NCT03302559

Study ID: SCRIC17-RET05

Title: Assessing the Cosmetic Changes in the Facial Skin Utilizing Non-Invasive In Vivo Skin Imaging Instrumentation After Use of a Topical Retinoid Product In Subjects With Moderate to Severe Photodamage

Protocol Amendment 1 Date: 15 November 2017

SkinMedica
An Allergan Company

Assessing the cosmetic changes in the facial skin utilizing non-invasive *in vivo* skin imaging instrumentation after use of a topical retinoid product in subjects with moderate to severe photodamage

PROTOCOL NUMBER	SCRIC17-RET05
ORIGINAL PROTOCOL	**DATE**: August 10, 2017
AMENDMENT #1	**AMENDMENT DATE:** November 15, 2017
INVESTIGATORS	[redacted] SkinMedica Clinical Research and Innovation Center 2525 Dupont Drive [redacted] Irvine, CA 92612 [redacted]
SUB-INVESTIGATORS	[redacted]
INSTITUTIONAL REVIEW BOARD	[redacted]
SPONSOR	SkinMedica Inc., an Allergan Company [redacted] SkinMedica Clinical Research and Innovation Center 2525 Dupont Drive, [redacted] Irvine, CA 92612 [redacted]

STUDY ACKNOWLEDGEMENT

I have read this protocol and agree that it contains all the details necessary to conduct the study as described. I will conduct this study following this protocol and will make a reasonable effort to complete the study in the time noted.

I will provide the contents of this protocol to study staff under my direct supervision that need to know the contents to conduct the study. I will discuss this information with the study staff to ensure they are fully informed about the study and the study medications.

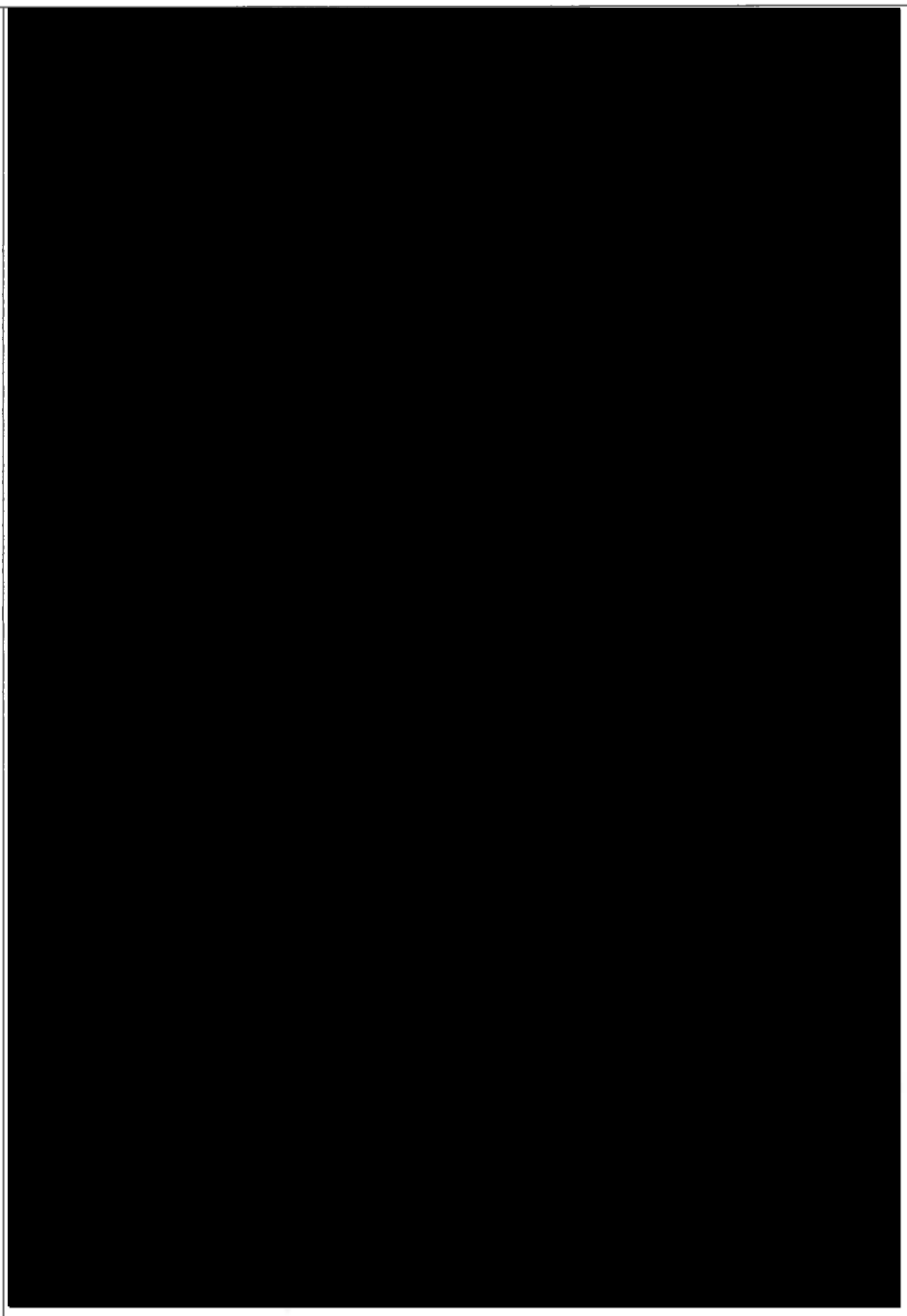
I will provide the contents of the protocol to the responsible IRB(s) or Ethics Committee(s).

[redacted]

Protocol number: SCRIC17-RET05

SYNOPSIS

Title	Assessing the cosmetic changes in the facial skin utilizing non-invasive *in vivo* skin imaging instrumentation after use of a topical retinoid product in subjects with moderate to severe photodamage.
Study Products	SkinMedica Retinol Complex 0.5 (cosmetic topical product)
Study Objectives	To utilize non-invasive skin imaging instrumentation including the [redacted] and [redacted] to observe and assess the cosmetic changes in the skin after clinical usage with SkinMedica Retinol Complex 0.5.
Study Regimen	Subjects will be instructed to remove all makeup from the face and cleanse the face at least 15 minutes prior to investigator assessments and use of skin instrumentation. • For standardization, this procedure will be performed with SkinMedica Facial Cleanser (to remove makeup and cleanse the face) for all the subjects. **Take home regimen during 2 week wash out period:** 1. SkinMedica Facial Cleanser (AM and PM) 2. Cetaphil Fragrance Free Moisturizing Lotion (AM and PM) 3. SkinMedica Essential Defense Mineral Shield Broad Spectrum SPF 35 Sunscreen (AM and as needed) **Take home regimen (Baseline – Week 12):** 1. SkinMedica Facial Cleanser (AM and PM) 2. SkinMedica Retinol Complex 0.5 (PM) 3. Cetaphil Fragrance Free Moisturizing Lotion (AM and PM) 4. SkinMedica Essential Defense Mineral Shield Broad Spectrum SPF 35 Sunscreen (AM and as needed)
Study Design	[redacted]

	 Subjects will complete multiple questionnaires including a self-assessment questionnaire on the test product, and questionnaires regarding their aging appearance, lines, satisfaction with their skin, social confidence, and psychological well-being. Any subject compensation will be provided to the subject at this visit.
Treatment Groups	After enrollment into the study and completion of the wash-out regimen, all subjects will receive the Test Product.

Duration of Study	Study Start Date: August 2017 Study End Date: August 2018
Study Population	Male or female subjects with Fitzpatrick skin types I-IV, ages 40-70 years old with moderate to severe facial photodamage.
Total Number of Subjects	Up to 50 subjects will be enrolled into the study.
Number of Sites	One site
Inclusion Criteria	1. Male or female subjects ages 40-70 years old, with Fitzpatrick skin type I-IV. 2. Subject has completed an appropriately administered informed consent process which includes signing the IRB approved consent form. 3. Presence of higher moderate to severe facial photodamage [redacted] 4. [redacted] 5. Willingness to cleanse the face and remove all makeup at least 15 minutes prior to each scheduled clinic visit. No other topical products should be applied to the face until the study visit has been completed. 6. [redacted] 7. Willingness to cooperate and participate by following study requirements (including using **only** the provided facial cleanser, treatment product, sunscreen and moisturizer) for the duration of the study and to report any adverse event symptoms or reactions immediately. 8. Willingness to not use any other products, including self-tanners, on their facial skin for the duration of the study. Subjects may continue to use regular cosmetic products (as long as they meet exclusion criteria #8), but may not begin the use of any new facial products other than the provided materials for the duration of the study. Regular use is defined as products used for a minimum of two weeks prior to enrollment without any incidence of irritation. 9. If subjects are taking hormone replacement or hormones for birth control, then they must be willing not to stop or change this medication for the duration of the study. Individuals who are not taking hormones at the start of the study must be willing not to start their use during the course of the study. 10. 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. 11. Women of childbearing potential must be willing to practice effective contraception for the duration of the study. Females on birth control pills (BCP) must be stable on the same type pill for at least three months prior to entering the study and must not change the type of BCP or dosing regimen during the study.
Exclusion Criteria	1. [redacted]

<table>
<tr>
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[redacted]
2. Individuals with known allergies or sensitivities to the ingredients in the study products.
3. Individuals with active symptoms of allergy, cold sore or warts, active psoriasis or eczema, rosacea, sunburn, open wounds, neurotic excoriations, excessive scarring, tattoos, or other skin conditions in the test areas that would interfere with the assessments of this study.
4. Individuals who are nursing, pregnant, or planning to become pregnant during the study.
5. Uncontrolled disease such as diabetes, hypertension, hyper or hypo-thyroidism, active hepatitis, immune deficiency, or autoimmune.
6. Individuals who have a pre-existing or dormant dermatologic condition (e.g., psoriasis, atopic dermatitis, rosacea, skin cancer, etc.).
7. Individuals who require electrolysis, waxing, or use depilatories on the face during conduct of the study.
8. Individuals who have routinely used any of the following topical products, prescription products, or had any of the listed treatments/procedures within the listed time frame prior to study entry or will use during study:
<table>
<tr><th>Medication/Product/Treatment</th><th>Time Frame</th></tr>
<tr><td>Any product that the investigator deems that could affect the study objectives. These include products that address skin imperfections. This does not include a basic cleanser, moisturizer and sunscreen.</td><td>2 weeks</td></tr>
<tr><td>Chemical peel or microdermabrasion</td><td>4 weeks</td></tr>
<tr><td>Retin-A®, Retin-A Micro®, Renova®, Avita®, Tazorac®, Avage® or Differin® or other similar prescription drugs</td><td>3 months</td></tr>
<tr><td>Cosmetic injections (filler and/or toxins, i.e. Juvederm, Radiesse, Botox, etc.), non-ablative laser or fractional laser resurfacing</td><td>6 months</td></tr>
<tr><td>Accutane® or other oral retinoid, Ablative procedures (i.e. laser, chemical, cosmetic surgeries)</td><td>12 months</td></tr>
</table>
9. Subjects who have planned surgeries or procedures.
10. [redacted]
11.

Individuals will be admitted to study at the discretion of the Investigator or designee based on medical history and findings of the pre-study interview and examination.
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<tr>
<td>Study Measurements</td>
<td>
<u>Investigator Assessments</u> will be performed as follows at all visits:

Overall Photodamage (0-9 scale)

None (0) = Facial skin is smooth to the touch, without significant fine/coarse lines or skin tone unevenness in any areas (periocular area, cheeks, forehead, and perioral area)
Mild (1- 3) = Facial skin shows 1 area (periocular area, cheeks, forehead, and perioral area) of significant roughness, or skin tone unevenness (red/brown), or fine/coarse lines
Moderate (4- 6) = Facial skin shows 2 areas (periocular area, cheeks, forehead, and perioral area) of significant roughness, skin tone unevenness (red/brown), or fine/coarse lines

</td>
</tr>
</table>

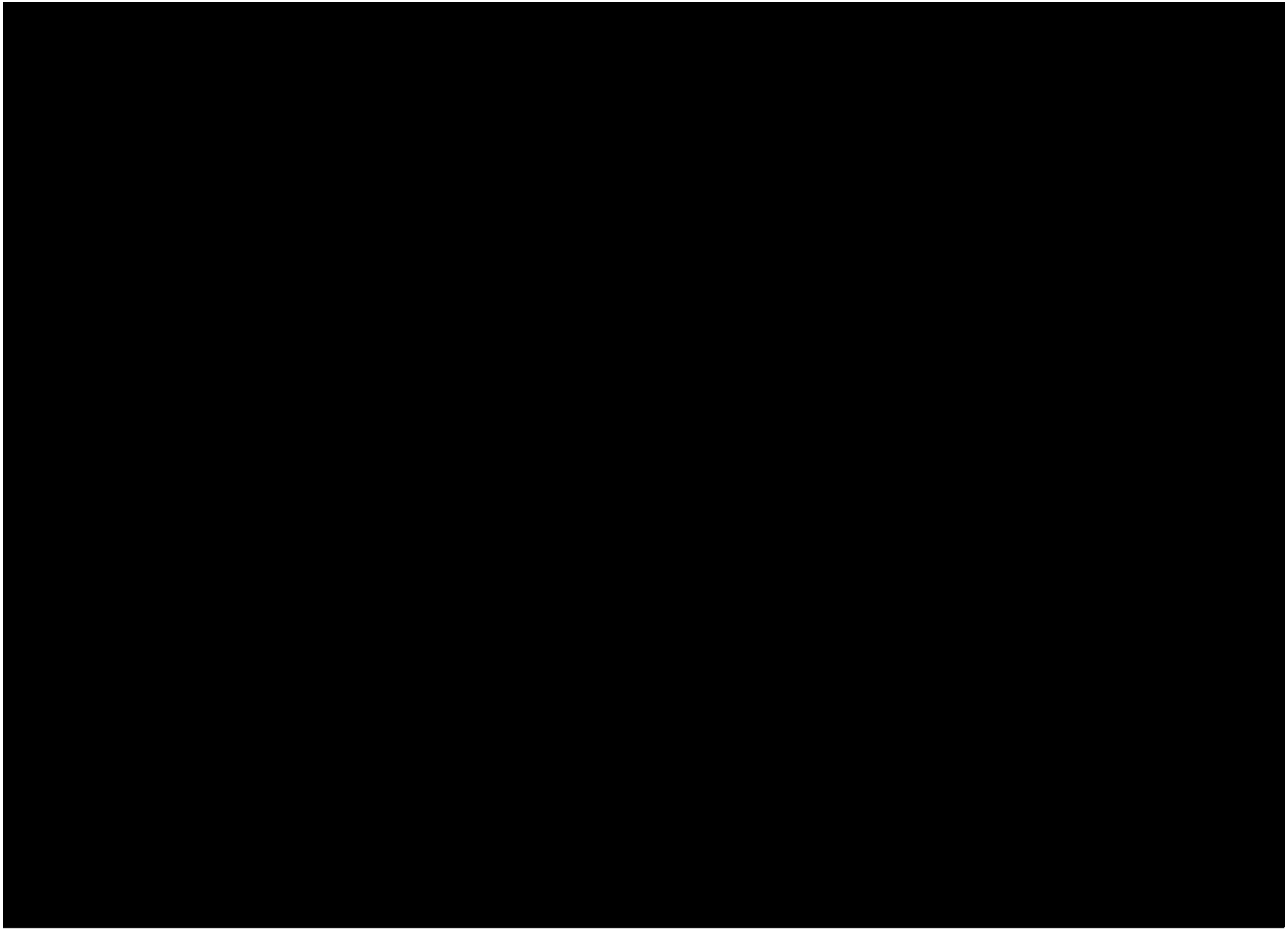
	• Severe (7- 9) = Facial skin shows 3 or more areas (periocular area, cheeks, forehead, and perioral area) of significant roughness, skin tone unevenness (red/brown), or fine/coarse lines  **Skin Roughness (0-4 scale)- Allergan Skin Roughness Visual Scale (Refer to Appendix I)** • None (0) = Smooth visual skin texture • Minimal (1) = Slightly coarse and uneven visual skin texture • Moderate (2) = Moderately coarse and uneven visual skin texture; may have early elastosis • Severe (3) = Severely coarse visual skin texture, crosshatched fine lines; may have some elastosis • Extreme (4) = Extremely coarse visual skin texture, crosshatched deep creases; extreme elastosis **Tactile Roughness (0-9 scale entire face)** • None (0) = No roughness of the treatment area; skin is completely smooth and pliable • Mild (1-3) = Some areas of slightly irregular roughness in the treatment area • Moderate (4-6) = Several areas of definite roughness of the treatment area • Severe (7-9) = Marked roughness of the treatment area associated with stiff feeling **Fine Lines (0-4 scale) - Allergan Fine Lines Visual Scale (Appendix II)** • None (0) = No fine lines • Minimal (1) = 1-2 superficial lines • Moderate (2) =3-5 superficial lines • Severe (3) = Greater than 5 superficial lines; no crosshatching • Diffuse (4) = Diffuse superficial lines; crosshatching **Fine Lines/Wrinkles - Forehead, Periocular, Cheeks, Perioral areas individually assessed (0-9 scale) (Refer to Appendix III)** • None (0) = No fine lines/wrinkles present; skin looks completely smooth and wrinkle-free • Mild (1-3) = Rare, presence of fine lines and wrinkles, widely spaced apart in the treatment area • Moderate (4-6) = Moderate number of fine lines/wrinkles in close

	proximity to each other in the treatment area • Severe (7-9) = Many fine lines/wrinkles densely packed together in the treatment area **Coarse Lines/Wrinkles - Forehead, Periocular, Cheeks, Perioral areas individually assessed (0-9 scale) (Refer to Appendix III)** • None (0) = No coarse lines/wrinkles present; skin looks completely smooth and wrinkle-free • Mild (1-3) = Rare, presence of coarse lines and wrinkles, widely spaced apart in the treatment area • Moderate (4-6) = Moderate number of coarse lines/wrinkles in close proximity to each other in the treatment area • Severe (7-9) = Many coarse lines/wrinkles densely packed together in the treatment area **Global Improvement in Overall Photodamage (0-4 scale; at follow-up visits only)** • None (0) = No change or worsening • Mild (1) = A noticeable improvement of the condition with a distinctive amount of signs/symptoms remaining (approximately 25% overall improvement) • Moderate (2) = A very noticeable improvement of the condition with a fair amount of signs/symptoms remaining (approximately 50% overall improvement) • Marked (3) = A distinctive improvement of the condition with some signs/symptoms remaining. (approximately 75% overall improvement) • Complete (4) = Almost complete improvement of the condition with a trace of signs/symptoms remaining (approximately 95% or better overall improvement) **Global Improvement in Fine Lines/Wrinkles – Forehead, Periocular, Cheeks, Perioral areas individually assessed (0-4 scale; at follow-up visits only)** • None (0) = No change or worsening • Mild (1) = Mild improvement in the appearance of fine lines/wrinkles (approximately 25% overall improvement) • Moderate (2) = Moderate improvement in the appearance of fine lines/wrinkles (approximately 50% overall improvement) • Marked (3) = Marked improvement in the appearance of fine lines/wrinkles (approximately 75% overall improvement) • Complete (4) = Complete clearing in the appearance of fine lines/wrinkles (approximately 95% or better overall improvement) **Global Improvement in Coarse Lines/Wrinkles – Forehead, Periocular, Cheeks, Perioral areas individually assessed (0-4 scale; at follow-up visits only)** • None (0) = No change or worsening • Mild (1) = Mild improvement in the appearance of coarse

	lines/wrinkles (approximately 25% overall improvement) • Moderate (2) = Moderate improvement in the appearance of coarse lines/wrinkles (approximately 50% overall improvement) • Marked (3) = Marked improvement in the appearance of coarse lines/wrinkles (approximately 75% overall improvement) • Complete (4) = Complete clearing in the appearance of coarse lines/wrinkles (approximately 95% or better overall improvement) **Global Improvement in Tactile Roughness (0-4 scale; at follow-up visits only)** • None (0) = No change or worsening • Mild (1) = Mild improvement in the appearance of tactile roughness (approximately 25% overall improvement) • Moderate (2) = Moderate improvement in the appearance of tactile roughness (approximately 50% overall improvement) • Marked (3) = Marked improvement in the appearance of tactile roughness (approximately 75% overall improvement) • Complete (4) = Complete clearing in the appearance of tactile roughness (approximately 95% or better overall improvement) [redacted]
Study Endpoints	• <u>Key Efficacy Endpoints</u> o Decreases in scores for the following parameters (which signifies an improvement in the parameter): ▪ Overall Photodamage ▪ Fine Lines/Wrinkles (Forehead, Periocular, Cheeks, Perioral areas individually assessed) ▪ Coarse Lines/Wrinkles (Forehead, Periocular, Cheeks, Perioral areas individually assessed) ▪ Tactile Roughness (entire face) ▪ Fine Lines - Allergan Fine Lines Visual Scale ▪ Skin Roughness - Allergan Skin Roughness Visual Scale [redacted]

	○ Increases in spectrophotometer L* values and global improvement scores (which signifies improvement): ▪ Global Improvement in Overall Photodamage ▪ Global Improvement in Fine Lines/Wrinkles (Forehead, Periocular, Cheeks, Perioral areas individually assessed) ▪ Global Improvement in Coarse Lines/Wrinkles (Forehead, Periocular, Cheeks, Perioral areas individually assessed) ▪ Global Improvement in Tactile Roughness [redacted]
Subject Compensation	Subjects who complete all of the required study visits will be compensated with SkinMedica products (up to $527 retail value). Completion of Baseline and Week 4 visits: **One** SkinMedica TNS Essential Serum ($281 retail value) Completion of Week 8 visit: **One** SkinMedica HA5 Rejuvenating Hydrator ($178 retail value) Completion of Week 12 visit: **One** SkinMedica sunscreen product of choice from options available (up to $68 retail value) To avoid noncompliance and use of the products during the study, these products will be provided at the final visit, regardless of study completion. Subjects will be notified of the retail value limits, which cannot be combined, and that the products will be provided, as available. SkinMedica chemical peels will not be eligible. Upon receipt of SkinMedica products, subjects will provide a signature confirming receipt of compensation.

Sample Size Determination	No sample size calculations will be performed.
Statistical Methods	Statistical analyses will be conducted on all subjects who complete the study. Summary statistics (i.e., mean etc.) will be conducted for all parameters collected during the study.



ABBREVIATIONS

AE	Adverse Event
CRA	Clinical Research Associate
CRF	Case Report Form
GCP	Good Clinical Practices
IRB	Independent Review Board
ITT	Intent-to-treat
PP	Per protocol
SAE	Serious Adverse Event
WOCBP	Women of Childbearing Potential

TABLE OF CONTENTS

1 BACKGROUND

One of the most apparent signs of aging include the appearance of lines and wrinkles on the facial skin. Retinoids have been shown to improve the visible signs of aging including the appearance of lines and wrinkles, uneven skin tone, and skin roughness (1, 2, 3).

2 RATIONALE

In a previous study, "A randomized, double-blind, split-face study comparing the efficacy and tolerability of three retinol-based products vs. three tretinoin-based products in subjects with moderate to severe facial photodamage" (Babcock, Mehta, & Makino, 2015), Retinol Complex 0.5 was shown to have comparable cosmetic improvements to Tretinoin 0.05% in overall photodamage, fine lines/wrinkles, coarse lines/wrinkles, skin tone brightness, mottled pigmentation, and tactile roughness. Kong et al. (2015) have also compared retinol with retinoic acid and for both products have shown an increase in epidermal thickening and clinically shown significant reductions in facial wrinkles after 12 weeks of topical use. In other clinical studies, topical retinol has also been shown to have significant improvements in fine lines. Although there are many studies that show the cosmetic effects of retinoids on improving the signs of aging, there is limited research looking at the cosmetic changes with skin imaging instrumentation after application of retinoids (1, 2, 3).

In this study, the purpose is to explore the cosmetic changes in the skin after using Retinol Complex 0.5 utilizing novel non-invasive *in vivo* skin imaging instrumentation including the

[redacted]

We would like to assess cosmetic changes after applying this test product once daily to improve the appearance of lines, texture, and skin tone evenness utilizing skin imaging instrumentation.

3 OBJECTIVES

To assess the cosmetic changes of a cosmetic topical retinoid product in subjects with moderate to severe photodamage utilizing skin imaging instrumentation.

[redacted]

Safety will be evaluated by adverse events reported during the study.

5 STUDY POPULATION

Male or female subjects with Fitzpatrick skin types I-IV, ages 40-70 years old with moderate to severe photodamage. Approximately 50 subjects will participate in this study.

5.1 Subject Eligibility

To be included in the study, subjects must meet the following inclusion/exclusion criteria.

5.1.1 Inclusion Criteria

1. Male or female subjects ages 40-70 years old, with Fitzpatrick skin type I-IV.

2. Subject has completed an appropriately administered informed consent process which includes signing the IRB approved consent form.
3. Presence of moderate to severe facial photodamage [redacted]
5. Willingness to cleanse the face and remove all makeup at least 15 minutes prior to each scheduled clinic visit. No other topical products should be applied to the face until the study visit has been completed.
[redacted]
7. Willingness to cooperate and participate by following study requirements (including using only the provided facial cleanser, treatment product, sunscreen and moisturizer) for the duration of the study and to report any adverse event symptoms or reactions immediately.
8. Willingness to not use any other products, including self-tanners, on their facial skin for the duration of the study. Subjects may continue to use regular cosmetic products (as long as they meet exclusion criteria #8), but may not begin the use of any new facial products other than the provided materials for the duration of the study. Regular use is defined as products used for a minimum of two weeks prior to enrollment without any incidence of irritation.
9. If subjects are taking hormone replacement or hormones for birth control, then they must be willing not to stop or change this medication for the duration of the study. Individuals who are not taking hormones at the start of the study must be willing not to start their use during the course of the study.
10. 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.
11. Women of childbearing potential must be willing to practice effective contraception for the duration of the study. Females on birth control pills (BCP) must be stable on the same type pill for at least three months prior to entering the study and must not change the type of BCP or dosing regimen during the study.

5.1.2 Exclusion Criteria

1. [redacted]
2. Individuals with known allergies or sensitivities to the ingredients in the study products.
3. Individuals with active symptoms of allergy, cold sore or warts, active psoriasis or eczema, rosacea, sunburn, open wounds, neurotic excoriations, excessive scarring, tattoos, or other skin conditions in the test areas that would interfere with the assessments of this study.
4. Individuals who are nursing, pregnant, or planning to become pregnant during the study.
5. Uncontrolled disease such as diabetes, hypertension, hyper or hypo-thyroidism, active hepatitis, immune deficiency, or autoimmune.
6. Individuals who have a pre-existing or dormant dermatologic condition (e.g., psoriasis, atopic dermatitis, rosacea, skin cancer, etc.).

7. Individuals who require electrolysis, waxing, or use depilatories on the face during conduct of the study.
8. Individuals who have routinely used any of the following topical products, prescription products, or had any of the listed treatments/procedures within the listed time frame prior to study entry or will use during study:

Medication/Product/Treatment	Time Frame
Any product that the investigator deems that could affect the study objectives. These include products that address skin imperfections. This does not include a basic cleanser, moisturizer and sunscreen.	2 weeks
Chemical peel or microdermabrasion	4 weeks
Retin-A®, Retin-A Micro®, Renova®, Avita®, Tazorac®, Avage® or Differin® or other similar prescription drugs	3 months
Cosmetic injections (filler and/or toxins, i.e. Juvederm, Radiesse, Botox, etc.), non-ablative laser or fractional laser resurfacing	6 months
Accutane® or other oral retinoid, Ablative procedures (i.e. laser, chemical, cosmetic surgeries)	12 months

9. Subjects who have planned surgeries or procedures.
10. [redacted]
11. [redacted]

Individuals will be admitted to study at the discretion of the Investigator or designee based on medical history and findings of the pre-study interview and examination.

5.1.3 Subject Withdrawal Criteria

Criteria and procedures for handling subjects who are discontinued from the study are described in Section 13.2. Subjects who are discontinued may be replaced.

6 STUDY REGIMEN PRODUCTS

6.1 Product Ingredients

SkinMedica® Facial Cleanser Ingredients:
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)

SkinMedica® Retinol Complex 0.5 (Test product)
Water/Aqua/Eau, Cetyl Ethylhexanoate, Glycine Soja Oil, Caprylic/Capric Triglyceride, Niacinamide, Polyacrylate-13, Squalane, Retinol, Palmitoyl Tripeptide-8, Dunaliella Salina Extract, Magnolia Grandiflora Bark Extract, Tocopherol, Tocotrienols, Ceramide 3, Bisabolol, Phytosterols, Squalene, Tocopheryl Acetate, Oryza Sativa Bran Cera, Glycerin, Polysorbate 20, Butylene Glycol, Cetyl Palmitate, Laureth-23, Trideceth-6 Phosphate, Sodium Hydroxide,

Dicaprylyl Ether, Lauryl Alcohol, Polyisobutene, Dextran, Potassium Sorbate, Disodium EDTA, Phenoxyethanol, Ethylhexylglycerin

Cetaphil Moisturizing Lotion
Water, glycerin, hydrogenated polyisobutene, cetearyl alcohol, ceteareth-20, Macadamia integrifolia seed oil (macadamia nut oil), dimethicone, tocopheryl acetate, stearoxytrimethylsilane, stearyl alcohol, panthenol, farnesol, benzyl alcohol, phenoxyethanol, acrylates/C10-30 alkyl acrylate crosspolymer, sodium hydroxide, citric acid

Essential Defense Mineral Shield Sunscreen SPF35
Active Ingredients: Titanium dioxide 5.0%, Zinc oxide 6.0%

Inactive Ingredients: 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, Tocopheryl Acetate, Sodium Citrate, Dimethicone/Vinyl Dimethicone Crosspolymer, Triethoxysilylethyl Polydimethylsiloxyethyl Hexyl Dimethicone, PEG/PPG-18/18 Dimethicone, Triethoxycaprylylsilance, Stearic Acid, Ethylhexylglycerin, Phenoxyethanol, Iron Oxides (CI 77491, CI 77492, CI 77499)

6.2 Warnings, Precautions and Contraindications
These study products are for topical use only. Care should be taken to avoid contact with eyes and all mucous membranes. If contact with eyes occurs, rinse thoroughly with water.

Mild redness, peeling and irritation are expected when using this product. Use of a sunscreen and limiting sun exposure is required while using the test product and for a week following discontinuation.

Subjects with a known allergy to any of the ingredients in the study products should not participate in this study.

There are no adequate and well-controlled studies of the Study Product ingredients in pregnant women. Also, it is not known whether the ingredients are excreted in human milk following use of topical products containing these ingredients. Women who are pregnant or lactating will be excluded from this study. Women of childbearing potential must not be pregnant or planning a pregnancy during the study period.

In case of accidental ingestion, subjects should contact the study staff immediately.

6.3 Storage, Handling and Dispensing the Study Medication
All study products should be stored at controlled room temperature [redacted]

6.4 Subject Regimen and Dosing Instructions
Wash-out period (2 weeks prior to Baseline)

- Every morning (AM):
    1. Subjects will gently wash their facial skin with Facial Cleanser.
    2. Apply approximately a nickel-sized amount of Cetaphil Moisturizing Lotion to their facial skin.

3. Apply Essential Defense Mineral Shield Sunscreen SPF 35 to their face and re-apply as needed throughout the day.

- Every evening (PM):
  1. Subjects will gently wash their facial skin with Facial Cleanser.
  2. Apply approximately a nickel-sized amount of Cetaphil Moisturizing Lotion to their facial skin.
- Subjects may apply cosmetic make-up if applicable.

The Test Product will be packaged in 1 oz. bottles with a pump. Subjects will apply the Test Product onto their facial skin once a day in the evening as per the below instructions:

- Every morning (AM):
  1. Subjects will gently wash their facial skin with Facial Cleanser.
  2. Apply approximately a nickel-sized amount of Cetaphil Moisturizing Lotion to their facial skin.
  3. Apply Essential Defense Mineral Shield Sunscreen SPF 35 to their face and re-apply as needed throughout the day.
- Every evening (PM):
  1. Subjects will gently wash their facial skin with Facial Cleanser.
  2. Immediately after cleansing, subjects will apply a nickel-sized amount of the Test Product onto their entire face avoiding the eye area. Product should not be applied on the eyelid. Care should be taken to prevent product from getting into the eyes. Allow product to absorb (30 seconds to 1 minute).
  3. Apply approximately a nickel-sized amount of Cetaphil Moisturizing Lotion to their facial skin.
- Subjects may apply cosmetic make-up if applicable.

Subjects will use the Test Product starting on the evening of the baseline visit.
Subjects will use the SkinMedica Facial Cleanser starting at the screening visit to remove makeup and cleanse the face.

6.5 Dose Modifications

Modifications of the Test Product dosing are allowed at the discretion of the investigator. If irritation develops, subjects will be instructed to contact the study staff.

7 RANDOMIZATION ASSIGNMENT

N/A

8 PRIOR AND CONCOMITANT THERAPIES

8.1 Prohibited Medications or Therapies

Medications or treatments that are prohibited during the duration of the study are as follows:
Prior to entry, into the study, subjects must **not** have:

- Used systemic retinoids at least 12 months prior to study entry.
- Used topical retinoids and/or all other topical medication (topical steroids, products containing benzoyl peroxide, alpha- or beta-hydroxy acids, hydroquinone, and/or any other OTC skin treatments to the facial area at least 14 days prior to study entry.
- Received a laser treatment of the face within 6 months prior to study entry.
- Received microdermabrasion or a chemical peel within 30 days of study entry.

- Been treated with another investigational device or drug within 30 days prior to study entry.

During the study, other chronic medications being used at the time of Screening Visit, with the exception of those specified in Section 5.1.2. can be continued at the discretion of the investigator.

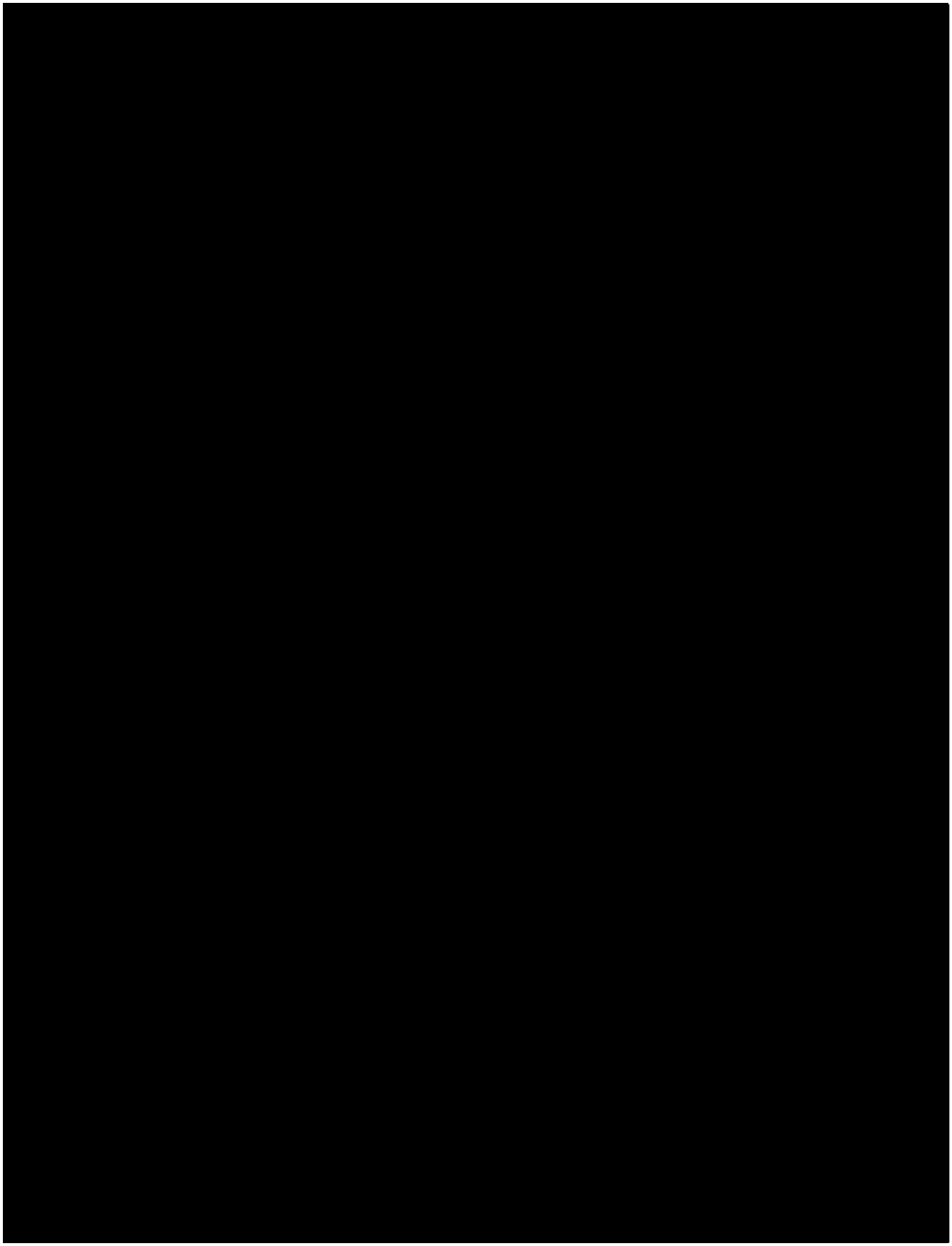
Subjects may not use any other topical products other than those provided for the study. The reason for any changes in concomitant therapies should be reported as, or in conjunction with, an adverse event.

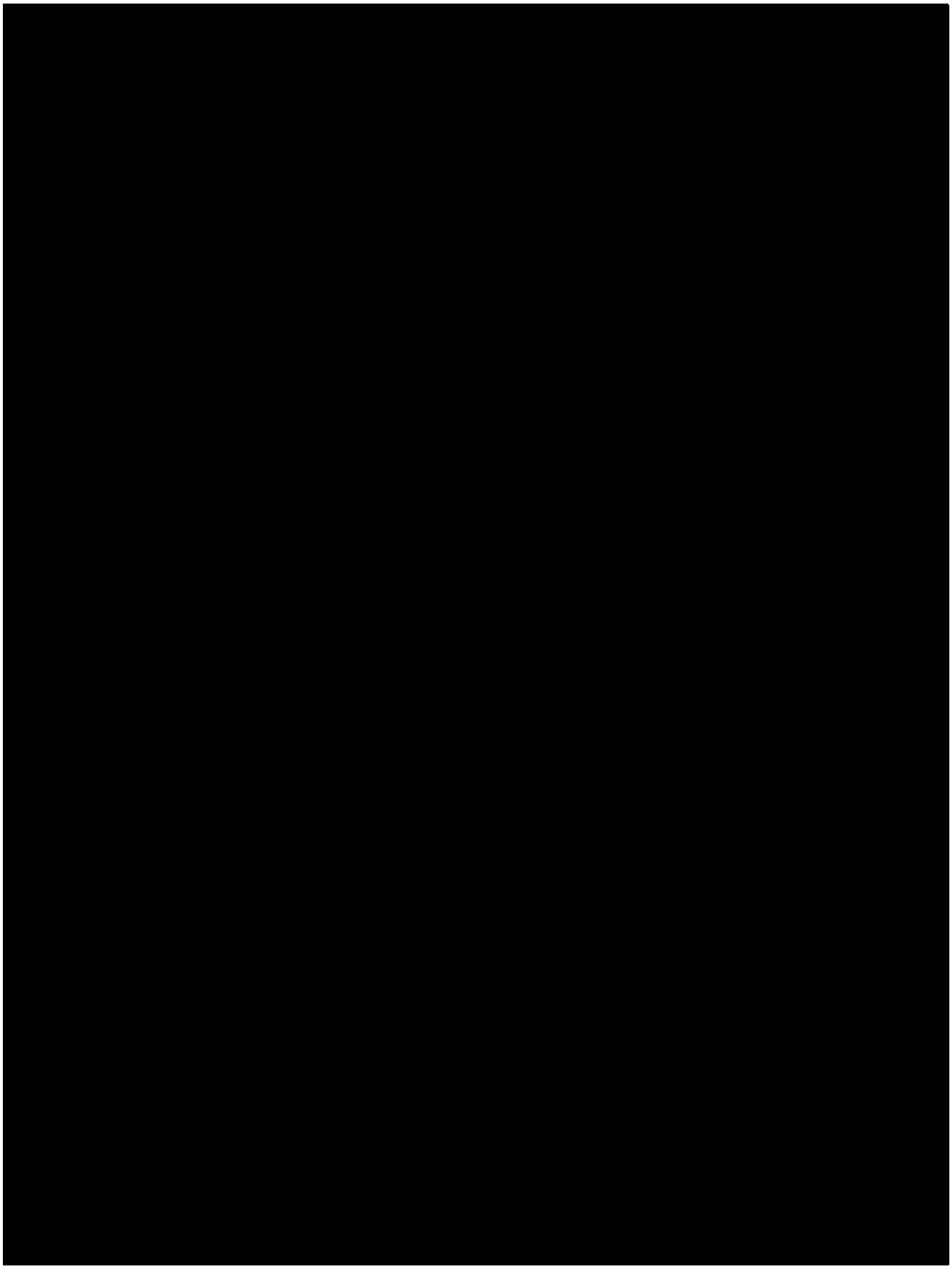
8.2 Allowed Medications or Treatments

No additional medications, including over-the-counter preparations, should be used without the knowledge and, if possible, permission of the investigator. Vitamins and mineral supplements are permitted at dosages considered by the investigator as reasonable for maintaining good health. The addition, discontinuation, or dose change of any concomitant medications will be documented in the source documents.

Medications will be permitted, at the discretion of the investigator, to treat local skin reactions, if applicable.

Cosmetic make-up can be used during the study as long as they meet exclusion criteria #8, and if the subjects has regularly used (defined as products used for a minimum of 2 weeks prior to enrollment) the make-up without any incidence of irritation.





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10 CLINICAL EVALUATIONS

The following clinical evaluations will be performed according to the schedule indicated during the study. The same grader should conduct the efficacy assessments for a subject at all visits, to prevent variations in grading.

10.1 Clinical Assessments

10.1.1 Investigator Assessments

Clinical efficacy assessments of the face will be performed as follows at all visits, unless otherwise specified. Whole numbers are allowed only (i.e. no half-points, or plus or minus designations).

Overall Photodamage (0-9 scale)

- None (0) = Facial skin is smooth to the touch, without significant fine/coarse lines or skin tone unevenness in any areas (periocular area, cheeks, forehead, and perioral area)
- Mild (1- 3) = Facial skin shows 1 area (periocular area, cheeks, forehead, and perioral area) of significant roughness, or skin tone unevenness (red/brown), or fine/coarse lines
- Moderate (4- 6) = Facial skin shows 2 areas (periocular area, cheeks, forehead, and perioral area) of significant roughness, skin tone unevenness (red/brown), or fine/coarse line
- Severe (7- 9) = Facial skin shows 3 or more areas (periocular area, cheeks, forehead, and perioral area) of significant roughness, skin tone unevenness (red/brown), or fine/coarse lines

[redacted]

Skin Roughness (0-4 scale)- Allergan Skin Roughness Visual Scale (Refer to Appendix I)

- None (0) = Smooth visual skin texture
- Minimal (1) = Slightly coarse and uneven visual skin texture
- Moderate (2) = Moderately coarse and uneven visual skin texture; may have early elastosis
- Severe (3) = Severely coarse visual skin texture, crosshatched fine lines; may have some elastosis
- Extreme (4) = Extremely coarse visual skin texture, crosshatched deep creases; extreme elastosis

Tactile Roughness (0-9 scale entire face)

- None (0) = No roughness of the treatment area; skin is completely smooth and pliable

- Mild (1-3) = Some areas of slightly irregular roughness in the treatment area
- Moderate (4-6) = Several areas of definite roughness of the treatment area
- Severe (7-9) = Marked roughness of the treatment area associated with stiff feeling

Fine Lines (0-4 scale) - Allergan Fine Lines Visual Scale (Appendix II)

- None (0) = No fine lines
- Minimal (1) = 1-2 superficial lines
- Moderate (2) =3-5 superficial lines
- Severe (3) = Greater than 5 superficial lines; no crosshatching
- Diffuse (4) = Diffuse superficial lines; crosshatching

Fine Lines/Wrinkles - Forehead, Periocular, Cheeks, Perioral areas individually assessed (0-9 scale) (Refer to Appendix III)

- None (0) = No fine lines/wrinkles present; skin looks completely smooth and wrinkle-free
- Mild (1-3) = Rare, presence of fine lines and wrinkles, widely spaced apart in the treatment area
- Moderate (4-6) = Moderate number of fine lines/wrinkles in close proximity to each other in the treatment area
- Severe (7-9) = Many fine lines/wrinkles densely packed together in the treatment area

Coarse Lines/Wrinkles - Forehead, Periocular, Cheeks, Perioral areas individually assessed (0-9 scale) (Refer to Appendix III)

- None (0) = No coarse lines/wrinkles present; skin looks completely smooth and wrinkle-free
- Mild (1-3) = Rare, presence of coarse lines and wrinkles, widely spaced apart in the treatment area
- Moderate (4-6) = Moderate number of coarse lines/wrinkles in close proximity to each other in the treatment area
- Severe (7-9) = Many coarse lines/wrinkles densely packed together in the treatment area

Global Improvement in Photodamage (0-4 scale; at follow-up visits only)

- None (0) = No change or worsening
- Mild (1) = A noticeable improvement of the condition with a distinctive amount of signs/symptoms remaining (approximately 25% overall improvement)
- Moderate (2) = A very noticeable improvement of the condition with a fair amount of signs/symptoms remaining (approximately 50% overall improvement)
- Marked (3) = A distinctive improvement of the condition with some signs/symptoms remaining. (approximately 75% overall improvement)
- Complete (4) = Almost complete improvement of the condition with a trace of signs/symptoms remaining (approximately 95% or better overall improvement)

Global Improvement in Fine Lines/Wrinkles – Forehead, Periocular, Cheeks, Perioral areas individually assessed (0-4 scale; at follow-up visits only)

- None (0) = No change or worsening
- Mild (1) = Mild improvement in the appearance of fine lines/wrinkles (approximately 25% overall improvement)
- Moderate (2) = Moderate improvement in the appearance of fine lines/wrinkles (approximately 50% overall improvement)
- Marked (3) = Marked improvement in the appearance of fine lines/wrinkles (approximately 75% overall improvement)
- Complete (4) = Complete clearing in the appearance of fine lines/wrinkles (approximately 95% or better overall improvement)

Global Improvement in Coarse Lines/Wrinkles – Forehead, Periocular, Cheeks, Perioral areas individually assessed (0-4 scale; at follow-up visits only)

- None (0) = No change or worsening
- Mild (1) = Mild improvement in the appearance of coarse lines/wrinkles (approximately 25% overall improvement)
- Moderate (2) = Moderate improvement in the appearance of coarse lines/wrinkles (approximately 50% overall improvement)
- Marked (3) = Marked improvement in the appearance of coarse lines/wrinkles (approximately 75% overall improvement)
- Complete (4) = Complete clearing in the appearance of coarse lines/wrinkles (approximately 95% or better overall improvement)

Global Improvement in Tactile Roughness (0-4 scale; at follow-up visits only)

- None (0) = No change or worsening
- Mild (1) = Mild improvement in the appearance of tactile roughness (approximately 25% overall improvement)
- Moderate (2) = Moderate improvement in the appearance of tactile roughness (approximately 50% overall improvement)
- Marked (3) = Marked improvement in the appearance of tactile roughness (approximately 75% overall improvement)
- Complete (4) = Complete clearing in the appearance of tactile roughness (approximately 95% or better overall improvement)

[redacted]

10.1.3 Instrumentation

Standardized digital photography will be taken of the subject's left, right and frontal facial views with the [redacted]

Triplicate 3D images of a designated area on the face will be taken with the [redacted] at baseline and all follow-up visits.

Non-invasive *in* vivo skin imaging will be conducted with the [redacted] and [redacted] on a designated target area on the face at baseline and all follow-up visits.

Triplicate measurements of the facial skin at a target location will be taken using a [redacted] at baseline and all follow-up visits.

[redacted]

10.2 Adverse Events

Adverse events (AEs) will be recorded in the AE section of the source documents. The start of adverse event collection will take place immediately after the subject completes their Screening visit (Day 0). Definitions and reporting requirements for serious AEs are depicted in Section 13.0.

11 BLINDING/UNBLINDING

Since this is an open-label study, there will be no blind.

12 END OF STUDY

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

12.1 Completion of the Study
Subjects who complete all 5 visits will have completed the study.

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

- Whenever the subject/care giver decides it is in their best interest to withdraw
- Whenever the investigator decides it is in the subject's best interest to be withdrawn
- Severe adverse events
- Intercurrent illness which may, in the investigator's opinion, significantly affect assessment of clinical status
- Non-compliance
- Pregnancy

If a subject does withdraw prematurely from the study, all procedures required for their current or "last visit" plus any additional final study requirements should be completed.

Subjects who are prematurely withdrawn or discontinued from the study may be replaced.

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

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

In the event that the Sponsor chooses to discontinue or terminate the study, appropriate notification will be given to the investigator.

13 ADVERSE EVENT REPORTING

13.1 Adverse Events
Any clinical findings determined by the Investigator to be important and/or unusual will be referred to as an adverse event (AE). Subjects are asked to contact the clinic staff immediately if they experience a reaction at any time during the study. The subject may be examined by the clinic's staff or by the study physician. The start of adverse event collection for this study will be immediately after the subject completes their Screening visit.

13.2 Definitions of Adverse Event and Serious Adverse Event

An adverse event is any untoward medical occurrence in a patient or a clinical investigational subject that is administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (for example an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product. Throughout the study, subjects will be monitored for signs and symptoms of adverse events. The condition must either not be present pre-study or must worsen in either intensity or frequency during the study.

A *serious adverse event* (SAE) is an untoward medical occurrence that at any dose:

- results in death;
- is life-threatening (NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.);
- requires in-patient 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.

An *unexpected adverse event* is any treatment-emergent adverse event, which is not identified in nature, severity, or frequency in current literature on the Test Product.

13.3 Reporting Requirements

- Serious and Unexpected Adverse Events

  Any serious, unexpected and treatment-related adverse event occurring in this study must be reported to [redacted] within 10 business days of awareness of the event using the Serious Adverse Event Report form [redacted]

- Adverse Event Reporting

  All adverse events must be recorded by the Investigator onto the Adverse Event page of the source documents. The Investigator will be required to describe the adverse event, onset and stop date, severity, opinion of causality, the course of action taken, if any, as well as any pertinent data necessary to allow a complete evaluation of the adverse event. For serious adverse events, an additional report (SAE Report Form) must be completed. The completed Adverse Event CRF and the SAE Report Form must be emailed to SkinMedica Medical Affairs at [redacted] within 24 hours of awareness.

- Follow-up and Final Reports

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

  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.
  References used:
  - International Conference of Harmonization (ICH) Guidelines: http://www.ich.org
  - E2A – Clinical Safety Data Management: Definitions and Standards for Expedited Reporting

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]

[redacted]

The Investigator will follow-up the case to assess the cause, effect, and severity of any AE, and findings will be documented on an AE form. If medical expenses are incurred by the subject in conjunction with the study, they will be billed separately to the Sponsor. If a physician is engaged to participate in any observations beyond scheduled visits, his fees will be billed separately to the Sponsor.

13.4 Pregnancy

Sexually active women of child bearing potential (WOCBP) must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

During the study, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period).

14 CLINICAL SUPPLIES

14.1 Study Test Product

- SkinMedica Retinol Complex 0.5 [SkinMedica, Inc., an Allergan Company]

14.2 Study Basic Skincare Products

- SkinMedica Facial Cleanser [SkinMedica, Inc., an Allergan Company]
- Cetaphil Moisturizing Lotion [Galderma Laboratories, L.P.]
- SkinMedica Essential Defense Mineral Shield Broad Spectrum SPF 35 [SkinMedica, Inc., an Allergan Company]

14.3 Return and Destruction of Study Medication Supplies

Since all the products used in this study are commercially-available cosmetic and OTC products, the subjects will not be required to return any used and/or unused product.

15 SUBJECT COMPENSATION

Subjects who complete all of the required study visits will be compensated with SkinMedica products (up to $527 retail value). Upon completion of the Baseline and Week 4 visits, subjects will be eligible to receive a credit for one SkinMedica TNS Essential Serum ($281 retail value). To avoid noncompliance and use of the products during the study, these products will be provided at the final visit, regardless of study completion.

Upon completion of the Week 8 visit, subjects will be eligible to receive one SkinMedica HA5 ($178 retail value) at their final Week 12 visit. At the Week 8 visit, subjects will be asked to select which SkinMedica products they would like to receive at their final (week 12) visit.

Upon completion of the Week 12 visit, subjects will be eligible to receive one SkinMedica sunscreen product (up to $68 retail value) at their final Week 12 visit. At the Week 8 visit, subjects will be asked to select which SkinMedica products they would like to receive at their final (week 12) visit.

Subjects will be notified of the retail value limits, which cannot be combined, and that the products will be provided, as available. SkinMedica chemical peels will not be eligible. Upon receipt of SkinMedica products, subjects will provide a signature confirming receipt of compensation.

16 STATISTICAL CONSIDERATIONS

16.1 Sample Size

No sample size calculations were performed for this pilot study.

16.2 Analysis Populations

An intent-to-treat (ITT) population will include all subjects who were enrolled and applied the Test Product.

A per-protocol (PP) population will include all subjects who completed all study visits without significant protocol violations. Subjects to be excluded from the PP analysis are subjects who have: 1) no efficacy evaluation at baseline, and/or have no follow-up visit; 2) used any prohibited medications during the study period which would interfere with the study objectives; 3) had any prohibited procedures during the study period which would interfere with the study objectives.

16.3 Statistical Methods

Statistical analyses will be conducted on all subjects who complete at least their baseline visit and subsequent follow-up assessment timepoint. Descriptive statistics (i.e., mean etc.) will be conducted for all subjects who have completed the Baseline and any follow-up visits.

Safety analyses will be performed in terms of incidence and severity adverse events. Concomitant medication/treatment will be listed by subject and study visit.

17 ETHICAL AND REGULATORY CONSIDERATIONS

17.1 Compliance with the Declaration of Helsinki

This study will be conducted in compliance with the principles of the Declaration of Helsinki, with the current Good Clinical Practice (GCP) guideline and with other applicable regulations. The investigator and all study staff will conduct the study in compliance with this protocol. The protocol, informed consent documents, recruitment advertisements and any amendments to these items will have Institutional Review Board (IRB) approval prior to study initiation. Voluntary informed consent will be given by every subject prior to the initiation of any study related procedures. The rights, safety and well-being of the study subjects are the most important considerations and prevail over the interests of science and society. All personnel involved in the conduct of this study must be qualified by education, training and experience to perform their assigned responsibilities.

17.2 Institutional Review Board/Ethics (IRB) and Informed Consent

Before study initiation, the investigator must have written and dated approval from the IRB/Ethics Committee for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subject/care givers. The investigator should also provide the IRB/Ethics Committee with a copy of the product labeling, information to be provided to subject/caregivers and any updates. The investigator will submit documentation of the IRB approval to SkinMedica, Inc., an Allergan Company.

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

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

Consent should be obtained before any protocol-required procedures are performed; including any procedure, that is not part of normal subject care (e.g. withdrawal of current medications etc.).

17.3 Protocol Compliance

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

17.4 Protocol Revisions

All protocol amendments must receive IRB/Ethics Committee approval prior to implementation. All administrative letters must be submitted to the IRB/Ethics Committee for their information. Copies of all correspondence with the IRB/Ethics Committee regarding this study must be sent to SkinMedica, Inc., an Allergan Company

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

17.5 Required Study Documents

The investigator must provide the following documents to SkinMedica, Inc., an Allergan Company before any subjects are enrolled and/or study medication may be shipped to the study site:

- The signed **STUDY ACKNOWLEDGEMENT** page from the IRB approved protocol
- Documentation of IRB approval of the protocol, informed consent form and any recruitment advertisements
- A copy of the IRB approved informed consent form
- A current IRB assurance number or a membership roster
- A current curriculum vitae and current medical license for the investigator and any sub-investigators

17.6 Record Retention

The investigator must maintain records related to this study for a minimum of two years.

17.7 Publication

SkinMedica, Inc., an Allergan Company or the principal investigators may publish and disseminate the results of their investigative research, however, publication of any such paper shall not be allowed without prior written approval by SkinMedica, Inc., an Allergan Company (sponsor). The principal investigators shall provide the sponsor with a copy of the papers prepared for publication at the earliest practicable time, but in any event not less than sixty (60) days prior to their submission to a scientific journal or presentation at scientific meetings and a reasonably detailed summary or abstract of any other oral or written publication not less than

sixty (60) days prior to their submission or presentation. The sponsor may freely use, copy and disseminate any such manuscript following its publication without further obligation to the principal investigators.

17.8 References

1. Babcock, M, Mehta, RC, Makino, ET. A randomized double-blind, split-face study comparing the efficacy and tolerability of three retinol-based products versus three tretinoin-based products in subjects with moderate to severe facial photodamage. J Drugs Derm. 2015 Jan;14(1):24-30.
2. Kong, Rong; Cui, Yilei; Fisher, Gary J.; Wang, Xiaojuan; Chen, Yinbei; Schneider, Louise M.; Majmudar, Gopa. J Cosm Derm. 2016 Mar, 15(1):49-57.
3. Varani J, Warner RL, Gharaee-Kermani M et al. Vitamin A antagonizes decreased cell growth and elevated collagen-degrading matrix metalloproteinases and stimulates collagen accumulation in naturally aged human skin1. J Investig Dermatol 2000; 114:480–6.