Supplement 1

This supplement contains the following items:

1. Study Protocol – pages 1 - 47
2. Statistical Analysis Plan – pages 48 - 59
3. Pharmacy Manual – pages 60 - 66
4. *Amended Study Protocol – pages 67 - 120
5. *Amended Analysis Plan – pages 121 - 132

*Note that this manuscript reports the results of Part 1, while both Part 1 and Part 2 clinical studies are described in the protocol. The attached protocol, statistical analysis plan and pharmacy manual are prespecified documents from before Part 1 was initiated. After completion of Part 1, some study design features for Part 2 were changed based on the results of Part 1 as also indicated in the original protocol. This was updated on Clinicaltrials.gov and also attached to this supplement as “Amended study protocol” (pages 67 - 120) and “Amended statistical analysis plan” (pages 121 - 132).

STUDY PROTOCOL

CLINICAL STUDY PROTOCOL

Assessment of the Human Systemic Absorption of Sunscreen Ingredients

PROTOCOL NO. SCR-005

Sponsor:	U.S. Food and Drug Administration White Oak Building #64, Room 2072 10903 New Hampshire Avenue Silver Spring, MD 20993
Sponsor Study Lead and Medical Monitor:	David Strauss, MD, PhD Director, Division of Applied Regulatory Science U.S. Food and Drug Administration Telephone: 301-796-6323 Email: david.strauss@fda.hhs.gov
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Study Monitor:	Jill Brown RIHSC Project Manager U.S. Food and Drug Administration
Version of Protocol:	1.2
Date of Protocol:	18 June 2018

Sponsor Signature Page

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki;
- International Council for Harmonisation (ICH) harmonised tripartite guideline E6 (R1): Good Clinical Practice; and
- All applicable laws and regulations, including without limitation, data privacy laws and compliance with appropriate regulations, including human subject research requirements set forth by the Research Involving Human Subjects Committee (RIHSC), the Institutional Review Board (IRB) of the U.S. Food and Drug Administration (FDA).

Digitally signed by David Strauss -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=David Strauss -S, 0.9.2342.19200300.100.1.1=2000507494
Date: 2018.07.05 17:13:25 -04'00'

David Strauss, MD, PhD
Director, Division of Applied Regulatory Science
U.S. Food and Drug Administration

Date

Investigator Signature Page

I confirm that I have read and that I understand this protocol, the investigator brochure, and other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki;
- ICH harmonised tripartite guideline E6 (R1): Good Clinical Practice;
- All applicable laws and regulations, including without limitation data privacy laws and regulations;
- Human subject research requirements set forth by the RIHSC, the IRB of the FDA;
- Regulatory requirements for reporting of serious adverse events (SAEs) defined in Section 5.7.2.1.2 of this protocol; and
- Terms outlined in the Clinical Study Site Agreement.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Section 8 of this protocol.

Carlos R. Sanabria, MD — 29 JUN 2018

Carlos Sanabria, MD
Principal Investigator

Date

Table of Contents

List of Tables

1. Protocol Synopsis

Protocol Number:	SCR-005
Title:	Assessment of the Human Systemic Absorption of Sunscreen Ingredients
Investigators:	Principal Investigator: Carlos Sanabria, MD
Study Phase:	1
Study Period:	This will be a single clinical study conducted in 2 parts. The duration of study participation will be approximately 37 days for each part, including a 30-day screening period, a 4-day treatment period (Days 1-4) and subjects leaving the clinic on the morning of Day 7 following completion of scheduled End-of-Study activities.
Study Site:	Spaulding Clinical Research LLC, 525 South Silverbrook Drive, West Bend, WI 53095
Background and Motivation:	Sunscreens prevent skin damage by reflecting or absorbing ultraviolet (UV) radiation and they are regulated as drug products in the United States (U.S.). Most active ingredients in sunscreens are organic chemicals and some have been shown to be absorbed through human skin with detectable levels in the blood or urine. As part of the safety evaluation for sunscreen products, the Food and Drug Administration (FDA) requests an assessment of systemic absorption in humans so that human blood levels can be compared with exposure levels obtained in nonclinical toxicology studies. If testing establishes that the sunscreen is not absorbed through the skin into the body, some aspects of toxicology testing may not be needed. Sunscreen products may be applied multiple times daily as both primary sunscreen products and as ingredients in cosmetic products, in substantial amounts for a lifetime starting at 6 months of age. The amount of sunscreen ingredient in a product can vary, but permitted levels can be as high as 10% for some organic active ingredients and application to the skin can accumulate to gram quantities in a day even with modest use. Because of the significant use of these sunscreens, even a low percentage of systemic absorption (e.g., 0.1%) could represent a significant systemic exposure in a single day and over a lifetime. The Surgeon General's Call to Action to Prevent Skin Cancer calls on partners in prevention from various sectors across the nation to address skin cancer as a major public health problem by increasing awareness of skin cancer and promoting actions to reduce its risk. Given the recognized public health benefits of sunscreen use, the FDA is committed to finding ways to facilitate the marketing of sunscreen products that include additional over-the-counter (OTC) sunscreen active ingredients. The FDA will continue to work with industry and other public health agencies to ensure that the sunscreens consumers use are safe and effective for daily, life-long use.

	In November 2016, the U.S. FDA finalized the guidance titled "Guidance for Industry: Nonprescription Sunscreen Drug Products Safety and Effectiveness Data" (sunscreen guidance). The guidance requests an assessment of the human systemic absorption of sunscreen ingredients with a Maximum Usage Trial (MUsT). The FDA sunscreen guidance notes that some nonclinical toxicity studies may be waived if results of an adequately conducted human pharmacokinetic (PK) MUsT show a steady-state blood level less than 0.5 ng/mL. Periodically, the FDA performs testing of products and formulations that the Agency sees as important for public health. This testing is not a reflection of rulemaking or other regulatory actions, but instead is done independently to measure the agency's understanding of the products' overall safety and effectiveness. This study is not intended to meet all requirements of MUsT studies as outlined in the FDA guidance referenced above, but will follow many of the principles.
Summary and Objectives:	**Part 1** is an open-label, randomized, 4-arm study in 24 healthy adult subjects with the primary objective: • To explore whether the active components (avobenzone, oxybenzone, ecamsule and octocrylene) of 4 sunscreen products (1 sunscreen product in each arm) are absorbed into the systemic circulation when a sunscreen product is applied under maximal-use conditions. One sunscreen product with the highest avobenzone exposure will be selected for the second part of the study. If there is no quantifiable exposure of avobenzone for any of the sunscreen products, the formulation with the highest oxybenzone exposure will be selected for Part 2. **Part 2** is an open-label, 1-arm study in 24 healthy adult subjects with the following primary objective: • To assess the pharmacokinetics of the active components (avobenzone, oxybenzone, octocrylene and/or ecamsule) in the selected product from Part 1.
Study Design:	**Part 1** Part 1 is an open-label, randomized, 4-arm pilot study to evaluate the effects of multiple applications of 4 different topical sunscreen formulations in healthy adult subjects. Each arm will include 6 subjects (3 male and 3 female) with 1 formulation. A total of 24 subjects (12 male and 12 female) from all 4 arms will be admitted to the clinical research unit (CRU) on Day 0. On the morning of Days 1 through 4, subjects will receive a topical application of the study drug at approximately 0900 hours. The study product will be weighed in advance and applied by a qualified person from the study team. Subjects will then receive 3 more topical applications on the same day at 2, 4, and 6 hours after the first dose.

	Part 2 Part 2 is an open-label, 1-arm confirmatory study to evaluate the pharmacokinetics of avobenzone, oxybenzone, octocrylene and/or ecamsule after multiple applications of a topical sunscreen formulation in healthy adult subjects. Part 2 will include 24 subjects (12 male and 12 female). The formulation in Part 2 will be selected based on the plasma exposure data from the pilot study (Part 1). A total of 24 subjects (12 male and 12 female) will be admitted to the CRU on Day 0. On the morning of Days 1 through 4, subjects will receive a topical application of the study product at approximately 0900 hours. The study drug will be weighed in advance and applied by a qualified person from the study team. Subjects will then receive 3 more topical applications on the same day at 2, 4, and 6 hours after the first dose. **Parts 1 and 2** In both parts, approximately 2 mg of active sunscreen ingredient per 1 cm^2 of body surface (calculation per method of Dubois) will be evenly applied 4 times per study day to areas of the body typically exposed to the sun: face, ears, neck, torso, arms, and legs (approximately 75% of the body surface area). The antecubital areas will be avoided when applying the sunscreen due to potential contamination of the sites used for intravenous PK blood sample collection. The topical applications of study drug will be administered with subjects in swim wear to simulate real-world settings as well as for easy application. In addition to swim wear, subjects may wear scrubs in between applications and at other times throughout the day/night. Subjects are required to shower each morning after the first PK blood sample collection (and before the first dose of the day), but not at other times during the day. Blood samples (approximately 10 mL per sample) will be collected for determination of avobenzone, oxybenzone, octocrylene and ecamsule plasma concentrations. Safety evaluations will include adverse event (AE) monitoring, vital sign measurements, and physical examinations. All AEs reported by the subject or observed by the investigator or clinical research unit (CRU) staff will be recorded. Any AE reported after the informed consent is signed and before study drug application will be recorded as medical history. Subjects will remain in the CRU after admission on Day 0 until the morning of Day 7 following completion of scheduled End-of-Study activities.
Inclusion Criteria:	Subjects who meet all of the following inclusion criteria will be eligible to participate in the study: 1. Subject signs an IRB-approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act authorization) before any study-related procedures are performed.

	2. Subject is a healthy man or woman, 18 to 60 years of age, inclusive, who has a body mass index of 18.5 to 29.9 kg/m^2, inclusive, at Screening. 3. Subject has normal medical history findings, clinical laboratory results, vital sign measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings at Screening or, if abnormal, the abnormality is not considered clinically significant (as determined and documented by the investigator or designee). 4. Subject must have a negative test result for alcohol and drugs of abuse at screening and Check-in (Day 0). 5. Subject has no known or suspected allergies or sensitivities to any components of the sunscreen formulation. 6. Female subjects must be of nonchildbearing potential or, if they are of childbearing potential, they must: 1) have been strictly abstinent for 1 month before Check-in (Day 0) and agree to remain strictly abstinent for the duration of the study and for at least 1 month after the last application of study drug; OR 2) be practicing 2 highly effective methods of birth control (as determined by the investigator or designee; one of the methods must be a barrier technique) from at least 1 month before Check-in (Day 0) until at least 1 month after the last application of study drug. 7. Female subjects must not be pregnant or lactating before enrollment in the study. 8. Male subjects must agree to practice 2 highly effective methods of birth control (as determined by the investigator or designee; one of the methods must be a barrier technique) from at least 1 month before Check-in (Day 0) until at least 1 month after the last application of study drug. 9. Subject is highly likely (as determined by the investigator) to comply with the protocol-defined procedures and to complete the study. Note: subjects with any skin type or skin pigment type may be eligible for the study.
Exclusion Criteria:	Subjects who meet any of the following exclusion criteria will not be eligible to participate in the study: 1. Subject has broken, irritated, or unhealed skin. 2. Subject has an active sunburn. 3. Subject has used a tanning bed in the previous 4 weeks. 4. Subject has known skin or autoimmune disease(s). 5. Subject is anemic or has any chronic condition(s) that may impact blood sample collection. 6. Subject has any underlying disease or surgical or medical condition (e.g., cancer, human immunodeficiency virus [HIV],

	severe hepatic or renal impairment) that could put the subject at risk or would normally prevent participation in a clinical study. 7. Subject has known or suspected allergies or sensitivities to any components of the sunscreen formulation. 8. Subject has clinical laboratory test results (hematology and serum chemistry) at Screening that are outside the reference ranges provided by the clinical laboratory and considered clinically significant by the investigator. 9. Subject has a positive test result at Screening for HIV 1 or 2 antibody, hepatitis C virus antibodies, or hepatitis B surface antigen. 10. Subject is unable or unwilling to undergo multiple venipunctures for blood sample collection because of poor tolerability or poor venous access. 11. Subject has received or applied the topical sunscreen formulations used in the current study, or any other product containing the active ingredients of the topical sunscreen formulations used in the current study, within 7 days before Check-in (Day 0). 12. Subject has used any personal care product(s) containing any active sunscreen ingredient, such sunscreen products, hand or body moisturizing lotion, makeup or foundation, lip balm, or lipstick, within 7 days before Check-in (Day 0). 13. Subject is unable or unwilling to tolerate the scent of sunscreen for the duration of the treatment period.
Study Drug, Dosage, and Route of Administration:	**Part 1** • La Roche Posay (Cream), Anthelios SX Daily Moisturizing Cream with Sunscreen, SPF 15 with Mexoryl SX • Hawaiian Tropic (Lotion); Island Sport Ultra-Light High Performance Sunscreen, SPF 50 • Neutrogena (Spray), Ultra Sheer Body Mist SPF 45 • Banana Boat (Spray); Sport Performance Coolzone Continuous Spray Sunscreen, SPF 50 Approximately 2 mg of sunscreen formulation per 1 cm^2 of body surface will be applied topically 4 times per day for 4 days to approximately 75% of the body surface area. **Part 2** The formulation in Part 2 will be selected based on the plasma exposure data from the pilot study (Part 1).
Reference Drug, Dosage, and Route of Administration:	Not applicable.

Pharmacokinetic Assessments:	Pharmacokinetic blood samples (approximately 10 mL per sample) will be collected for determination of avobenzone, oxybenzone, ecamsule and octocrylene plasma concentrations at the following time points: • Day 1: *0 and 0.5, 1, 1.5, *2, *4, *6, 8, 9, 10, 12, and 14 hours after initial dose • Day 2: 23, *28, 33 h • Day 3: 47, *52, 57 h • Day 4: 71, 73, *74, *76, *78, 81, 82, 84 and 86 h • Day 5: 95 hours • Day 6: 120 hours • Day 7: 144 hours * when a time point corresponds with sunscreen administration, the PK sample will be collected before sunscreen administration. The following PK parameters will be determined for each subject: <u>Day 1</u> • Maximum concentration (observed peak drug concentration) (C_{max}) • Time at which C_{max} occurs (T_{max}) • AUC from time 0 to the sampling time corresponding to the last quantifiable concentration (C_{last}) (AUC_{0-t}) <u>Days 2 and 3</u> • Residual drug concentration (predose level) (C_{trough}) • 3 h post dose concentration <u>Day 4</u> • Maximum concentration (observed peak drug concentration) (C_{max}) • Time at which C_{max} occurs (T_{max}) • Elimination rate constant (K_{el}) • Terminal half-life ($t_{1/2}$) • AUC from time 0 to the sampling time corresponding to the last quantifiable concentration (C_{last}) (AUC_{0-t}) • AUC from time 0 extrapolated to infinity (AUC_{0-inf}) <u>Day 5, 6 and 7</u> • Residual drug concentration (C_{trough})
Safety Assessments:	Safety will be evaluated in terms of AEs, vital sign measurements (blood pressure, heart rate, respiratory rate, and oral body temperature), and physical examination findings.

Sample Size:	Approximately 48 healthy subjects are planned for enrollment, of which 24 subjects will be enrolled and randomized in Part 1 and 24 subjects will be enrolled in Part 2. The sample size was determined empirically and is typical for exploratory investigations of this type.
Statistical Methods:	All data will be presented in data listings. Data from subjects excluded from an analysis population will be presented in the data listings but not included in the calculation of summary statistics. The number of subjects who enroll in the study and the number and percentage of subjects who complete each assessment will be presented. The frequency and percentage of subjects who withdraw or discontinue from the study and the reason for withdrawal or discontinuation will be summarized. Demographic and baseline characteristics will be summarized overall and by treatment for all subjects. Descriptive statistics will be used to summarize demographic and baseline subject characteristics. For continuous variables, the mean, median, standard deviation (SD), minimum, and maximum values will be reported. For categorical (nominal) variables, the number and percentage of subjects (or observations) will be reported. **Pharmacokinetics:** The PK population will include all subjects who receive study drug and have at least 1 estimable PK parameter after dosing. Plasma concentrations and PK parameters of avobenzone, oxybenzone, ecamsule and octocrylene will be listed and summarized using descriptive statistics (n, arithmetic mean, SD, minimum, median, and maximum) by nominal PK sampling time. **Safety:** The safety population will include all subjects who receive at least 1 dose of any of the study drugs. Any AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of AEs, organized by system organ class and preferred term, will be summarized with a focus on treatment-emergent AEs. Vital sign measurements will be summarized using descriptive statistics by time point. All values will be evaluated for clinically notable results. Data for additional safety parameters (e.g., physical examination findings) will be listed.
Date of Protocol:	18 June 2018

2. List of Abbreviations

Abbreviation	Definition
AE	adverse event
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from time 0 through 24 hours after dosing
AUC_{0-inf}	area under the concentration-time curve from time 0 extrapolated to infinity
AUC_{0-t}	area under the concentration-time curve from time 0 to the sampling time corresponding to the last quantifiable concentration
CFR	Code of Federal Regulations
C_{last}	time corresponding to the last quantifiable concentration
C_{max}	maximum concentration (observed peak drug concentration)
CRU	clinical research unit
C_{trough}	residual drug concentration (predose level)
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IAA	IRB Authorization Agreement
ICH	International Council for Harmonisation
IRB	institutional review board
IV	intravenous
K_{el}	elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
MUsT	Maximum Usage Trial
OTC	over the counter
PK	pharmacokinetic
RIHSC	Research Involving Human Subjects Committee
SAE	serious adverse event
SD	standard deviation
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
T_{max}	time at which C_{max} occurs
UV	ultraviolet
U.S.	United States

3. Introduction

Sunscreens prevent skin damage by reflecting or absorbing ultraviolet (UV) radiation and they are regulated as drug products in the United States (U.S.). Most active ingredients in sunscreens are organic chemicals and some have been shown to be absorbed through human skin with detectable levels in the blood or urine. As part of the safety evaluation for sunscreen products, the Food and Drug Administration (FDA) requests an assessment of systemic absorption in humans so that human blood levels can be compared with exposure levels obtained in nonclinical toxicology studies. If testing establishes that the sunscreen is not absorbed through the skin into the body, some aspects of toxicology testing may not be needed.

Sunscreen products may be applied multiple times daily as both primary sunscreen products and as ingredients in cosmetic products, in substantial amounts for a lifetime starting at 6 months of age. The amount of sunscreen ingredient in a product can vary, but permitted levels can be as high as 10% for some organic active ingredients and application to the skin can accumulate to gram quantities in a day even with modest use. Because of the significant use of these sunscreens, even a low percentage of systemic absorption (e.g., 0.1%) could represent a significant systemic exposure in a single day and over a lifetime.

The Surgeon General's Call to Action to Prevent Skin Cancer calls on partners in prevention from various sectors across the nation to address skin cancer as a major public health problem by increasing awareness of skin cancer and promoting actions to reduce its risk. Given the recognized public health benefits of sunscreen use, the FDA is committed to finding ways to facilitate the marketing of sunscreen products that include additional over-the-counter (OTC) sunscreen active ingredients. The FDA will continue to work with industry and other public health agencies to ensure that the sunscreens consumers use are safe and effective for daily, life-long use.

In November 2016, the U.S. FDA finalized the guidance titled "Guidance for Industry: Nonprescription Sunscreen Drug Products Safety and Effectiveness Data" (sunscreen guidance) (DHHS, 2016). The guidance requests an assessment of the human systemic absorption of sunscreen ingredients with a Maximum Usage Trial (MUsT). The FDA sunscreen guidance notes that some nonclinical toxicity studies may be waived if results of an adequately conducted human pharmacokinetic (PK) MUsT shows a steady-state blood level less than 0.5 ng/mL.

Periodically, the FDA performs testing of products and formulations that the Agency sees as important for public health. This testing is not a reflection of rulemaking or other regulatory actions, but instead is done independently to measure the agency's understanding of the products' overall safety and effectiveness.

This study is not intended to meet all requirements of MUsT studies as outlined in the FDA guidance referenced above, but will follow many of the principles.

4. Study Objectives

4.1. Primary Objectives

4.1.1 Part 1

Part 1 is an open-label, randomized, 4-arm study in 24 healthy adult subjects with the primary objective:

- To explore whether the active components (avobenzone, oxybenzone, ecamsule and octocrylene) of 4 sunscreen products (1 sunscreen product in each arm) are absorbed into the systemic circulation when sunscreen is applied under maximal-use conditions.

One sunscreen product with the highest avobenzone exposure will be selected for the second part of the study. If there is no quantifiable exposure of avobenzone for any of the sunscreen products, the formulation with the highest oxybenzone exposure will be selected for Part 2.

4.1.2 Part 2

Part 2 is an open-label, 1-arm study in 24 healthy adult subjects with the following primary objective:

- To assess the pharmacokinetics of the active components (avobenzone, oxybenzone, octocrylene and/or ecamsule) in the selected product from Part 1.

5. Investigational Plan

5.1. Study Design

This will be a single clinical study conducted in 2 parts. The duration of study participation will be approximately 37 days for each part, including a 30-day screening period, a 4-day treatment period (Days 1-4) with the subjects confined to the clinic, and subjects not leaving the clinic until Day 7 following completion of scheduled End-of-Study activities.

Part 1

Part 1 is an open-label, randomized, 4-arm pilot study to evaluate the effects of multiple applications of 4 different topical sunscreen formulations in healthy adult subjects. Each arm will include 6 subjects (3 male and 3 female) with 1 formulation. A total of 24 subjects (12 male and 12 female) from all 4 arms will be admitted to the clinical research unit (CRU) on Day 0.

On the morning of Days 1 through 4, subjects will receive a topical application of the study product at approximately 0900 hours. The study drug will be weighed in advance and applied by a qualified person from the study team. Subjects will then receive 3 more topical applications on the same day at 2, 4, and 6 hours after the first dose.

5.1.1 Part 2

Part 2 is an open-label, 1-arm confirmatory study to evaluate the pharmacokinetics of avobenzone, oxybenzone, octocrylene and/or ecamsule after multiple applications of a topical sunscreen formulation in healthy adult subjects. Part 2 will include 24 subjects (12 male and 12 female). The formulation in Part 2 will be selected based on the plasma exposure data from the pilot study (Part 1). A total of 24 subjects (12 male and 12 female) will be admitted to the CRU on Day 0.

On the morning of Days 1 through 4, subjects will receive a topical application of the study product at approximately 0900 hours. The study drug will be weighed in advance and applied by a qualified person from the study team. Subjects will then receive 3 more topical applications on the same day at 2, 4, and 6 hours after the first dose.

5.1.2 Common Procedures

Details of study visits and study procedures are described in Section 5.6 and Section 5.7, respectively, and the overall Schedule of Events for both parts of the study is presented in Section 10.1.

In both parts of the study, approximately 2 mg of sunscreen per 1 cm^2 of body surface (calculation per method of Dubois) will be evenly applied 4 times per study day to areas of the body typically exposed to the sun: face, ears, neck, torso, arms, and legs (approximately 75% of the body surface area). The antecubital areas will be avoided when applying the sunscreen due to potential contamination of the sites used for intravenous (IV) PK blood sample collection. The topical applications of the study drug will be administered with subjects in swim wear to simulate real world settings as well as for easy application. In addition to swim wear, subjects may wear scrubs in between applications and at other times throughout the day/night. Subjects are required to shower each morning after the first PK blood sample collection (and before the first sunscreen application for that day), but not at other times during the day. And, subjects should not use any personal care products which contain avobenzone, oxybenzone, ecamsule or octocrylene during the study.

Blood samples (approximately 10 mL per sample) will be collected for determination of avobenzone, oxybenzone, octocrylene and/or ecamsule plasma concentrations.

Safety evaluations will include adverse event (AE) monitoring, vital sign measurements, and physical examinations. All AEs reported by the subject or observed by the

investigator or CRU staff will be recorded. Any AE reported after the informed consent is signed and before study drug application will be recorded as medical history.

Subjects will remain in the CRU after admission on Day 0 until the morning of Day 7 following completion of scheduled End-of-Study activities.

5.1.3 Risk/Benefit

Subjects will be informed that participation in a human PK study like the present one cannot be of benefit to healthy volunteers. Nevertheless, the information from the physical examination, vital sign measurements, and ECG results may be shared with the subject's personal physician if this is the subject's choice. Subjects will be informed that it is also their choice to inform their personal physician that they are participating in this research study.

Subjects will be informed that their contribution to the study is of major importance to agencies like the U.S. FDA for helping this agency better evaluate the effects of human systemic absorption of sunscreen ingredients. However, since this is a study involving healthy volunteers, subjects will be informed that they have the alternative not to participate.

Subjects will be informed that they may be exposed to risks associated with the pharmacological properties of the study drugs and the study procedures.

The study sunscreen products will not be administered to anyone who is pregnant. All women must take a pregnancy test before receiving any study drug in this study. All men and all women of childbearing potential enrolled in this study will be informed that they must use 2 highly effective birth control methods (as determined by the investigator or designee; one of the methods must be a barrier technique) during the study and for at least 1 month after the last application of study drug. Subjects will be informed that they must notify the investigator if they or their female partners become pregnant during the course of the study.

Subjects will be informed that insertion of an IV catheter may be required for blood sample collection on Days 1 and 4 and, during insertion of the catheter, soreness, bruising, or infection at the insertion site are possible but unlikely. Subjects will also be informed that dizziness and lightheadedness may occur during direct venipuncture, insertion of the IV catheter, or during blood collection.

Subjects will be informed that they may eat only meals and snacks that are provided during periods of their stay in the study clinic, and that they must consume all of each meal that is served at a reasonable pace (within 25 minutes).

Subjects will be informed that the confidentiality of their data will be respected at all times according to state law, and the study personnel handling their study data are bound by confidentiality agreements.

Subjects will be informed that the study drug and all tests, procedures, and visits required by the study are provided at no cost to them. If subjects become ill or physically injured because of participation in this study, they will be informed that costs of treatment will not be covered by the sponsor.

If a subject becomes pregnant, she will be informed that neither Spaulding Clinical Research nor the sponsor will be responsible for the cost of any obstetric or related care, or for the child's care.

Subjects will be informed by the Investigator of significant new findings that may develop during the course of this research study that may relate to their willingness to continue participation in the study.

5.2. Selection of Study Population

Subjects will be screened and the data collected will be reviewed by the principal investigator. Only those subjects who meet all of the eligibility criteria will be enrolled.

5.2.1 Inclusion Criteria

Subjects who meet all of the following inclusion criteria will be eligible to participate in the study:

1. Subject signs an institutional review board (IRB)-approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act authorization) before any study-related procedures are performed.
2. Subject is a healthy man or woman, 18 to 60 years of age, inclusive, who has a body mass index of 18.5 to 29.9 kg/m^2, inclusive, at Screening.
3. Subject has normal medical history findings, clinical laboratory results, vital sign measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings at Screening or, if abnormal, the abnormality is not considered clinically significant (as determined and documented by the investigator or designee).
4. Subject must have a negative test result for alcohol and drugs of abuse at screening and Check-in (Day 0)
5. Subject has no known or suspected allergies or sensitivities to any components of the sunscreen formulation.
6. Female subjects must be of nonchildbearing potential or, if they are of childbearing potential, they must: 1) have been strictly abstinent for 1 month before Check-in (Day 0) and agree to remain strictly abstinent for the duration of the study and for at least 1 month after the last application of study drug; OR 2) be practicing 2 highly effective methods of birth control (as determined by the investigator or designee; one

of the methods must be a barrier technique) from at least 1 month before Check-in (Day 0) until at least 1 month after the last application of study drug.

7. Female subjects must not be pregnant or lactating before enrollment in the study.
8. Male subjects must agree to practice 2 highly effective methods of birth control (as determined by the investigator or designee; one of the methods must be a barrier technique) from at least 1 month before Check-in (Day 0) until at least 1 month after the last application of study drug.
9. Subject is highly likely (as determined by the investigator) to comply with the protocol-defined procedures and to complete the study.

Note: subjects with any skin type or skin pigment type may be eligible for the study.

5.2.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will not be eligible to participate in the study:

1. Subject has broken, irritated, or unhealed skin.
2. Subject has an active sunburn.
3. Subject has used a tanning bed in the previous 4 weeks.
4. Subject has known skin or autoimmune disease(s).
5. Subject is anemic or has any chronic condition(s) that may impact blood sample collection.
6. Subject has any underlying disease or surgical or medical condition (e.g., cancer, human immunodeficiency virus [HIV], severe hepatic or renal impairment) that could put the subject at risk or would normally prevent participation in a clinical study.
7. Subject has known or suspected allergies or sensitivities to any components of the sunscreen formulation.
8. Subject has clinical laboratory test results (hematology and serum chemistry) at Screening that are outside the reference ranges provided by the clinical laboratory and considered clinically significant by the investigator.
9. Subject has a positive test result at Screening for HIV 1 or 2 antibody, hepatitis C virus antibodies, or hepatitis B surface antigen.
10. Subject is unable or unwilling to undergo multiple venipunctures for blood sample collection because of poor tolerability or poor venous access.
11. Subject has received or applied the topical sunscreen formulations used in the current study, or any other product containing the active ingredients of the topical sunscreen formulations used in the current study, within 7 days before Check-in (Day 0).

12. Subject has used any personal care product(s) containing any active sunscreen ingredient, such sunscreen products, hand or body moisturizing lotion, makeup or foundation, lip balm, or lipstick, within 7 days before Check-in (Day 0).
13. Subject is unable or unwilling to tolerate the scent of sunscreen for the duration of the treatment period.

5.3. Screening Failures

Subjects who sign and date the informed consent form but who fail to meet the inclusion and exclusion criteria are defined as screening failures. A screening log, which documents the subject initials and reason(s) for screening failure, will be maintained by the investigator for all screening failures. A copy of the log should be retained in the investigator's study files.

If a subject fails the screening process because of an abnormal laboratory result, they can receive a copy of the results upon request. The investigator will determine if follow up for the abnormal laboratory result is needed, and will encourage the subject to follow up with his or her personal physician as appropriate. All subjects will be informed as to the reason(s) they are excluded from study participation, even if follow up is not required. If a subject fails the screening process because of a positive test result for human immunodeficiency virus or hepatitis, the positive result will be reported to local health authorities as required by law.

5.4. Termination of Study or Investigational Site

5.4.1 Criteria for Termination of the Study

The study will be completed as planned unless one of the following criteria is satisfied that requires early termination of the study:

- New information regarding the safety or efficacy of the study product(s) that indicates a change in the known risk profile for the study drug(s), such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objective or compromises subject safety.

5.4.2 Criteria for Termination of Investigational Site

The study site may be terminated if the site (including the investigator) is found in significant violation of GCP, the protocol, the contractual agreement, or is unable to ensure adequate performance of the study.

In the event that the sponsor elects to terminate the study or the investigational site, a study-specific procedure for early termination will be provided by the sponsor; the

procedure will be followed by the applicable investigational site during the course of termination.

5.5. Criteria for Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn by the investigator without the approval of the subject based on the investigator's clinical judgment. A subject is not required to provide a written request to withdraw from the study; however, a written request is required if a subject withdraws consent for his or her personal data to be used for study-related purposes.

A subject may be discontinued for any of the following reasons:

- AE: The subject has experienced an AE that, in the opinion of the investigator, requires early termination. The appropriate electronic case report form (eCRF) must be completed for each AE. If a subject is discontinued from the study due to an AE, the investigator is required to follow up with the subject until the event resolves or becomes stable. If a subject dies during the study, the cause of death must be reported as a serious AE (SAE), with an outcome of death noted in the eCRF.
- Protocol Violation: The subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unnecessary risk to the subject's health.
- Withdrawal by Subject: The subject (or other responsible individual [e.g., caregiver]) wishes to withdraw from the study in the absence of a medical need.

  NOTE: Withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category.
- Study Terminated by Sponsor: The sponsor, IRB, FDA, or other regulatory agency terminates the study.
- Pregnancy: The subject is found to be pregnant.

  NOTE: If the subject is found to be pregnant, the subject must be withdrawn immediately. The pregnancy will be followed up to term, and the outcome, including any premature termination will be recorded. All live births must be followed for a minimum of 30 days or until the first well baby visit.
- Other.

  NOTE: This category records withdrawals caused by an accidental or a medical emergency, unblinding, and other rare cases. The specific reason should be recorded in the comment space of the eCRF.

5.5.1 Handling of Withdrawals

The investigator may terminate a subject's study participation at any time during the study when the subject meets the criteria described in Section 5.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Subjects will be informed that their participation in the study is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Should a subject's participation be discontinued, the primary reason for termination must be recorded. In addition, efforts should be made to perform all procedures scheduled for the early termination visit. Any data and samples collected before subject withdrawal will become the property of the sponsor.

5.5.2 Replacement Subjects

Approximately 48 healthy subjects are planned for enrollment, of which 24 subjects will be enrolled and randomized in Part 1 and 24 subjects will be enrolled in Part 2. Up to 12 subjects may be qualified as replacements. Thus, a maximum of 60 subjects may be exposed to study drugs and procedures during the study.

5.6. Study Visits

5.6.1 Recruitment

Recruitment materials (e.g., internet, radio, and print advertisements, social media posts) will be approved by the local IRB and FDA Research Involving Human Subjects Committee (RIHSC) before telephone screening. The sponsor is responsible for registration of the study on clinicaltrials.gov; however, this may not occur until RIHSC has approved the final study protocol.

5.6.1.1 Compensation

Subjects will be offered payment for Screening; however, if the results of their alcohol and drug screening tests are positive, they will not be compensated. Subjects who complete the entire study (Day 0 to Day 7 in either Part 1 or Part 2) will receive payment according to the schedule provided in the informed consent form. No special incentives are offered. Final payment will not be released until all follow-up procedures have been completed and accepted by the investigator.

If a subject chooses to withdraw from the study prematurely, he or she will only be compensated for completed days. If subjects are withdrawn for medical reasons or if the study is halted temporarily or permanently, the subjects will receive compensation proportional to the time spent in the study. No compensation will be provided if a subject

is dismissed from the study for noncompliance (e.g., improper conduct, ingesting alcohol and/or drugs [including recreational drugs], tampering with the study drug, consuming any prohibited foods or beverages).

If subjects are required to stay in the clinic for a longer period for safety reasons, they will be compensated at a rate proportional to the entire compensation for the study. If a subject becomes ill or physically injured because of participation in this study, the subject will be referred for treatment.

5.6.2 Screening

The following procedures and assessments will be performed at Screening (Day –30 to Day –1):

- Obtain informed consent/HIPAA authorization (The informed consent process will be performed by a clinical research nurse in a private room. The subject will be given unlimited time to ask questions regarding study participation, and each subject will be questioned to ensure their understanding.)

After informed consent is obtained:

- Review inclusion/exclusion criteria to confirm subject eligibility
- Record demographic information
- Measure height, weight, and calculate body mass index
- Perform serology screening (hepatitis B surface antigen, hepatitis C virus antibodies, and HIV antibody 1/2 antigen/antibody combination test)
- Record medical history, including social history and smoking habits
- Perform drug and alcohol screening (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, alcohol, opiates, phencyclidine, propoxyphene, and methadone)
- Perform a serum pregnancy test (female subjects only)
- Record prior medications
- Monitor for AEs
- Perform clinical laboratory tests (hematology, serum chemistry, and urinalysis)
- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature)
- Perform a safety 12-lead ECG
- Perform a complete physical examination

5.6.3 Study Periods

Part 1 of this study has an open-label, randomized, 4-arm design and Part 2 has an open-label, 1-arm design. Both parts of the study have 1 treatment period and 2 follow-up days. Subjects stay in the clinic for the full treatment and follow-up period.

5.6.3.1 Check-in

The following procedures and assessments will be performed at Check-in (Day 0) as outlined in Appendix A: Schedule of Events:

- Review inclusion/exclusion criteria to confirm subject eligibility
- Perform drug and alcohol screening (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, alcohol, opiates, phencyclidine, propoxyphene, and methadone)
- Perform a serum pregnancy test (female subjects only)
- Perform Fitzpatrick skin type assessment
- Admit subject to the study clinic
- Randomization (after completion of check-in procedures on Day 0 or just before dosing on Day 1)
- Record concomitant medications
- Monitor for AEs

5.6.3.2 Treatment

The following procedures and assessments will be performed during the treatment period (Days 1 through 4) according to the Schedule of Events (Section 10.1):

- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature) before dosing
- Collect PK blood sample (10 mL) before and after dosing (see Section 5.7)
- Application of topical sunscreen (according to the randomization schedule for Part 1) at approximately 0900 hours and again at 2, 4, and 6 hours after the first dose
- Physical examination of skin at the sites of topical application for signs of irritation
- Record concomitant medications
- Monitor for AEs

5.6.3.3 Washout

Not applicable.

5.6.4 Discharge (or Early Termination)

The following procedures and assessments will be performed before the subject is discharged from the study (morning of Day 7) or upon early termination:

- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature)
- Physical examination of skin at the sites of topical application for signs of irritation
- Record concomitant medications
- Monitor for AEs
- Discharge subject from the study clinic after completion of all study procedures

5.6.5 Follow-up

The following procedures and assessments will be performed on Days 6 and 7:

- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature)
- Collect PK blood samples (10 mL) after dosing as follows:
  - Day 6: 120 hours after first dose on Day 1
  - Day 7: 144 hours after first dose on Day 1
- Physical examination of skin at the sites of topical application for signs of irritation
- Symptom-directed brief physical examination at the investigator's discretion
- Record concomitant medications
- Monitor for AEs

5.7. Study Procedures

5.7.1 Pharmacokinetic Assessments

5.7.1.1 Pharmacokinetic Sample Collection

Pharmacokinetic blood samples (approximately 10 mL per sample) will be collected for determination of avobenzone, oxybenzone, ecamsule and octocrylene plasma concentrations at the following time points (the time limit for PK sample draws can be +/- 5 minutes from the nominal time):

- Day 1: *0 and 0.5, 1, 1.5, *2, *4, *6, 8, 9, 10, 12, and 14 hours after initial dose
- Day 2: 23, *28, 33 h
- Day 3: 47, *52, 57 h
- Day 4: 71, 73, *74, *76, *78, 81, 82, 84 and 86 h
- Day 5: 95 hours
- Day 6: 120 hours
- Day 7: 144 hours

  * when a time point corresponds with sunscreen administration, the PK sample will be collected before sunscreen administration.

The specific dosing and PK schedule may be adjusted for Part 2 based on the results of Part 1 in a pre-specified manner.

5.7.1.2 Pharmacokinetic Specimen Handling

The PK blood samples (10 mL each) will be collected into tubes containing K_2EDTA, inverted several times to mix the blood with the anticoagulant, and placed in an ice bath. Within 30 minutes of collection, the samples will be centrifuged for 10 minutes, at 3000 revolutions per minute, at 4°C, by a study team member.

The plasma will be separated using a disposable plastic pipette and approximately half of the plasma will be transferred into duplicate cryotube vials labeled as Aliquot A (primary) and Aliquot B (backup). The plasma samples will be appropriately labeled and stored frozen at –70°C or below until shipment. Temperature monitoring logs should be maintained and accessible for review by the study monitor.

The Aliquot A samples (primary) will be shipped first, on dry ice, to the bioanalytical laboratory at FDA for processing when requested by the sponsor. The Aliquot B samples (backup) will be held for a second shipment at a time after the completion of all Aliquot A sample shipment(s) and the timing of the Aliquot B shipment communicated by the sponsor. None of the PK blood samples will be stored at clinical facility for future use, however the sponsor will store them for analytical purposes of this study only.

Plasma concentrations of avobenzone, oxybenzone, ecamsule and octocrylene will be assayed using a validated liquid chromatography with tandem mass spectrometry method.

5.7.1.3 Pharmacokinetic Parameters

The following PK parameters will be determined for each subject:

Days 1

- Maximum concentration (observed peak drug concentration) (C_{max})
- Time at which C_{max} occurs (T_{max})
- AUC from time 0 to the sampling time corresponding to the last quantifiable concentration (C_{last}) (AUC_{0-t}), calculated by the mixed linear logarithmic trapezoidal method

Days 2 and 3

- Residual drug concentration (predose level) (C_{trough})
- 3 h post dose concentration

Day 4

- Elimination rate constant (K_{el}), obtained by linear regression of the log-linear terminal phase of the concentration-time profile using at least 3 data points, excluding C_{max}, otherwise K_{el} will not be determined. The acceptability criteria for determination of K_{el} will be a coefficient of regression more than or equal to 0.98. When K_{el} will not be determined, AUC_{0-inf} and $t_{1/2}$ will not be reported.
- Terminal half-life ($t_{1/2}$), calculated using the equation ln2/k after the last study drug application (on Day 4)
- Accumulation ratios, calculated using the following formula:

  $R_1 = AUC_{0-23}$ Day 4 / AUC_{0-23} Day 1
- AUC from time 0 extrapolated to infinity (AUC_{0-inf}), calculated by the mixed linear-logarithmic trapezoidal method as:

  $AUC_{0-inf} = AUC_{0-t} + C_{last} / K_{el}$

  When the extrapolation represents more than 20%, AUC_{0-inf} and $t_{1/2}$ will not be reported.

Days 5, 6 and 7

- Residual drug concentration (predose level) (C_{trough})

5.7.2 Safety Assessments

Safety will be evaluated in terms of AEs, vital sign measurements (blood pressure, heart rate, respiratory rate, and oral body temperature), and physical examination findings.

5.7.2.1 Adverse Events

5.7.2.1.1 Adverse Event Definitions

An AE is defined as any untoward and/or unintended sign, including an abnormal clinical laboratory finding, symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug. Events or conditions that increase in frequency or severity during or as a consequence of use of a drug in human clinical trials will also be considered AEs.

A treatment-emergent adverse event (TEAE) is defined as an AE that begins after study drug administration.

An unexpected AE is any AE having a specificity or severity not consistent with the current investigator's brochure for the study drug(s).

An SAE is defined as any AE occurring at any dose that meets the following criteria:

- Results in death,
- Is life threatening,
- Requires hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity,
- Is a congenital anomaly/birth defect, or
- Is an important medical event that may not meet the previous criteria but, based upon appropriate medical judgment, jeopardizes the subject or requires medical or surgical intervention to prevent one of the outcomes listed previously.

5.7.2.1.2 Adverse Event Reporting

The recording of AEs will begin after the subject signs the informed consent form and will continue until discharge (or early termination). All AEs, whether serious or nonserious and whether or not related to the study drug, must be recorded in the eCRF. Study subjects will be instructed to warn study staff if he or she has any unexpected symptoms. In addition, all subjects will receive a reminder telephone call approximately 24 hours before Check-in.

Any SAE (whether expected or unexpected) must be entered into the eCRF system and reported by facsimile to the medical monitor or designee using the SAE Reporting Form within 24 hours of the investigator or study clinic staff becoming aware of the event. It is the responsibility of the investigator to report all SAEs to the medical monitor, to provide

the most complete report possible, and to assess each SAE for its relationship to the study drug. The investigator is responsible for obtaining follow-up information on all SAEs and submitting follow-up SAE data. Any unexpected SAEs must be reported promptly to the investigator's IRB as per the IRB's requirements.

In the event of a fatal or life-threatening SAE, the sponsor will notify the appropriate FDA authorities by telephone or facsimile within 7 calendar days of receipt of the report. The sponsor will follow all 7-day alert reports with a written report within 10 working days of receipt of the case. Serious AE cases that concern nonfatal, nonlife-threatening events that are unexpected and at least possibly related to the study drug will be submitted in writing to the FDA within 10 working days of receipt.

Furthermore, any AEs that are not expected, occur at a higher frequency, or would require modification of the study protocol and/or informed consent must be reported to the FDA within 10 working days.

Adverse events that are assessed by the investigator as possibly or probably related to the study drug will be followed until they resolve or stabilize. All SAEs will be followed until resolution.

5.7.2.1.3 Assessment of Severity

The investigator will assess the severity of each AE using the following scale:

- Mild: The subject is aware of the AE but is still able to perform all activities; minimal or no medical intervention or therapy is required.
- Moderate: The subject has to discontinue some activities due to the AE; minimal or no medical intervention or therapy is required.
- Severe: The subject is incapacitated by the AE and is unable to perform normal activities; significant medical intervention or therapy is required and hospitalization is possible.

5.7.2.1.4 Assessment of Causality

The investigator will assess the causal relationship/relatedness of each AE to the study drug using the following scale:

- Not Related: Onset of the AE has no reasonable temporal relationship to administration of the study drug, a causal relationship to administration of the study drug is biologically implausible, or the event is attributed to an alternative etiology.
- Unlikely Related: Onset of the AE has a reasonable temporal relationship to study drug administration and although a causal relationship is unlikely, it is biologically plausible.

- Possibly Related: Onset of the AE has a strong temporal relationship to administration of the study drug, cannot be explained by the subject's clinical state or other factors, and a causal relationship is biologically plausible.
- Probably Related: Onset of the AE shows a distinct temporal relationship to administration of the study drug that cannot be explained by the subject's clinical state or other factors, the AE is a known reaction to the product or chemical group, or can be predicted by the product's pharmacology.

5.7.2.1.5 Pregnancy

A serum pregnancy test will be performed for female subjects at the time points presented in the Schedule of Events (Section 10.1). If a subject becomes pregnant while on the study, this should be reported immediately to the investigator, the subject will be withdrawn from the study and the medical monitor and the subject will be instructed to follow-up with his or her personal physician. All pregnancies are to be reported as an AE and followed for outcome.

5.7.2.2 Clinical Laboratory Tests

Clinical laboratory and diagnostic screening tests will be performed at the time points presented in the Schedule of Events (Section 10.1) and will be collected in accordance with acceptable laboratory procedures. Clinical laboratory testing will be performed by Spaulding Clinical Laboratory, West Bend, Wisconsin, and Laboratory Corporation of America (LabCorp), Dublin, Ohio. The clinical laboratory tests that will be performed are presented in Table 5-1. Unused clinical laboratory test samples will not be stored for future use.

Clinical laboratory results will be reviewed by the investigator or designee together with data in the eCRF. Any values outside the reference range will be evaluated for clinical significance. If a value is determined to be clinically significant, the subject will be instructed to follow-up with his or her personal physician. The investigator or designee may repeat the clinical laboratory tests if deemed appropriate. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Table 5-1 Clinical Laboratory and Diagnostic Screening Tests

Hematology	Serum Chemistry	Urinalysis
Complete blood count Hematocrit Hemoglobin Platelet count Red blood cell count White blood cell count (with automated differential)	Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Bicarbonate Blood urea nitrogen Calcium Chloride Direct bilirubin Glucose Lactic dehydrogenase Magnesium Phosphorus Potassium Serum creatinine Sodium Total bilirubin Total protein Uric acid	Appearance Bilirubin Color Glucose Ketones Leukocyte esterase Microscopic examination: red blood cells; white blood cells; epithelial cells; bacteria, crystals, casts, etc. (if present) Nitrite Occult blood pH Protein Specific gravity Urobilinogen

Diagnostic Screening Tests:	
Serum	**Urine**
Hepatitis panel (hepatitis B surface antigen and hepatitis C virus antibody) and human immunodeficiency virus antibody 1/2 antigen/antibody combination test	Drug screen including: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, ethanol, opiates, phencyclidine, propoxyphene, and methadone
Serum human chorionic gonadotropin pregnancy test for all female subjects	

5.7.2.3 Vital Sign Measurements

Vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature) will be measured using an automated device at the time points presented in the Schedule of Events (Section 10.1). The subject should be in a supine position, if possible, for a minimum of 5 minutes before vital signs are measured.

5.7.2.4 Safety 12-Lead Electrocardiograms

Safety 12-lead ECGs will be performed at the time points presented in the Schedule of Events (Section 10.1). The subject should be in a supine position, if possible, for approximately 10 minutes before safety 12-lead ECGs are measured. The safety 12-lead ECGs will be reviewed by the investigator at the study clinic to detect any immediate safety concerns.

5.7.2.5 Physical Examinations

Physical examinations will be performed at the time points presented in the Schedule of Events (Section 10.1).

The complete physical examination at Screening will include, but not be limited to, assessments of the head, eyes, ears, nose, throat, skin, thyroid, nervous system, respiratory system, cardiovascular system, abdomen (liver and spleen), lymph nodes, and extremities. Height, weight (without shoes and wearing the lightest possible clothing), and calculation of body mass index (kg/m^2) will be performed at Screening only.

During the study, skin at the sites of topical application of the study drug will be examined for signs of irritation during the treatment period, upon discharge (or early termination), and at the follow-up visits. At the follow-up visits, a symptom-directed brief physical examination may be performed at the investigator's discretion

If an abnormality is observed upon physical examination, the subject will be instructed to follow up with his or her personal physician.

5.7.3 Demographics and Medical History

Demographic data (date of birth, gender, race, and ethnicity) will be collected at Screening.

Each subject will provide a complete medical history at Screening that will be reviewed at Check-in. Specific information relating to any prior or existing medical conditions/surgical procedures will be recorded in the subject's eCRF.

5.8. Study Treatments

5.8.1 Treatments Administered

Part 1

- La Roche Posay (Cream), Anthelios SX Daily Moisturizer Cream, Face Sunscreen SPF 15 with Mexoryl SX
- Hawaiian Tropic (Lotion); Island Sport Ultra-Light High Performance Sunscreen, SPF 50
- Neutrogena (Spray), Ultra Sheer Body Mist SPF 45
- Banana Boat (Spray); Sport Performance Coolzone Continuous Spray Sunscreen, SPF 50

Approximately 2 mg of sunscreen formulation per 1 cm^2 of body surface will be applied topically 4 times per day for 4 days to approximately 75% of the body surface area.

Part 2

The formulation in Part 2 will be selected based on the plasma exposure data from the pilot study (Part 1).

Parts 1 and 2

On the morning of Days 1 through 4, subjects will receive a topical application of the study drug (for Part 1 this will be according to the randomization schedule; not applicable in Part 2) at approximately 0900 hours. The study drug will be weighed in advance and applied by a qualified person from the study team. Subjects will then receive 3 more topical applications on the same day at 2, 4, and 6 hours after the first dose. Based on the results of Part 1, the dosing schedule may be adjusted for Part 2.

The antecubital areas will be avoided when applying the sunscreen due to potential contamination of the sites used for IV PK blood sample collection.

5.8.2 Method Assigning Subjects to Treatment

5.8.2.1 Randomization Process

Part 1

The FDA project biostatistician will create the specifications that will be used to generate the randomization schedule. The specifications will be based on the protocol requirements and appropriate statistical programming with consideration for study design, number of treatments, number of subjects planned for enrollment, stratification, and blocking.

Based on these specifications, the project biostatistician (or designee) will generate a dummy randomization schedule. The schedule is generated by a SAS® or R program, which produces output file(s) and/or SAS or R dataset(s).

The project biostatistician (or designee) distributes the 'dummy' randomization schedule to specified personnel for review. Any change (e.g., change in block size, change in stratification levels) that requires an update to the specifications will reset this process. Minor changes (e.g., display formatting) will not require a change to the specifications.

No transfer is necessary if the unblinded randomization biostatistician also created the 'dummy' randomization.

The randomization biostatistician is responsible for generating the final randomization schedule.

Randomization (Part 1 only) will occur after informed consent is obtained, either after completion of check-in procedures on Day 0 or just before dosing on Day 1. Unique subject numbers will be used in sequential order based on each subject's order of qualification.

Subjects in Part 1 will be randomly assigned to 1 of 4 different treatments, thus each subject will receive one of the following treatments by the end of Part 1: 1) La Roche Posay (Cream), Anthelios SX Daily Moisturizer Cream, Face Sunscreen SPF 15 with

Mexoryl SX; 2) Hawaiian Tropic (Lotion); Island Sport Ultra-Light High Performance Sunscreen, SPF 50; 3) Neutrogena (Spray) Ultra Sheer Body Mist SPF 45 ; or 4) Banana Boat (Spray); Sport Performance Coolzone Continuous Spray Sunscreen, SPF 50. Replacement subjects (if needed) will be assigned to the treatment group of the subject they are replacing.

The treatment groups in Part 1 are presented in Table 5-2.

Table 5-2 Part 1 Treatment Groups

Subjects (n)	Treatment Group	Treatment
6	A	La Roche Posay (Cream), Anthelios SX Daily Moisturizer Cream, Face Sunscreen SPF 15 with Mexoryl SX
6	B	Hawaiian Tropic (Lotion); Island Sport Ultra-Light High Performance Sunscreen, SPF 50
6	C	Neutrogena (Spray) Ultra Sheer Body Mist SPF 45
6	D	Banana Boat (Spray); Sport Performance Coolzone Continuous Spray Sunscreen, SPF 50

All randomization information will be secured and housed in a locked storage area, accessible only by the randomization personnel and the assigned pharmacist and his or her verifier.

5.8.3 Identity of Study Drug

The topical sunscreen formulations described in Section 5.8.1 are commercially available OTC products containing the active components avobenzone, oxybenzone, octocrylene and/or ecamsule.

5.8.4 Management of Clinical Supplies

5.8.4.1 Study Drug Packaging and Storage

The topical sunscreen formulations will be obtained from commercial sources and stored according to the manufacturer's directions.

5.8.4.2 Study Drug Accountability

Good clinical documentation practices will be employed to record the receipt, storage conditions, accountability, and use or return of the study drug. The study drug will be stored in a secure location with access to the study personnel who will be managing the storage, dispensing, and accountability of the study drug.

Upon completion or termination of the study, final accountability review by the study monitor, and written authorization from the sponsor, all unused and/or partially used study drug should be returned or destroyed at the study clinic. It is the investigator's

responsibility to ensure that the sponsor has provided written authorization for study drug disposal, the disposal process follows the study clinic's standard operating procedures, and appropriate records of the disposal are documented and maintained. No unused study drug may be disposed until fully accounted for by the study monitor (or designee). Documentation of unused study drug should include subject number, medication identity (medication #, period #), date, and quantity of study drug used.

5.8.5 Blinding

Both parts of this study are open-label; therefore, blinding is not applicable.

5.8.6 Treatment Compliance

At Screening, as part of the eligibility assessment, it will be confirmed that subjects can comply with the protocol-defined procedure of topical study drug application. All applications of the study drug will be administered in the study clinic either under direct observation of or administered by clinic personnel, and recorded in the eCRF.

5.8.7 Prior and Concomitant Medications

Subjects are prohibited from having received or applied the topical sunscreen formulations used in the current study within 7 days before Check-in (Day 0). Subjects are also prohibited from having used any personal care product(s) containing any active sunscreen ingredient, such sunscreen products, hand or body moisturizing lotion, makeup or foundation, lip balm, or lipstick, within 7 days before Check-in (Day 0).

Subjects will be instructed not to take any medications, including OTC products, without first consulting with the investigator.

5.8.8 Subject Restrictions

At Screening, as part of the eligibility assessment, it will be confirmed that subjects have not used a tanning bed in the previous 4 weeks before the study. As part of the medical history assessment at Screening, subjects will be asked about their smoking history. Subject responses will be recorded on the eCRF.

Subjects must be willing to comply with study rules throughout the duration of the study.

5.9. Statistical Methods

5.9.1 Sample Size

Approximately 48 healthy subjects are planned for enrollment, of which 24 subjects will be enrolled and randomized in Part 1 and 24 subjects will be enrolled in Part 2. The sample size was determined empirically and is typical for exploratory investigations of this type.

5.9.2 Analysis Populations

The PK population will include all subjects who receive study drug and have at least 1 estimable PK parameter after dosing.

The safety population will include all subjects who receive at least 1 dose of any of the study drugs.

5.9.3 General Statistical Considerations

All data will be presented in data listings. Data from subjects excluded from an analysis population will be presented in the data listings but not included in the calculation of summary statistics.

5.9.4 Subject Disposition

The number of subjects who enroll in the study and the number and percentage of subjects who complete each assessment will be presented. The frequency and percentage of subjects who withdraw or discontinue from the study and the reason for withdrawal or discontinuation will be summarized.

5.9.5 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized overall and by treatment for all subjects.

5.9.6 Pharmacokinetic Analyses

Plasma concentrations and PK parameters of avobenzone, oxybenzone, ecamsule and octocrylene will be listed and summarized using descriptive statistics (n, arithmetic mean, SD, minimum, median, and maximum) by nominal PK sampling time.

5.9.7 Safety Analyses

5.9.7.1 Adverse Events

Any AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of AEs, organized by system organ class and frequency, will be summarized by seriousness, severity, relationship to treatment, and by treatment, with a focus on TEAEs. A detailed listing of serious AEs and TEAEs leading to withdrawal will also be provided.

5.9.7.2 Clinical Laboratory Tests

Clinical laboratory results (hematology, serum chemistry, and urinalysis) will be summarized using descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum). Clinical laboratory results will be classified as normal or

abnormal, according to the reference ranges of the individual parameter. The number and percentage of subjects with abnormal laboratory results will be provided. No statistical testing will be performed on clinical laboratory data.

5.9.7.3 Vital Sign Measurements

Vital sign measurements and changes from Baseline will be summarized using descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum) by treatment and time point.

5.9.7.4 Safety 12-Lead Electrocardiograms

Safety 12-lead ECG data will be summarized using descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum).

5.9.7.5 Physical Examinations

Physical examination findings will be presented in a data listing, and abnormal physical examination findings will be recorded as AEs.

5.9.7.6 Other Safety Data

All concomitant medication usage and medications that changed in daily dose, frequency, or both since the subject provided informed consent will be summarized for each subject.

5.9.8 Interim Analyses

No interim analyses are planned.

5.9.9 Missing Data

Missing data will not be imputed. Data that are excluded from the descriptive or inferential analyses will be included in the subject data listings. This will include data from subjects not in the particular analysis population, measurements from unscheduled visits, or extra measurements that may arise from 2 or more analyses of a plasma sample at the same time point.

5.10. Data Quality Assurance

Completed eCRFs are required for each subject randomly assigned to study drug. Electronic data entry will be accomplished through the ClinSpark® remote electronic data capture system, which allows for on-site data entry and data management. This system provides immediate, direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and subsequently any

investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records.

Furthermore, the investigator retains full responsibility for the accuracy and authenticity of all data entered into the electronic data capture system. The completed dataset and their associated files are the sole property of the sponsor and should not be made available in any form to third parties, except for appropriate governmental health or regulatory authorities, without written permission of the sponsor.

6. Ethical Considerations

6.1. Ethical Conduct of the Study

This study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, 1964 and later revisions, as well as, United States Title 45 Code of Federal Regulations (CFR) Part 46 GCP, and International Council for Harmonisation (ICH) guidelines describing technical requirements for registration of pharmaceuticals for human use.

7. Institutional Review Board (IRB)

The investigator will provide both the local IRB and the FDA IRB with all required documents, including the study protocol and informed consent form and recruitment materials. The study will not be initiated until appropriate IRB approval is obtained. The sponsor will provide either a copy of the FDA IRB approval letter or signed IRB Authorization Agreement (IAA) to the investigator or designee before the study is initiated. The subjects will be informed that they have the right to contact the local IRB or Office for Human Research Protections if they have any questions, concerns, complaints, or believe they have been harmed by the participation in this research study as a result of investigator negligence. Subjects will be given the address and phone number of the local IRB.

8. Administrative Procedures

8.1. Responsibilities of the Investigator

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes may be reported to the IRB but will not result in protocol amendments.

8.1.1 Form FDA 1572

The investigator will complete and sign the Form FDA 1572.

8.1.2 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with the ICH E6(R1) and all applicable guidelines and regulations.

8.1.3 Reporting Requirements

By participating in this study, the investigator agrees to submit reports of SAEs according to the time line and method outlined in the protocol (Section 5.7.2.1.2). In addition, the investigator agrees to submit reports to the IRB as appropriate. The investigator also agrees to provide the sponsor with an adequate report shortly after completion of the investigator's participation in the study.

8.1.4 Source Documentation

By participating in this study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories.

8.1.5 Retention of Records

The investigator agrees to keep the records stipulated in this protocol and those documents that include (but are not limited to) the study-specific documents, identification log of all participating subjects, medical records, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent form), copies of all eCRFs, query responses, and detailed records of drug disposition, to enable evaluations or audits from regulatory authorities, the sponsor, or its designees.

Furthermore, ICH 4.9.5 requires the investigator to retain essential documents specified in ICH E6(R1) (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the clinical study site agreement between the investigator and sponsor.

Refer to the clinical study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

8.1.6 Financial Disclosure and Obligations

The investigator is required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 45 CFR 45. In addition, the investigator must provide to the sponsor a

commitment to update this information promptly if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.

Neither the sponsor nor the study clinic is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process.

8.2. Confidentiality and Disclosure of Data

All subjects will sign a HIPAA-compliant authorization form containing the mandated core elements and requirements before participation in this clinical study. The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's electronic data capture system database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes such as gender, age or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires that the investigator allow review of the subject's original medical records (source data or documents) by the study monitor, representatives from any regulatory authority (e.g., FDA), the sponsor's designated auditors, and the appropriate IRB. These medical records will include, but will not be limited to, clinical laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process.

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected in the subject's eCRF).

Data will be maintained and backed up in the electronic data capture system. All access to the data is protected by username and password, and each staff member and all sponsor staff will have separate access that requires a separate username and password. Access is only given to site staff and requested sponsor staff who have completed the appropriate training.

8.3. Certificate of Confidentiality

In order to protect the privacy of subjects, Certificates of Confidentiality will be obtained prior to the initiation of the study.

8.4. Subject Consent

Written informed consent in compliance with 45 CFR 46 will be obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. An informed consent template may be provided by the sponsor to the study clinic. If any institution-specific modifications to study-related procedures are proposed or made by the study clinic, the consent should be reviewed by the sponsor or its designee or both before IRB submission. Once reviewed, the consent will be submitted by the investigator to the IRB for review and approval before the start of the study. If the informed consent form is revised during the course of the study, all active participating subjects must sign the revised form.

Before enrollment, each prospective subject will be given a full explanation of the study and be allowed to read the approved informed consent form. The informed consent process will be performed by a clinical research nurse in a private room. The subject will be given unlimited time to ask questions regarding study participation, and each subject will be questioned to ensure their understanding. Once the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing the informed consent form.

The investigator will provide a copy of the signed informed consent form to the subject. The original form will be maintained in the subject's medical records at the site.

8.5. Data Collection

Full details of procedures for data collection and handling will be documented in the data management plan, which is initiated with the final protocol receipt. The data management plan is a changing document that evolves over the course of the study and is finalized by database lock.

8.6. Publications

No information related to or generated by this study will be released to the public until it has been reviewed by the sponsor. The sponsor shall own intellectual rights for the data and analysis resulting from this study and results cannot be presented or published without written permission from the sponsor. Authorship on publications will be determined by standard journal requirements.

9. Study Management

9.1. Release of Study Drug to the Study Clinic

Before the study drug can be released to the study clinic, the following documents will be collected from the study clinic by the clinical research organization, retained in the trial master file, and a study drug shipment approval form will be completed by the clinical research organization:

- Protocol signature page signed by the investigator
- IRB approval of the protocol and informed consent form and IRB membership list
- Completed Form FDA 1572, curriculum vitae, and medical licenses from each investigator
- Financial disclosure and debarment certification from each investigator
- Executed contract with investigator and study clinic

9.2. Monitoring

9.2.1 Monitoring of the Study

The sponsor or its designee will monitor the study to ensure that it is being conducted according to the protocol, GCP standards, and applicable region-specific requirements, and to ensure that study initiation, conduct, and closure are adequate. The investigators and the study clinic staff will be expected to cooperate fully with the study monitors and personnel or agents of the sponsor, and be available during monitoring visits to answer questions sufficiently and to provide any missing information. The investigators and their institutions will permit direct access to source data/documents for study-related monitoring activities, audits, IRB reviews, and regulatory inspections.

During any on-site visits, the study monitor will:

- Check and assess the progress of the study
- Review all informed consent forms
- Review study data collected
- Conduct source document verification
- Identify any issues and address their resolution
- Verify that the facility remains acceptable
- Conduct study drug accountability

These monitoring activities will be done in order to verify that the:

- Data are authentic, accurate, and complete.
- The safety and rights of the subjects are being protected.
- The study is being conducted in accordance with the currently approved protocol (including any amendments), GCP, and all applicable regulatory requirements.

In addition, the sponsor, designated auditors, and government inspectors must be allowed access to eCRFs, source documents, and other study files that may be required to evaluate the conduct of the study.

9.3. Management of Protocol Amendments and Deviations

9.3.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent immediate hazard to the subject, must be submitted to the sponsor or designee and reviewed and approved by the IRB before implementation. Amendments to the protocol must be submitted in writing to the IRB for approval before subjects are enrolled into an amended protocol.

9.3.2 Protocol Violations and Deviations

Any significant protocol deviations that the investigator or study clinic staff believes are of major importance (e.g., incorrect randomizations, subject enrolled but not eligible) should be reported to the IRB as soon as possible. Significant protocol deviations may include the following:

- Deviations from the inclusion/exclusion criteria that may affect subject safety
- Deviations (omission or delay) of safety monitoring procedures
- Deviations in the administration of the study drug
- Deviations in obtaining informed consent

All subjects who are enrolled and receive the study drug, regardless of whether they have a major protocol violation, must continue to be followed for safety for all follow-up study visits.

10. Appendices

10.1. Appendix A: Schedule of Events

Table 10-1 Overall Schedule of Events (Parts 1 and 2)

	Screening	Check-in	Treatment and Follow-Up Period (In House)						Discharge or Early Termination
Study Procedure	**Days –30 to–1**	**Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Informed consent/HIPAA authorization	X								
Eligibility assessment	X	X							
Demographics	X								
Height, weight, body mass index	X								
Serology	X								
Medical history[a]	X								
Drug and alcohol screening	X	X							
Serum pregnancy test (female subjects)	X	X							
Fitzpatrick skin type assessment		X							
Admission to study clinic		X							
Randomization[b]		X							
Prior and concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X
Clinical laboratory tests[c]	X								
Vital sign measurements[d]	X		X	X	X	X	X	X	X
Safety 12-lead ECG[e]	X								
Physical examination[f]	X		X	X	X	X	X	X	X
Study drug administration[g]			X	X	X	X			
PK blood sample collection[h]			X	X	X	X	X	X	X
Discharge from study clinic									X

Abbreviations: ECG, electrocardiogram; HIPAA, Health Insurance Portability and Accountability Act; PK, pharmacokinetic.

a Medical history assessment will also include social history and smoking habits.

b Randomization (Part 1 only) will occur either after completion of check-in procedures on Day 0 or just before dosing on Day 1.

c Clinical laboratory testing will include hematology, serum chemistry, and urinalysis.

d Vital signs measurements will include blood pressure, heart rate, respiratory rate, and oral body temperature. The subject should be in a supine position, if possible, for a minimum of 5 minutes before vital signs are measured. During the treatment period, vital signs will be measured before dosing.

e The subject should be in a supine position, if possible, for approximately 10 minutes before the safety 12-lead ECG is measured.

f A complete physical examination will be performed at Screening. The skin at the sites of topical application of the study drug will be examined for signs of irritation during the treatment period, upon discharge (or early termination), and at the follow-up visits. At the follow-up visits, a symptom-directed brief physical examination may be performed at the investigator's discretion.

g Topical sunscreen will be applied (according to the randomization schedule) at approximately 0900 hours and again at 2, 4, and 6 hours after the first dose.

h Pharmacokinetic blood samples (approximately 10 mL per sample) will be collected at the following time points:

- Day 1: *0 and 0.5, 1, 1.5, *2, *4, *6, 8, 9, 10, 12, and 14 hours after initial dose
- Day 2: 23, *28, 33 h
- Day 3: 47, *52, 57 h
- Day 4: 71, 73, *74, *76, *78, 81, 82, 84 and 86 h
- Day 5: 95 hours
- Day 6: 120 hours
- Day 7: 144 hours

Note: *when a time point corresponds with sunscreen administration, the PK sample will be collected before sunscreen administration.

11. Reference List

Department of Health and Human Services, Food and Drug Administration (US), Center for Drug Evaluation and Research (CDER). Guidance for Industry: Nonprescription Sunscreen Drug Products – Safety and Effectiveness Data. November 2016.

Statistical Analysis Plan

Statistical Analysis Plan

SCR-005: Assessment of the Human Systemic Absorption of Sunscreen Ingredients

Sponsor: U.S. Food and Drug Administration
White Oak Building #64, Room 2072
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sponsor Study Lead and Medical Monitor: David Strauss, MD, PhD
Director, Division of Applied Regulatory Science
U.S. Food and Drug Administration
Telephone: 301-796-6323
Email: david.strauss@fda.hhs.gov

FDA RIHSC Sponsor: David Strauss, MD, PhD

Project Managers: Murali Matta, PhD
U.S. Food and Drug Administration
Telephone: 240-402-5325
Email: murali.matta@fda.hhs.gov

Robbert Zusterzeel, MD, PhD, MPH
U.S. Food and Drug Administration
Telephone: 301-796-3750
Email: robbert.zusterzeel@fda.hhs.gov

Study Monitor: Jill Brown
RIHSC Project Manager
U.S. Food and Drug Administration

Version of SAP: 1.1

Date of SAP: 16 July 2018

CONFIDENTIAL

Sponsor Signatures Page

Prepared by

Robbert Zusterzeel -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001114905, cn=Robbert Zusterzeel -S
Date: 2018.07.16 10:47:03 -04'00'

July 16, 2018

Robbert Zusterzeel, MD, PhD, MPH
Staff Fellow Medical Officer
Division of Applied Regulatory Science
U.S. Food and Drug Administration

Date

Reviewed by

Murali K. Matta -S

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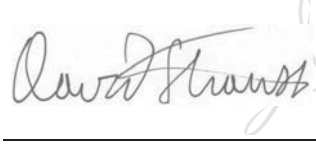
Date: 2018.07.16 11:05:13 -04'00'

July 16, 2018

Murali Matta, PhD
Visiting Associate
Division of Applied Regulatory Science
U.S. Food and Drug Administration

Date



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Date: 2018.07.16 12:09:14 -04'00'

July 16, 2018

Approved by

David Strauss, MD, PhD
Director
Division of Applied Regulatory Science
U.S. Food and Drug Administration

Date

Contents

1 Study Objectives

The primary objective of this study is:

1. To explore whether the active components (avobenzone, oxybenzone, ecamsule and octocrylene) of sunscreen products are absorbed into the systemic circulation when a sunscreen product is applied under maximal-use conditions.

1.1 Primary Objective (Part 1)

Part 1 is an open-label, randomized, 4-arm study in 24 healthy adult subjects with the primary objective:

- To explore whether the active components (avobenzone, oxybenzone, ecamsule and octocrylene) of 4 sunscreen products (1 sunscreen product in each arm) are absorbed into the systemic circulation when a sunscreen product is applied under maximal-use conditions.

One sunscreen product with the highest avobenzone exposure will be selected for the second part of the study. If there is no quantifiable exposure of avobenzone for any of the sunscreen products, the formulation with the highest oxybenzone exposure will be selected for Part 2.

1.2 Primary Objective (Part 2)

Part 2 is an open-label, 1-arm study in 24 healthy adult subjects with the following primary objective:

- To assess the pharmacokinetics of the active components (avobenzone, oxybenzone, octocrylene and/or ecamsule) in the selected product from Part 1.

More detailed information about the study (inclusion/exclusion criteria and schedule of events) can be found in the study protocol.

2 Sample Size

Approximately 48 healthy subjects are planned for enrollment, of which 24 will be assigned to Part 1 (randomized to 4 arms of 6 participants each) and 24 will be assigned to Part 2 (only 1 arm). Subjects are considered enrolled after determination by the Principal Investigator on Day 0 that they meet all eligibility criteria and are subsequently assigned a randomization/study identification number. The sample size was determined empirically and is typical for exploratory investigations of this type.

3 Analysis Populations

The analysis population will include all subjects who receive at least 1 dose of any of the study drugs and have PK sample data for the treatment period collected before dosing and at 1 or more time points after dosing.

The safety population will include all subjects who receive at least 1 dose of any of the study drugs.

4 General Statistical Considerations, Subject Disposition and Demographics and Baseline Characteristics

All data will be presented in data listings. Data from subjects excluded from an analysis population will be presented in the data listings but not included in the calculation of summary statistics. The number of subjects who enroll in the study and the number and percentage of subjects who complete each assessment will be presented. The frequency and percentage of subjects who withdraw or discontinue from the study and the reason for withdrawal or discontinuation will be summarized. Continuous demographic and baseline characteristic variables (age, height, weight, body mass index) will be summarized overall and by treatment using descriptive statistics (number of subjects, mean, standard deviation [SD], median, and minimum and maximum). The number and percentage of subjects in each class of categorical demographic and baseline characteristic variables will also be summarized.

5 Pharmacokinetic (PK) Analyses and Primary/Secondary Outcomes

The PK sampling schedule for this study is summarized in Appendix A. The following PK parameters will be determined for each subject in Part 1 and Part 2:

Day 1

- Maximum concentration (observed peak drug concentration) (C_{max})
- Time at which C_{max} occurs (T_{max})
- AUC from time 0 to the 23 hour time point (C_{last}) (AUC_{0-23})

Days 2 and 3

- Residual drug concentration (predose level) (C_{trough})
- Concentration 3 hours after the last dose of the day

Day 4

- Maximum concentration (observed peak drug concentration) (C_{max})
- Time at which C_{max} occurs (T_{max})
- Elimination rate constant (K_{el}) and terminal half-life ($t_{1/2}$); calculated after final dose using all the available data up to 144 hours
- AUC from time 71 to the 95 hour time point (AUC_{73-95})
- AUC from time 0 extrapolated to infinity (AUC_{0-inf}) and/or last observed time point

Day 5, 6 and 7

Residual drug concentration (C_{trough})

The primary and secondary outcomes of this study are as follows:

Primary Outcome:

1. Maximum* Avobenzone concentration (C_{max})

Secondary Outcomes:

1. Maximum* Oxybenzone concentration (C_{max})
2. Maximum* Octocrylene concentration (C_{max})
3. Maximum* Ecamsule concentration (C_{max})

* observed maximum

Note that Cmax could occur on any of the days of the study. PK parameters C_{max}, C_{last}, C_{trough}, T_{max}, AUC_{0-t}, K_{el}, $t_{1/2}$ and AUC_{0-inf}, will be summarized using descriptive statistics (number of subjects, mean, standard deviation [SD], coefficient of variation [CV], median, minimum, and

maximum) for the days above for avobenzone, oxybenzone, octocrylene and/or ecamsule (depending on whether the specific sunscreen formulation contains each of the active ingredients; see Attachment B) in Part 1 and 2. The PK parameters will be analyzed using non-compartmental methods based on actual sampling times. Mean and individual concentration-time profiles will be presented in graphs.

NOTE: The PK timepoints and days of dosing for Part 2 may be adjusted based on the results of Part 1, but there will be no changes to the statistical methods for Part 2 other than a potential adjustment to which days detailed PK parameters would be calculated if the number of dosing days or PK sampling schedule changes.

6 Safety Analyses

All AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of treatment-emergent adverse events (TEAEs), organized by system organ class and frequency, will be summarized by seriousness, severity, relationship to treatment, and by treatment at onset of the TEAE. A detailed listing of serious AEs and TEAEs leading to withdrawal will also be provided.

Clinical laboratory results (hematology, serum chemistry, and urinalysis) will be summarized using descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum). Clinical laboratory results will be classified as normal or abnormal, according to the reference ranges of the individual parameter. The number and percentage of subjects with abnormal laboratory results will be provided. No statistical testing will be performed on clinical laboratory data.

Vital sign measurements (blood pressure, heart rate, respiratory rate, and oral body temperature), safety 12-lead ECG results, and changes from Baseline for these parameters will be summarized by treatment and time point using descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum). Physical examination findings will be presented in a data listing, and abnormal physical examination findings will be recorded as AEs.

All concomitant medication usage and medications that changed in daily dose, frequency, or both since the subject provided informed consent will be summarized for each subject.

7 Missing Data

Missing data will not be imputed. Data that are excluded from the descriptive or inferential analyses will be included in the subject data listings. This will include data from subjects not in the particular analysis population, measurements from unscheduled visits, or extra measurements that may arise from 2 or more analyses of a plasma sample at the same time point.

8 Data Quality Assurance

Completed eCRFs are required for each subject randomly assigned to study drug. Electronic data entry will be accomplished through the ClinSpark remote electronic data capture (EDC) system, which allows for on-site data entry and data management. This system provides immediate, direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records.

Furthermore, the investigator retains full responsibility for the accuracy and authenticity of all data entered into the electronic data capture system. The completed dataset and their associated files are the sole property of the sponsor and should not be made available in any form to third parties, except for appropriate governmental health or regulatory authorities, without written permission of the sponsor.

Attachment A. Pharmacokinetic Sample Collection Schedule

Pharmacokinetic blood samples (approximately 10 mL per sample) will be collected for determination of avobenzone, oxybenzone, ecamsule and octocrylene plasma concentrations at the following time points (the time limit for PK sample draws can be +/- 5 minutes from the nominal time):

- Day 1: *0 and 0.5, 1, 1.5, *2, *4, *6, 8, 9, 10, 12, and 14 hours after initial dose
- Day 2: 23, *28, 33 h
- Day 3: 47, *52, 57 h
- Day 4: 71, 73, *74, *76, *78, 81, 82, 84 and 86 h
- Day 5: 95 hours
- Day 6: 120 hours
- Day 7: 144 hours

  * when a time point corresponds with sunscreen administration, the PK sample will be collected before sunscreen administration.

The specific dosing and PK schedule may be adjusted for Part 2 based on the results of Part 1 in a pre-specified manner.

Attachment B. Randomization Schedule

Randomization in this study is unblinded and only applicable to Part 1.

After screening, 24 subjects will be randomized to participate in one of the 4 treatment sequences of the study in Part 1. Example of treatment codes from the study protocol:

- Treatment sequences of Part 1:
  - A: La Roche Posay (Cream), Anthelios SX Daily Moisturizing Cream with Sunscreen, SPF 15 with Mexoryl SX (6 subjects): Avobenzone (2%), Ecamsule (2%) and Octocrylene (10%)
  - B: Hawaiian Tropic (Lotion); Island Sport Ultra-Light High Performance Sunscreen, SPF 50 (6 subjects): Avobenzone (3%), Oxybenzone (4%) and Octocrylene (6%)
  - C: Neutrogena (Spray), Ultra Sheer Body Mist SPF 45 (6 subjects): Avobenzone (3%), Oxybenzone (6%), Octocrylene (2.35%), Homosalate (15%) and Octisalate (5%)
  - D: Banana Boat (Spray); Sport Performance Coolzone Continuous Spray Sunscreen, SPF 50 (6 subjects): Avobenzone (3%), Oxybenzone (5%) and Octocrylene (10%)

- Treatment sequences of Part 2:
  - E: One sunscreen product with the highest avobenzone exposure will be selected for the second part of the study (24 subjects). If there is no quantifiable exposure of avobenzone for any of the sunscreen products, the formulation with the highest oxybenzone exposure will be selected for Part 2.

The script performs randomization across treatment groups, all subjects in Part 1 will be studied in 1 cohort. For Part 2 there is no randomization but allocated randomization IDs (RANDID) are still assigned in the table below for consistency.

Treatment schedule

RANDID	PART	COHORT	SEQ
1001	1	1	D
1002	1	1	A
1003	1	1	C
1004	1	1	B
1005	1	1	D
1006	1	1	B
1007	1	1	A
1008	1	1	C
1009	1	1	C
1010	1	1	B

1011	1	1	A
1012	1	1	D
1013	1	1	B
1014	1	1	A
1015	1	1	D
1016	1	1	C
1017	1	1	B
1018	1	1	A
1019	1	1	C
1020	1	1	D
1021	1	1	A
1022	1	1	D
1023	1	1	C
1024	1	1	B
2001	2	2	E
2002	2	2	E
2003	2	2	E
2004	2	2	E
2005	2	2	E
2006	2	2	E
2007	2	2	E
2008	2	2	E
2009	2	2	E
2010	2	2	E
2011	2	2	E
2012	2	2	E
2013	2	2	E
2014	2	2	E
2015	2	2	E
2016	2	2	E
2017	2	2	E
2018	2	2	E
2019	2	2	E
2020	2	2	E
2021	2	2	E

2022	2	2	E
2023	2	2	E
2024	2	2	E

Pharmacy Manual

spaulding clinical
RESEARCH BEYOND RESULTS

PHARMACY MANUAL

Assessment of the Human Systemic Absorption of Sunscreen Ingredients

1.0 Contact details of Sponsor

Sponsor Study Lead and Medical Monitor	Name:	David Strauss, MD, PhD
	Telephone:	301-796-6323
	Email:	david.strauss@fda.hhs.gov

2.0 Study Medication/Supplies

Product Code	Product Type	Product Name	Supplied By
A	Investigational Product	La Roche Posay (Cream), Anthelios SX Daily Moisturizer Cream, Face Sunscreen SPF 15 with Mexoryl SX	Spaulding Clinical
B	Investigational Product	Hawaiian Tropic (Lotion); Island Sport Ultra-Light High Performance Sunscreen, SPF 50	Spaulding Clinical
C	Investigational Product	Neutrogena (Spray), Ultra Sheer Body Mist SPF 45	Spaulding Clinical
D	Investigational Product	Banana Boat (Spray); Sport Performance Coolzone Continuous Spray Sunscreen, SPF 50	Spaulding Clinical

2.1 Storage

All investigational product will be stored in the controlled-access, temperature and humidity monitored pharmacy. The conditions of storage include protection from light, moisture, freezing, and excessive heat unless otherwise noted.

All investigational product will be stored at USP-defined controlled room temperature of 20°-25° (68°-77° F); and that allows for excursions between 15° and 30° (59° and 86° F).

2.2 Labeling

Investigational products shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), and/or other local regulations.

2.3 Stability

To ensure stability, prior to dose preparation, investigational products should not be stored in a container other than the container in which they were supplied.

3.0 Study Design

Part 1 is an open-label, randomized, 4-arm pilot study to evaluate the effects of multiple applications of 4 different topical sunscreen formulations in healthy adult subjects. Each arm will include 6 subjects (3 male and 3 female) with 1 formulation.

Treatments

- 2 mg of La Roche Posay (Cream), Anthelios SX Daily Moisturizer Cream, Face Sunscreen SPF 15 with Mexoryl SX per 1 cm^2 of body surface will be applied topically 4 times per day for 4 days to approximately 75% of the body surface area.
- 2 mg of Hawaiian Tropic (Lotion); Island Sport Ultra-Light High Performance Sunscreen, SPF 50 per 1 cm^2 of body surface will be applied topically 4 times per day for 4 days to approximately 75% of the body surface area.
- 2 mg of Neutrogena (Spray), Ultra Sheer Body Mist SPF 45 per 1 cm^2 of body surface will be applied topically 4 times per day for 4 days to approximately 75% of the body surface area.
- 2 mg of Banana Boat (Spray); Sport Performance Coolzone Continuous Spray Sunscreen, SPF 50 per 1 cm^2 of body surface will be applied topically 4 times per day for 4 days to approximately 75% of the body surface area.

Part 2 is an open-label, 1-arm confirmatory study to evaluate the pharmacokinetics of the ingredients contained in the formulation of a product from Part 1 after multiple applications of a topical sunscreen formulation in healthy adult subjects. Part 2 will include 24 subjects (12 male and 12 female). The formulation in Part 2 will be selected based on the plasma exposure data from the pilot study (Part 1).

Treatment

- 2 mg of sunscreen identified from Part 1 per 1 cm^2 of body surface will be applied topically 4 times per day for 4 days to approximately 75% of the body surface area.

4.0 Randomization/Blinding

The FDA project biostatistician will create the specifications that will be used to generate the randomization schedule. Randomization (Part 1 only) will occur after informed consent is obtained, either after completion of check-in procedures on Day 0 or just before dosing on Day 1.

Subjects in Part 1 will be randomly assigned to 1 of 4 different treatments, thus each subject will receive one of the treatments outlined in the table below by the end of Part 1. Replacement subjects (if needed) will be assigned to the treatment group of the subject they are replacing.

Subjects (n)	Treatment Group	Treatment
6	A	La Roche Posay (Cream), Anthelios SX Daily Moisturizer Cream, Face Sunscreen SPF 15 with Mexoryl SX

6	B	Hawaiian Tropic (Lotion); Island Sport Ultra-Light High Performance Sunscreen, SPF 50
6	C	Neutrogena (Spray), Ultra Sheer Body Mist SPF 45
6	D	Banana Boat (Spray); Sport Performance Coolzone Continuous Spray Sunscreen, SPF 50

All randomization information will be secured and housed in a locked storage area, accessible only by the randomization personnel and the assigned pharmacist and his or her verifier.

Both parts of this study are open-label; therefore, blinding is not applicable.

5.0 Dispensing

The topical sunscreen formulations described in Section 2 are commercially available over-the-counter products containing the active components avobenzone, oxybenzone, octocrylene and/or ecamsule.

The height and weight of each subject will be provided to pharmacy. Pharmacy will calculate each subject's Body Surface Area using the Mosteller formula:

$$\text{Mosteller}^{1}\ BSA\ (m^2) = \sqrt{\frac{Height\ (cm) \times Weight\ (kg)}{3600}}$$

The following formula will then be applied to determine the amount of investigational product dispensed and applied to each subject at each dose:

$$IP\ (g) = \frac{BSA\ (m^2\ \times 10{,}000\ \times 0.75\ \times 2)}{1000}$$

The cream and lotion products will be supplied on glassine weighing paper placed in a weigh boat. The spray products will be sprayed into a beaker and the resulting liquid extracted into a syringe which will then be capped to reduce any further evaporation.

The dose dispensed must be within 0.2 g of the calculated quantity.

Each dose will be prepared and labeled with a unique barcode, study number, screening/enrollment number, study day and nominal dosing time within 8 hours of investigational product administration.

After dose preparation, investigational product will be stored in the controlled access pharmacy under USP-defined storage conditions (cream and lotion at controlled room temperature of 20°-25° (68°-77° F), spray formulation at controlled cold temperature of 2°-8° (36°-46° F)) until taken to the floor within 1 hour prior to administration.

[1] Mosteller RD. **Simplified Calculation of Body Surface Area.** *N Engl J Med.* 1987 Oct 22;317(17):1098

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PHARMACY MANUAL

At least two bottles/tubes (un-opened) of each investigational product will be shipped to sponsor as per the product specific transportation recommendation

6.0 Retention/Destruction

Upon completion of termination of the study, final accountability review by the study monitor, and written authorization from the sponsor, all unused and/or partially used investigational product should be returned or destroyed at the study clinic. It is the investigator's responsibility to ensure that the sponsor has provided written authorization for investigational product disposal, the disposal process follows the study clinic's standard operating procedures, and appropriate records of the disposal are documented and maintained. No unused investigational product may be disposed until fully accounted for by the study monitor (or designee). Documentation of unused investigational product should include subject number, medication identity (medication #, period #), date, and quantity of investigational product used.

7.0 Hazards

Consideration should be given to handling, preparation, and disposal through measures that minimize investigational product contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

8.0 Forms/Templates

Spaulding T.PH-501A Master Study Drug Accountability Log

Spaulding F.PH-501C Drug Preparation and Dispensing Log

Approval:

ANTHONY GODFREY		02AUG18
Print Name	Signature	Date

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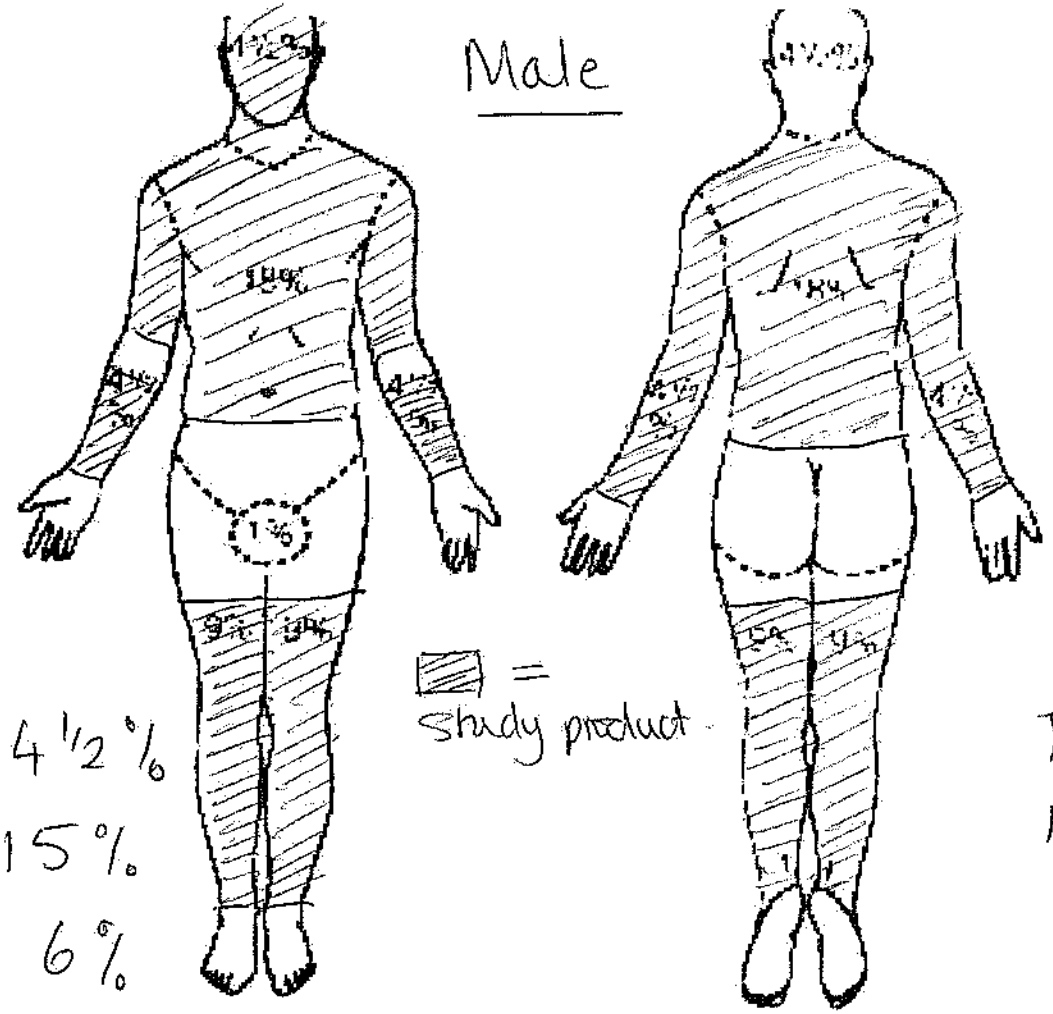
PHARMACY MANUAL

Pharmacy Manual Review By signing this you confirm to have read and understood the Pharmacy Manual, and you have the experience and skills necessary for all tasks appropriate to the Study Role.				
Name	Study Role	Initials	Signature	Date

Male



▨ = study product

Face = 4 ½ %
Torso ≃ 15 %
Arms ≃ 6 %
Legs ≃ 15 %

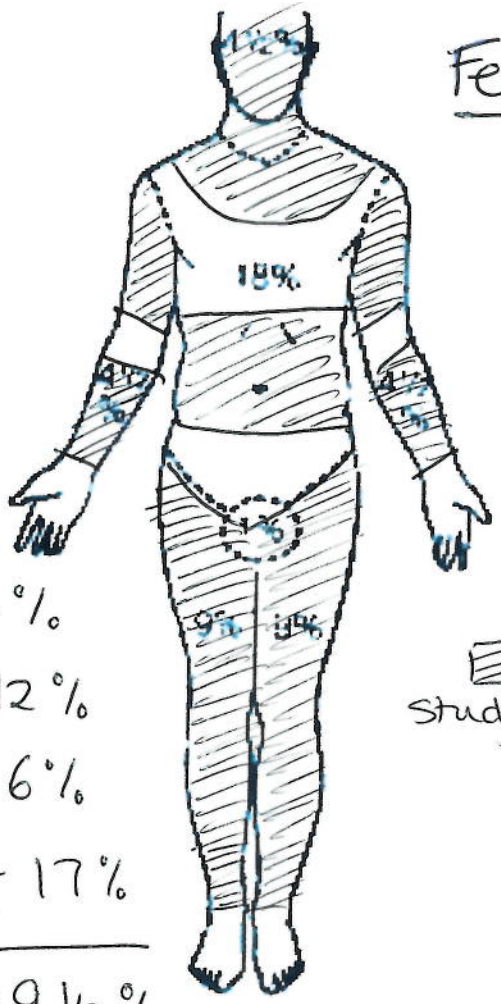
40 ½ %

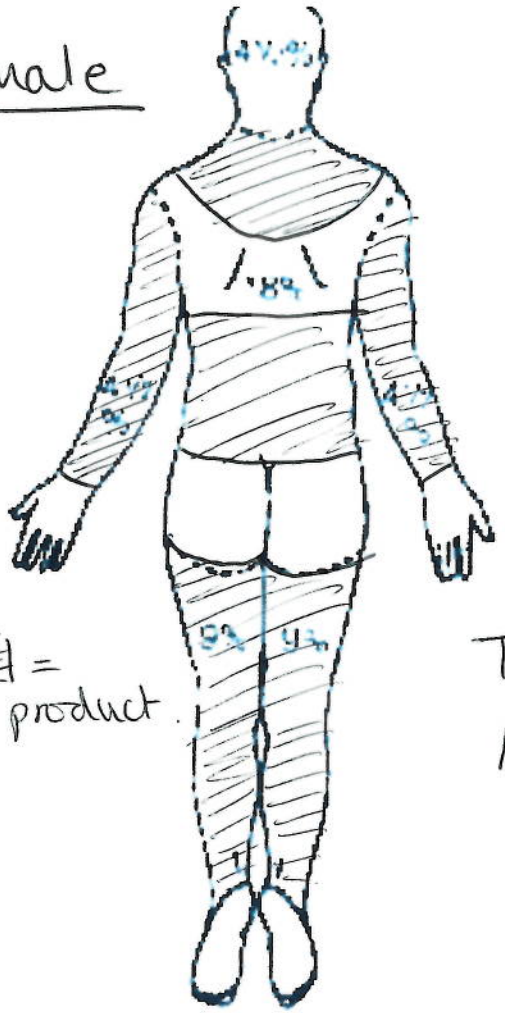
Torso ≃ 14 %
Arms ≃ 8 %
Legs ≃ 15 %

37 %

Total = 77 ½ %

Female





= study product

Face = 4%
Torso ≃ 12%
Arms ≃ 6%
Legs ≃ 17%

39½%

Torso ≃ 12%
Arms ≃ 8%
Legs ≃ 17%

37%

Total = 76½%

Amended Study Protocol

CLINICAL STUDY PROTOCOL

Assessment of the Human Systemic Absorption of Sunscreen Ingredients

PROTOCOL NO. SCR-005

Sponsor:	U.S. Food and Drug Administration White Oak Building #64, Room 2072 10903 New Hampshire Avenue Silver Spring, MD 20993
Sponsor Study Lead and Medical Monitor:	David Strauss, MD, PhD Director, Division of Applied Regulatory Science U.S. Food and Drug Administration Telephone: 301-796-6323 Email: david.strauss@fda.hhs.gov
Project Managers:	Murali Matta, PhD U.S. Food and Drug Administration Telephone: 240-402-5325 Email: murali.matta@fda.hhs.gov Robbert Zusterzeel, MD, PhD, MPH U.S. Food and Drug Administration Telephone: 301-796-3750 Email: robbert.zusterzeel@fda.hhs.gov
Study Monitor:	Jill Brown RIHSC Project Manager U.S. Food and Drug Administration
Version of Protocol:	1.4
Date of Protocol:	13 December 2018

Sponsor Signature Page

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki;
- International Council for Harmonisation (ICH) harmonised tripartite guideline E6 (R1): Good Clinical Practice; and
- All applicable laws and regulations, including without limitation, data privacy laws and compliance with appropriate regulations, including human subject research requirements.

Digitally signed by David Strauss -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=David Strauss -S, 0.9.2342.19200300.100.1.1=2000507494
Date: 2018.12.28 10:37:15 -05'00'

David Strauss, MD, PhD
Director, Division of Applied Regulatory Science
U.S. Food and Drug Administration

Date

Investigator Signature Page

I confirm that I have read and that I understand this protocol, the investigator brochure, and other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki;
- ICH harmonised tripartite guideline E6 (R1): Good Clinical Practice;
- All applicable laws and regulations, including without limitation data privacy laws and regulations;
- Human subject research requirements;
- Regulatory requirements for reporting of serious adverse events (SAEs) defined in Section 5.7.2.1.2 of this protocol; and
- Terms outlined in the Clinical Study Site Agreement.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Section 8 of this protocol.

Carlos R. Sanabria, MD

Carlos Sanabria, MD
Principal Investigator

20 DEC 2018
Date

Table of Contents

List of Tables

1. Protocol Synopsis

Protocol Number:	SCR-005
Title:	Assessment of the Human Systemic Absorption of Sunscreen Ingredients
Investigators:	Principal Investigator: Carlos Sanabria, MD
Study Phase:	1
Study Period:	This will be a single clinical study conducted in 2 parts. The duration of study participation will be approximately 37 days for part 1, including a 30-day screening period, a 4-day treatment period (Days 1-4) and subjects leaving the clinic on the morning of Day 7 following completion of scheduled End-of-Study activities. For part 2, the duration of participation will be approximately 51 days, including a 30-day screening period, a 4-day treatment period (Days 1-4) and subjects leaving the clinic on the morning of Day 7. Subjects in part 2 will then return to the clinical for follow-up visits on Days 10, 14 and 21 after which End-of-Study activities will be completed.
Study Site:	Spaulding Clinical Research LLC, 525 South Silverbrook Drive, West Bend, WI 53095
Background and Motivation:	Sunscreens prevent skin damage by reflecting or absorbing ultraviolet (UV) radiation and they are regulated as drug products in the United States (U.S.). Most active ingredients in sunscreens are organic chemicals and some have been shown to be absorbed through human skin with detectable levels in the blood or urine. As part of the safety evaluation for sunscreen products, the Food and Drug Administration (FDA) requests an assessment of systemic absorption in humans so that human blood levels can be compared with exposure levels obtained in nonclinical toxicology studies. If testing establishes that the sunscreen is not absorbed through the skin into the body, some aspects of toxicology testing may not be needed. Sunscreen products may be applied multiple times daily as both primary sunscreen products and as ingredients in cosmetic products, in substantial amounts for a lifetime starting at 6 months of age. The amount of sunscreen ingredient in a product can vary, but permitted levels can be as high as 15% for some organic active ingredients and application to the skin can accumulate to gram quantities in a day even with modest use. Because of the significant use of these sunscreens, even a low percentage of systemic absorption (e.g., 0.1%) could represent a significant systemic exposure in a single day and over a lifetime. The Surgeon General's Call to Action to Prevent Skin Cancer calls on partners in prevention from various sectors across the nation to address skin cancer as a major public health problem by increasing awareness of skin cancer and promoting actions to reduce its risk. Given the recognized public health benefits of sunscreen use, the

	FDA is committed to finding ways to facilitate the marketing of sunscreen products that include additional over-the-counter (OTC) sunscreen active ingredients. The FDA will continue to work with industry and other public health agencies to ensure that the sunscreens consumers use are safe and effective for daily, life-long use. In November 2016, the U.S. FDA finalized the guidance titled "Guidance for Industry: Nonprescription Sunscreen Drug Products Safety and Effectiveness Data" (sunscreen guidance). The guidance requests an assessment of the human systemic absorption of sunscreen ingredients with a Maximum Usage Trial (MUsT). The FDA sunscreen guidance notes that some nonclinical toxicity studies may be waived if results of an adequately conducted human pharmacokinetic (PK) MUsT show a steady-state blood level less than 0.5 ng/mL. Periodically, the FDA performs testing of products and formulations that the Agency sees as important for public health. This testing is not a reflection of rulemaking or other regulatory actions, but instead is done independently to measure the agency's understanding of the products' overall safety and effectiveness. This study is not intended to meet all requirements of MUsT studies as outlined in the FDA guidance referenced above, but will follow many of the principles.
Summary and Objectives:	**Part 1** is an open-label, randomized, 4-arm study in 24 healthy adult subjects with the primary objective: • To explore whether the active components (avobenzone, oxybenzone, ecamsule and octocrylene) of 4 sunscreen products (1 sunscreen product in each arm) are absorbed into the systemic circulation when a sunscreen product is applied under maximal-use conditions. One sunscreen product with the highest avobenzone exposure will be selected for the second part of the study. If there is no quantifiable exposure of avobenzone for any of the sunscreen products, the formulation with the highest oxybenzone exposure will be selected for Part 2. In addition, 3 new sunscreen products are being included in Part 2. **Part 2** is an open-label, 4-arm study in 48 healthy adult subjects with the following primary objective: • To assess the systemic absorption and pharmacokinetics of the active components (avobenzone, oxybenzone, octocrylene, ecamsule, homosalate, octisalate and octinoxate, where applicable [Part 2 products will not contain ecamsule]) of 4 sunscreen products (1 sunscreen product in each arm) under maximal-use conditions.

Study Design:	**Part 1** Part 1 is an open-label, randomized, 4-arm pilot study to evaluate the effects of multiple applications of 4 different topical sunscreen formulations in healthy adult subjects. Each arm will include 6 subjects (3 male and 3 female) with 1 formulation. A total of 24 subjects (12 male and 12 female) from all 4 arms will be admitted to the clinical research unit (CRU) on Day 0. On the morning of Days 1 through 4, subjects will receive a topical application of the study drug at approximately 0900 hours. The study product will be weighed in advance and applied by a qualified person from the study team. Subjects will then receive 3 more topical applications on the same day at 2, 4, and 6 hours after the first dose.

	Part 2 Part 2 is an open-label, 4-arm study to evaluate the pharmacokinetics of avobenzone, oxybenzone, octocrylene, homosalate, octisalate and octinoxate (where applicable [Part 2 products will not contain ecamsule]) after multiple applications of a topical sunscreen formulation in healthy adult subjects. Part 2 will include 48 subjects (24 male and 24 female) and each arm will include 12 subjects (6 male and 6 female). One of the formulations in Part 2 will be selected based on the plasma exposure data from the pilot study (Part 1) along with 3 additional formulations. A total of 48 subjects (24 male and 24 female) will be admitted to the CRU on Day 0. On the morning of Days 1 through 4, subjects will receive a topical application of the study product at approximately 0900 hours. The study drug will be weighed in advance and applied by a qualified person from the study team. Subjects will only receive one application on Day 1. On Days 2, 3 and 4, subjects will receive an initial dose and 3 more topical applications on the same day at 2, 4, and 6 hours after the first dose. **Parts 1 and 2** In both parts, approximately 2 mg of active sunscreen ingredient per 1 cm^2 of body surface (calculation per method of Dubois) will be evenly applied 4 times per study day (except for a one-time application on the first day in part 2) to areas of the body typically exposed to the sun: face, ears, neck, torso, arms, and legs (approximately 75% of the body surface area). The antecubital areas will be avoided when applying the sunscreen due to potential contamination of the sites used for intravenous PK blood sample collection. The topical applications of study drug will be administered with subjects in swim wear to simulate real-world settings as well as for easy application. In addition to swim wear, subjects may wear scrubs in between applications and at other times throughout the day/night. Subjects are required to shower each morning after the first PK blood sample collection (and before the first dose of the day), but not at other times during the day. Blood samples (approximately 10 mL per sample) will be collected for determination of plasma concentrations for all active ingredients (avobenzone, oxybenzone, octocrylene, ecamsule, homosalate, octisalate and octinoxate, where applicable). Safety evaluations will include adverse event (AE) monitoring, vital sign measurements, and physical examinations. All AEs reported by the subject or observed by the investigator or clinical research unit (CRU) staff will be recorded. Any AE reported after the informed consent is signed and before study drug application will be recorded as medical history. Subjects will remain in the CRU after admission on Day 0 until the morning of Day 7 following completion of scheduled End-of-Study activities for part 1. For part 2, subjects will undergo the same

	schedule but will return to the clinic for follow-up visits on Days 10, 14 and 21. Subjects will then be discharged following completion of End-of-Study activities. Subjects are not allowed to use products containing any of these active ingredients from 7 days before check-in until completion of End-of-Study procedures.
Inclusion Criteria:	Subjects who meet all of the following inclusion criteria will be eligible to participate in the study: 1. Subject signs an IRB-approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act authorization) before any study-related procedures are performed. 2. Subject is a healthy man or woman, 18 to 60 years of age, inclusive, who has a body mass index of 18.5 to 29.9 kg/m^2, inclusive, at Screening. 3. Subject has normal medical history findings, clinical laboratory results, vital sign measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings at Screening or, if abnormal, the abnormality is not considered clinically significant (as determined and documented by the investigator or designee). 4. Subject must have a negative test result for alcohol and drugs of abuse at screening and Check-in (Day 0). 5. Subject has no known or suspected allergies or sensitivities to any components of the sunscreen formulation. 6. Female subjects must be of nonchildbearing potential or, if they are of childbearing potential, they must: 1) have been strictly abstinent for 1 month before Check-in (Day 0) and agree to remain strictly abstinent for the duration of the study and for at least 1 month after the last application of study drug; OR 2) be practicing 2 highly effective methods of birth control (as determined by the investigator or designee; one of the methods must be a barrier technique) from at least 1 month before Check-in (Day 0) until at least 1 month after the last application of study drug. 7. Female subjects must not be pregnant or lactating before enrollment in the study. 8. Male subjects must agree to practice 2 highly effective methods of birth control (as determined by the investigator or designee; one of the methods must be a barrier technique) from at least 1 month before Check-in (Day 0) until at least 1 month after the last application of study drug. 9. Subject is highly likely (as determined by the investigator) to comply with the protocol-defined procedures and to complete the study.

	Note: subjects with any skin type or skin pigment type may be eligible for the study.
Exclusion Criteria:	Subjects who meet any of the following exclusion criteria will not be eligible to participate in the study: 1. Subject has broken, irritated, or unhealed skin. 2. Subject has an active sunburn. 3. Subject has used a tanning bed in the previous 4 weeks. 4. Subject has known skin or autoimmune disease(s). 5. Subject is anemic or has any chronic condition(s) that may impact blood sample collection. 6. Subject has any underlying disease or surgical or medical condition (e.g., cancer, human immunodeficiency virus [HIV], severe hepatic or renal impairment) that could put the subject at risk or would normally prevent participation in a clinical study. 7. Subject has known or suspected allergies or sensitivities to any components of the sunscreen formulation. 8. Subject has clinical laboratory test results (hematology and serum chemistry) at Screening that are outside the reference ranges provided by the clinical laboratory and considered clinically significant by the investigator. 9. Subject has a positive test result at Screening for HIV 1 or 2 antibody, hepatitis C virus antibodies, or hepatitis B surface antigen. 10. Subject is unable or unwilling to undergo multiple venipunctures for blood sample collection because of poor tolerability or poor venous access. 11. Subject has received or applied the topical sunscreen formulations used in the current study, or any other product containing the active ingredients of the topical sunscreen formulations used in the current study, within 7 days before Check-in (Day 0). 12. Subject has used any personal care product(s) containing any active sunscreen ingredient, such sunscreen products, hand or body moisturizing lotion, makeup or foundation, lip balm, or lipstick, within 7 days before Check-in (Day 0). 13. Subject is unable or unwilling to tolerate the scent of sunscreen for the duration of the treatment period.
Study Drug, Dosage, and Route of Administration:	**<u>Part 1</u>** • La Roche Posay (Cream), Anthelios SX Daily Moisturizing Cream with Sunscreen, SPF 15 with Mexoryl SX • Hawaiian Tropic (Lotion); Island Sport Ultra-Light High Performance Sunscreen, SPF 50 • Neutrogena (Spray), Ultra Sheer Body Mist SPF 45

	• Banana Boat (Spray); Sport Performance Coolzone Continuous Spray Sunscreen, SPF 50 Approximately 2 mg of sunscreen formulation per 1 cm^2 of body surface will be applied topically 4 times per day for 4 days to approximately 75% of the body surface area. **Part 2** • Hawaiian Tropic (Lotion); Island Sport Ultra-Light High Performance Sunscreen, SPF 50 • Neutrogena (Aerosol Spray), Ultra Sheer Body Mist SPF 100 • Supergoop (Non-Aerosol Spray), Sunscreen Mist with Vitamin C SPF 50 • Supergoop (Pump Spray), Sun Defying Sunscreen Oil with Meadowfoam SPF 50 Approximately 2 mg of sunscreen formulation per 1 cm^2 of body surface will be applied topically once on Day 1 and 4 times per day (over eight hours) on Days 2-4 to approximately 75% of the body surface area.
Reference Drug, Dosage, and Route of Administration:	Not applicable.

Pharmacokinetic Assessments:	Pharmacokinetic blood samples (approximately 10 mL per sample) will be collected for determination of avobenzone, oxybenzone, octocrylene, ecamsule, homosalate, octisalate and octinoxate plasma concentrations, where applicable to the different sunscreen formulations, at the following time points: • Day 1: 0 and 0.5, 1, 1.5, 2, 3 (Part 2 only), 4, 6, 8, 9, 10, 12, and 14 hours after initial dose • Day 2: 23, 28, 33 h • Day 3: 47, 52, 57 h • Day 4: 71, 73, 74, 76, 78, 81, 82, 84 and 86 h • Day 5: 95 hours • Day 6: 120 hours • Day 7: 144 hours • Day 10: 216 hours (Part 2 only) • Day 14: 312 hours (Part 2 only) • Day 21: 480 hours (Part 2 only) NOTE: when a time point corresponds with sunscreen administration, the PK sample will be collected before sunscreen administration. The following PK parameters will be determined for each subject for each sunscreen active ingredient: <u>Across all study days</u> • Maximum concentration (observed peak drug concentration) (C_{max}) <u>Day 1</u> • Maximum concentration (observed peak drug concentration) (C_{max}) • Time at which C_{max} occurs (T_{max}) • AUC from time 0 to the sampling time corresponding to the last quantifiable concentration (C_{last}) (AUC_{0-t}) <u>Days 2 and 3</u> • Residual drug concentration (predose level) (C_{trough}) • 3 h post dose concentration <u>Day 4</u> • Maximum concentration (observed peak drug concentration) (C_{max}) • Time at which C_{max} occurs (T_{max}) • Elimination rate constant (K_{el}) • Terminal half-life ($t_{1/2}$)

	• AUC from time 0 to the sampling time corresponding to the last quantifiable concentration (C_{last}) (AUC_{0-t}) • AUC from time 0 extrapolated to infinity (AUC_{0-inf}) <u>Day 5, 6, 7, 10 (Part 2 only), 14 (Part 2 only) and 21 (Part 2 only)</u> • Residual drug concentration (C_{trough}) <u>Tape Stripping to Determine Residual Skin Concentration</u> In addition, skin tape stripping of the lower back (around 3.8 cm^2 area) will be conducted once on Days 7 and 14 in part 2 to determine residual sunscreen active ingredients in the superficial layers of the skin.
Safety Assessments:	Safety will be evaluated in terms of AEs, vital sign measurements (blood pressure, heart rate, respiratory rate, and oral body temperature), and physical examination findings.
Sample Size:	Approximately 72 healthy subjects are planned for enrollment, of which 24 subjects will be enrolled and randomized in Part 1 and 48 subjects will be enrolled and randomized in Part 2. The sample size was determined empirically and is typical for exploratory investigations of this type.
Statistical Methods:	All data will be presented in data listings. Data from subjects excluded from an analysis population will be presented in the data listings but not included in the calculation of summary statistics. The number of subjects who enroll in the study and the number and percentage of subjects who complete each assessment will be presented. The frequency and percentage of subjects who withdraw or discontinue from the study and the reason for withdrawal or discontinuation will be summarized. Demographic and baseline characteristics will be summarized overall and by treatment for all subjects. Descriptive statistics will be used to summarize demographic and baseline subject characteristics. For continuous variables, the mean, median, standard deviation (SD), minimum, and maximum values will be reported. For categorical (nominal) variables, the number and percentage of subjects (or observations) will be reported. **Pharmacokinetics:** The PK population will include all subjects who receive study drug and have at least 1 estimable PK parameter after dosing. Plasma concentrations and PK parameters of avobenzone, oxybenzone, octocrylene, ecamsule, homosalate, octisalate and octinoxate, where applicable, will be listed and summarized using descriptive statistics (n, arithmetic mean, SD, minimum, median, and maximum) by nominal PK sampling time. **Safety:** The safety population will include all subjects who receive at least 1 dose of any of the study drugs. Any AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of AEs, organized by system organ class and preferred

	term, will be summarized with a focus on treatment-emergent AEs. Vital sign measurements will be summarized using descriptive statistics by time point. All values will be evaluated for clinically notable results. Data for additional safety parameters (e.g., physical examination findings) will be listed.
Date of Protocol:	13 December 2018

2. List of Abbreviations

Abbreviation	Definition
AE	adverse event
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from time 0 through 24 hours after dosing
AUC_{0-inf}	area under the concentration-time curve from time 0 extrapolated to infinity
AUC_{0-t}	area under the concentration-time curve from time 0 to the sampling time corresponding to the last quantifiable concentration
CFR	Code of Federal Regulations
C_{last}	time corresponding to the last quantifiable concentration
C_{max}	maximum concentration (observed peak drug concentration)
CRU	clinical research unit
C_{trough}	residual drug concentration (predose level)
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IAA	IRB Authorization Agreement
ICH	International Council for Harmonisation
IRB	institutional review board
IV	intravenous
K_{el}	elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
MUsT	Maximum Usage Trial
OTC	over the counter
PK	pharmacokinetic
SAE	serious adverse event
SD	standard deviation
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
T_{max}	time at which C_{max} occurs
UV	ultraviolet
U.S.	United States

3. Introduction

Sunscreens prevent skin damage by reflecting or absorbing ultraviolet (UV) radiation and they are regulated as drug products in the United States (U.S.). Most active ingredients in sunscreens are organic chemicals and some have been shown to be absorbed through human skin with detectable levels in the blood or urine. As part of the safety evaluation for sunscreen products, the Food and Drug Administration (FDA) requests an assessment of systemic absorption in humans so that human blood levels can be compared with exposure levels obtained in nonclinical toxicology studies. If testing establishes that the sunscreen is not absorbed through the skin into the body, some aspects of toxicology testing may not be needed.

Sunscreen products may be applied multiple times daily as both primary sunscreen products and as ingredients in cosmetic products, in substantial amounts for a lifetime starting at 6 months of age. The amount of sunscreen ingredient in a product can vary, but permitted levels can be as high as 15% for some organic active ingredients and application to the skin can accumulate to gram quantities in a day even with modest use. Because of the significant use of these sunscreens, even a low percentage of systemic absorption (e.g., 0.1%) could represent a significant systemic exposure in a single day and over a lifetime.

The Surgeon General's Call to Action to Prevent Skin Cancer calls on partners in prevention from various sectors across the nation to address skin cancer as a major public health problem by increasing awareness of skin cancer and promoting actions to reduce its risk. Given the recognized public health benefits of sunscreen use, the FDA is committed to finding ways to facilitate the marketing of sunscreen products that include additional over-the-counter (OTC) sunscreen active ingredients. The FDA will continue to work with industry and other public health agencies to ensure that the sunscreens consumers use are safe and effective for daily, life-long use.

In November 2016, the U.S. FDA finalized the guidance titled "Guidance for Industry: Nonprescription Sunscreen Drug Products Safety and Effectiveness Data" (sunscreen guidance) DHHS, 2016) [1]. The guidance requests an assessment of the human systemic absorption of sunscreen ingredients with a Maximum Usage Trial (MUsT). The FDA sunscreen guidance notes that some nonclinical toxicity studies may be waived if results of an adequately conducted human pharmacokinetic (PK) MUsT shows a steady-state blood level less than 0.5 ng/mL.

Periodically, the FDA performs testing of products and formulations that the Agency sees as important for public health. This testing is not a reflection of rulemaking or other regulatory actions, but instead is done independently to measure the agency's understanding of the products' overall safety and effectiveness.

This study is not intended to meet all requirements of MUsT studies as outlined in the FDA guidance referenced above, but will follow many of the principles.

4. Study Objectives

4.1. Primary Objectives

4.1.1 Part 1

Part 1 is an open-label, randomized, 4-arm study in 24 healthy adult subjects with the primary objective:

- To explore whether the active components (avobenzone, oxybenzone, ecamsule and octocrylene) of 4 sunscreen products (1 sunscreen product in each arm) are absorbed into the systemic circulation when sunscreen is applied under maximal-use conditions.

One sunscreen product with the highest avobenzone exposure will be selected for the second part of the study. If there is no quantifiable exposure of avobenzone for any of the sunscreen products, the formulation with the highest oxybenzone exposure will be selected for Part 2.

4.1.2 Part 2

Part 2 is an open-label, 4-arm study in 48 healthy adult subjects with the following primary objective:

- To assess, where applicable, the pharmacokinetics and systemic absorption of the active components (avobenzone, oxybenzone, octocrylene, ecamsule, homosalate, octisalate and octinoxate) of 4 sunscreen products (1 sunscreen product in each arm) under maximal-use conditions.

5. Investigational Plan

5.1. Study Design

This will be a single clinical study conducted in 2 parts. The duration of study participation will be approximately 37 days for part 1, including a 30-day screening period, a 4-day treatment period (Days 1-4) and subjects leaving the clinic on the morning of Day 7 following completion of scheduled End-of-Study activities. For part 2, the duration of participation will be approximately 51 days, including a 30-day screening period, a 4-day treatment period (Days 1-4) and subjects leaving the clinic on the morning of Day 7. Subjects in part 2 will then return to the clinical for follow-up visits on Days 10, 14 and 21 after which End-of-Study activities will be completed.

5.1.1 Part 1

Part 1 is an open-label, randomized, 4-arm pilot study to evaluate the effects of multiple applications of 4 different topical sunscreen formulations in healthy adult subjects. Each arm will include 6 subjects (3 male and 3 female) with 1 formulation. A total of 24 subjects (12 male and 12 female) from all 4 arms will be admitted to the clinical research unit (CRU) on Day 0.

On the morning of Days 1 through 4, subjects will receive a topical application of the study product at approximately 0900 hours. The study drug will be weighed in advance and applied by a qualified person from the study team. Subjects will then receive 3 more topical applications on the same day at 2, 4, and 6 hours after the first dose.

5.1.2 Part 2

Part 2 is an open-label, 4-arm-study to evaluate the pharmacokinetics of avobenzone, oxybenzone, octocrylene, homosalate, octisalate and octinoxate (Part 2 products will not contain ecamsule) after multiple applications of a topical sunscreen formulation in healthy adult subjects. Part 2 will include 48 subjects (24 male and 24 female) and 12 subjects in each arm (6 male and 6 female). One of the formulations in Part 2 will be selected based on the plasma exposure data from the pilot study (Part 1). In addition, 3 new formulations will be added.

On the morning of Days 1 through 4, subjects will receive a topical application of the study product at approximately 0900 hours. The study drug will be weighed in advance and applied by a qualified person from the study team. Subjects will only receive one application on Day 1. On Days 2, 3 and 4, subjects will receive an initial dose and 3 more topical applications on the same day at 2, 4, and 6 hours after the first dose.

5.1.3 Tape Stripping

For Part 2 only, skin tape stripping (6 consecutive strippings) of the lower back (area: around 3.8 cm^2) will be conducted once on Days 7 and 14 to determine residual sunscreen active ingredients in the superficial layers of the skin. The intention of the stripping is to determine the concentration of sunscreen active ingredients in superficial layers to estimate the potential skin deposit and 6-8 strips will be required to remove most of the stratum corneum layer [2-3]. The number of strips is restricted to 6 to minimize any skin irritation or skin rash [2-3].

5.1.4 Common Procedures

Details of study visits and study procedures are described in Section 5.6 and Section 5.7, respectively, and the overall Schedule of Events for both parts of the study is presented in Section 10.1.

In both parts of the study, approximately 2 mg of sunscreen per 1 cm^2 of body surface (calculation per method of Dubois) will be evenly applied 4 times per study day (except for a one-time application on the first day in part 2) to areas of the body typically exposed to the sun: face, ears, neck, torso, arms, and legs (approximately 75% of the body surface area). The antecubital areas will be avoided when applying the sunscreen due to potential contamination of the sites used for intravenous (IV) PK blood sample collection. The topical applications of the study drug will be administered with subjects in swim wear to simulate real world settings as well as for easy application. In addition to swim wear, subjects may wear scrubs in between applications and at other times throughout the day/night. Subjects are required to shower each morning after the first PK blood sample collection (and before the first sunscreen application for that day), but not at other times during the day. And, subjects should not use any personal care products which contain avobenzone, oxybenzone, ecamsule, octocrylene, homosalate, octisalate or octinoxate during the study.

Blood samples (approximately 10 mL per sample) will be collected for determination of avobenzone, oxybenzone, octocrylene, ecamsule, homosalate, octisalate and octinoxate (where applicable) plasma concentrations.

Safety evaluations will include adverse event (AE) monitoring, vital sign measurements, and physical examinations. All AEs reported by the subject or observed by the investigator or CRU staff will be recorded. Any AE reported after the informed consent is signed and before study drug application will be recorded as medical history.

Subjects will remain in the CRU after admission on Day 0 until discharge on the morning of Day 7. In Part 2, subjects will return to the clinic on Day 10, 14 and 21 for follow-up PK sampling (Days 10, 14 and 21) and tape stripping (Days 14).

Subjects are not allowed to use products containing any of the active ingredients from 7 days before check-in until completion of End-of-Study procedures.

5.1.5 Risk/Benefit

Subjects will be informed that participation in a human PK study like the present one cannot be of benefit to healthy volunteers. Nevertheless, the information from the physical examination, vital sign measurements, and ECG results may be shared with the subject's personal physician if this is the subject's choice. Subjects will be informed that

it is also their choice to inform their personal physician that they are participating in this research study.

Subjects will be informed that their contribution to the study is of major importance to agencies like the U.S. FDA for helping this agency better evaluate the effects of human systemic absorption of sunscreen ingredients. However, since this is a study involving healthy volunteers, subjects will be informed that they have the alternative not to participate.

Subjects will be informed that they may be exposed to risks associated with the pharmacological properties of the study drugs and the study procedures.

The study sunscreen products will not be administered to anyone who is pregnant. All women must take a pregnancy test before receiving any study drug in this study. All men and all women of childbearing potential enrolled in this study will be informed that they must use 2 highly effective birth control methods (as determined by the investigator or designee; one of the methods must be a barrier technique) during the study and for at least 1 month after the last application of study drug. Subjects will be informed that they must notify the investigator if they or their female partners become pregnant during the course of the study.

Subjects will be informed that insertion of an IV catheter may be required for blood sample collection on Days 1 and 4 and, during insertion of the catheter, soreness, bruising, or infection at the insertion site are possible but unlikely. Subjects will also be informed that dizziness and lightheadedness may occur during direct venipuncture, insertion of the IV catheter, or during blood collection.

Subjects will be informed that tape stripping applied to the skin may cause mild pain or irritation and skin rash at the area of tape stripping after the procedure.

Subjects will be informed that they may eat only meals and snacks that are provided during periods of their stay in the study clinic, and that they must consume all of each meal that is served at a reasonable pace (within 25 minutes).

Subjects will be informed that the confidentiality of their data will be respected at all times according to state law, and the study personnel handling their study data are bound by confidentiality agreements.

Subjects will be informed that the study drug and all tests, procedures, and visits required by the study are provided at no cost to them. If subjects become ill or physically injured because of participation in this study, they will be informed that costs of treatment will not be covered by the sponsor.

If a subject becomes pregnant, she will be informed that neither Spaulding Clinical Research nor the sponsor will be responsible for the cost of any obstetric or related care, or for the child's care.

Subjects will be informed by the Investigator of significant new findings that may develop during the course of this research study that may relate to their willingness to continue participation in the study.

5.2. Selection of Study Population

Subjects will be screened and the data collected will be reviewed by the principal investigator. Only those subjects who meet all of the eligibility criteria will be enrolled.

5.2.1 Inclusion Criteria

Subjects who meet all of the following inclusion criteria will be eligible to participate in the study:

1. Subject signs an institutional review board (IRB)-approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act authorization) before any study-related procedures are performed.
2. Subject is a healthy man or woman, 18 to 60 years of age, inclusive, who has a body mass index of 18.5 to 29.9 kg/m^2, inclusive, at Screening.
3. Subject has normal medical history findings, clinical laboratory results, vital sign measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings at Screening or, if abnormal, the abnormality is not considered clinically significant (as determined and documented by the investigator or designee).
4. Subject must have a negative test result for alcohol and drugs of abuse at screening and Check-in (Day 0)
5. Subject has no known or suspected allergies or sensitivities to any components of the sunscreen formulation.
6. Female subjects must be of nonchildbearing potential or, if they are of childbearing potential, they must: 1) have been strictly abstinent for 1 month before Check-in (Day 0) and agree to remain strictly abstinent for the duration of the study and for at least 1 month after the last application of study drug; OR 2) be practicing 2 highly effective methods of birth control (as determined by the investigator or designee; one of the methods must be a barrier technique) from at least 1 month before Check-in (Day 0) until at least 1 month after the last application of study drug.
7. Female subjects must not be pregnant or lactating before enrollment in the study.

8. Male subjects must agree to practice 2 highly effective methods of birth control (as determined by the investigator or designee; one of the methods must be a barrier technique) from at least 1 month before Check-in (Day 0) until at least 1 month after the last application of study drug.
9. Subject is highly likely (as determined by the investigator) to comply with the protocol-defined procedures and to complete the study.

Note: subjects with any skin type or skin pigment type may be eligible for the study.

5.2.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will not be eligible to participate in the study:

1. Subject has broken, irritated, or unhealed skin.
2. Subject has an active sunburn.
3. Subject has used a tanning bed in the previous 4 weeks.
4. Subject has known skin or autoimmune disease(s).
5. Subject is anemic or has any chronic condition(s) that may impact blood sample collection.
6. Subject has any underlying disease or surgical or medical condition (e.g., cancer, human immunodeficiency virus [HIV], severe hepatic or renal impairment) that could put the subject at risk or would normally prevent participation in a clinical study.
7. Subject has known or suspected allergies or sensitivities to any components of the sunscreen formulation.
8. Subject has clinical laboratory test results (hematology and serum chemistry) at Screening that are outside the reference ranges provided by the clinical laboratory and considered clinically significant by the investigator.
9. Subject has a positive test result at Screening for HIV 1 or 2 antibody, hepatitis C virus antibodies, or hepatitis B surface antigen.
10. Subject is unable or unwilling to undergo multiple venipunctures for blood sample collection because of poor tolerability or poor venous access.
11. Subject has received or applied the topical sunscreen formulations used in the current study, or any other product containing the active ingredients of the topical sunscreen formulations used in the current study, within 7 days before Check-in (Day 0).

12. Subject has used any personal care product(s) containing any active sunscreen ingredient, such sunscreen products, hand or body moisturizing lotion, makeup or foundation, lip balm, or lipstick, within 7 days before Check-in (Day 0).
13. Subject is unable or unwilling to tolerate the scent of sunscreen for the duration of the treatment period.

5.3. Screening Failures

Subjects who sign and date the informed consent form but who fail to meet the inclusion and exclusion criteria are defined as screening failures. A screening log, which documents the subject initials and reason(s) for screening failure, will be maintained by the investigator for all screening failures. A copy of the log should be retained in the investigator's study files.

If a subject fails the screening process because of an abnormal laboratory result, they can receive a copy of the results upon request. The investigator will determine if follow up for the abnormal laboratory result is needed, and will encourage the subject to follow up with his or her personal physician as appropriate. All subjects will be informed as to the reason(s) they are excluded from study participation, even if follow up is not required. If a subject fails the screening process because of a positive test result for human immunodeficiency virus or hepatitis, the positive result will be reported to local health authorities as required by law.

5.4. Termination of Study or Investigational Site

5.4.1 Criteria for Termination of the Study

The study will be completed as planned unless one of the following criteria is satisfied that requires early termination of the study:

- New information regarding the safety or efficacy of the study product(s) that indicates a change in the known risk profile for the study drug(s), such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objective or compromises subject safety.

5.4.2 Criteria for Termination of Investigational Site

The study site may be terminated if the site (including the investigator) is found in significant violation of GCP, the protocol, the contractual agreement, or is unable to ensure adequate performance of the study.

In the event that the sponsor elects to terminate the study or the investigational site, a study-specific procedure for early termination will be provided by the sponsor; the procedure will be followed by the applicable investigational site during the course of termination.

5.5. Criteria for Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn by the investigator without the approval of the subject based on the investigator's clinical judgment. A subject is not required to provide a written request to withdraw from the study; however, a written request is required if a subject withdraws consent for his or her personal data to be used for study-related purposes.

A subject may be discontinued for any of the following reasons:

- AE: The subject has experienced an AE that, in the opinion of the investigator, requires early termination. The appropriate electronic case report form (eCRF) must be completed for each AE. If a subject is discontinued from the study due to an AE, the investigator is required to follow up with the subject until the event resolves or becomes stable. If a subject dies during the study, the cause of death must be reported as a serious AE (SAE), with an outcome of death noted in the eCRF.
- Protocol Violation: The subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unnecessary risk to the subject's health.
- Withdrawal by Subject: The subject (or other responsible individual [e.g., caregiver]) wishes to withdraw from the study in the absence of a medical need.

  NOTE: Withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category.
- Study Terminated by Sponsor: The sponsor, IRB, FDA, or other regulatory agency terminates the study.
- Pregnancy: The subject is found to be pregnant.

  NOTE: If the subject is found to be pregnant, the subject must be withdrawn immediately. The pregnancy will be followed up to term, and the outcome, including any premature termination will be recorded. All live births must be followed for a minimum of 30 days or until the first well baby visit.
- Other.

NOTE: This category records withdrawals caused by an accidental or a medical emergency, unblinding, and other rare cases. The specific reason should be recorded in the comment space of the eCRF.

5.5.1 Handling of Withdrawals

The investigator may terminate a subject's study participation at any time during the study when the subject meets the criteria described in Section 5.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Subjects will be informed that their participation in the study is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Should a subject's participation be discontinued, the primary reason for termination must be recorded. In addition, efforts should be made to perform all procedures scheduled for the early termination visit. Any data and samples collected before subject withdrawal will become the property of the sponsor.

5.5.2 Replacement Subjects

Approximately 72 healthy subjects are planned for enrollment, of which 24 subjects will be enrolled and randomized in Part 1 and 48 subjects will be enrolled and randomized in Part 2. Up to 18 subjects may be qualified as replacements. Thus, a maximum of 90 subjects may be exposed to study drugs and procedures during the study.

5.6. Study Visits

5.6.1 Recruitment

Recruitment materials (e.g., internet, radio, and print advertisements, social media posts) will be approved by the local IRB before telephone screening. The sponsor is responsible for registration of the study on clinicaltrials.gov; however, this may not occur until the IRB has approved the final study protocol.

5.6.1.1 Compensation

Subjects will be offered payment for Screening; however, if the results of their alcohol and drug screening tests are positive, they will not be compensated. Subjects who complete the entire study (Day 0 to Day 7 in Part 1 or Day 0 to Day 21 in Part 2) will receive payment according to the schedule provided in the informed consent form. No special incentives are offered. Final payment will not be released until all follow-up procedures have been completed and accepted by the investigator.

If a subject chooses to withdraw from the study prematurely, he or she will only be compensated for completed days. If subjects are withdrawn for medical reasons or if the study is halted temporarily or permanently, the subjects will receive compensation proportional to the time spent in the study. No compensation will be provided if a subject is dismissed from the study for noncompliance (e.g., improper conduct, ingesting alcohol and/or drugs [including recreational drugs], tampering with the study drug, consuming any prohibited foods or beverages).

If subjects are required to stay in the clinic for a longer period for safety reasons, they will be compensated at a rate proportional to the entire compensation for the study. If a subject becomes ill or physically injured because of participation in this study, the subject will be referred for treatment.

5.6.2 Screening

The following procedures and assessments will be performed at Screening (Day –30 to Day –1):

- Obtain informed consent/HIPAA authorization (The informed consent process will be performed by a clinical research nurse in a private room. The subject will be given unlimited time to ask questions regarding study participation, and each subject will be questioned to ensure their understanding.)

After informed consent is obtained:

- Review inclusion/exclusion criteria to confirm subject eligibility
- Record demographic information
- Measure height, weight, and calculate body mass index
- Perform serology screening (hepatitis B surface antigen, hepatitis C virus antibodies, and HIV antibody 1/2 antigen/antibody combination test)
- Record medical history, including social history and smoking habits
- Perform drug and alcohol screening (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, alcohol, opiates, phencyclidine, propoxyphene, and methadone)
- Perform a serum pregnancy test (female subjects only)
- Record prior medications
- Monitor for AEs
- Perform clinical laboratory tests (hematology, serum chemistry, and urinalysis)

- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature)
- Perform a safety 12-lead ECG
- Perform a complete physical examination

5.6.3 Study Periods

Part 1 and Part 2 of this study are open-label, randomized, 4-arm designs. Part 1 of the study has 1 treatment period and 3 follow-up days; subjects stay in the clinic for the full treatment and follow-up period. Part 2 of the study has 1 treatment period and 6 follow-up days; subjects stay in the clinic for the full treatment period and the first 3 follow-up days (total of 7 days) and will then return to the clinic for one-day visits on the subsequent 3 days of follow-up (Day 10, 14 and 21).

5.6.3.1 Check-in

The following procedures and assessments will be performed at Check-in (Day 0) as outlined in Appendix A: Schedule of Events:

- Review inclusion/exclusion criteria to confirm subject eligibility
- Perform drug and alcohol screening (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, alcohol, opiates, phencyclidine, propoxyphene, and methadone)
- Perform a serum pregnancy test (female subjects only)
- Perform Fitzpatrick skin type assessment
- Admit subject to the study clinic
- Randomization (after completion of check-in procedures on Day 0 or just before dosing on Day 1)
- Record concomitant medications
- Monitor for AEs

5.6.3.2 Treatment

The following procedures and assessments will be performed during the treatment period (Days 1 through 4) according to the Schedule of Events (Section 10.1):

- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature) before dosing
- Collect PK blood sample (10 mL) before and after dosing (see Section 5.7)

- Application of topical sunscreen for Part 1 at approximately 0900 hours and again at 2, 4, and 6 hours after the first dose. Application of topical sunscreen for Part 2 at approximately 0900 hours on Day 1 and again at approximately 0900 hours on Days 2, 3 and 4 followed by an additional 3 applications at 2, 4, and 6 hours after the first dose on Days 2, 3 and 4.
- Physical examination of skin at the sites of topical application for signs of irritation
- Record concomitant medications
- Monitor for AEs

5.6.3.3 Washout

Not applicable.

5.6.4 Discharge (or Early Termination)

The following procedures and assessments will be performed before the subject is discharged from the study or upon early termination:

- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature)
- Physical examination of skin at the sites of topical application for signs of irritation
- Record concomitant medications
- Monitor for AEs
- Discharge subject from the study clinic after completion of all study procedures

5.6.5 Follow-up

The following procedures and assessments will be performed on Days 10, 14 and 21 for Part 2:

- Measure vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature)
- Collect PK blood samples (10 mL) after dosing as follows:
  - Day 10: 216 hours after first dose on Day 1 (Part 2 only)
  - Day 14: 312 hours after first dose on Day 1 (Part 2 only)
  - Day 21: 480 hours after first dose on Day 1 (Part 2 only)
- Physical examination of skin at the sites of topical application for signs of irritation
- Symptom-directed brief physical examination at the investigator's discretion

- Record concomitant medications
- Monitor for AEs

5.7. Study Procedures

5.7.1 Pharmacokinetic Assessments

5.7.1.1 Pharmacokinetic Sample Collection

Pharmacokinetic blood samples (approximately 10 mL per sample) will be collected for determination of avobenzone, oxybenzone, octocrylene, ecamsule, homosalate, octisalate and octinoxate plasma concentrations (where applicable to the different sunscreen formulations) at the following time points (the time limit for PK sample draws can be +/- 5 minutes from the nominal time):

- Day 1: 0 and 0.5, 1, 1.5, 2, 3 (Part 2 only), 4, 6, 8, 9, 10, 12, and 14 hours after initial dose
- Day 2: 23, 28, 33 h
- Day 3: 47, 52, 57 h
- Day 4: 71, 73, 74, 76, 78, 81, 82, 84 and 86 h
- Day 5: 95 hours
- Day 6: 120 hours
- Day 7: 144 hours
- Day 10: 216 hours (Part 2 only)
- Day 14: 312 hours (Part 2 only)
- Day 21: 480 hours (Part 2 only)

NOTE: when a time point corresponds with sunscreen administration, the PK sample will be collected before sunscreen administration.

5.7.1.2 Tape Stripping Sample Collection

For Part 2 only, tape stripping of the lower back to an area of around 3.8 cm^2 will be conducted once on Days 7 and 14 to determine residual sunscreen active ingredients in the superficial layers of the skin. Tape stripping will be applied to different areas of the lower back on Day 7 vs. Day 14 to prevent false sampling.

The area on the lower back for each subject will be marked with a skin marker. Before executing the tape stripping, hair on the marked area will be removed with the 3M trimmer (no razors as this would damage the skin and could lead to false sampling). A pre-weighed standard tape (Standard D-Squame ® adhesive tape) will be applied to a marked area under constant pressure of 225 g/cm^2 for 5 seconds using a D-Squame ®

Pressure device. The tape will be removed swiftly and placed in a standard tape rack after weighing. Tape stripping will be performed 6 additional consecutive times in the same area with sampling intervals of 1 ± 0.5 minutes.

5.7.1.3 Pharmacokinetic Specimen Handling

The PK blood samples (10 mL each) will be collected into tubes containing K_2EDTA, inverted several times to mix the blood with the anticoagulant, and placed in an ice bath. Within 30 minutes of collection, the samples will be centrifuged for 10 minutes, at 3000 revolutions per minute, at 4°C, by a study team member.

The plasma will be separated using a disposable plastic pipette and approximately half of the plasma will be transferred into duplicate cryotube vials labeled as Aliquot A (primary) and Aliquot B (backup). The plasma samples will be appropriately labeled and stored frozen at –70°C or below until shipment. Temperature monitoring logs should be maintained and accessible for review by the study monitor.

The Aliquot A samples (primary) will be shipped first, on dry ice, to the bioanalytical laboratory at FDA for processing when requested by the sponsor. The Aliquot B samples (backup) will be held for a second shipment at a time after the completion of all Aliquot A sample shipment(s) and the timing of the Aliquot B shipment communicated by the sponsor. None of the PK blood samples will be stored at clinical facility for future use, however the sponsor will store them for analytical purposes of this study only.

The tape strips will be transferred to pre-labeled D Squame ® standard storage cards and stored frozen at –70°C or below until shipment.

Both plasma and skin concentrations of avobenzone, oxybenzone, ecamsule, octocrylene, homosalate, octisalate and octinoxate (where applicable) will be assayed using a validated liquid chromatography with tandem mass spectrometry method.

5.7.1.4 Pharmacokinetic Parameters

The following PK parameters will be determined for each subject for each active ingredient:

<u>Across all study days (Primary Endpoint)</u>

- Maximum concentration (observed peak drug concentration) (C_{max})

<u>Days 1</u>

- Maximum concentration (observed peak drug concentration) (C_{max})
- Time at which C_{max} occurs (T_{max})

- AUC from time 0 to the sampling time corresponding to the last quantifiable concentration (C_{last}) (AUC_{0-t}), calculated by the mixed linear logarithmic trapezoidal method

Days 2 and 3

- Residual drug concentration (predose level) (C_{trough})
- 3 h post dose concentration

Day 4

- Elimination rate constant (K_{el}), obtained by linear regression of the log-linear terminal phase of the concentration-time profile using at least 3 data points, excluding C_{max}, otherwise K_{el} will not be determined. The acceptability criteria for determination of K_{el} will be a coefficient of regression more than or equal to 0.98. When K_{el} will not be determined, AUC_{0-inf} and $t_{1/2}$ will not be reported.
- Terminal half-life ($t_{1/2}$), calculated using the equation ln2/k after the last study drug application (on Day 4)
- Accumulation ratios, calculated using the following formula:

  $R_1 = AUC_{0-23}$ Day 4 / AUC_{0-23} Day 1
- AUC from time 0 extrapolated to infinity (AUC_{0-inf}), calculated by the mixed linear-logarithmic trapezoidal method as:

  $AUC_{0-inf} = AUC_{0-t} + C_{last} / K_{el}$

  When the extrapolation represents more than 20%, AUC_{0-inf} and $t_{1/2}$ will not be reported.

Days 5, 6, 7, 10 (Part 2 only), 14 (Part 2 only) and 21 (Part 2 only)

- Residual drug concentration (C_{trough})

5.7.2 Safety Assessments

Safety will be evaluated in terms of AEs, vital sign measurements (blood pressure, heart rate, respiratory rate, and oral body temperature), and physical examination findings.

5.7.2.1 Adverse Events

5.7.2.1.1 Adverse Event Definitions

An AE is defined as any untoward and/or unintended sign, including an abnormal clinical laboratory finding, symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug. Events or conditions that

increase in frequency or severity during or as a consequence of use of a drug in human clinical trials will also be considered AEs.

A treatment-emergent adverse event (TEAE) is defined as an AE that begins after study drug administration.

An unexpected AE is any AE having a specificity or severity not consistent with the current investigator's brochure for the study drug(s).

An SAE is defined as any AE occurring at any dose that meets the following criteria:

- Results in death,
- Is life threatening,
- Requires hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity,
- Is a congenital anomaly/birth defect, or
- Is an important medical event that may not meet the previous criteria but, based upon appropriate medical judgment, jeopardizes the subject or requires medical or surgical intervention to prevent one of the outcomes listed previously.

5.7.2.1.2 Adverse Event Reporting

The recording of AEs will begin after the subject signs the informed consent form and will continue until discharge (or early termination). All AEs, whether serious or nonserious and whether or not related to the study drug, must be recorded in the eCRF. Study subjects will be instructed to warn study staff if he or she has any unexpected symptoms. In addition, all subjects will receive a reminder telephone call approximately 24 hours before Check-in.

Any SAE (whether expected or unexpected) must be entered into the eCRF system and reported by facsimile to the medical monitor or designee using the SAE Reporting Form within 24 hours of the investigator or study clinic staff becoming aware of the event. It is the responsibility of the investigator to report all SAEs to the medical monitor, to provide the most complete report possible, and to assess each SAE for its relationship to the study drug. The investigator is responsible for obtaining follow-up information on all SAEs and submitting follow-up SAE data. Any unexpected SAEs must be reported promptly to the investigator's IRB as per the IRB's requirements.

In the event of a fatal or life-threatening SAE, the sponsor will notify the appropriate FDA authorities by telephone or facsimile within 7 calendar days of receipt of the report. The sponsor will follow all 7-day alert reports with a written report within 10 working days of receipt of the case. Serious AE cases that concern nonfatal, nonlife-threatening

events that are unexpected and at least possibly related to the study drug will be submitted in writing to the FDA within 10 working days of receipt.

Furthermore, any AEs that are not expected, occur at a higher frequency, or would require modification of the study protocol and/or informed consent must be reported to the FDA within 10 working days.

Adverse events that are assessed by the investigator as possibly or probably related to the study drug will be followed until they resolve or stabilize. All SAEs will be followed until resolution.

5.7.2.1.3 Assessment of Severity

The investigator will assess the severity of each AE using the following scale:

- Mild: The subject is aware of the AE but is still able to perform all activities; minimal or no medical intervention or therapy is required.
- Moderate: The subject has to discontinue some activities due to the AE; minimal or no medical intervention or therapy is required.
- Severe: The subject is incapacitated by the AE and is unable to perform normal activities; significant medical intervention or therapy is required and hospitalization is possible.

5.7.2.1.4 Assessment of Causality

The investigator will assess the causal relationship/relatedness of each AE to the study drug using the following scale:

- Not Related: Onset of the AE has no reasonable temporal relationship to administration of the study drug, a causal relationship to administration of the study drug is biologically implausible, or the event is attributed to an alternative etiology.
- Unlikely Related: Onset of the AE has a reasonable temporal relationship to study drug administration and although a causal relationship is unlikely, it is biologically plausible.
- Possibly Related: Onset of the AE has a strong temporal relationship to administration of the study drug, cannot be explained by the subject's clinical state or other factors, and a causal relationship is biologically plausible.
- Probably Related: Onset of the AE shows a distinct temporal relationship to administration of the study drug that cannot be explained by the subject's clinical state or other factors, the AE is a known reaction to the product or chemical group, or can be predicted by the product's pharmacology.

5.7.2.1.5 Pregnancy

A serum pregnancy test will be performed for female subjects at the time points presented in the Schedule of Events (Section 10.1). If a subject becomes pregnant while on the study, this should be reported immediately to the investigator, the subject will be withdrawn from the study and the medical monitor and the subject will be instructed to follow-up with his or her personal physician. All pregnancies are to be reported as an AE and followed for outcome.

5.7.2.2 Clinical Laboratory Tests

Clinical laboratory and diagnostic screening tests will be performed at the time points presented in the Schedule of Events (Section 10.1) and will be collected in accordance with acceptable laboratory procedures. Clinical laboratory testing will be performed by Spaulding Clinical Laboratory, West Bend, Wisconsin, and Laboratory Corporation of America (LabCorp), Dublin, Ohio. The clinical laboratory tests that will be performed are presented in Table 5-1. Unused clinical laboratory test samples will not be stored for future use.

Clinical laboratory results will be reviewed by the investigator or designee together with data in the eCRF. Any values outside the reference range will be evaluated for clinical significance. If a value is determined to be clinically significant, the subject will be instructed to follow-up with his or her personal physician. The investigator or designee may repeat the clinical laboratory tests if deemed appropriate. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Table 5-1 Clinical Laboratory and Diagnostic Screening Tests

Hematology	Serum Chemistry	Urinalysis
Complete blood count Hematocrit Hemoglobin Platelet count Red blood cell count White blood cell count (with automated differential)	Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Bicarbonate Blood urea nitrogen Calcium Chloride Direct bilirubin Glucose Lactic dehydrogenase Magnesium Phosphorus Potassium Serum creatinine Sodium Total bilirubin Total protein Uric acid	Appearance Bilirubin Color Glucose Ketones Leukocyte esterase Microscopic examination: red blood cells; white blood cells; epithelial cells; bacteria, crystals, casts, etc. (if present) Nitrite Occult blood pH Protein Specific gravity Urobilinogen

Diagnostic Screening Tests:	
Serum	**Urine**
Hepatitis panel (hepatitis B surface antigen and hepatitis C virus antibody) and human immunodeficiency virus antibody 1/2 antigen/antibody combination test	Drug screen including: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, ethanol, opiates, phencyclidine, propoxyphene, and methadone
Serum human chorionic gonadotropin pregnancy test for all female subjects	

5.7.2.3 Vital Sign Measurements

Vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature) will be measured using an automated device at the time points presented in the Schedule of Events (Section 10.1). The subject should be in a supine position, if possible, for a minimum of 5 minutes before vital signs are measured.

5.7.2.4 Safety 12-Lead Electrocardiograms

Safety 12-lead ECGs will be performed at the time points presented in the Schedule of Events (Section 10.1). The subject should be in a supine position, if possible, for approximately 10 minutes before safety 12-lead ECGs are measured. The safety 12-lead ECGs will be reviewed by the investigator at the study clinic to detect any immediate safety concerns.

5.7.2.5 Physical Examinations

Physical examinations will be performed at the time points presented in the Schedule of Events (Section 10.1).

The complete physical examination at Screening will include, but not be limited to, assessments of the head, eyes, ears, nose, throat, skin, thyroid, nervous system, respiratory system, cardiovascular system, abdomen (liver and spleen), lymph nodes, and extremities. Height, weight (without shoes and wearing the lightest possible clothing), and calculation of body mass index (kg/m^2) will be performed at Screening only.

During the study, skin at the sites of topical application of the study drug will be examined for signs of irritation during the treatment period, upon discharge (or early termination), and at the follow-up visits. At the follow-up visits, a symptom-directed brief physical examination may be performed at the investigator's discretion

If an abnormality is observed upon physical examination, the subject will be instructed to follow up with his or her personal physician.

5.7.3 Demographics and Medical History

Demographic data (date of birth, gender, race, and ethnicity) will be collected at Screening.

Each subject will provide a complete medical history at Screening that will be reviewed at Check-in. Specific information relating to any prior or existing medical conditions/surgical procedures will be recorded in the subject's eCRF.

5.8. Study Treatments

5.8.1 Treatments Administered

Part 1

- La Roche Posay (Cream), Anthelios SX Daily Moisturizer Cream, Face Sunscreen SPF 15 with Mexoryl SX
- Hawaiian Tropic (Lotion); Island Sport Ultra-Light High Performance Sunscreen, SPF 50
- Neutrogena (Spray), Ultra Sheer Body Mist SPF 45
- Banana Boat (Spray); Sport Performance Coolzone Continuous Spray Sunscreen, SPF 50

Approximately 2 mg of sunscreen formulation per 1 cm^2 of body surface will be applied topically 4 times per day for 4 days to approximately 75% of the body surface area.

Part 2

- Hawaiian Tropic (Lotion); Island Sport Ultra-Light High Performance Sunscreen, SPF 50
- Neutrogena (Aerosol Spray), Ultra Sheer Body Mist SPF 100
- Supergoop (Non-Aerosol Spray), Sunscreen Mist with Vitamin C SPF 50
- Supergoop (Pump Spray), Sun Defying Sunscreen Oil with Meadowfoam SPF 50

Approximately 2 mg of sunscreen formulation per 1 cm^2 of body surface will be applied topically once on Day 1 and 4 times per day on Days 2-4 to approximately 75% of the body surface area.

The antecubital areas will be avoided when applying the sunscreen due to potential contamination of the sites used for IV PK blood sample collection.

5.8.2 Method Assigning Subjects to Treatment

5.8.2.1 Randomization Process

Part 1 and Part 2

The FDA project biostatistician will create the specifications that will be used to generate the randomization schedule. The specifications will be based on the protocol requirements and appropriate statistical programming with consideration for study design, number of treatments, number of subjects planned for enrollment, stratification, and blocking.

Based on these specifications, the project biostatistician (or designee) will generate a dummy randomization schedule. The schedule is generated by a SAS®/ R or other program, which produces output file(s) and/or SAS or R dataset(s).

The project biostatistician (or designee) distributes the 'dummy' randomization schedule to specified personnel for review. Any change (e.g., change in block size, change in stratification levels) that requires an update to the specifications will reset this process. Minor changes (e.g., display formatting) will not require a change to the specifications.

No transfer is necessary if the unblinded randomization biostatistician also created the 'dummy' randomization.

The randomization biostatistician is responsible for generating the final randomization schedule.

Randomization will occur after informed consent is obtained, either after completion of check-in procedures on Day 0 or just before dosing on Day 1. Unique subject numbers will be used in sequential order based on each subject's order of qualification.

In both Part 1 and Part 2 of the study, subjects will be randomly assigned to 1 of 4 different treatments, thus each subject will receive one of the sunscreen formulations by the end of the study. For subjects in Part 1: 1) La Roche Posay (Cream), Anthelios SX Daily Moisturizer Cream, Face Sunscreen SPF 15 with Mexoryl SX; 2) Hawaiian Tropic (Lotion); Island Sport Ultra-Light High Performance Sunscreen, SPF 50; 3) Neutrogena (Spray) Ultra Sheer Body Mist SPF 45; or 4) Banana Boat (Spray); Sport Performance Coolzone Continuous Spray Sunscreen, SPF 50. For subjects in Part 2: 1) Hawaiian Tropic (Lotion); Island Sport Ultra-Light High Performance Sunscreen, SPF 50 ; 2) Neutrogena (Aerosol Spray), Ultra Sheer Body Mist SPF 100; 3) Supergoop (Non-Aerosol Spray), Sunscreen Mist with Vitamin C SPF 50 ; or 4) Supergoop (Pump Spray), Sun Defying Sunscreen Oil with Meadowfoam SPF 50.

Replacement subjects (if needed) will be assigned to the treatment group of the subject they are replacing.

The treatment groups are presented in Table 5-2.

Table 5-2 Treatment Groups

Study Part	Subjects (n)	Treatment Group	Treatment
1	6	A	La Roche Posay (Cream), Anthelios SX Daily Moisturizer Cream, Face Sunscreen SPF 15 with Mexoryl SX
1	6	B	Hawaiian Tropic (Lotion); Island Sport Ultra-Light High Performance Sunscreen, SPF 50
1	6	C	Neutrogena (Spray) Ultra Sheer Body Mist SPF 45
1	6	D	Banana Boat (Spray); Sport Performance Coolzone Continuous Spray Sunscreen, SPF 50
2	12	E	Hawaiian Tropic (Lotion); Island Sport Ultra-Light High Performance Sunscreen, SPF 50
2	12	F	Neutrogena (Aerosol Spray), Ultra Sheer Body Mist SPF 100
2	12	G	Supergoop (Non-Aerosol Spray), Sunscreen Mist with Vitamin C SPF 50
2	12	H	Supergoop (Pump Spray), Sun Defying Sunscreen Oil with Meadowfoam SPF 50

All randomization information will be secured and housed in a locked storage area, accessible only by the randomization personnel and the assigned pharmacist and his or her verifier.

5.8.3 Identity of Study Drug

The topical sunscreen formulations described in Section 5.8.1 are commercially available OTC products containing the active components avobenzone, oxybenzone, octocrylene, ecamsule, homosalate, octisalate and octinoxate, where applicable.

5.8.4 Management of Clinical Supplies

5.8.4.1 Study Drug Packaging and Storage

The topical sunscreen formulations will be obtained from commercial sources and stored according to the manufacturer's directions.

5.8.4.2 Study Drug Accountability

Good clinical documentation practices will be employed to record the receipt, storage conditions, accountability, and use or return of the study drug. The study drug will be stored in a secure location with access to the study personnel who will be managing the storage, dispensing, and accountability of the study drug.

Upon completion or termination of the study, final accountability review by the study monitor, and written authorization from the sponsor, all unused and/or partially used study drug should be returned or destroyed at the study clinic. It is the investigator's responsibility to ensure that the sponsor has provided written authorization for study drug disposal, the disposal process follows the study clinic's standard operating procedures, and appropriate records of the disposal are documented and maintained. No unused study drug may be disposed until fully accounted for by the study monitor (or designee). Documentation of unused study drug should include subject number, medication identity (medication #, period #), date, and quantity of study drug used.

5.8.5 Blinding

Both parts of this study are open-label; therefore, blinding is not applicable.

5.8.6 Treatment Compliance

At Screening, as part of the eligibility assessment, it will be confirmed that subjects can comply with the protocol-defined procedure of topical study drug application. All applications of the study drug will be administered in the study clinic either under direct observation of or administered by clinic personnel, and recorded in the eCRF.

5.8.7 Prior and Concomitant Medications

Subjects are prohibited from having received or applied the topical sunscreen formulations used in the current study within 7 days before Check-in (Day 0). Subjects are also prohibited from having used any personal care product(s) containing any active

sunscreen ingredient, such sunscreen products, hand or body moisturizing lotion, makeup or foundation, lip balm, or lipstick, within 7 days before Check-in (Day 0).

Subjects will be instructed not to take any medications, including OTC products, without first consulting with the investigator.

5.8.8 Subject Restrictions

At Screening, as part of the eligibility assessment, it will be confirmed that subjects have not used a tanning bed in the previous 4 weeks before the study. As part of the medical history assessment at Screening, subjects will be asked about their smoking history. Subject responses will be recorded on the eCRF.

Subjects must be willing to comply with study rules throughout the duration of the study.

5.9. Statistical Methods

5.9.1 Sample Size

Approximately 72 healthy subjects are planned for enrollment, of which 24 subjects will be enrolled and randomized in Part 1 and 48 subjects will be enrolled and randomized in Part 2. The sample size was determined empirically and is typical for exploratory investigations of this type.

5.9.2 Analysis Populations

The PK population will include all subjects who receive study drug and have at least 1 estimable PK parameter after dosing.

The safety population will include all subjects who receive at least 1 dose of any of the study drugs.

5.9.3 General Statistical Considerations

All data will be presented in data listings. Data from subjects excluded from an analysis population will be presented in the data listings but not included in the calculation of summary statistics.

5.9.4 Subject Disposition

The number of subjects who enroll in the study and the number and percentage of subjects who complete each assessment will be presented. The frequency and percentage of subjects who withdraw or discontinue from the study and the reason for withdrawal or discontinuation will be summarized.

5.9.5 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized overall and by treatment for all subjects.

5.9.6 Pharmacokinetic Analyses

Plasma concentrations and PK parameters of avobenzone, oxybenzone, octocrylene, ecamsule, homosalate, octisalate and octinoxate (where applicable) will be listed and summarized using descriptive statistics (n, arithmetic mean, SD, minimum, median, and maximum) by nominal PK sampling time.

5.9.7 Safety Analyses

5.9.7.1 Adverse Events

Any AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of AEs, organized by system organ class and frequency, will be summarized by seriousness, severity, relationship to treatment, and by treatment, with a focus on TEAEs. A detailed listing of serious AEs and TEAEs leading to withdrawal will also be provided.

5.9.7.2 Clinical Laboratory Tests

Clinical laboratory results (hematology, serum chemistry, and urinalysis) will be summarized using descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum). Clinical laboratory results will be classified as normal or abnormal, according to the reference ranges of the individual parameter. The number and percentage of subjects with abnormal laboratory results will be provided. No statistical testing will be performed on clinical laboratory data.

5.9.7.3 Vital Sign Measurements

Vital sign measurements and changes from Baseline will be summarized using descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum) by treatment and time point.

5.9.7.4 Safety 12-Lead Electrocardiograms

Safety 12-lead ECG data will be summarized using descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum).

5.9.7.5 Physical Examinations

Physical examination findings will be presented in a data listing, and abnormal physical examination findings will be recorded as AEs.

5.9.7.6 Other Safety Data

All concomitant medication usage and medications that changed in daily dose, frequency, or both since the subject provided informed consent will be summarized for each subject.

5.9.8 Interim Analyses

No interim analyses are planned.

5.9.9 Missing Data

Missing data will not be imputed. Data that are excluded from the descriptive or inferential analyses will be included in the subject data listings. This will include data from subjects not in the particular analysis population, measurements from unscheduled visits, or extra measurements that may arise from 2 or more analyses of a plasma sample at the same time point.

5.10. Data Quality Assurance

Completed eCRFs are required for each subject randomly assigned to study drug. Electronic data entry will be accomplished through the ClinSpark® remote electronic data capture system, which allows for on-site data entry and data management. This system provides immediate, direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records.

Furthermore, the investigator retains full responsibility for the accuracy and authenticity of all data entered into the electronic data capture system. The completed dataset and their associated files are the sole property of the sponsor and should not be made available in any form to third parties, except for appropriate governmental health or regulatory authorities, without written permission of the sponsor.

6. Ethical Considerations

6.1. Ethical Conduct of the Study

This study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, 1964 and later revisions, as

well as, United States Title 45 Code of Federal Regulations (CFR) Part 46 GCP, and International Council for Harmonisation (ICH) guidelines describing technical requirements for registration of pharmaceuticals for human use.

7. Institutional Review Board (IRB)

The investigator will provide the local IRB with all required documents, including the study protocol and informed consent form and recruitment materials. The study will not be initiated until appropriate IRB approval is obtained. The subjects will be informed that they have the right to contact the local IRB or Office for Human Research Protections if they have any questions, concerns, complaints, or believe they have been harmed by the participation in this research study as a result of investigator negligence. Subjects will be given the address and phone number of the local IRB.

8. Administrative Procedures

8.1. Responsibilities of the Investigator

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes may be reported to the IRB but will not result in protocol amendments.

8.1.1 Form FDA 1572

The investigator will complete and sign the Form FDA 1572.

8.1.2 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with the ICH E6(R1) and all applicable guidelines and regulations.

8.1.3 Reporting Requirements

By participating in this study, the investigator agrees to submit reports of SAEs according to the time line and method outlined in the protocol (Section 5.7.2.1.2). In addition, the investigator agrees to submit reports to the IRB as appropriate. The investigator also agrees to provide the sponsor with an adequate report shortly after completion of the investigator's participation in the study.

8.1.4 Source Documentation

By participating in this study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories.

8.1.5 Retention of Records

The investigator agrees to keep the records stipulated in this protocol and those documents that include (but are not limited to) the study-specific documents, identification log of all participating subjects, medical records, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent form), copies of all eCRFs, query responses, and detailed records of drug disposition, to enable evaluations or audits from regulatory authorities, the sponsor, or its designees.

Furthermore, ICH 4.9.5 requires the investigator to retain essential documents specified in ICH E6(R1) (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the clinical study site agreement between the investigator and sponsor.

Refer to the clinical study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

8.1.6 Financial Disclosure and Obligations

The investigator is required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 45 CFR 45. In addition, the investigator must provide to the sponsor a commitment to update this information promptly if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.

Neither the sponsor nor the study clinic is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process.

8.2. Confidentiality and Disclosure of Data

All subjects will sign a HIPAA-compliant authorization form containing the mandated core elements and requirements before participation in this clinical study. The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's electronic data capture system database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes such as gender, age or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires that the investigator allow review of the subject's original medical records (source data or documents) by the study monitor, representatives from any regulatory authority (e.g., FDA), the sponsor's designated auditors, and the appropriate IRB. These medical records will include, but will not be limited to, clinical laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process.

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected in the subject's eCRF).

Data will be maintained and backed up in the electronic data capture system. All access to the data is protected by username and password, and each staff member and all sponsor staff will have separate access that requires a separate username and password. Access is only given to site staff and requested sponsor staff who have completed the appropriate training.

8.3. Certificate of Confidentiality

In order to protect the privacy of subjects, Certificates of Confidentiality will be obtained prior to the initiation of the study.

8.4. Subject Consent

Written informed consent in compliance with 45 CFR 46 will be obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. An informed consent template may be provided by the sponsor to the study clinic. If any institution-specific modifications to study-related procedures are proposed or made by the study clinic, the consent should be reviewed by the sponsor or its designee or both before IRB submission. Once reviewed, the consent will be submitted by the investigator to the IRB for review and approval before the start of the study. If the informed consent form is revised during the course of the study, all active participating subjects must sign the revised form.

Before enrollment, each prospective subject will be given a full explanation of the study and be allowed to read the approved informed consent form. The informed consent process will be performed by a clinical research nurse in a private room. The subject will be given unlimited time to ask questions regarding study participation, and each subject will be questioned to ensure their understanding. Once the investigator is assured that the

subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing the informed consent form.

The investigator will provide a copy of the signed informed consent form to the subject. The original form will be maintained in the subject's medical records at the site.

8.5. Data Collection

Full details of procedures for data collection and handling will be documented in the data management plan, which is initiated with the final protocol receipt. The data management plan is a changing document that evolves over the course of the study and is finalized by database lock.

8.6. Publications

No information related to or generated by this study will be released to the public until it has been reviewed by the sponsor. The sponsor shall own intellectual rights for the data and analysis resulting from this study and results cannot be presented or published without written permission from the sponsor. Authorship on publications will be determined by standard journal requirements.

9. Study Management

9.1. Release of Study Drug to the Study Clinic

Before the study drug can be released to the study clinic, the following documents will be collected from the study clinic by the clinical research organization, retained in the trial master file, and a study drug shipment approval form will be completed by the clinical research organization:

- Protocol signature page signed by the investigator
- IRB approval of the protocol and informed consent form and IRB membership list
- Completed Form FDA 1572, curriculum vitae, and medical licenses from each investigator
- Financial disclosure and debarment certification from each investigator
- Executed contract with investigator and study clinic

9.2. Monitoring

9.2.1 Monitoring of the Study

The sponsor or its designee will monitor the study to ensure that it is being conducted according to the protocol, GCP standards, and applicable region-specific requirements,

and to ensure that study initiation, conduct, and closure are adequate. The investigators and the study clinic staff will be expected to cooperate fully with the study monitors and personnel or agents of the sponsor, and be available during monitoring visits to answer questions sufficiently and to provide any missing information. The investigators and their institutions will permit direct access to source data/documents for study-related monitoring activities, audits, IRB reviews, and regulatory inspections.

During any on-site visits, the study monitor will:

- Check and assess the progress of the study
- Review all informed consent forms
- Review study data collected
- Conduct source document verification
- Identify any issues and address their resolution
- Verify that the facility remains acceptable
- Conduct study drug accountability

These monitoring activities will be done in order to verify that the:

- Data are authentic, accurate, and complete.
- The safety and rights of the subjects are being protected.
- The study is being conducted in accordance with the currently approved protocol (including any amendments), GCP, and all applicable regulatory requirements.

In addition, the sponsor, designated auditors, and government inspectors must be allowed access to eCRFs, source documents, and other study files that may be required to evaluate the conduct of the study.

9.3. Management of Protocol Amendments and Deviations

9.3.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent immediate hazard to the subject, must be submitted to the sponsor or designee and reviewed and approved by the IRB before implementation. Amendments to the protocol must be submitted in writing to the IRB for approval before subjects are enrolled into an amended protocol.

9.3.2 Protocol Violations and Deviations

Any significant protocol deviations that the investigator or study clinic staff believes are of major importance (e.g., incorrect randomizations, subject enrolled but not eligible)

should be reported to the IRB as soon as possible. Significant protocol deviations may include the following:

- Deviations from the inclusion/exclusion criteria that may affect subject safety
- Deviations (omission or delay) of safety monitoring procedures
- Deviations in the administration of the study drug
- Deviations in obtaining informed consent

All subjects who are enrolled and receive the study drug, regardless of whether they have a major protocol violation, must continue to be followed for safety for all follow-up study visits.

10. Appendices

10.1. Appendix A: Schedule of Events

Table 10-1 Overall Schedule of Events (Parts 1 and 2)

	Screening	Check-in	Treatment and Follow-Up Period (In House)						In House Discharge or Early Termination	Follow-Up Visit (Part 2 only)	Follow-Up Visit (Part 2 only)	Follow-Up Visit (Part 2 only)
Study Procedure	**Days –30 to–1**	**Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 10**	**Day 14**	**Day 21**
Informed consent/HIPAA authorization	X											
Eligibility assessment	X	X										
Demographics	X											
Height, weight, body mass index	X											
Serology	X											
Medical history[a]	X											
Drug and alcohol screening	X	X										
Serum pregnancy test (female subjects)	X	X										
Fitzpatrick skin type assessment		X										
Admission to study clinic		X										
Randomization[b]		X										
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests[c]	X											
Vital sign measurements[d]	X		X	X	X	X	X	X	X	X	X	X
Safety 12-lead ECG[e]	X											

Physical examination[f]	X		X	X	X	X	X	X	X	X	X	X
Study drug administration[g]			X	X	X	X						
PK blood sample collection[h]			X	X	X	X	X	X	X	X	X	X
Tape stripping (Part 2 only)[i]									X		X	
Discharge from study clinic									X	X	X	X

Abbreviations: ECG, electrocardiogram; HIPAA, Health Insurance Portability and Accountability Act; PK, pharmacokinetic.

a Medical history assessment will also include social history and smoking habits.

b Randomization (Part 1 only) will occur either after completion of check-in procedures on Day 0 or just before dosing on Day 1.

c Clinical laboratory testing will include hematology, serum chemistry, and urinalysis.

d Vital signs measurements will include blood pressure, heart rate, respiratory rate, and oral body temperature. The subject should be in a supine position, if possible, for a minimum of 5 minutes before vital signs are measured. During the treatment period, vital signs will be measured before dosing.

e The subject should be in a supine position, if possible, for approximately 10 minutes before the safety 12-lead ECG is measured.

f A complete physical examination will be performed at Screening. The skin at the sites of topical application of the study drug will be examined for signs of irritation during the treatment period, upon discharge (or early termination), and at the follow-up visits. At the follow-up visits, a symptom-directed brief physical examination may be performed at the investigator's discretion.

g Topical sunscreen will be applied (according to the randomization schedule) at approximately 0900 hours and again at 2, 4, and 6 hours after the first dose.

h Pharmacokinetic blood samples (approximately 10 mL per sample) will be collected at the following time points:

- Day 1: 0 and 0.5, 1, 1.5, 2, 3 (Part 2 only), 4, 6, 8, 9, 10, 12, and 14 hours after initial dose
- Day 2: 23, 28, 33 h
- Day 3: 47, 52, 57 h
- Day 4: 71, 73, 74, 76, 78, 81, 82, 84 and 86 h
- Day 5: 95 hours
- Day 6: 120 hours
- Day 7: 144 hours
- Day 10: 216 hours (Part 2 only)
- Day 14: 312 hours (Part 2 only)
- Day 21: 480 hours (Part 2 only)

NOTE: when a time point corresponds with sunscreen administration, the PK sample will be collected before sunscreen administration.

i Tape stripping timepoints to determine residual concentration of active ingredients in the superficial layers of the skin

11. Reference List

1) Department of Health and Human Services, Food and Drug Administration (US), Center for Drug Evaluation and Research (CDER). Guidance for Industry: Nonprescription Sunscreen Drug Products – Safety and Effectiveness Data. November 2016.

2) Variation in stratum corneum protein content as a function of anatomical site and ethnic group, International Journal of Cosmetic Sciences, 38 (2016) 224-31.

3) The tape stripping procedure – evaluation of some critical parameters, European Journal of Pharmaceutics and Biopharmaceutics 72 (2009) 317-323.

Amended Statistical Analysis Plan

Statistical Analysis Plan

SCR-005: Assessment of the Human Systemic Absorption of Sunscreen Ingredients

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Date of SAP: 20 November 2018

CONFIDENTIAL

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Contents

1 Study Objectives

The primary objective of this study is:

1. To explore whether the active components (avobenzone, oxybenzone, ecamsule and octocrylene) of sunscreen products are absorbed into the systemic circulation when a sunscreen product is applied under maximal-use conditions.

1.1 Primary Objective (Part 1)

Part 1 is an open-label, randomized, 4-arm study in 24 healthy adult subjects with the primary objective:

- To explore whether the active components (avobenzone, oxybenzone, ecamsule and octocrylene) of 4 sunscreen products (1 sunscreen product in each arm) are absorbed into the systemic circulation when a sunscreen product is applied under maximal-use conditions.

One sunscreen product with the highest avobenzone exposure will be selected for the second part of the study. If there is no quantifiable exposure of avobenzone for any of the sunscreen products, the formulation with the highest oxybenzone exposure will be selected for Part 2.

1.2 Primary Objective (Part 2)

Part 2 is an open-label, 4-arm study in 48 healthy adult subjects with the following primary objective:

- To assess, where applicable, the pharmacokinetics and systemic absorption of the active components (avobenzone, oxybenzone, octocrylene, ecamsule, homosalate, octisalate and octinoxate, of 4 sunscreen products (1 sunscreen product in each arm) under maximal-use conditions.

Part 2 will include the sunscreen product with maximal avobenzone exposure from Part 1 and 3 additional new sunscreen formulations. More detailed information about the study (inclusion/exclusion criteria and schedule of events) can be found in the study protocol.

2 Sample Size

Approximately 72 healthy subjects are planned for enrollment, of which 24 will be assigned to Part 1 (randomized to 4 arms of 6 participants each) and 48 will be assigned to Part 2 (randomized to 4 arms of 12 participants each). Subjects are considered enrolled after determination by the Principal Investigator on Day 0 that they meet all eligibility criteria and are subsequently assigned a randomization/study identification number. The sample size was determined empirically and is typical for exploratory investigations of this type.

3 Analysis Populations

The analysis population will include all subjects who receive at least 1 dose of any of the study drugs and have PK sample data for the treatment period collected before dosing and at 1 or more time points after dosing.

The safety population will include all subjects who receive at least 1 dose of any of the study drugs.

4 General Statistical Considerations, Subject Disposition and Demographics and Baseline Characteristics

All data will be presented in data listings. Data from subjects excluded from an analysis population will be presented in the data listings but not included in the calculation of summary statistics. The number of subjects who enroll in the study and the number and percentage of subjects who complete each assessment will be presented. The frequency and percentage of subjects who withdraw or discontinue from the study and the reason for withdrawal or discontinuation will be summarized. Continuous demographic and baseline characteristic variables (age, height, weight, body mass index) will be summarized overall and by treatment using descriptive statistics (number of subjects, mean, standard deviation [SD], median, interquartile range [IQR], and minimum and maximum). The number and percentage of subjects in each class of categorical demographic and baseline characteristic variables will also be summarized.

5 Pharmacokinetic (PK) Analyses and Primary/Secondary Outcomes

The PK sampling schedule for this study is summarized in Appendix A. The following PK parameters will be determined for each subject in Part 1 and Part 2:

Across all study days

- Maximum concentration (observed peak drug concentration) (C_{max})

Day 1

- Maximum concentration (observed peak drug concentration) (C_{max})
- Time at which C_{max} occurs (T_{max})
- AUC from time 0 to the 23 hour time point (C_{last}) (AUC_{0-23})

Days 2 and 3

- Residual drug concentration (predose level) (C_{trough})
- Concentration 3 hours after the last dose of the day

Day 4

- Maximum concentration (observed peak drug concentration) (C_{max})
- Time at which C_{max} occurs (T_{max})
- Elimination rate constant (K_{el}) and terminal half-life ($t_{1/2}$); calculated after final dose using all the available data up to last study sample (144 hours for Part 1; 432 hours for Part 2)
- AUC from time 71 to the 95 hour time point (AUC_{73-95})
- AUC from time 0 extrapolated to infinity (AUC_{0-inf}) and/or last observed time point

Day 5, 6, 7, 10 (Part 2 only), 14 (Part 2 only) and 21 (Part 2 only)

- Residual drug concentration (C_{trough})

The primary and secondary outcomes of this study are as follows:

Primary Outcome:

1. Maximum* Avobenzone concentration (C_{max})

Secondary Outcomes:

1. Maximum* Oxybenzone concentration (C_{max})
2. Maximum* Octocrylene concentration (C_{max})
3. Maximum* Ecamsule concentration (C_{max})
4. Maximum* Homosalate concentration (C_{max})
5. Maximum* Octisalate concentration (C_{max})

6. Maximum* Octinoxate concentration (C_{max}) (Part 2 Only)

* observed maximum;

Note that Cmax could occur on any of the days of the study. PK parameters C_{max}, C_{last}, C_{trough}, T_{max}, AUC_{0-t}, K_{el}, $t_{1/2}$ and AUC_{0-inf}, will be summarized using descriptive statistics (number of subjects, mean, standard deviation [SD], coefficient of variation [CV], median, minimum, and maximum) for the days above for avobenzone, oxybenzone, octocrylene, ecamsule, homosalate, octisalate and/or octinoxate (depending on whether the specific sunscreen formulation contains each of the active ingredients; see Attachment B) in Part 1 and 2. The PK parameters will be analyzed using non-compartmental methods based on actual sampling times. Mean and individual concentration-time profiles will be presented in graphs.

6 Safety Analyses

All AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of treatment-emergent adverse events (TEAEs), organized by system organ class and frequency, will be summarized by seriousness, severity, relationship to treatment, and by treatment at onset of the TEAE. A detailed listing of serious AEs and TEAEs leading to withdrawal will also be provided.

Clinical laboratory results (hematology, serum chemistry, and urinalysis) will be summarized using descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum). Clinical laboratory results will be classified as normal or abnormal, according to the reference ranges of the individual parameter. The number and percentage of subjects with abnormal laboratory results will be provided. No statistical testing will be performed on clinical laboratory data.

Vital sign measurements (blood pressure, heart rate, respiratory rate, and oral body temperature), safety 12-lead ECG results, and changes from Baseline for these parameters will be summarized by treatment and time point using descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum). Physical examination findings will be presented in a data listing, and abnormal physical examination findings will be recorded as AEs.

All concomitant medication usage and medications that changed in daily dose, frequency, or both since the subject provided informed consent will be summarized for each subject.

7 Missing Data

Missing data will not be imputed. Data that are excluded from the descriptive or inferential analyses will be included in the subject data listings. This will include data from subjects not in

the particular analysis population, measurements from unscheduled visits, or extra measurements that may arise from 2 or more analyses of a plasma sample at the same time point.

8 Data Quality Assurance

Completed eCRFs are required for each subject randomly assigned to study drug. Electronic data entry will be accomplished through the ClinSpark remote electronic data capture (EDC) system, which allows for on-site data entry and data management. This system provides immediate, direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records.

Furthermore, the investigator retains full responsibility for the accuracy and authenticity of all data entered into the electronic data capture system. The completed dataset and their associated files are the sole property of the sponsor and should not be made available in any form to third parties, except for appropriate governmental health or regulatory authorities, without written permission of the sponsor.

Attachment A. Pharmacokinetic Sample Collection Schedule

Pharmacokinetic blood samples (approximately 10 mL per sample) will be collected for determination of avobenzone, oxybenzone, octocrylene, ecamsule, homosalate, octisalate and octinoxate plasma concentrations (where applicable to the different sunscreen formulations), at the following time points (the time limit for PK sample draws can be +/- 5 minutes from the nominal time):

- Day 1: 0 and 0.5, 1, 1.5, 2, 3 (Part 2 only), 4, 6, 8, 9, 10, 12, and 14 hours after initial dose
- Day 2: 23, 28, 33 h
- Day 3: 47, 52, 57 h
- Day 4: 71, 73, 74, 76, 78, 81, 82, 84 and 86 h
- Day 5: 95 hours
- Day 6: 120 hours
- Day 7: 144 hours
- Day 10: 216 hours (Part 2 only)
- Day 14: 312 hours (Part 2 only)
- Day 21: 480 hours (Part 2 only)

NOTE: when a time point corresponds with sunscreen administration, the PK sample will be collected before sunscreen administration.

Attachment B. Randomization Schedule

Randomization in this study is unblinded.

After screening, subjects will be randomized to one of 4 treatment sequences in either Part 1 (24 subjects) or Part 2 (48 subjects). Example of treatment codes from the study protocol:

- Treatment sequences of Part 1:
  - A: La Roche Posay (Cream), Anthelios SX Daily Moisturizing Cream with Sunscreen, SPF 15 with Mexoryl SX (6 subjects): Avobenzone (2%), Ecamsule (2%) and Octocrylene (10%)
  - B: Hawaiian Tropic (Lotion); Island Sport Ultra-Light High Performance Sunscreen, SPF 50 (6 subjects): Avobenzone (3%), Oxybenzone (4%) and Octocrylene (6%)
  - C: Neutrogena (Spray), Ultra Sheer Body Mist SPF 45 (6 subjects): Avobenzone (3%), Oxybenzone (6%), Octocrylene (2.35%), Homosalate (15%) and Octisalate (5%)
  - D: Banana Boat (Spray); Sport Performance Coolzone Continuous Spray Sunscreen, SPF 50 (6 subjects): Avobenzone (3%), Oxybenzone (5%) and Octocrylene (10%)

- Treatment sequences of Part 2:
  - E: Hawaiian Tropic (Lotion); Island Sport Ultra-Light High Performance Sunscreen, SPF 50 (12 subjects): Avobenzone (3%), Oxybenzone (4%) and Octocrylene (6%)
  - F: Neutrogena (Aerosol Spray), Ultra Sheer Body Mist SPF 100 (12 subjects): Avobenzone (3%), Oxybenzone (6%), Octocrylene (10%), Homosalate (15%) and Octisalate (5%)
  - G: Supergoop (Non-Aerosol Spray), Sunscreen Mist with Vitamin C SPF 50 (12 subjects): Avobenzone (3%), Octocrylene (10%), Homosalate (10%), Octisalate (5%) and Octinoxate (7.5%)
  - H: Supergoop (Pump Spray), Sun Defying Sunscreen Oil with Meadowfoam SPF 50 (12 subjects): Avobenzone (3%), Homosalate (10%),Octisalate (5%) and Octinoxate (7.5%)

The script performs randomization across treatment groups; all subjects in Part 1 will be studied in 1 cohort (cohort 1) and subjects in part 2 will be studied in 2 cohorts (cohorts 2 and 3).

Treatment schedule

RANDID	PART	COHORT	SEQ
1001	1	1	D
1002	1	1	A
1003	1	1	C
1004	1	1	B

1005	1	1	D
1006	1	1	B
1007	1	1	A
1008	1	1	C
1009	1	1	C
1010	1	1	B
1011	1	1	A
1012	1	1	D
1013	1	1	B
1014	1	1	A
1015	1	1	D
1016	1	1	C
1017	1	1	B
1018	1	1	A
1019	1	1	C
1020	1	1	D
1021	1	1	A
1022	1	1	D
1023	1	1	C
1024	1	1	B
2001	2	2	G
2002	2	2	E
2003	2	2	F
2004	2	2	H
2005	2	2	E
2006	2	2	G
2007	2	2	F
2008	2	2	H
2009	2	2	G
2010	2	2	E
2011	2	2	H
2012	2	2	F
2013	2	2	F
2014	2	2	G

2015	2	2	E
2016	2	2	H
2017	2	2	H
2018	2	2	E
2019	2	2	G
2020	2	2	F
2021	2	2	E
2022	2	2	F
2023	2	2	G
2024	2	2	H
2025	2	3	F
2026	2	3	H
2027	2	3	G
2028	2	3	E
2029	2	3	G
2030	2	3	H
2031	2	3	E
2032	2	3	F
2033	2	3	G
2034	2	3	E
2035	2	3	H
2036	2	3	F
2037	2	3	H
2038	2	3	E
2039	2	3	F
2040	2	3	G
2041	2	3	G
2042	2	3	E
2043	2	3	F
2044	2	3	H
2045	2	3	G
2046	2	3	E
2047	2	3	H
2048	2	3	F