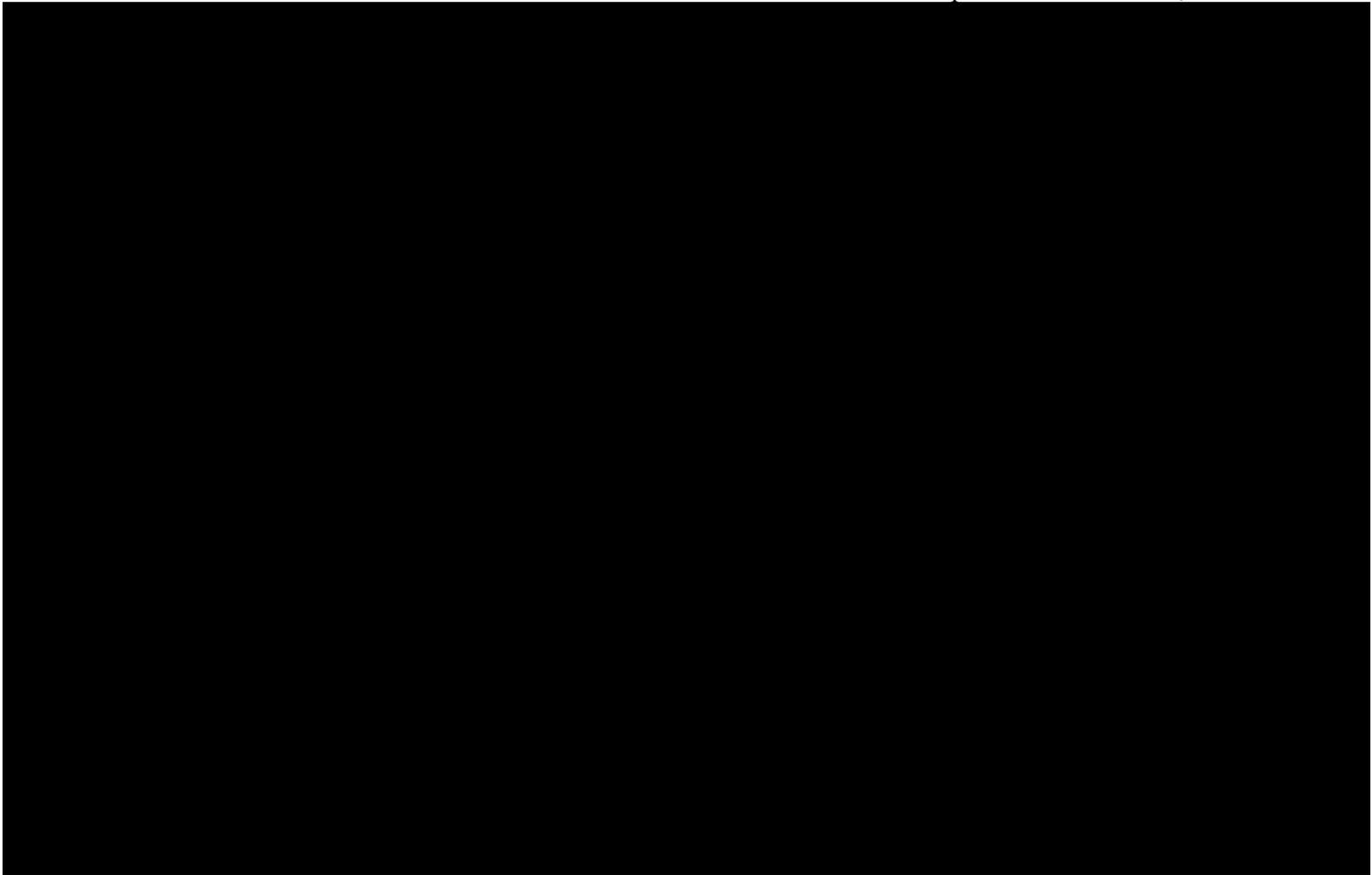
#### **4.3 Concomitant Medications**

Systemic and topical medications being used at baseline that are considered necessary for the subject's welfare and will not interfere with the study may be used. Administration of these drugs must be reported on the appropriate case report form and any alterations in the use of the medication during the study will be carefully noted. Administration of a prohibited drug (*see section 4.2 of protocol*) in an emergency situation is done with the safety of the study participant as the prime consideration. All topical and systemic medications that the subject receives during the study will be recorded. Any alterations will be noted.

#### **4.4 Treatment Group Randomization**

Subjects will be randomized in a 1:1 fashion to receive treatment with SkinMedica's cosmetic topical brightener or 4% hydroquinone. A randomization table will be provided by the sponsor and used to determine which facial side will be treated with Test Product A (cosmetic topical serum "Lytera 2.0") and Test Product B (4% hydroquinone) for each subject.





- Randomization and distribution of study products by the Unblinded study staff

[REDACTED]



## 6.0 ASSESSMENTS

### 6.1 Clinical Grading of Efficacy Parameters

Clinical grading of the efficacy parameter will be performed at the study visits indicated. Hyperpigmentation will be assessed on **the left and the right side** of each subject's face separately.

#### **Melasma Severity Rating Scale:**

At the screening/baseline visit and the end of treatment visit (week 12), the Investigator will assess the subject's facial skin for the severity of symmetrical facial melasma using the following Melasma Severity Rating Scale on the left and right facial sides. Subjects must present with a score of 2 for the left and the right facial sides to be enrolled into the study.

Score	Hyperpigmentation Status
0	Cleared: color of melasma lesions approximately equivalent to surrounding normal skin or with minimal residual hyperpigmentation
1	Mild: color slightly darker than the surrounding normal skin
2	Moderate: color moderately darker than the surrounding normal skin
3	Severe: color markedly darker than the surrounding normal skin



**Overall Hyperpigmentation Scale:**

At all visits (baseline, weeks 4, 8 and 12), the Investigator will globally assess the subject's left and right facial sides for overall hyperpigmentation using the following ten point scale (0 – 9):

<b>None</b> (Score of 0)	Skin is normal in color with no evidence of hyperpigmentation
<b>Mild</b> (Score of 1, 2 or 3)	Several brown spots with increased pigmentation; they are small in size and slightly darker than surrounding skin
<b>Moderate</b> (Score of 4, 5 or 6)	Many brown spots with increased pigmentation; they are medium in size and much darker than surrounding skin
<b>Severe</b> (Score of 7, 8 or 9)	Many large brown spots with increased pigmentation; they are large in size and markedly darker than surrounding skin

**Half-face Evaluation of Melasma Area Severity Index (MASI) Score**

At all visits, (baseline, weeks 4, 8 and 12), the Investigator will assign a grade for the left and right facial sides, for each of the below units, for the variable A (percentage of each area involved), D (darkness of pigment) and P (pattern of involvement), as described in detail below.

Calculations will be conducted by the sponsor upon receipt of the completed CRFs.

**3 variables are assessed for each half- facial unit:**

- Total Area Involved (**A**)
- Darkness of pigment (**D**)
- Homogeneity (**H**)

**Variable Definitions:**

***A = A numerical value is assigned for the corresponding percentage of the total area of the facial segment being assessed.***

This value represents ONLY the percent of the area involved, not the pattern or darkness of the pigment.

- 0**= No involvement
- 1**= <10% involvement
- 2**= 10-29% involvement
- 3**= 30-49% involvement
- 4**= 50-69% involvement
- 5**= 70-89% involvement
- 6**= 90-100% involvement

**D = Darkness of the pigment compared to adjacent normal pigment.**

- 0= Normal skin color
- 1= Slightly darker than normal color
- 2 = Mild hyperpigmentation
- 3= Moderate hyperpigmentation, clearly and distinctly darker than normal pigment
- 4 = Severe hyperpigmentation, virtually black pigment

**H = The homogeneity of the pigmentation will be assessed using the below scale:**

- 0= Normal skin color without evidence of hyperpigmentation
- 1= Specks of involvement
- 2 = Small patchy areas of involvement < 1.5 cm diameter
- 3 = Patches of involvement > 2 cm diameter
- 4 = Uniform skin involvement without any clear areas

Calculation of the half-face MASI score:

To calculate the half-face MASI score, the sum of the severity grade for darkness (D) and homogeneity (H) is multiplied by the numerical value of the areas (A) involved and by the percentages of the four facial areas (10-30%).

Total Half-Face MASI score:

Half Forehead  $0.15(D+H)A$  + One Malar Side  $0.3(D+H)A$  + Half Chin  $0.05(D+H)A$

**Investigator's Global Improvement Assessment- Overall Hyperpigmentation:**

The expert grader will also score an Investigator's Global Improvement Assessment for Overall Hyperpigmentation on the left and right facial sides at all follow-up visits (weeks 4, 8, and 12).

- 0=No change or worsening
- 1=Mild improvement (~25% overall improvement)
- 2=Moderate improvement (~50% overall improvement)
- 3=Marked improvement (~75% overall improvement)
- 4=Complete clearing/Dramatic improvement (~95%+ overall improvement)

**6.2 Investigator's Tolerability Assessment**

Tolerability of the test products will be assessed through the capture of adverse events reported throughout the study period. Any adverse event(s) experienced by the subject

during the study period, whether related to the treatment or not, will be recorded in the “Case Report Form.”

### **6.3 Subject MELASQOL Assessment**

Subjects will complete the MELASQOL assessment regarding their full face at the baseline visit and their left and right facial sides at week 12. The MELASQOL is a validated assessment to help measure the emotional and psychological impact of melasma (3). This questionnaire is found in [REDACTED]

### **6.4 Subject Self-Assessment Questionnaires**

Subjects will complete a Sponsor-provided self-assessment questionnaire at follow-up visits at weeks 4, 8, and 12. The assessment consists in a personal and subjective evaluation of their facial skin quality on the left and right side during and after the treatment by the subject. In addition, the assessment serves to evaluate the self-perceived cosmetic efficacy of the treatment and the product attributes. This questionnaire is found in [REDACTED]

### **6.5 Imaging Procedures**

Photographs will be taken at all visits utilizing standardized conditions for all subjects. The skin must be cleansed prior to photography to remove any makeup, including foundation makeup, lipstick/gloss and eye shadow. The settings for the exposure, lighting, flash, and focal length will be maintained constant over the course of the study.

Ensure that subjects jewelry is removed from ears/neck and hair is pushed back away from the face, ensuring that no stray hairs are in the facial area.

Subjects will be photographed using an appropriate clinical digital photography system [REDACTED] at highest resolution in a consistent position. Importantly, the photography should be taken to enable comparison of baseline photos with later photos taken at the end of the treatment period. For instance, if available, the overlay function must be used. As each photograph is being taken, it should be viewed to ensure that it is in focus and is similar to its baseline counterpart in all technical aspects, including lighting, distance and angle. In addition, the face should be captured in neutral facial expressions and neutral angles (e.g., avoiding hypo- or hyperextension of the neck).

Photos using the [REDACTED] will be taken from three angles to enable the improvement to be clearly noticed: full frontal (0°) and at profile from the left (45°) and from the right side (45°). Photos will be taken at controlled distances under standard room lighting. Cross-polarized, parallel- polarized and visible light images will be acquired along with both blue fluorescence and ultraviolet fluorescence images. During the photography, the subjects will be asked to keep their eyes closed.

### **6.6 Mexameter Instrumentation Procedures**

Two target hyperpigmented lesions will be selected from the left (1) and the right (2) malar facial areas and measured by the mexameter, and instrument that measures

melanin content. Measurements at subsequent visits must be taken from the same target lesion locations as at the baseline visit within each subject.

One target “normal” measurement will also be taken from an unaffected skin area on the face representing normal skin. The values from the target hyperpigmented lesions will be compared to the normal lesion value.

## **7.0 STATISTICS**

Statistical analyses will be conducted by the sponsor on an intent-to-treat basis (ex: all enrolled subjects, with at least one follow-up visit, will be included in the analysis).

## **8.0 RESPONSIBILITIES OF THE INVESTIGATOR**

### **8.1 Adherence to the Study Protocol**

The Investigator must ensure adherence to the procedures outlined in this Study Protocol. The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Investigator abides by GCP as described in the ICH Guidelines Topic E6: “Guideline for Good Clinical Practice.” Compliance with these regulations also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. The study will also be carried out in keeping with local legal and regulatory requirements.

### **8.2 Data Handling and Record Keeping**

The Investigator must ensure that proper source documentation for all study activities are diligently maintained and securely kept. The Investigator will transfer all relevant data to the Case Report Form as stipulated in this Study Protocol and his/her signature on the Case Report Form guarantees completeness and integrity of these data. The Investigator will store all study related supplies in a secure and locked location. In addition, the Investigator will ensure that all Case Report Forms will be maintained for a period of two years after the conclusion of the study.

## **9.0 REGULATORY OBLIGATIONS**

### **9.1 Institutional Review Board**

The study protocol, informed consent forms (all versions), and any specific advertising will be submitted to and approved by Independent Investigational Review Board before the start of the study. A form must be signed by the chairman or designee of the IRB noting the approvals. This notification will be provided to SkinMedica for notification of study initiation.

**9.2 Protocol**

The Investigator signing the protocol signature page will act as the Principal Investigator at this site. Protocols will be noted as approved by the Investigator by placement of his signature on the Investigator's Signature Page. Copies of the IRB approved protocol and informed consents will be provided to SkinMedica.

**9.3 Informed Consent**

An Informed Consent Form (ICF) that includes all of the relevant elements currently required by FDA or state regulations will be provided to each prospective study subject at screening and before enrollment into the study. The type and method of study, any potential or possible hazards, and the subject's right to withdraw from the study at any time will be explained to the subjects by the Investigator or Designee. Once the Investigator or Designee is assured that an individual candidate understands the implications of participating in this study, the subject will be asked to give consent by signing and dating in the appropriate areas of the Informed Consent Form. The Investigator or Designee will also sign and date the ICF. A copy of the IRB approved ICF will be given to the subject for the subject's records and the original will be filed in the subject's binder or folder.

**9.4 Protocol and Informed Consent Changes**

Changes to the protocol or Informed Consent Forms will be implemented as amendments to the original document and approved by the IRB. The approvals will be processed in accordance with the established IRB procedures. Copies of all protocol and ICF amendments/revisions, along with letters noting IRB approval, will be submitted to SkinMedica, as this may affect safety. Any addenda, amendment or revision that substantially alters the study design or increases potential risk to the subject will require the subject's consent to continue in the study.

**9.5 Study Monitoring**

The site will be responsible for internal verification of complete and accurate data collection and confirming adherence to the protocol throughout the study. The study may be monitored by Sponsor representatives to ensure that the protocol and GCP guidelines are being followed and to assist in resolving any difficulties encountered while the study is in progress. The monitoring may include site visits and frequent communications (telephone, fax, email, letters).

## **10.0 CONFIDENTIALITY OF RECORDS**

Information about the subject's health taken during this study may be used and given to others by the study coordinators, the medical staff, the respective study center and by the subject's doctors and their other healthcare providers. The subject's doctors and their healthcare providers may share health information about the subject with the investigator and study coordinator. The study coordinator and the providers may share that information with researchers participating in this study's laboratories conducting tests for this study. A final study report may be shared with SkinMedica, Inc.; The U.S. Food and Drug Administration (FDA); Department of Health and Human Services (DHHS) agencies; other U.S. and foreign government agencies that watch over quality, safety and effectiveness of research.

All research related personnel will ensure subject confidentiality is maintained. All subject related documents will be identified by subject initials and subject identification numbers. All subject related documents will be filed in individual subject binders or folders and stored in confidence by the site only to be accessed by research related personnel.

## **11.0 DELEGATION OF INVESTIGATOR RESPONSIBILITIES**

The Investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions. The investigator should maintain a list of sub-investigators and other appropriately qualified persons to whom he has delegated significant trial-related duties.

## **12.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

The Investigator must ensure that institutional regulations, the Informed Consent Form, and the HIPAA Authorization clearly permit study-related monitoring, audits, IRB review, and regulatory inspections providing direct access to source data and documents.

## **13.0 ADVERSE EVENTS AND REPORTING**

### **13.1 Serious And/Or Adverse Event Reporting**

A serious adverse event is any untoward medical occurrence, that, at any dose:

- results in death;
- is life-threatening;

- requires in-subject hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- is an important medical event.

Throughout the study, subjects will be monitored for signs and symptoms of adverse events. An adverse event is any pathological or unintended change in the structure, function or chemistry of the body that occurs during the study, irrespective of causality, including any illness, injury, toxicity, sensitivity, or sudden death. The condition must either not be present pre-study or must worsen in either intensity or frequency during the study.

An unanticipated adverse study drug event is any drug-related adverse event, which is not identified in nature, severity, or frequency in current literature on the test article.

All adverse events, including serious and study drug related or unanticipated adverse drug events, must be recorded and assessed by the Investigator. In the event of an adverse event, serious adverse event or unanticipated adverse drug event, the physician will provide optimal subject care.

Subjects who have had a serious adverse event must be followed clinically until all parameters, including laboratory values, have either returned to normal or are otherwise explained.

Any serious adverse event or unanticipated adverse drug event occurring in this study will be analyzed and identified by the investigator and reported to the IRB within 10 business days, as per IND regulations and FDA Guidance. The investigator will also determine the event related to the study drug and report that event to the manufacture of the device, if necessary.

Serious adverse events will be reported to the Sponsor within 24 hours (or the next working day). The main Sponsor contact for serious adverse events is:

[REDACTED]

If death was the outcome of the event on the initial SAE Report, a Follow-up/Final Report, including autopsy report, when performed, must be completed.

### **13.2 Pregnancy During The Study**

If a subject of childbearing potential becomes pregnant at any time while participating during the study, the pregnancy will be deemed an Adverse Event and the subject will stop all protocol related procedures. The investigator will follow-up with the subject until the pregnancy reaches term or until the pregnancy has been resolved.

The Investigator will report the Adverse Event of pregnancy to the IRB within 24 hours of awareness of the event and follow-up reports will be filed with the IRB as information with changes of the pregnancy becomes available.

### **13.3 Anticipated Reactions**

All test materials have the potential to cause some minor side-effects or other reactions. Possible reactions to the test material(s) may include (but are not limited to) subjective sensations (such as itching, burning, stinging, tingling), scaling/dryness, and redness. Additionally, test material(s) applied to the eye areas have the potential to cause eye watering/tearing, redness of the eyes, corneal erosions, and foreign body sensation in the eyes.

Symptoms of mild to moderate irritation, including the examples discussed above, will not be treated as adverse reactions if they are mild in nature. These conditions may or may not resolve over time. Symptoms that are persistent and moderate to severe in nature, or that involve elevation (e.g. edema, papules, vesicles, spreading) will be considered AEs.

In rare cases, it is possible for a subject to develop allergic reactions to the test material(s). This risk is increased for individuals with a history of allergies, and individuals with asthma and/or a history of hives may also be affected. Subjects will be instructed to notify the clinic immediately if they experience an allergic reaction including rash, hives, and itching.

The Investigator or designee will have the final authorization to determine if a reaction will be considered an AE.

### **13.4 Unknown/Unforeseeable Risks**

In addition to the risks listed above, there may be some unknown or infrequent and unforeseeable risks associated with the use of the assigned study products. Subjects will be informed both verbally and in writing in a timely manner of any new information, findings or changes to the way the research will be performed that might influence their willingness to continue their participation in this study.

**Pregnancy/Fetal Risks:** The effects of SkinMedica Facial Cleanser, Rejuvenative Moisturizer, Essential Defense Mineral Shield Broad Spectrum SPF 35, Test Product A (Lytera 2.0) and Test Product B (4% Hydroquinone) have not been studied in pregnancy and therefore may be hazardous.

If a subject thinks that she may be pregnant or have become pregnant during the study she is to inform the study doctor immediately. If a subject becomes pregnant or thinks they may be pregnant, they will be removed from the study and the study doctor will refer the subject to seek obstetric care and may request to track their pregnancy and will report to the IRB.

### **13.5 Unblinding**

In the event that a subject experiences an Adverse Event or Serious Adverse Event, the Investigator and/or Sub-Investigator will become unblinded.

## **14.0 REFERENCES**

1. Melasma: a clinical and epidemiological review\* Ana Carolina Handel, Luciane Donida Bartoli Miot, and Hélio Amante Miot, *An Bras Dermatol*. 2014 Sep-Oct; 89(5): 771–782.
2. Melasma. Etiologic and Therapeutic Considerations, Pearl E. Grimes, MD, *Arch Dermatol*. 1995;131(12):1453-1457.
3. Development and validation of a health-related quality of life instrument for women with melasma. R. Balkrishnan, et.al. *Br J Dermatol*. 2003;149:572-577.

[REDACTED]

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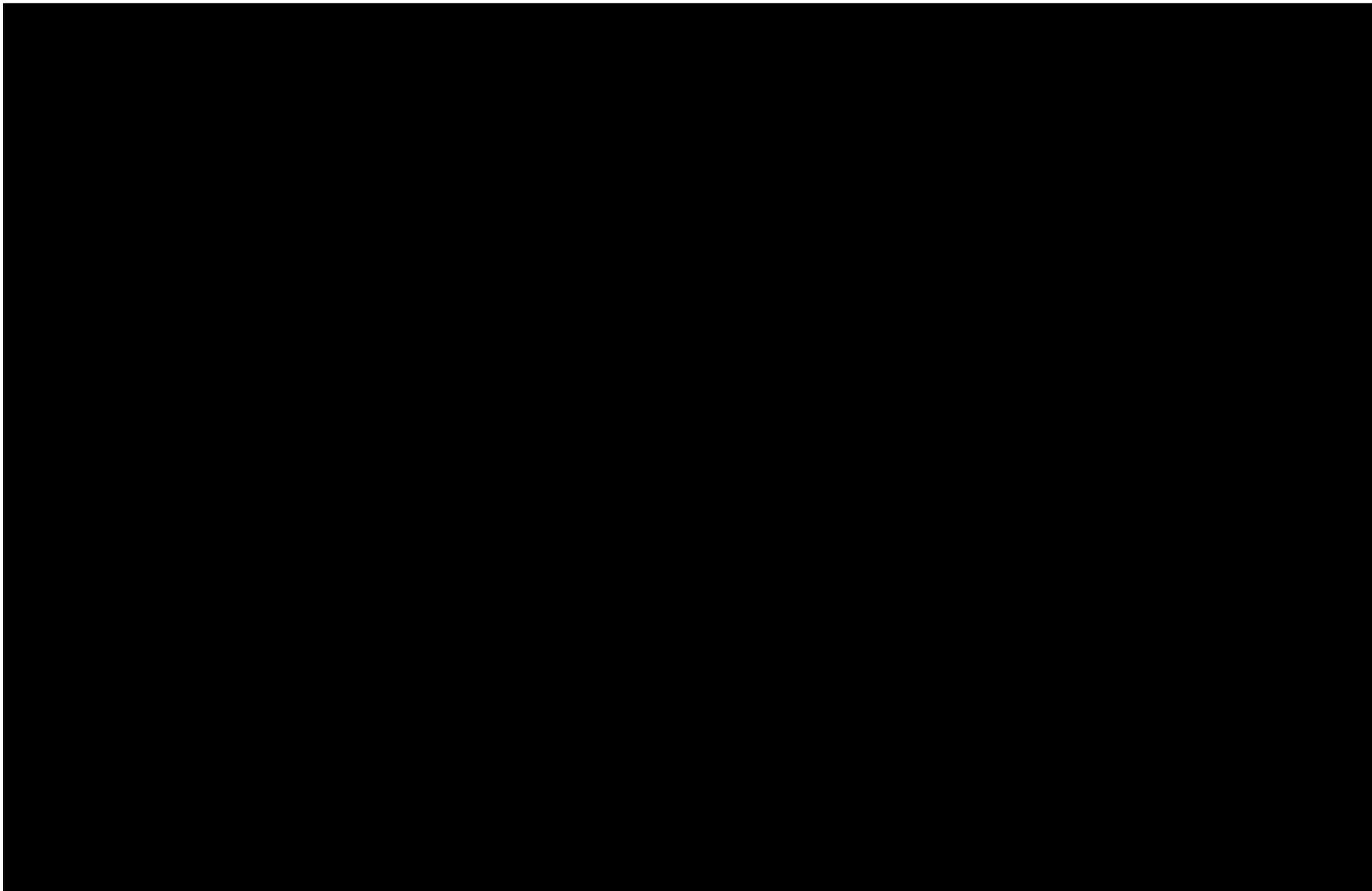
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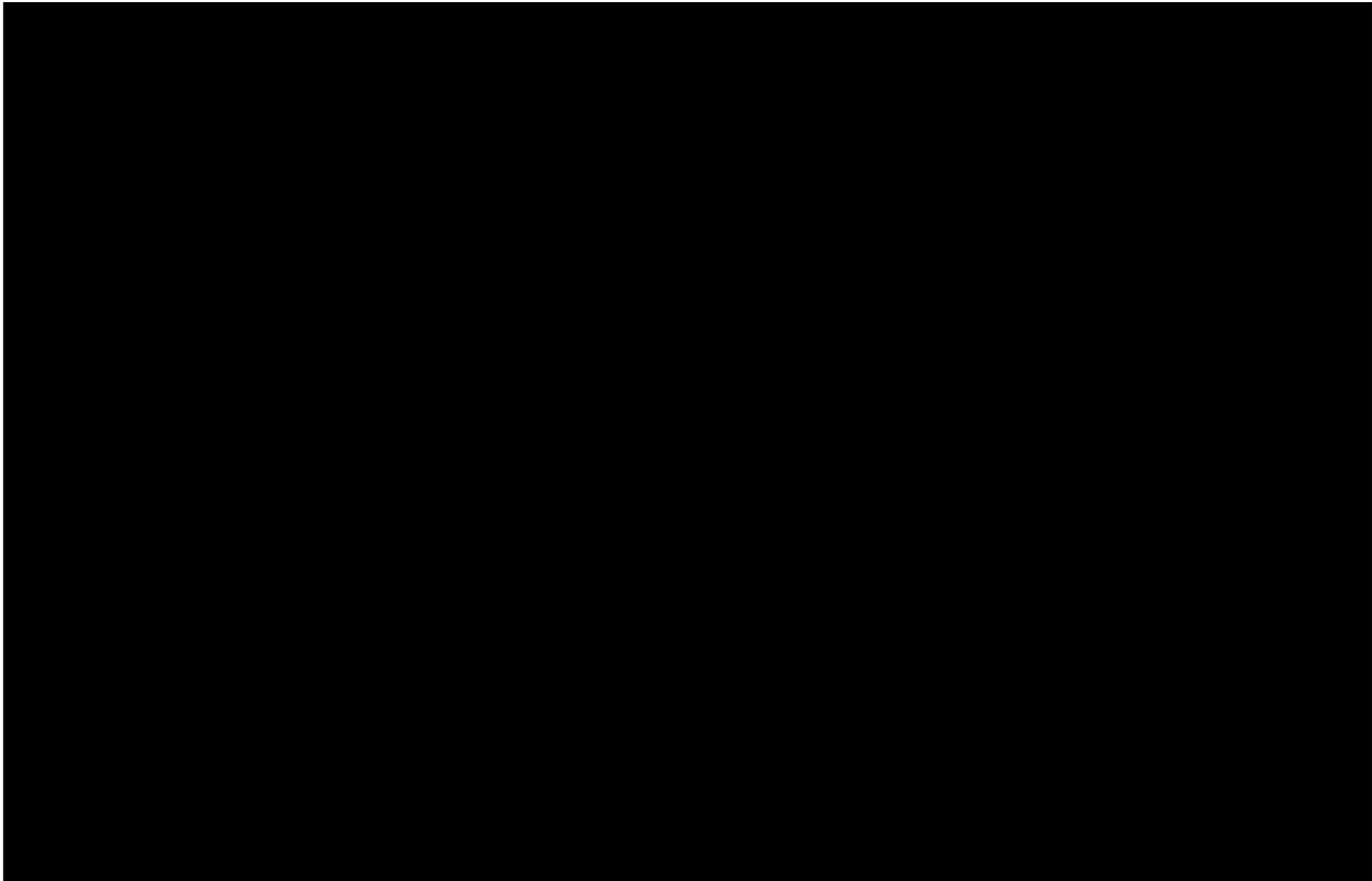
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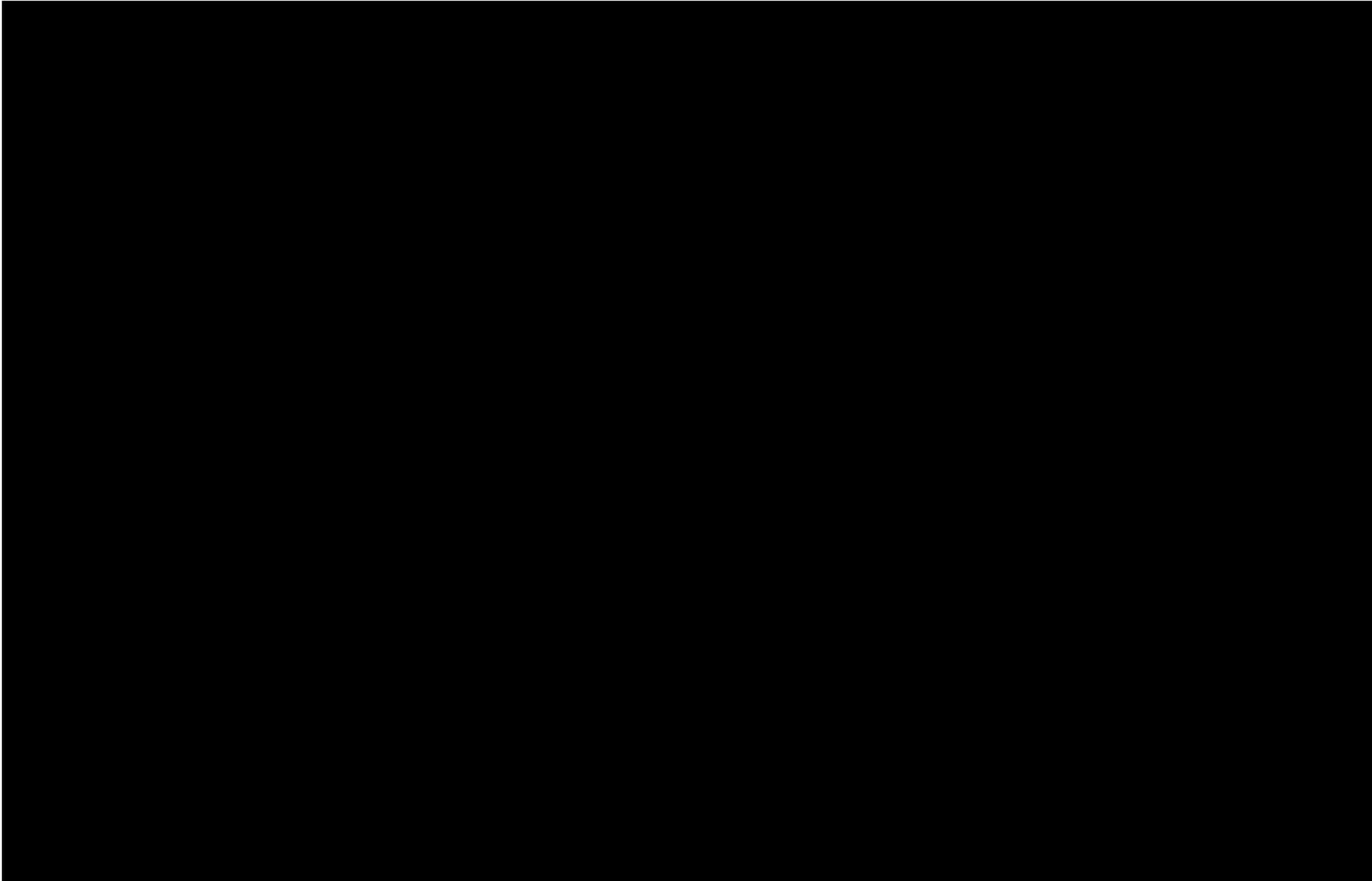
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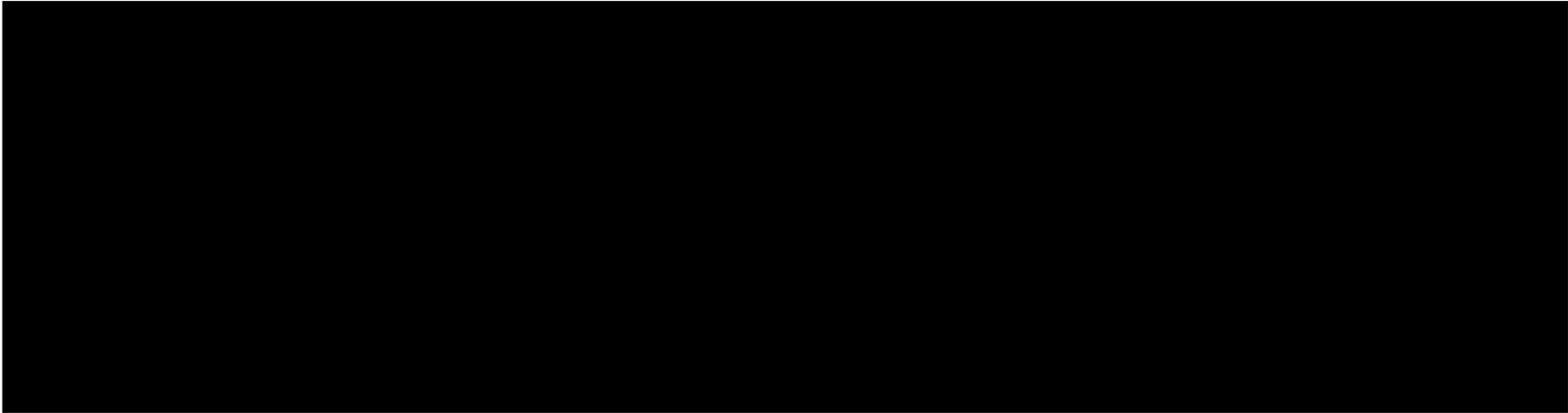
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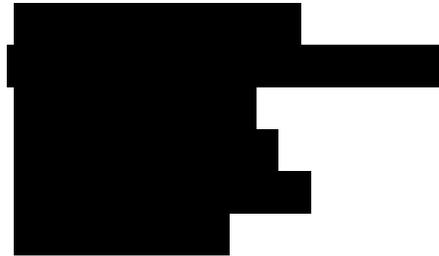


**Randomized, Double-blinded, Split-face Study comparing the  
Cosmetic Efficacy and Tolerability of Two Topical Products  
in Subjects with Moderate Facial Melasma**

**PROTOCOL NUMBER: SKM16-LYT-MEL**

**FUNDING SPONSOR:** SkinMedica Inc., an Allergan Company  
2525 Dupont Drive  
Irvine, CA 92612

**PRINCIPAL INVESTIGATOR:**



**PROTOCOL DATE:** 10/Aug/2016

The study will be conducted according to the protocol and in compliance with International Conference of Harmonisation Good Clinical Practice Guidelines and all other applicable regulatory requirements.

**CONFIDENTIALITY STATEMENT**

THE INFORMATION PROVIDED IN THIS STUDY PROTOCOL IS INTENDED FOR REVIEW BY THE PRINCIPAL INVESTIGATOR, ALL RESEARCH RELATED PERSONNEL, ETHICS COMMITTEE(S) AND HEALTH AUTHORITIES. INFORMATION PROVIDED AND CAPTURED IN THIS PROTOCOL IS STRICTLY CONFIDENTIAL AND WILL ONLY BE DISCLOSED WITH WRITTEN CONSENT FROM THE SPONSORS.



**PROTOCOL SIGNATURE PAGE**

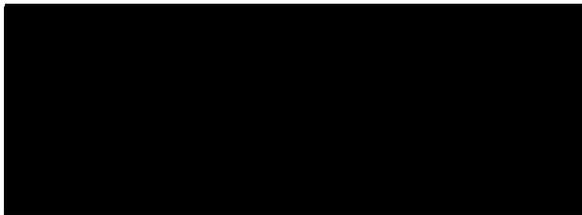
**Randomized, Double-blinded, Split-face Study comparing the  
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2525 Dupont Drive  
Irvine, CA 92612

**PRINCIPAL INVESTIGATOR:**



New York, NY 10025

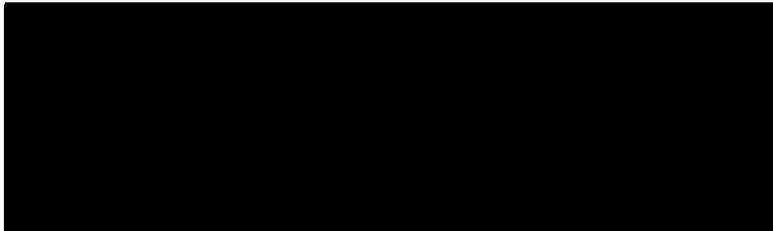
**PROTOCOL DATE:**

10/Aug/2016

I,  agree to conduct protocol "**Randomized, Investigator-blinded, Split-face Study comparing the Cosmetic Efficacy and Tolerability of Two Topical Products in Subjects with Moderate Facial Melasma**" in accordance and compliance with International Conference of Harmonisation Good Clinical Practice Guidelines and all applicable regulatory requirements.

**ACCEPTED AND AGREED:**

Principal Investigator Signature:





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**STUDY SYNOPSIS**

<b>Protocol Number</b>	SKM16-LYT-MEL
<b>Protocol Title</b>	Randomized, Double-blinded, Split-face Study comparing the Cosmetic Efficacy and Tolerability of Two Topical Products in Subjects with Moderate Facial Melasma
<b>Study Duration</b>	3 months (12 Weeks)
<b>Study Population</b>	20 healthy subjects with Fitzpatrick Skin Types III-VI
<b>Objectives</b>	To evaluate and compare the efficacy and tolerability of two topical products in the improvement of facial melasma
<b>Study Design</b>	Single site, investigator-initiated, double-blinded, parallel arm, randomized treatment, split-face, 12-week study comparing the efficacy and tolerability of SkinMedica's cosmetic topical brightener versus generic hydroquinone 4% topical prescription cream. A total of 20 healthy subjects will be enrolled into this study. Subjects will be screened and randomized at Baseline and will return for visits at Weeks 4, 8 and 12. The test products will be applied only to the affected areas (dark patches) twice a day, morning and evening, every day for 12 weeks. Ancillary products will be provided for basic daily skincare regimen use.
<b>Study Products</b>	<ul style="list-style-type: none"> <li>• SkinMedica Facial Cleanser</li> <li>• SkinMedica Rejuvenative Moisturizer</li> <li>• SkinMedica Essential Defense Mineral Shield Broad Spectrum SPF 35 Sunscreen</li> <li>• Test Product A (Lytera 2.0)</li> <li>• Test Product B (4% Hydroquinone Topical Cream-)</li> </ul>
<b>Eligibility Criteria</b>	Subjects aged 18+ with [REDACTED] symmetrical moderate facial melasma.

**1.0 BACKGROUND**

Melasma is a common disorder of hyperpigmentation which typically presents as brown or grayish brown macules on the face, including the forehead, malar region, upper lip and chin. Melasma is commonly observed in women with Fitzpatrick skin types III to V (1), especially Asian and Hispanic women, although all skin types can be affected.

Contributing causes of melasma may include ultraviolet irradiation, oral contraceptives, hormone replacement therapy, pregnancy, and thyroid dysfunction (2) however the exact etiology are not yet fully understood.

Many patients find the uneven skin tone appearance caused by melasma to be cosmetically unacceptable. Finding a successful treatment remains challenging and frustrating. Therapies include broad-spectrum sunscreens, hydroquinone, tretinoin, kojic acid, alpha hydroxy acids, salicylic acid, and chemical peels.

The treatment of hyperpigmentation associated with skin aging and melasma is challenging due to the prolonged time to respond and its high relapse rate when therapy is discontinued. Patients are also required to avoid sunlight to improve therapeutic results. Hydroquinone is currently the gold standard for the topical treatment of hyperpigmentation and melasma.

## 2.0 STUDY OBJECTIVE

The objective of this study is to evaluate the efficacy and tolerability of SkinMedica's cosmetic topical brightener versus 4% hydroquinone in the improvement of the appearance of moderate facial melasma over the course of 12 weeks.

## 3.0 STUDY POPULATION

Twenty (20) healthy subjects presenting with symmetrical moderate facial melasma, who meet all inclusion and exclusion criteria will be eligible to participate in this study.

### 3.1 Inclusion Criteria

A subject will be eligible to participate if they meet all of the following inclusion criteria:

1. Female or male aged 18+ years [REDACTED]
2. Individuals with symmetrical (with at least left and right malar region involvement) moderate melasma [REDACTED]
3. Individuals that are willing to provide written informed consent and are able to read, speak, write, and understand English.
4. Individuals willing to sign a photography release.
5. Willing to withhold all facial treatments during the course of the study including botulinum toxin, injectable fillers, microdermabrasion, IPL, peels, facials, waxing, laser treatments and tightening treatments. Threading is allowed but not facial laser hair removal.

6. Willingness to cooperate and participate by following study requirements for the duration of the study and to report any changes in health status or medications, adverse event symptoms, or reactions immediately.
7. Willingness to not begin using any new cosmetic facial make-up during the study. If regular users of cosmetic facial make-up, they must have used the product(s) without any tolerability issues for at least 2 weeks prior to starting the study.
8. Willingness to avoid as much as possible, direct and prolonged sun exposure for the duration of the study (including tanning beds), especially from 10 AM to 2 PM. Subjects are asked to wear protective clothing prior to and during exposure. Any extended sun exposure must be recorded in the source documents.

### **3.2 Exclusion Criteria**

A subject will not be eligible to participate if they meet any of the following exclusion criteria.

1. Individuals diagnosed with known allergies to study provided skin care products.
2. Individuals who are nursing, pregnant, or planning to become pregnant during the study according to subject self-report.
3. Individuals with a history of skin cancer.
4. Individuals having a health condition and/or pre-existing or dormant dermatologic disease on the face (e.g., psoriasis, rosacea, acne, eczema, seborrheic dermatitis, severe excoriations etc.) that the Investigator or designee deems inappropriate for participation or could interfere with the outcome of the study.
5. Individuals with a history of immunosuppression/immune deficiency disorders (including HIV infection or AIDS) or currently using immunosuppressive medications (e.g., azathioprine, belimumab, cyclophosphamide, Enbrel, Imuran, Humira, mycophenolate mofetil, methotrexate, prednisone, Remicade, Stelara.) and/or radiation as determined by study documentation that the Investigator or designee deems inappropriate for participation or could interfere with the outcome of the study.
6. Individuals with an uncontrolled disease such as asthma, diabetes, hypertension, hyperthyroidism, or hypothyroidism. Individuals having multiple health conditions may be excluded from participation even if the conditions are controlled by diet, medication, etc.
7. Individuals with any planned surgeries and/or invasive medical procedures during the course of the study.

8. Individuals who are currently participating in any other facial usage study or have participated in any clinical trial within 4 weeks prior to inclusion into the study.
9. Individuals who have observable suntan, scars, nevi, excessive hair, etc. or other dermal conditions on the face that might influence the test results in the opinion of the Investigator or designee.
10. Individuals who started hormone replacement therapies (HRT) or hormones for birth control less than 3 months prior to study entry or who plan on starting, stopping, or changing doses of HRT or hormones for birth control during the study.
11. Individuals who used any of the following medications or had any of the listed procedures within the listed time frame prior to the study start date:
  - Retin-A®, Retin-A Micro®, Renova®, Avita®, Tazorac®, Soriatane®, or Differin® within 4 months
  - Had a chemical peel, dermabrasion, non-ablative laser or fractional laser resurfacing of the face and neck within 1 month.
  - Accutane® within 12 months
  - Prescription strength skin lightening products (e.g. hydroquinone, tretinoin, AHA, BHA and polyhydroxy acids, 4-hydroxyanisole alone or in combination with tretinoin, etc.) within 3 months
  - Any anti-wrinkle, skin lightening products, or any other product or topical or systemic medication known to affect skin aging or dyschromia (products containing alpha/beta/poly-hydroxy acids, vitamin C, soy, Q-10, hydroquinone; systemic or licorice extract (topically), Tego® Cosmo C250, gigawhite, lemon juice extract (topically), emblica extract, etc.) within 2 weeks.
  - Have undergone a regimen of Thermage treatments or an equivalent type of high energy treatments, plastic surgery, or ablative laser resurfacing of the face and neck within 12 months
  - Had facial treatment with a botulinum toxin base injectable (Botox), injectable fillers, or a fat transfer within 6 months.

#### 4.0 METHODS AND MATERIALS





#### 4.2 Study Products

SkinMedica Facial Cleanser: Water/Aqua/Eau, Disodium Laureth Sulfosuccinate, Cocamidopropyl Hydroxysultaine, Sodium Lauryl Sulfoacetate, Camellia Oleifera Leaf Extract, Glycerin, Panthenol, Butylene Glycol, Ethylhexylglycerin, PEG-150 Pentaerythrityl Tetrastearate, PEG-6, Caprylic/Capric, Glycerides, Disodium EDTA, Phenoxyethanol, Parfum/Fragrance, Blue 1 (CI 42090), Yellow 10 (CI 47005)

Test Product A (Cosmetic topical serum "Lytera 2.0"): Water/Aqua/Eau, Butylene Glycol, Glycerin, Niacinamide, Polyacrylate-13, Phenylethyl Resorcinol, Tranexamic Acid, Vitis Vinifera (Grape) Flower Cell Extract, Plankton Extract, Tetrapeptide-30, Artemisia Capillaris Flower Extract, Vibrio Alginolyticus Ferment Filtrate, Alteromonas Ferment Extract, Tocopheryl Acetate, Polyisobutene, Polysorbate 20, Caprylic/Capric Triglyceride, Hydroxyacetophenone, Phytic Acid, Diethylhexyl Syringylidenemalonate, Disodium EDTA, Ethylhexylglycerin, Phenoxyethanol

SkinMedica Rejuvenative Moisturizer: Water/Aqua/Eau, Caprylic/Capric Triglyceride, Tocopheryl Acetate, Diglycerin, Isostearyl Behenate, Glycerol



Stearate, PEG-100 Stearate, Tetrahexyldecyl Ascorbate, Butyrospermum Parkii Butter, Panthenol, Phytosterols, Tocopherol, Tocotrienols, Squalene, Oryza Sativa Bran Cera, Aloe Barbadensis Leaf Juice, Algae Extract, Bisabolol, Ginkgo Biloba Leaf Extract, Avena Sativa Kernel Extract, Sodium Hyaluronate, Stearyl Glycyrhethinate, Retinyl Palmitate, Glycerin, Glyceryl Polyacrylate, Dimethicone, Cetyl Alcohol, Cetearyl Alcohol, Cetareth-20, Caprylyl Methicone, Carbomer, Tromethamine, Disodium EDTA, Potassium Sorbate, Phenoxyethanol, Ethylhexylglycerin, Parfum/Fragrance

SkinMedica Essential Defense Mineral Shield Broad Spectrum SPF 35

Sunscreens: Water, Cyclopentasiloxane, Dimethicone, Polyglyceryl-3 Polydimethylsiloxyethyl Dimethicone, Butylene Glycol, Aluminum Hydroxide, Dimethicone/PEG-10/15 Crosspolymer, PEG-9 Polydimethylsiloxyethyl Dimethicone, Sodium Chloride, Caffeine, Camellia oleifera Leaf Extract, Sodium Citrate, Dimethicone/Vinyl Dimethicone Crosspolymer, Triethoxysilylethyl Polydimethylsiloxyethyl Hexyl Dimethicone, Stearic Acid, Ethylhexylglycerin, Phenoxyethanol

Test Product B (4% Hydroquinone Topical Prescription Cream):

[Ingredients TBD depending on Pharmacy]

#### **4.3 Subject Compliance**

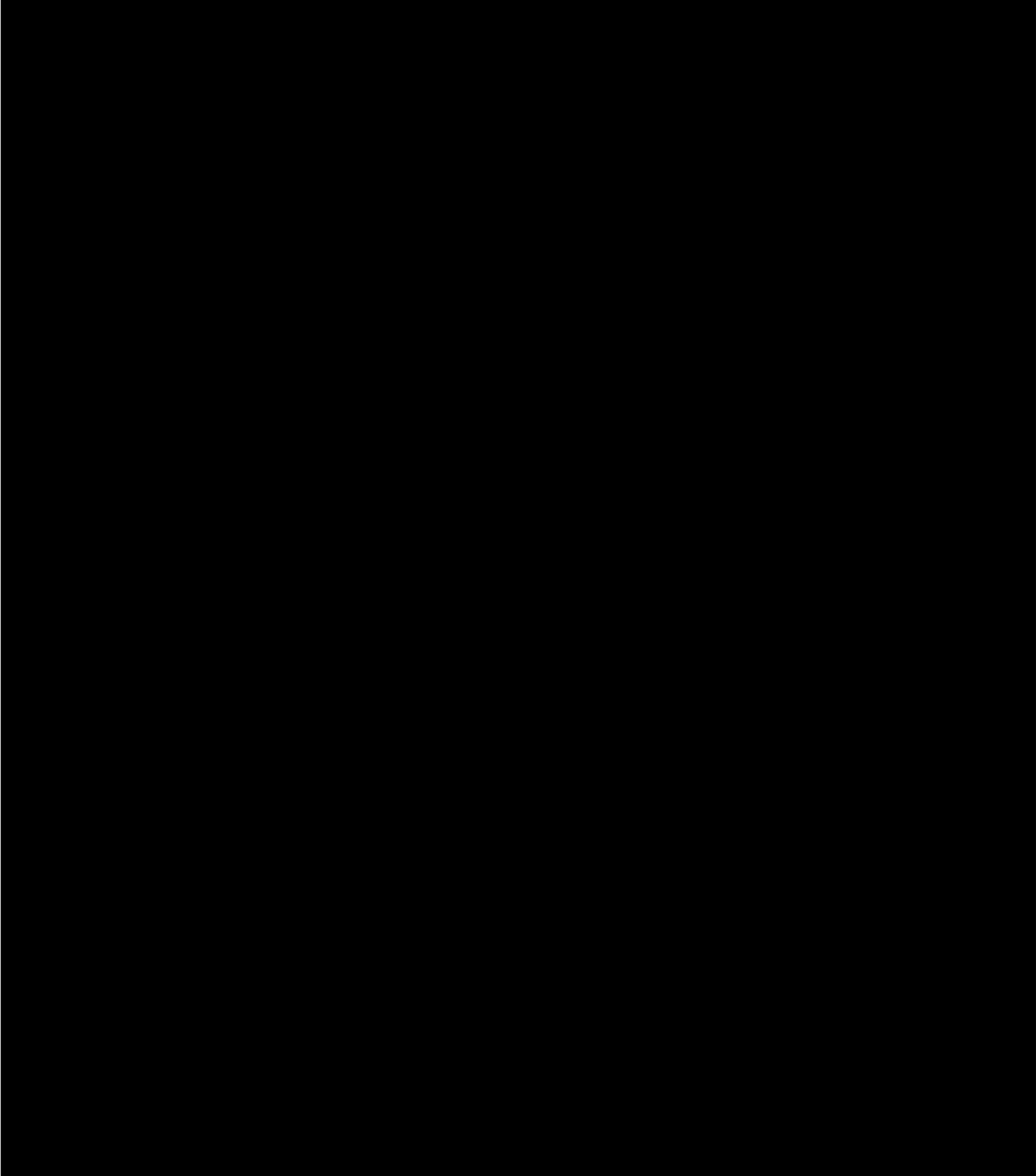
Subject compliance to the study treatment regimen will be verbally assessed; study personnel will ask each subject whether they missed any applications of study treatment since the previous visit and will quantify the subject's response.

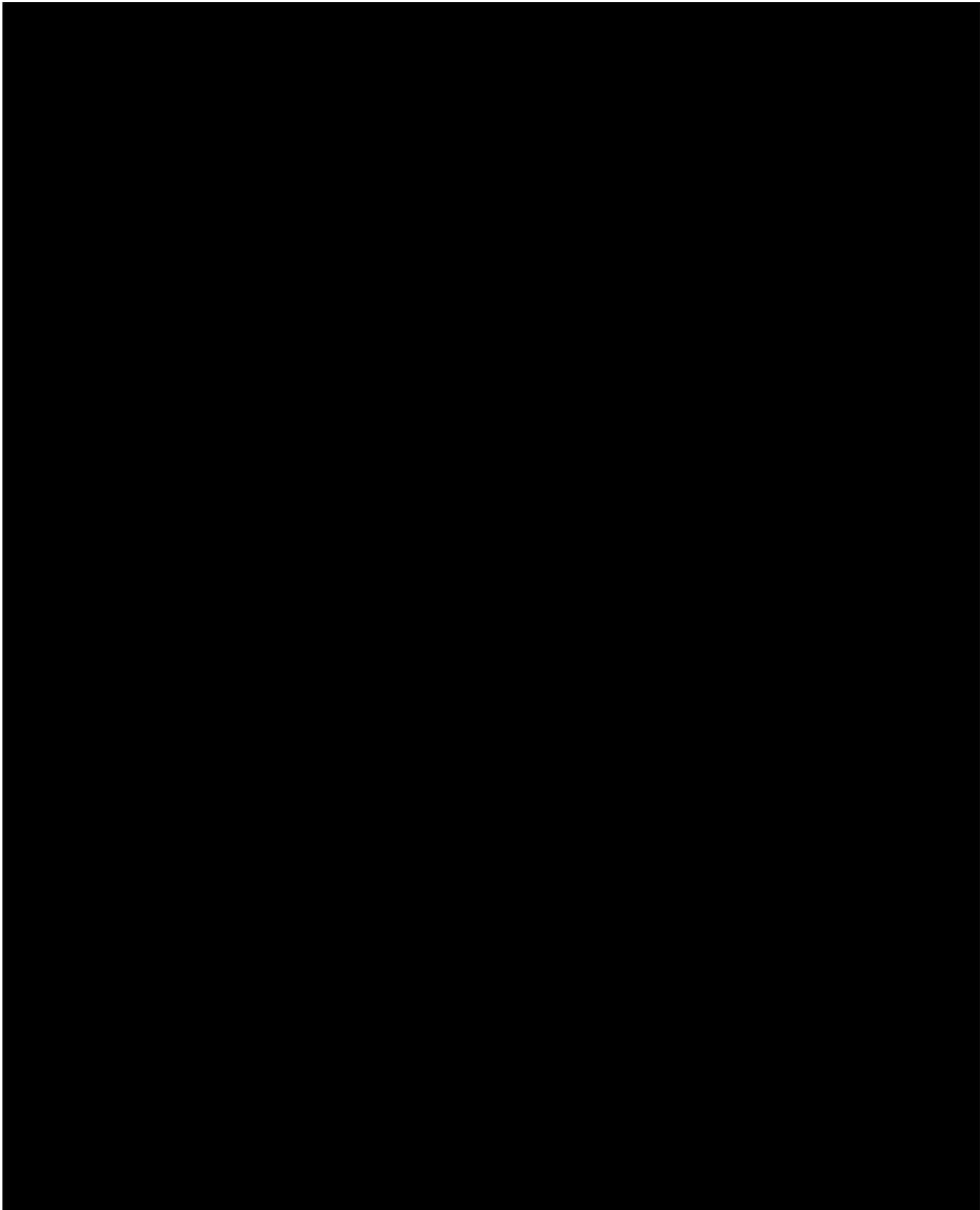
#### **4.4 Concomitant Medications**

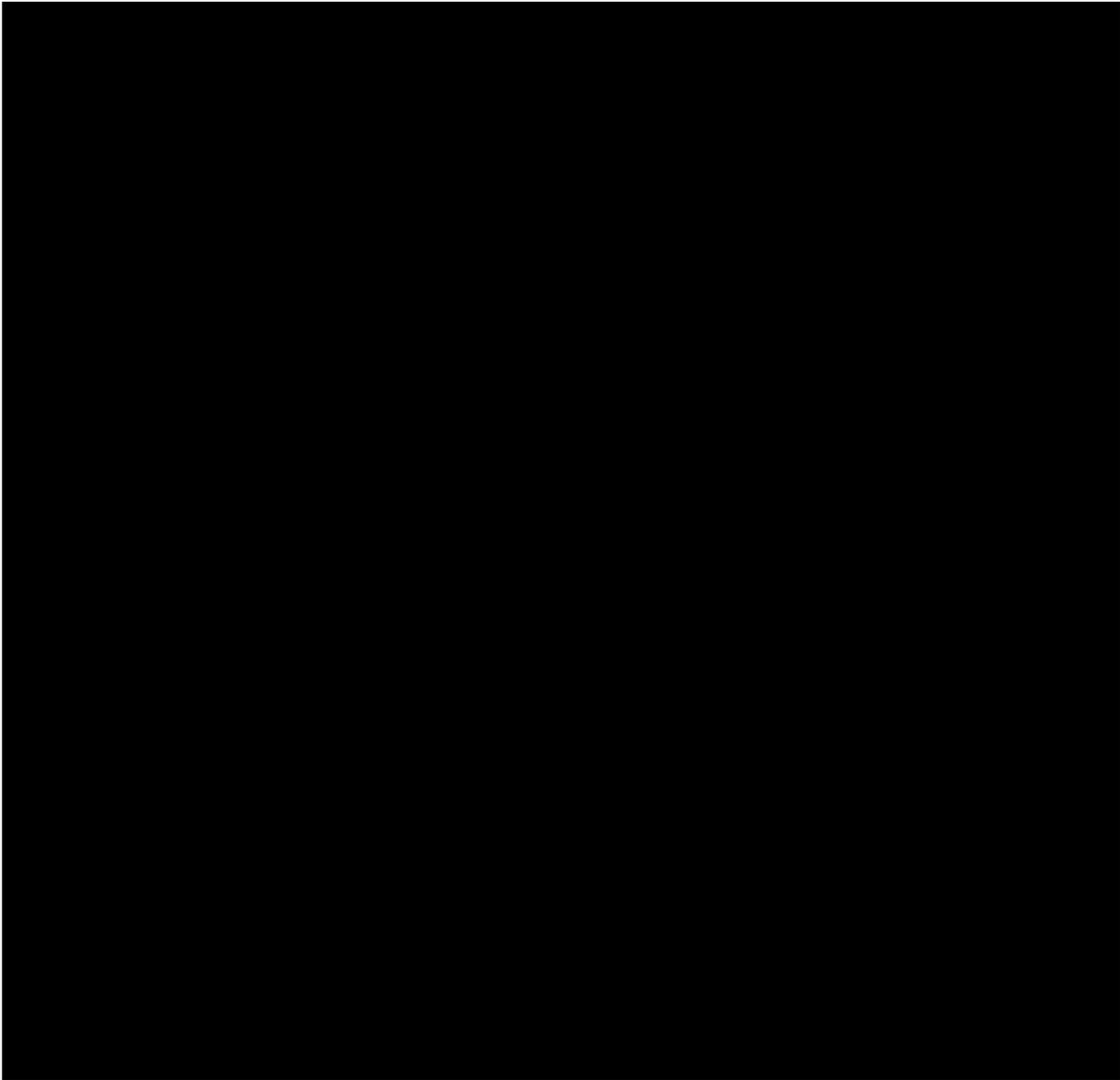
Systemic and topical medications being used at baseline that are considered necessary for the subject's welfare and will not interfere with the study may be used. Administration of these drugs must be reported on the appropriate case report form and any alterations in the use of the medication during the study will be carefully noted. Administration of a prohibited drug (*see section 4.2 of protocol*) in an emergency situation is done with the safety of the study participant as the prime consideration. All topical and systemic medications that the subject receives during the study will be recorded. Any alterations will be noted.

#### **4.5 Treatment Group Randomization**

Subjects will be randomized in a 1:1 fashion to receive treatment with SkinMedica's cosmetic topical brightener or 4% hydroquinone. A randomization table will be provided by the sponsor and used to determine which facial side will be treated with Test Product A (cosmetic topical serum "Lytera 2.0") and Test Product B (4% hydroquinone) for each subject.







## **6.0 ASSESSMENTS**

### **6.1 Clinical Grading of Efficacy Parameters**

Clinical grading of the efficacy parameter will be performed at the study visits indicated. Hyperpigmentation will be assessed on **the left and the right side** of each subject's face separately.

#### **Melasma Severity Rating Scale:**



At the screening/baseline visit and the end of treatment visit (week 12), the Investigator will assess the subject's facial skin for the severity of symmetrical facial melasma using the following Melasma Severity Rating Scale on the left and right facial sides. Subjects must present with a score of 2 for the left and the right facial sides to be enrolled into the study.

Score	Hyperpigmentation Status
0	Cleared: color of melasma lesions approximately equivalent to surrounding normal skin or with minimal residual hyperpigmentation
1	Mild: color slightly darker than the surrounding normal skin
2	Moderate: color moderately darker than the surrounding normal skin
3	Severe: color markedly darker than the surrounding normal skin

#### **Overall Hyperpigmentation Scale:**

At all visits (baseline, weeks 4, 8 and 12), the Investigator will globally assess the subject's left and right facial sides for overall hyperpigmentation using the following ten point scale (0 – 9):

<b>None</b> (Score of 0)	Skin is normal in color with no evidence of hyperpigmentation
<b>Mild</b> (Score of 1, 2 or 3)	Several brown spots with increased pigmentation; they are small in size and slightly darker than surrounding skin
<b>Moderate</b> (Score of 4, 5 or 6)	Many brown spots with increased pigmentation; they are medium in size and much darker than surrounding skin
<b>Severe</b> (Score of 7, 8 or 9)	Many large brown spots with increased pigmentation; they are large in size and markedly darker than surrounding skin

#### **Half-face Evaluation of Melasma Area Severity Index (MASI) Score**

At all visits, (baseline, weeks 4, 8 and 12), the Investigator will assign a grade for the left and right facial sides, for each of the below units, for the variable A (percentage of each area involved), D (darkness of pigment) and P (pattern of involvement), as described in detail below.

Calculations will be conducted by the sponsor upon receipt of the completed CRFs.

**3 variables are assessed for each half- facial unit:**

- Total Area Involved (**A**)
- Darkness of pigment (**D**)
- Homogeneity (**H**)

**Variable Definitions:**

***A = A numerical value is assigned for the corresponding percentage of the total area of the facial segment being assessed.***

This value represents ONLY the percent of the area involved, not the pattern or darkness of the pigment.

- 0**= No involvement
- 1**= <10% involvement
- 2**= 10-29% involvement
- 3**= 30-49% involvement
- 4**= 50-69% involvement
- 5**= 70-89% involvement
- 6**= 90-100% involvement

***D = Darkness of the pigment compared to adjacent normal pigment.***

- 0**= Normal skin color
- 1**= Slightly darker than normal color
- 2** = Mild hyperpigmentation
- 3**= Moderate hyperpigmentation, clearly and distinctly darker than normal pigment
- 4** = Severe hyperpigmentation, virtually black pigment

***H = The homogeneity of the pigmentation will be assessed using the below scale:***

- 0**= Normal skin color without evidence of hyperpigmentation
- 1**= Specks of involvement
- 2** = Small patchy areas of involvement < 1.5 cm diameter
- 3** = Patches of involvement > 2 cm diameter
- 4** = Uniform skin involvement without any clear areas

Calculation of the half-face MASI score:

To calculate the half-face MASI score, the sum of the severity grade for darkness (D) and homogeneity (H) is multiplied by the numerical value of the areas (A) involved and by the percentages of the four facial areas (10-30%).

Total Half-Face MASI score:

Half Forehead  $0.15(D+H)A$  + One Malar Side  $0.3(D+H)A$  + Half Chin  $0.05(D+H)A$

**Investigator's Global Improvement Assessment- Overall****Hyperpigmentation:**

The expert grader will also score an Investigator's Global Improvement Assessment for Overall Hyperpigmentation on the left and right facial sides at all follow-up visits (weeks 4, 8, and 12).

0=No change or worsening

1=Mild improvement (~25% overall improvement)

2=Moderate improvement (~50% overall improvement)

3=Marked improvement (~75% overall improvement)

4=Complete clearing/Dramatic improvement (~95%+ overall improvement)

**6.2 Investigator's Tolerability Assessment**

Tolerability of the test products will be assessed through the capture of adverse events reported throughout the study period. Any adverse event(s) experienced by the subject during the study period, whether related to the treatment or not, will be recorded in the "Case Report Form."

**6.3 Subject MELASQOL Assessment**

Subjects will complete the MELASQOL assessment regarding the left and their right facial sides at the baseline visit and at week 12 only. The MELASQOL is a validated assessment to help measure the emotional and psychological impact of melasma (3). This questionnaire is found in [REDACTED].

**6.4 Subject Self-Assessment Questionnaires**

Subjects will complete a Sponsor-provided self-assessment questionnaire at follow-up visits at weeks 4, 8, and 12. The assessment consists in a personal and subjective evaluation of the facial skin quality during and after the treatment by the subject. In addition, the assessment serves to evaluate the self-perceived cosmetic efficacy of the treatment and the product attributes. This questionnaire is found in [REDACTED].

**6.5 Imaging Procedures**

Photographs will be taken at all visits utilizing standardized conditions for all subjects.

The skin must be cleansed prior to photography to remove any makeup, including foundation makeup, lipstick/gloss and eye shadow. The settings for the exposure, lighting, flash, and focal length will be maintained constant over the course of the study.

Ensure that subjects jewelry is removed from ears/neck and hair is pushed back away from the face, ensuring that no stray hairs are in the facial area.

Subjects will be photographed using an appropriate clinical digital photography system [REDACTED] at highest resolution in a consistent position. Importantly, the photography should be taken to enable comparison of baseline photos with later photos taken at the end of the treatment period. For instance, if available, the overlay function must be used. As each photograph is being taken, it should be viewed to ensure that it is in focus and is similar to its baseline counterpart in all technical aspects, including lighting, distance and angle. In addition, the face should be captured in neutral facial expressions and neutral angles (e.g., avoiding hypo- or hyperextension of the neck).

Photos using the [REDACTED] will be taken from three angles to enable the improvement to be clearly noticed: full frontal (0°) and at profile from the left (45°) and from the right side (45°). Photos will be taken at controlled distances under standard room lighting. Cross-polarized, parallel- polarized and visible light images will be acquired along with both blue fluorescence and ultraviolet fluorescence images. During the photography, the subjects will be asked to keep their eyes closed.

## **6.6 Mexameter Instrumentation Procedures**

Two target hyperpigmented lesions will be selected from the left (1) and the right (2) malar facial areas and measured by the mexameter, and instrument that measures melanin content. Measurements at subsequent visits must be taken from the same target lesion locations as at the baseline visit within each subject.

One target “normal” measurement will also be taken from an unaffected skin area on the face representing normal skin. The values from the target hyperpigmented lesions will be compared to the normal lesion value.

## **7.0 STATISTICS**

Statistical analyses will be conducted by the sponsor on an intent-to-treat basis (ex: all enrolled subjects, with at least one follow-up visit, will be included in the analysis).

## **8.0 RESPONSIBILITIES OF THE INVESTIGATOR**

### **8.1 Adherence to the Study Protocol**

The Investigator must ensure adherence to the procedures outlined in this Study Protocol. The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Investigator abides by GCP as described in the ICH Guidelines Topic E6:

“Guideline for Good Clinical Practice.” Compliance with these regulations also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. The study will also be carried out in keeping with local legal and regulatory requirements.

## **8.2 Data Handling and Record Keeping**

The Investigator must ensure that proper source documentation for all study activities are diligently maintained and securely kept. The Investigator will transfer all relevant data to the Case Report Form as stipulated in this Study Protocol and his/her signature on the Case Report Form guarantees completeness and integrity of these data. The Investigator will store all study related supplies in a secure and locked location. In addition, the Investigator will ensure that all Case Report Forms will be maintained for a period of two years after the conclusion of the study.

## **9.0 REGULATORY OBLIGATIONS**

### **9.1 Institutional Review Board**

The study protocol, informed consent forms (all versions), and any specific advertising will be submitted to and approved by Independent Investigational Review Board before the start of the study. A form must be signed by the chairman or designee of the IRB noting the approvals. This notification will be provided to SkinMedica for notification of study initiation.

### **9.2 Protocol**

The Investigator signing the protocol signature page will act as the Principal Investigator at this site. Protocols will be noted as approved by the Investigator by placement of his signature on the Investigator’s Signature Page. Copies of the IRB approved protocol and informed consents will be provided to SkinMedica.

### **9.3 Informed Consent**

An Informed Consent Form (ICF) that includes all of the relevant elements currently required by FDA or state regulations will be provided to each prospective study subject at screening and before enrollment into the study. The type and method of study, any potential or possible hazards, and the subject’s right to withdraw from the study at any time will be explained to the subjects by the Investigator or Designee. Once the Investigator or Designee is assured that an individual candidate understands the implications of participating in this study,

the subject will be asked to give consent by signing and dating in the appropriate areas of the Informed Consent Form. The Investigator or Designee will also sign and date the ICF. A copy of the IRB approved ICF will be given to the subject for the subject's records and the original will be filed in the subject's binder or folder.

#### **9.4 Protocol and Informed Consent Changes**

Changes to the protocol or Informed Consent Forms will be implemented as amendments to the original document and approved by the IRB. The approvals will be processed in accordance with the established IRB procedures. Copies of all protocol and ICF amendments/revisions, along with letters noting IRB approval, will be submitted to SkinMedica, as this may affect safety. Any addenda, amendment or revision that substantially alters the study design or increases potential risk to the subject will require the subject's consent to continue in the study.

#### **9.5 Study Monitoring**

The site will be responsible for internal verification of complete and accurate data collection and confirming adherence to the protocol throughout the study. The study may be monitored by Sponsor representatives to ensure that the protocol and GCP guidelines are being followed and to assist in resolving any difficulties encountered while the study is in progress. The monitoring may include site visits and frequent communications (telephone, fax, email, letters).

### **10.0 CONFIDENTIALITY OF RECORDS**

Information about the subject's health taken during this study may be used and given to others by the study coordinators, the medical staff, the respective study center and by the subject's doctors and their other healthcare providers. The subject's doctors and their healthcare providers may share health information about the subject with the investigator and study coordinator. The study coordinator and the providers may share that information with researchers participating in this study's laboratories conducting tests for this study. A final study report may be shared with SkinMedica, Inc.; The U.S. Food and Drug Administration (FDA); Department of Health and Human Services (DHHS) agencies; other U.S. and foreign government agencies that watch over quality, safety and effectiveness of research.

All research related personnel will ensure subject confidentiality is maintained. All subject related documents will be identified by subject initials and subject identification numbers. All subject related documents will be filed in individual subject binders or

folders and stored in confidence by the site only to be accessed by research related personnel.

## **11.0 DELEGATION OF INVESTIGATOR RESPONSIBILITIES**

The Investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions. The investigator should maintain a list of sub-investigators and other appropriately qualified persons to whom he has delegated significant trial-related duties.

## **12.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

The Investigator must ensure that institutional regulations, the Informed Consent Form, and the HIPAA Authorization clearly permit study-related monitoring, audits, IRB review, and regulatory inspections providing direct access to source data and documents.

## **13.0 ADVERSE EVENTS AND REPORTING**

### **13.1 Serious And/Or Adverse Event Reporting**

A serious adverse event is any untoward medical occurrence, that, at any dose:

- results in death;
- is life-threatening;
- requires in-subject hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- is an important medical event.

Throughout the study, subjects will be monitored for signs and symptoms of adverse events. An adverse event is any pathological or unintended change in the structure, function or chemistry of the body that occurs during the study, irrespective of causality, including any illness, injury, toxicity, sensitivity, or sudden death. The condition must either not be present pre-study or must worsen in either intensity or frequency during the study.

An unanticipated adverse study drug event is any drug-related adverse event, which is not identified in nature, severity, or frequency in current literature on the test article.

All adverse events, including serious and study drug related or unanticipated adverse drug events, must be recorded and assessed by the Investigator. In the event of an adverse event, serious adverse event or unanticipated adverse drug event, the physician will provide optimal subject care.

Subjects who have had a serious adverse event must be followed clinically until all parameters, including laboratory values, have either returned to normal or are otherwise explained.

Any serious adverse event or unanticipated adverse drug event occurring in this study will be analyzed and identified by the investigator and reported to the IRB within 10 business days, as per IND regulations and FDA Guidance. The investigator will also determine the event related to the study drug and report that event to the manufacture of the device, if necessary.

Serious adverse events will be reported to the Sponsor within 24 hours (or the next working day). The main Sponsor contact for serious adverse events is:



If death was the outcome of the event on the initial SAE Report, a Follow-up/Final Report, including autopsy report, when performed, must be completed.

### **13.2 Pregnancy During The Study**

If a subject of childbearing potential becomes pregnant at any time while participating during the study, the pregnancy will be deemed an Adverse Event and the subject will stop all protocol related procedures. The investigator will follow-up with the subject until the pregnancy reaches term or until the pregnancy has been resolved.

The Investigator will report the Adverse Event of pregnancy to the IRB within 24 hours of awareness of the event and follow-up reports will be filed with the IRB as information with changes of the pregnancy becomes available.

### **13.3 Anticipated Reactions**

All test materials have the potential to cause some minor side-effects or other reactions. Possible reactions to the test material(s) may include (but are not limited to) subjective sensations (such as itching, burning, stinging, tingling),

scaling/dryness, and redness. Additionally, test material(s) applied to the eye areas have the potential to cause eye watering/tearing, redness of the eyes, corneal erosions, and foreign body sensation in the eyes.

Symptoms of mild to moderate irritation, including the examples discussed above, will not be treated as adverse reactions if they are mild in nature. These conditions may or may not resolve over time. Symptoms that are persistent and moderate to severe in nature, or that involve elevation (e.g. edema, papules, vesicles, spreading) will be considered AEs.

In rare cases, it is possible for a subject to develop allergic reactions to the test material(s). This risk is increased for individuals with a history of allergies, and individuals with asthma and/or a history of hives may also be affected. Subjects will be instructed to notify the clinic immediately if they experience an allergic reaction including rash, hives, and itching.

The Investigator or designee will have the final authorization to determine if a reaction will be considered an AE.

#### **13.4 Unknown/Unforeseeable Risks**

In addition to the risks listed above, there may be some unknown or infrequent and unforeseeable risks associated with the use of the assigned study products. Subjects will be informed both verbally and in writing in a timely manner of any new information, findings or changes to the way the research will be performed that might influence their willingness to continue their participation in this study.

**Pregnancy/Fetal Risks:** The effects of SkinMedica Facial Cleanser, Rejuvenative Moisturizer, Essential Defense Mineral Shield Broad Spectrum SPF 35, Test Product A (Lytera 2.0) and Test Product B (4% Hydroquinone) have not been studied in pregnancy and therefore may be hazardous.

If a subject thinks that she may be pregnant or have become pregnant during the study she is to inform the study doctor immediately. If a subject becomes pregnant or thinks they may be pregnant, they will be removed from the study and the study doctor will refer the subject to seek obstetric care and may request to track their pregnancy and will report to the IRB.

#### **13.5 Unblinding**

In the event that a subject experiences an Adverse Event or Serious Adverse Event, the Investigator and/or Sub-Investigator will become unblinded.

## **14.0 REFERENCES**

1. Melasma: a clinical and epidemiological review\* Ana Carolina Handel, Luciane Donida Bartoli Miot, and Hélio Amante Miot, *An Bras Dermatol.* 2014 Sep-Oct; 89(5): 771–782.

2. Melasma. Etiologic and Therapeutic Considerations, Pearl E. Grimes, MD, *Arch Dermatol.* 1995;131(12):1453-1457.
3. Development and validation of a health-related quality of life instrument for women with melasma. R. Balkrishnan, et.al. *Br J Dermatol.* 2003;149:572-577.

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