CLINICAL TRIAL PROTOCOL

Protocol Status	Final
Version	1
Protocol Title	Evaluation of Topically Applied Bemotrizinol for Human Photoallergic Potential
Protocol Identification Number	DSM PA 2020
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CRL Study Number	CRLNJ2020-0495
Investigational Product	• SU E 101413 85: Sunscreen oil with 6% BEMT (PARSOL® Shield) and 10% ethanol as penetration enhancer • SU E 101413 91: Sunscreen oil vehicle with 10% ethanol as penetration enhancer without BEMT (BEMT replaced by Isopropylmyristate) • SU-E-101413-82: Dispersion of 6% BEMT (PARSOL® Shield) in petrolatum
US IND Number:	146892

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DOCUMENT HISTORY	
Document	**Date**
Original, Version 2	26 October 2020
Amendment 1, Version 7	25 February 2021
Amendment 2, Version 1 – Final Protocol	17 December 2021

Note: Only major changes to the protocol are presented in this summary of changes. Administrative changes have been made throughout the document to reflect change in version number and date of issue. Corrections of minor typographical errors and inconsistencies, grammar, or formatting changes are not listed here.

Amendment 2, Version 1 – Final Protocol (17 December 2021):

Section # and Name	**Description of Change**	**Brief Rationale**
Title Page, Section 1.0 (Background Information); Section 2.0 (Trial Objectives and Purpose); Section 3.4 (Treatment and Dosage); Section 5.0 (Treatment of Subjects); Section 7.0 (Assessment of Safety); Appendix II	Formulation numbers SU-E-101413-70 and SU-E-101413-81 replaced with SU E 101413 85 and SU E 101413 91, respectively	To address FDA feedback to potential effects of butyloctyl salicylate in the sunscreen oil formulations and the new IVPT results
Section 1.0 (Background information)	New IVPT results considered	See above
Appendix II – Quantitative Composition of Investigational Products	Butyloctyl salicylate replaced by higher oil contents in SU E 101413 85 and SU E 101413 91	See above

Amendment 1, Version 7 (25 February 2021):

Section # and Name	Description of Change	Brief Rationale
Section 3.2.1 (Re-Challenge Phase); Section 3.2 (Study Design)	Procedure for the re-challenge phase same as the challenge phase was added	to assist in interpretation of positive results, a re-challenge phase was added according to FDA guidance
Section 3.4 (Treatment and Dosage)	section was added describing sample preparation	To define sample preparation process in more detail
Section 3.2 (Study Design)	irradiation exposure redefined: Induction Phase 2 MED (full spectrum), challenge phase 10 J/cm^2 UVA	To account the nature of the PT according to guidance
Title Page, Section 3.4 (Treatment and Dosage)	SU-E-101413-83: Petrolatum vehicle was omitted	to not unnecessarily harm subjects, this vehicle control was skipped

1.0 BACKGROUND INFORMATION

The investigational product is 6% bemotrizinol (BEMT) either in a basic sunscreen oil formulation or in petrolatum as vehicle. BEMT is a photostable broad-spectrum filter, which efficiently contributes to UVB and UVA protection across the full range of application forms at low concentrations. Such sunscreen UV-filters contribute to public health by preventing skin damage (sunburn), reducing skin photoaging and helping reduce the risk of developing skin cancer by absorbing UV radiation. As a sunscreen active ingredient bemotrizinol is intended to be formulated for topical sunscreen use in permitted dosage forms, dosing regimens and conditions described under FDA's Sunscreen monograph for Drug Products for OTC Human Use (21 CFR Part 352).

Bemotrizinol is chemically stable, does not photodegrade under high UV exposures, has very limited bioavailability and is metabolically stable under physiological conditions. Therefore, metabolites or moieties of concern are not known from any of the completed tests with the usual purity (>99%) of BEMT as is used in consumer products.

DSM Nutritional Products (DSM) has been providing BEMT (under the tradename of PARSOL® Shield) as a UV light absorber for use in sunscreens and personal care cosmetic products globally since 2016, whereas BEMT has globally been used as a UV light absorber since 1999. From completed nonclinical safety testing results, BEMT at concentrations up to 10% has been shown to be safe for use in human topically applied products for all age groups.

The large body of nonclinical evidence available for BEMT indicates that BEMT is not a toxicologically active substance and does not indicate concern for human adverse effects from prolonged topical use in clinical studies at a maximum concentration of 6%. A review of the body of non-clinical legacy test data for BEMT available in FDA Docket 2005-N-0453 and of DSM in vitro test reports does not indicate adverse effects in single oral and topical applications. The substance is not genotoxic with or without UV irradiation, it is not photoallergic topically and is not a skin contact sensitizer with or without irradiation. Prolonged topical dosing of BEMT for 40 weeks to hairless mice also exposed to daily doses of UV radiation demonstrated a protective effect in that BEMT did not increase the UV-induced carcinogenic response in mice, and actually increased the time to tumor onset and decreased the potency of the UV radiation. Repeated oral dosing through the full reproductive cycle of rodents did not reveal adverse effects and rabbits did not show effects to key developmental parameters (Segment II study); endocrine system interactions or modulations did not reveal any adverse indications.

1.0 BACKGROUND INFORMATION (CONTINUED)

Chronic topical dosing to minipigs did not reveal dermal or systemic toxicity at a highest achievable dosage. Furthermore, prolonged administration by oral (up to 13 weeks) or dermal routes (up to two years) did not produce any indications for systemic target organ effects or an increased carcinogenic response. The DSM in vitro study results for local tolerance by skin irritation and sensitization and bacterial mutagenicity did not reveal differences from the related legacy studies and supports an interpretation of representative equivalency to USP grade bemotrizinol for the tested endpoints.

Clinical testing has not demonstrated adverse events (AEs) for topical applications to assess local tolerance including skin irritation and sensitization without or with UV radiation exposures. Regulatory agencies including those in Europe, Japan, Canada, and others, have reviewed the safety data and granted approval for use in topical products sold in their respective markets.

In the US market, BEMT is currently not approved as an active over-the-counter OTC sunscreen ingredient but is being reviewed by the Food and Drug Administration (FDA or Agency) for inclusion under the OTC Sunscreen Monograph via the Time and Extent Application (TEA) regulatory pathway. As part of the review process, FDA recommends that specific data regarding the safety and effectiveness of topical sunscreen actives are needed in order to determine whether a nonprescription (OTC) sunscreen active ingredient is generally recognized as safe and effective (GRASE).[1] According the FDA guidance human dermal safety studies for topical products in which exposure to light after application is anticipated generally consist of two sets of studies—those conducted without specific exposure to light and those conducted to assess reactions after ultraviolet exposure (photosafety studies). These study sets usually consist of dermal irritation patch testing, dermal sensitization patch testing, dermal photoallergy testing, and dermal photoallergenicity testing.

1.0 BACKGROUND INFORMATION (CONTINUED)

In the present photoallergy testing study we intend to test a concentration of 6% BEMT which will be the maximal concentration nominated for the OTC Sunscreen monograph as well. The testing will follow FDA's general recommendations for photoallergy testing contained presented in their S10 Photosafety Evaluation of Pharmaceuticals Guidance for Industry.[2.]

Previously, five formulations were tested in an *in vitro* percutaneous permeation test (IVPT) study. The formulations represented "market image" dosage forms with BEMT as the only active ingredient and contained commonly used and safe inactive ingredients for sunscreens. Based on FDA recommendation, the formulation chosen for evaluation in the pilot study was the one identified from the IVPT that demonstrated the highest skin absorption with a permeation enhancer. Since IVPT results did not show a statistically significant difference between the highest skin penetration from the sunscreen oil formulation compared to the same formulation type containing a permeation enhancer, the sunscreen oil containing 10% ethanol as skin penetration enhancer was selected to be tested in the pilot MUsT study. This formulation contained butyloctyl salicylate which is a commonly used ingredient with good solubility, viscosity, and permittivity attributes.

Upon FDA recommendation, a second IVPT was conducted to investigate the effect of butyloctyl salicylate on dermal penetration/absorption of BEMT. The formulations tested in the second IVPT (with or without butyloctyl salicylate) showed that the penetration/absorption of BEMT was similar and in the same range as in the first IVPT study. However, to rule out any possibility of effect of butyloctyl salicylate having an effect on the dermal penetration/absorption of BEMT, butyloctyl salicylate was removed from all formulations to be used in the pivotal MUsT. To that end, and to maintain "linkage" between the human bioavailability and pharm-tox data, the formulation shown to have the highest in vivo absorption is expected to be the formulation (i.e., SU E 101413 85) incorporated into dermal safety testing.

In addition to the sunscreen oil formulation, we intend to test 6% BEMT in a single solvent/dispersing agent as well, to rule out the possibility of cross-reactivities from the inactive ingredients used in the sunscreen oil formulation, resulting in unexpected false positive results. Petrolatum was found to be a suitable and common excipient for UV filters tested human dermal safety studies.

1.0 BACKGROUND INFORMATION (CONTINUED)

A photoallergic effect occurs only after repeated exposure to an offending agent. In photoallergy, the photosensitizing molecule, as with photoallergic molecules, absorbs ultraviolet light of a specific wavelength (short wave - UVB spectra; 290-320 nm). The activated state leads to a photochemical change in the molecule itself which then results in the formation of an allergic compound. A photoallergic effect is induced by UVB spectra during an Induction Phase and elicited by long wave UVA wavelengths (320-400 nm) during the Challenge Phase. The clinical manifestations of photoallergy can be eczematous, urticarial, lichen planus-like, and/or sunburn-like reactions.

Photoallergy testing presents minimal risk of causing skin irritation, or the potential benefit of the material warrants the testing.[2] Reactions may consist of mild to heavy erythema, swelling, itching, cracking, peeling, or, in rare cases, blistering and /or an allergic reaction may occur of the test site. Reactions to the tape adhesive may also be observed.[3]

Subjects will be generally healthy adults who have no known allergies to cosmetic products or formulation ingredients. Attempts will be made to stratify the study population for sex, age, and race. Each subject's back will be evaluated to ensure that the skin is free from clinically evident dermatoses, injuries, or any other disorders that may compromise the subject's participation in the study.

There is no direct benefit to subjects participating in this clinical trial. Subjects will be compensated for their participation in the clinical trial, as outlined on the Informed Consent Form. Subject participation in the clinical trial is voluntary. Subjects may withdraw from participation at any time.

This clinical trial will be conducted in compliance with this clinical trial protocol, applicable Good Clinical Practices, and applicable regulatory requirement(s).

2.0 TRIAL OBJECTIVES AND PURPOSE

The objective of this study is to evaluate the potential of investigational product, 6% Bemotrizinol in a suitable vehicle (i.e. sunscreen oil SU E 101413 85) or petrolatum (SU-E-101413-82) to produce a photoallergic response after application to the skin of human subjects followed by exposure to UV radiation. The purpose of this clinical trial is to evaluate the safety of the investigational products to determine whether bemotrizinol under the SIA is generally recognized as safe and effective (GRASE).[1]

3.0 TRIAL DESIGN

3.1. STUDY ENDPOINT

The primary endpoint of this clinical trial is to evaluate the potential of a test material to produce a photoallergic response.

3.2. STUDY DESIGN

This clinical trial will assess the photoallergic potential of a test material, compared to a vehicle control and a negative control.

Subjects will arrive to the laboratory on the day of study initiation. Informed consent will be obtained and Inclusion/exclusion criteria will be verified. Visual assessment of the skin of each subject's back will be performed. Qualified subjects will be enrolled.

On this visit, a site on the lower back, isolated from the actual test site, will be chosen to determine the subject's Minimal Erythema Dose (MED). The MED of each subject is assessed by applying a progressive geometric sequence of UV radiation exposures to five sub-sites, each of which is graduated incrementally by 25% over the previous site. The MED is evaluated 16 to 24 hours after ultraviolet radiation.

Duplicate test sites on the back (each approximately 4 cm^2) will be identified. A body map demonstrating application sites is listed in Appendix I. Test material will be applied to designated patches and affixed to both sides of the back. One side will be designated for irradiation, and the other is used as a treated/non-irradiated control.

Approximately 24 hours after application, the patches will be removed and the skin will be gently wiped. The MED will be determined from the five UV-treated sub-sites and all of the test sites will be evaluated according to the erythema grading scale. The sites designated for irradiation will be then irradiated with solar simulated light by two times an individual's MED.

The remaining site serves as the non-irradiated control. Test sites are delineated with a marking pen to ensure continuity of patch application and patch site location.

3.0 TRIAL DESIGN (CONTINUED)

3.2.1. Induction Phase

This procedure is carried out twice weekly for a total of six applications/post-irradiation readings. However, the schedule may be modified to accommodate inclement weather, holidays, or missed applications. At the discretion of the Principal Investigator, the test material may then be applied, the sites irradiated and scored on two consecutive days during the Induction Phase. If a patch and or irradiation is missed, a 3-day sequence of patch/irradiation/score will be added at the end of the Induction Phase. Subjects must have no fewer than 5 evaluations at the end of the Induction phase. Only one rescheduled patch or irradiation procedure is permitted. Subjects missing a second visit are discontinued from the study due to non-compliance with the study protocol.

Irradiated area within the treated sites and control sites are examined approximately 24 hours following irradiation of the test sites and graded. Skin condition of the sites will be evaluated at each visit for possible skin reactions to the test material. Any reaction will be documented on the source document.

If a 2+ reaction or greater occurs on a site, the application of the test material may be discontinued for the remainder of the Induction Phase, but may be challenged on the appropriate day of the study.

At the discretion of the Principal Investigator, subjects exhibiting a significant reaction at the beginning of the Induction Phase may be considered to be “pre-sensitized” to an ingredient(s) of the test product and may be discontinued from the patching and irradiation of that test material for the remainder of the study.

3.2.2. Challenge Phase

Approximately 10 to 21 days following the last induction application, duplicate patches are applied to sites previously unexposed to the test material. In addition 2 sets of patches without test material will be also applied on 2 sides of the back. Approximately 24 hours later, the patches are removed, the test sites are evaluated. The test sites on one side of the back are irradiated with a non-erythrogenic dose of UVA radiation (wavelengths 320-400 nm) equivalent to approximately 10 J/cm^2. The sites on the other side of the back serve as a test material treated, non-irradiated control site and non-treated non irradiated control. The challenge sites are graded at 24, 48, and 72 hours following irradiation according to the dermal grading scale.

3.0 TRIAL DESIGN (CONTINUED)

3.2.3. Re-Challenge Phase

At the discretion of the Investigator, and with the Sponsor's approval, a subject may be re-challenged with the test material if reactions indicative of sensitization or photo sensitization are observed during the Challenge Phase. The subject(s) will be asked to return to the laboratory no sooner than two weeks following the conclusion of the PA study and the Challenge procedures will be repeated. One patch of the test material will be applied to the subject's back and allowed to remain in direct contact with the skin for 24 hours. The subject will return after 24 hours for removal of the patch and grading of the site, without irradiation if sensitization is suspected or with irradiation of an additional treated site (24 hour exposure) if reactions suggestive of photosensitization are observed during the study. Subjects will return for a 48 hour and 72 hour post-patch application grading and additional 96 hour evaluation if a reaction persists. If the sites are irradiated after patch removal, subjects will return for evaluation at 24 hour, 48 hour and 72 hour post UV exposure.

Additional products (usually a breakdown of components of the original test product or "omission" products) may be challenged simultaneously or following the re-challenge of the original product by agreement between the Sponsor and Principal Investigator.

3.0 TRIAL DESIGN (CONTINUED)

3.2 STUDY DESIGN (CONTINUED)

The following dermal scoring system will be used to evaluate the irradiated area within the treated test site after UV exposure. Any other reaction on the treated/irradiated site outside the irradiated area will be scored and recorded.

Grading scale for Erythema	Description
0	No visible skin reaction
±	Barely perceptible erythema
1+	Mild erythema
2+	Well defined erythema
3+	Severe erythema

Grading Scale for dermal response	
e	= Edema
P	= Peeling
S	= Spreading of reaction beyond irradiated site.
Sc	= Scabbing
d	= Dryness/scaling
D	= Oozing, crusting, and/or superficial erosions
I	= Itching
Pa	= Papules
V	= Vesicle
W	= Weeping
Hr	= Hyperpigmentation
Ho	= Hypopigmentation
M	= Missed Visit

If a grade ≥2+ erythema is observed after patch removal on the site designated for irradiation, the site will not be irradiated, regardless of the dermal response of the non-irradiated site and the subjects will be discontinued by the Principal Investigator from the study. The dermal response will be followed up until resolution or until the end of the study.

LIGHT SOURCE

A Xenon Arc Solar Simulator (150w, Model 15S or 16S, Solar Light Company, Philadelphia, PA)[4] is used as a source of ultraviolet light irradiation and filtered to provide a basic solar-like spectrum in compliance with the ISO 17166 CIE S 007/E entitled "Erythema reference action spectrum and standard erythema dose," dated 1999 (First edition, 1999-12-15; corrected and reprinted 2000-11-15).

3.0 TRIAL DESIGN (CONTINUED)

3.2 STUDY DESIGN (CONTINUED)

For evaluation of photoallergy, during the Induction Phase, the sites are irradiated with 2 times the subject's MED (full spectrum wavelengths UVB 290–320 nm and UVA 320-400 nm) J/cm^2 UVA.

During the challenge phase, the sites will be irradiated with a dose of 10 J/cm2 of UVA light (320-400nm) using a Schott WG-345 and UG11/1 mm filter to block UVB wavelength 290-320 nanometers.

The lamp output is measured immediately prior to the start of each subject's testing with a UV Intensity Meter (Model DCS-1 DCS- 2, Solar Light Company, Philadelphia, PA). The spectral distributions of the optical output of the solar simulators are validated annually by Rapid Precision Testing Laboratories.

A subject may be required to return to the laboratory for a Re-Challenge Test if reactions indicative of sensitization are observed during the Challenge Phase. During the Re-Challenge Phase, the test material will be applied to a naive site under the same conditions of the Challenge Phase, and the subject will be examined for dermal reactions.

A study schedule appears below.

Procedure	Induction Phase															Challenge Phase				
																		24 h	48 h	72 h
Visit➔	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Informed Consent obtained	X																			
Inclusion/exclusion criteria verified	X																			
Confirmatory MED Evaluation	X	X																		
Test sites examined for eligibility	X																			
Patches applied	X		X			X		X			X		X			X†				
Patches removed		X		X			X		X			X		X			X			
Specified sites irradiated		X		X			X		X			X		X			X			
Sites graded for dermal irritation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

†Virgin sites

3.0 TRIAL DESIGN (CONTINUED)

3.3. RANDOMIZATION AND BLINDING

Randomization is not required for this study.

Subjects will be blinded to the name of the investigational products. The Investigatory staff will not be blinded. Investigational products will be labeled with unique CRL study identification and panel codes and subject numbers upon receipt by CRL.

3.4. TREATMENT AND DOSAGE

The investigational products will be identified by Eurofins | CRL, Inc. (CRL) study and panel numbers. Investigational product identification is as follows:

Sponsor Identification	CRL Identification Number
SU E 101413 85: Sunscreen oil with 6% BEMT (PARSOL® Shield) and 10% ethanol as penetration enhancer	CRLNJ2020-0495-01
SU E 101413 91: Sunscreen oil vehicle with 10% ethanol as penetration enhancer without BEMT (BEMT replaced by Isopropylmyristate)	CRLNJ2020-0495-02
SU-E-101413-82: Dispersion of 6% BEMT (PARSOL® Shield) in petrolatum	CRLNJ2020-0495-03

The Sponsor assumes responsibility for the purity, stability, characterization, and adequate preservation of the test materials. The Sponsor has provided assurance that the test materials submitted have been determined to be safe for use in humans.

A technician will measure approximately 0.15 g (using a weighting bowl) or 0.15 ml (using a 1.0 ml syringe) of each investigational product and the vehicle controls and then apply to the fabric portion of separate patches. A tongue depressor may be used to help spreading the test products is necessary. This application will be performed in the lab, withing 30 minutes before the patch is placed on the back. The negative control will be an undosed patch.

The patches to be used for this clinical trial will be occlusive strips (manufactured by Strukmyer LLC, Mesquite, TX or equivalent), consisting of a breathable tape with non-breathable adhesive and center portion of 1.9 cm x 1.9 cm fabric.

3.0 TRIAL DESIGN (CONTINUED)

3.5. STUDY DURATION

This clinical trial will require subject involvement for 20 days for 4 weeks in a 6-week period. Subjects will report to the laboratory on Day 1 for informed consent, verification of enrollment criteria, dermal grading, MED Irradiation and application of the investigational products and vehicle control under occlusive patches. Subjects will return approximately 24 hours later on Day 2 for patch removal, dermal grading of the sites, MED evaluation, and test site irradiation. Subjects will return to the laboratory for dermal grading and patch application.

This procedure is carried out twice weekly for a total of six applications and post-irradiation grading. Approximately two weeks after the last induction visit, subjects return to the clinic for patch application. After approximately 24 hours the patches are removed and the sites are graded followed by the UVA irradiation of the designated sites. The sites are evaluated 24, 48 and 72 hours after the UVA exposure

In the event of an adverse event related to the clinical trial, follow up contact with the subject will be maintained by the investigational staff until the adverse event has been resolved.

3.6. STUDY TERMINATION AND SUBJECT DISCONTINUATION

In the event that the investigational products or vehicle control elicits a dermal irritation score of ≥ 2+ erythema in more than 5 subjects after patch removal, the exposure of the site to the UV light will be discontinued. The Sponsor will be notified and termination of the study will be discussed. Subjects will be asked to return to the clinic for a follow up of the dermal response until resolution. The subjects, and the Institutional Review Board will be notified. A clinical study report will be generated and submitted to the Sponsor.

If a grade ≥ 2+ erythema is observed after patch removal prior to irradiation, the subject will be discontinued by the Principal Investigator from the study.

3.7. INVESTIGATIONAL PRODUCT ACCOUNTABILITY

Investigational product accountability will be executed in accordance with CRL SOP L1.1, as outlined below.

Upon investigational product delivery to the Lab Materials and Records Department, all correspondence will be dated. Investigational product deliveries will be stored in the Lab Materials and Records Department office behind a locked door if the deliveries are unable to be processed the same day; these deliveries will be processed the following business day.

3.0 TRIAL DESIGN (CONTINUED)

3.7 INVESTIGATIONAL PRODUCT ACCOUNTABILITY (CONTINUED)

The investigational product and accompanying documentation (description, identification, amount of test material, and condition) will be reviewed for consistent information. All pertinent information (codes, randomization numbers, quantity, expiration dates, and storage condition) will be recorded on the test material log. Documents will be placed in the study binder. Instructions for testing, number of subjects to be tested, type of patches to be used (occlusive or semi-occlusive), and if dilution is required will be included with test materials to be used for patch studies and will be confirmed. The test material will be placed in the appropriate storage area under conditions listed in in CRL SOP L1.2 (outlined below). If items are associated with the photo biology or microbiology department, notify designated staff to store test material in the appropriate locker for the study duration. A study number will be assigned to each individual test material in numerical sequence upon receipt. The study number will be recorded in the CRL Study Number Log Book, Panel Number Log Book (if applicable), Test Material Log Sheet, as well as in Study Tracker. The study number will be documented on the test material container. Multiple test materials received concurrently from the same sponsor may be assigned a CRL number with sub-number identification, dash, and number. The test material description, including the condition (if damaged), will be recorded on the Test Material Log Sheet. The test material container will be weighed as received and the weight will be recorded on the Test Material Log Sheet. Copies of the appropriate documents (Test Material Log Sheets and Submission Forms) will be forwarded to the project manager for inclusion in the study folder and entered into the computer database.

Clinical study staff will acquire the test materials from the designated storage area prior to study start. The test material dispensing log will be completed and signed prior to removal from the storage room. All test materials will continue to be stored according to storage requirements in CRL SOP L 1.2.

Upon study completion, the sponsor will be contacted to determine the method of mailing/hand delivery and need for MSDS documentation. The method and date of shipment will be kept on file and a copy of the final dispensing log or similar document, listing the number of units being returned and the exact identity of the units (including any sponsor-assigned numbers), must be enclosed with the shipment. The original Test Material Dispensing/Accountability Log will be retained in the study binder. The test material will be returned within 30 days of study completion.

Controlled storage of the investigational product will be executed in accordance with CRL SOP L 1.2, as outlined below.

3.0 TRIAL DESIGN (CONTINUED)

3.7 INVESTIGATIONAL PRODUCT ACCOUNTABILITY (CONTINUED)

The test material storage room and Lab Materials and Records Office are locked via a coded keypad, requiring lab staff to enter a pre-determined confidential code to enter the room to acquire test material. Room temperature will be maintained at 55 °F to 85 °F (12 °C to 29 °C) and 10% to 60% humidity. Temperature and humidity thermometers are monitored daily by lab department staff based on room location of the thermometer. Temperature and humidity is not monitored by staff on weekends, holidays, or unscheduled closure days (e.g. weather related, emergency, etc). Temperature and humidity levels are recorded into a logbook. Excursions outside of normal temperature and/or humidity ranges require corrective action.

3.8. DATA RECORDING

Dermal evaluations will be recorded on the Case Report Forms. Informed consent and Inclusion/Exclusion criteria will be documented on Case Report Forms. Adverse events will be documented and reported to the Sponsor.

3.9. PROTOCOL ADHERENCE

Neither the testing facility nor the Sponsor will modify this clinical trial protocol. In the event that the protocol must be changed, a protocol amendment or administrative change will be documented. A protocol amendment will be submitted when changes in the existing protocol are required that significantly affect safety of subjects, scope of the investigation, or scientific quality of the clinical trial. Protocol amendments will be submitted to the Sponsor and the Investigational Review Board (IRB) for review and signature, and will be signed and implemented by the Principal Investigator. Minor changes to the existing protocol that do not significantly affect safety of subjects, scope of the investigation, or scientific quality of the clinical trial will be documented as administrative changes to the protocol, and will be maintained in the clinical trial master file. Administrative changes will be approved and signed by the Sponsor. Unplanned or unexpected non-compliances with the protocol will be documented as protocol deviations. Protocol deviations should be avoided whenever possible, and will be documented in the clinical trial master file and reported to the Sponsor and IRB.

4.0 SELECTION AND WITHDRAWAL OF SUBJECTS

Up to 50 subjects will be enrolled in the study in an attempt to complete with 45 subjects. All subjects will be initially identified by a permanent CRL identification number. Once the subject meets qualification criteria, a study subject number will be assigned. This study subject number will be assigned in sequence as subjects are enrolled in the clinical trial.

Attempts will be made to stratify the study population for sex, age and race. Each subject's back will be evaluated to ensure that the skin is free from clinically evident dermatoses, injuries, or any other disorders that may compromise the subject's participation in the study.

4.0 SELECTION AND WITHDRAWAL OF SUBJECTS (CONTINUED)

4.1. SUBJECT INCLUSION CRITERIA

A subject may be eligible for clinical trial participation if all of the following criteria are met:

a) Subject is male or female between 18 and 75 years of age;
b) Subject has a Fitzpatrick Skin Types I – III, based on the first 30 to 45 minutes of sun exposure after a winter season of no sun exposure according to the following criteria;
   I Always burns easily; never tans (sensitive)
   II Always burns easily; tans minimally (sensitive)
   III Burns moderately; tans gradually (normal)
c) Subject agrees to avoid excessive sun exposure of the test sites and to refrain from visits to tanning salons during the course of this study;
d) Subject does not exhibit any skin diseases or abnormalities which might be confused with a skin reaction from the test material;
e) Subject agrees not to introduce any new cosmetic or toiletry products during the study;
f) Subject agrees to refrain from getting patches wet and from scrubbing or washing the test area with soap or applying powders, lotions or personal care products to the area during the course of the study;
g) Subject is dependable and able to follow directions as outlined in the protocol and anticipates being available for all study visits;
h) Subject is willing to participate in all study evaluations;
i) Subject is in generally good health and has a current Panelist Profile Form on file at CRL;
j) Subject has completed a HIPAA Authorization Form in conformance with 45 CFR Parts 160 and 164;
k) Subject understands and is willing to sign an Informed Consent Form in conformance with 21 CFR Part 50: “Protection of Human Subjects.”

4.0 SELECTION AND WITHDRAWAL OF SUBJECTS (CONTINUED)

4.2. SUBJECT EXCLUSION CRITERIA

A subject is not eligible for clinical trial participation if any of the following criteria are met:

a) Female subject is pregnant, nursing, planning a pregnancy, or not using adequate birth control;
b) Subjects with a prior history of phototoxic or photoallergic reactions or those taking medication which might produce an abnormal response to sunlight;
c) Subject has received treatment with sympathomimetics, antihistamines, vasoconstrictors, non-steroidal anti-inflammatory agents, and/or systemic or topical corticosteroids within one week prior to initiation of the study;
d) Subject has a history of acute or chronic dermatologic, medical, and/or physical conditions which would preclude application of the test material and/or could influence the outcome of the study;
e) Subject is under treatment for a skin and/or systemic bacterial infection;
f) Subject reports a history of allergies to tape adhesives;
g) Subject is currently taking certain medications which, in the opinion of the Principal Investigator, may interfere with the study;
h) Subject has known allergies to sunscreen, skin treatment products or cosmetics, toiletries, and/or topical drugs;
i) Subject has a known communicable disease (e.g., HIV, sexually transmitted diseases, Hepatitis B, Hepatitis C, etc.);
j) Subject has insulin-dependent diabetes;
k) Subject has a history of cancer;
l) Subject is currently taking certain medications which, in the opinion of the Principal Investigator, may interfere with the study;
m) Subject exhibits sunburn, suntan, uneven skin tone, blemishes, moles or excess hair in the test site area.

4.0 SELECTION AND WITHDRAWAL OF SUBJECTS (CONTINUED)

4.3. SUBJECT TERMINATION AND WITHDRAWAL

If a grade ≥ 2+ erythema is observed after patch removal prior to irradiation, the subject will be discontinued by the Principal Investigator from the study. A subject's participation may be terminated if a protocol deviation occurs during the study. A subject may be discontinued from clinical trial participation at any time if the Principal Investigator or designated medical staff feels that it is not in the subject's best interest to continue. When a subject is discontinued for reasons related to the investigational products of the clinical trial, the subject will be informed that they are discontinued from the study. The subject will be compensated as outlined in the Informed Consent form. Discontinued subject data will be removed from the data set but will be reported in the clinical study report.

Subjects who are discontinued from study participation will not be replaced. As with all clinical studies, it is beyond the control of the test facility to guarantee the number of subjects that will actually complete the study. It is the responsibility of the Sponsor to commission a sufficient number of subjects in order to maximize the probability of ending with the intended target number.

In the event of an adverse event related to the clinical trial, follow up contact with the subject will be maintained by the investigational staff until the adverse event has been resolved.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. Reasonable attempts will be made by the Principal Investigator or designee to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the clinical trial will be specified in the subject's source documents and included in the final report.

5.0 TREATMENT OF SUBJECTS

The investigational product for this study is 6% bemotrizinol (BEMT) in a basic sunscreen oil formulation (SU E 101413 85) and petrolatum (SU-E-101413-82). One vehicle controls, i.e. sunscreen oil vehicle (SU E 101413 91), and a negative control will also be used as comparators in this clinical trial.

Approximately 0.15 g or 0.15 ml of each investigational product and the vehicle control will be applied to the fabric portion of the patch. Two doses (one irradiated and one non-irradiated) of the investigational products and two doses (one irradiated and one non-irradiated) of the vehicle controls will be applied to back of each subject once on Day 1 under occlusive patches. Patches will remain in place for approximately 24 hours and will be removed by clinical study staff on Day 2. During the challenge phase, two undosed negative control occlusive patches will also be also applied. Subjects will return to the laboratory 24 hours and 48 hours post-irradiation for dermal evaluations.

The patches to be used for this clinical trial will be occlusive strips (manufactured by Strukmyer LLC, Mesquite, TX or equivalent), consisting of a breathable tape with non-breathable adhesive and center portion of ¾-inch x ¾-inch fabric.

Subjects who have received treatment with sympathomimetics, antihistamines, vasoconstrictors, non-steroidal anti-inflammatory agents, and/or systemic or topical corticosteroids within one week prior to initiation of the study will be excluded from study participation. Subjects will be discontinued if they use sympathomimetics, antihistamines, vasoconstrictors, non-steroidal anti-inflammatory agents, and/or systemic or topical corticosteroids during the study, and will be discontinued from study participation if they use these interventions during the study.

6.0 ASSESSMENT OF EFFICACY

No efficacy evaluations will be performed during this study.

7.0 ASSESSMENT OF SAFETY

Dermal scores obtained during the challenge phase will be reported for each site. The results obtained will determine if 6% bemotrizinol (BEMT) either in a basic sunscreen oil formulation SU E 101413 85 or as dispersion in petrolatum (SU-E-101413-82) elicit a photoallergic response based on a comparison of the reactions obtained on treated/irradiated, treated/non-irradiated and non-treated control sites as listed below. SU E 101413 91: Sunscreen oil vehicle with 10% ethanol as penetration enhancer without BEMT (BEMT replaced by Isopropylmyristate) photoallergy potential will also be determined.

Test Site				Conclusion*
Treated (Irradiated)	**Treated (Non-irradiated)**	**Non-treated(Non-irradiated**	**Non-Treated (Irradiated)**	
■	☐	☐	☐	Photoallergic Response
☐	☐	☐	☐	Not a contact sensitizer or photoallergen

■ = positive response ☐ = no reaction

*Clinically significant reactions other than photoallergic reactions will be recorded and interpreted accordingly.

Safety of the investigational product will be monitored by evaluating adverse event reporting.

7.1. ADVERSE EVENTS

7.1.1. Definition of an Adverse Event

An adverse event is any untoward medical occurrence, whether or not it is considered clinical trial related, including death, experienced by a subject. An event may consist of a disease, an exacerbation of a pre-existing illness or condition, an occurrence of an intermittent illness or condition, a set of related symptoms or signs, or a single symptom or sign. Any subject that presents with a dermal reaction of 3+ or greater will be considered as an adverse event and documented accordingly.

7.0 ASSESSMENT OF SAFETY (CONTINUED)

7.1.2. Definition of a Serious Adverse Event

A serious adverse event is any event in which the subject is, in the view of the Principal Investigator, at immediate risk of death or persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions. Note that this definition does not include an event that, had it occurred in a more serious form, might have caused death or persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions. Examples of serious adverse events include, but are not limited to death due to any cause, whether or not it is felt to be related to the clinical trial; events that require subject hospitalization; or events that result in a congenital anomaly or birth defect.

7.1.3. Documentation and Reporting of Adverse Events

All adverse events will be promptly recorded and sufficiently documented by the Principal Investigator or designated medical staff in the source documentation and case report form, even if the adverse event is assessed as unlikely to be related to the clinical trial by the Principal Investigator or designated medical staff. The Principal Investigator or designated medical staff will report the occurrence of any serious adverse event to the Sponsor's representative and the IRB within one business day, regardless of the causal relationship to the clinical trial, and follow-up with written documentation within three business days. All adverse events, serious or not serious, related or not related to the Investigational Product, will be summarized and reported in the final report. All adverse events will be followed up until resolved, stabilized, the subject is lost to follow-up, or the event is otherwise explained.

7.2. ANTICIPATED REACTION

Topical application of the test material to the skin may be associated to the following reactions:

Mild to well defined erythema, itching and swelling. Other minor skin irritations including dry skin, exfoliation, burning/stinging/ sensation, and skin discoloration (hyperpigmentation/hypopigmentation). Typically these reactions are temporary and do not extend beyond site of application.

8.0 STATISTICS

Statistical analysis will not be performed for this study. Investigational product safety will be determined through interpretation of the dermal evaluation scores.

All subjects who complete the study will be included in safety conclusion. Discontinued subjects will be removed from the data set, but will be included in the safety conclusion, if appropriate.

9.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents. Trial-related monitoring and audits will be conducted remotely.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE

This clinical trial will be conducted in accordance with the clinical trial protocol and CRL SOPs. The clinical trial master file will be reviewed for compliance with the clinical trial protocol, CRL SOPs, and applicable guidelines and regulations by the Principal Investigator and the Quality Assurance representative.

11.0 ETHICS

11.1. ETHICAL CONDUCT OF THE CLINICAL TRIAL

CRL follows established, standardized procedures for clinical testing designed to ensure the wellbeing of clinical trial subjects and the generation of reliable clinical trial data. The clinical trial Sponsor is responsible for ensuring the clinical trial complies with applicable Drug, Cosmetic or Medical Device regulations, which vary by product.

11.2. ETHICS COMMITTEE AND REGULATORY APPROVAL

The Institutional Review Board (IRB) will review and approve the clinical trial protocol, investigational test product formulas, and Informed Consent Form prior to clinical trial initiation in accordance with Title 21 of the Code of Federal Regulations (CFR), Parts 50 and 56. Additional clinical trial documentation may be submitted to the IRB for review and approval at the discretion of the Principal Investigator or at the request of the IRB.

11.0 ETHICS (CONTINUED)

11.3. INFORMED CONSENT

Each subject will be given a copy of the IRB-approved Informed Consent Form (ICF) and have the nature and the purpose of the clinical trial explained by CRL personnel. Prior to entry into the clinical trial, the subject must give voluntary written consent to participate by signing the ICF. The Principal Investigator must retain the original signed Informed Consent Form in the subject's file and must give a copy of the Informed Consent Form to the subject.

11.4. SUBJECT CONFIDENTIALITY

The Principal Investigator must ensure that the research subject's confidentiality is maintained. Subjects will be identified by a study ID number only. Documents will be kept in strict confidence by the Principal Investigator. Any use of personally identifiable data or private health information must be justified by the Principal Investigator and approved by the IRB.

12.0 DATA HANDLING AND RECORDKEEPING

Per the request of the Sponsor, the study folder will be retained for at least ten years.

Record keeping will be executed in accordance with CRL SOP L 2.1, as outlined below.

A copy of the report will be retained electronically indefinitely. This applies to reports signed electronically and those hand signed (scanned and saved when being hand signed). Study documents and related media must be identifiable by panel number, CRL number, and type of study. Each study folder will be stored in a designated box labeled by year and panel number and filed in numerical order by panel number. Once the study report has been sent to the Sponsor and the study folder and accompanying photos (if applicable) have been archived, a log entry will be made that includes CRL study number and archive box number. Upon completion of the required retention period, shredding of the documents will be performed by a third-party shredding company.

12.0 DATA HANDLING AND RECORDKEEPING (CONTINUED)

Dearchiving of study records will be executed in accordance with CRL SOP L 2.2, as outlined below.

A request for the removal of test materials and/or documents from archives is made by completing and submitting a Product/Records Request Form to the Lab Materials and Records Department. If the sections of the Product/Records Request Form under the responsibility of the requester are not completed in their entirety, the form will be given back to the requester to be completed before requested materials are removed. Upon receipt of a completed Product/Records Request Form, Lab Materials and Records staff will obtain the requested materials from the appropriate storage area, and complete the appropriate sections of the Product/Records Request Form, indicating the date of removal, CRL Study number and/or panel number, title, and/or description of test material or documents removed, and name of the retriever. The information will be transcribed on the product/records request form in to the "Retrieval Comments" section of Study Tracker that is associated with the CRL NJ study number in question and corresponds with the item requested and will enter the date removed from archives.

All items must be returned to the Lab Materials and Records Department within 24 hours (or as soon as possible). Items will be returned to their appropriate archive locations. The return and re-archiving of the removed items will be documented in the Study Tracker under the CRLNJ study number that corresponds with the item requested, along with date returned to archives. The information will be transcribed on the product/records request form in to the "Retrieval Comments" section of study tracker. Upon completion, the original product/records request form will be destroyed.

13.0 FINANCING AND INSURANCE

Financing and insurance are addressed in the FRAMEWORK AGREEMENT for SERVICES – DSM SOURCING B.V. & EUROFINS CLF SPECIALISED NUTRITION TESTING SERVICES GMBH (effective July 1, 2020).

14.0 PUBLICATION POLICY

With a view to safeguard the Sponsor's interests, any publication, lecture, manuscript, poster presentation, or other disclosure or dissemination of the data or results of the study by CRL or the Principal Investigator shall be excluded.

The Sponsor might, after prior written approval and after review of the wording, grant CRL or the Principal Investigator the right to disclose certain parts of the results upon its sole discretion.

15.0 SUPPLEMENTS

Not applicable.

16.0 CLINICAL TRIAL REPORTING

An audited topline will be submitted to the Sponsor approximately 10 business days of clinical trial completion. A draft clinical study report including a calibration record should be referenced and a summary of lamp output will be issued within approximately 4 weeks of clinical trial completion. Clinical trial-related documents, including source documents or raw data, will be reviewed by the Principal Investigator and/or designated clinical trial staff prior to issuance of the final report. The report will summarize the clinical trial objective(s) and test methodology. Clinical trial data will be reported as described in the Data Tabulation section. A PDF file of the signed final report will be delivered upon completion of Quality Assurance audit procedures and Sponsor approval of the draft report.

17.0 COVID-19 FACE MASK REQUIREMENT

Subjects will be required to wear face masks during their laboratory visits. Staff are not permitted to remove their face masks at any time during the study visit. Face masks should fit snugly but comfortably against the sides of the face. The masks should be secured with ties or ear loops and should completely cover the mouth and the nose, making sure that it extends from the top of the nose, as close as possible to the eyes without obstructing sight, to under the chin. The masks should cover the face side-to-side, well past the opening of the mouth.

In the context of the Coronavirus (COVID-19) pandemic, the clinical site will follow all FDA, Centers for Disease Control and Prevention (CDC), and institutional review board (IRB) recommendations in its oversight and conduct of the trial. This may include changing the schedule of follow-up visits if it is considered necessary after a full risk/benefit analysis.

18.0 REFERENCES

1. DHHS 2016. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry: Nonprescription Sunscreen Drug Products – Safety and Effectiveness Data. November 2016. Available at: https://www.fda.gov/media/94513/download

2. FOOD & DRUG ADMINISTRATION, H. H. S. 2015. International Conference on Harmonisation; S10 Photosafety Evaluation of Pharmaceuticals; guidance for industry; availability. Notice. Fed Regist, 80, 4282-3. https://www.fda.gov/media/85076/download

3. U.S. Department of Health and Human Services. Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs: Guidance for Industry. 2018

4. Berger, D.S. (1969). Specification and Design of Solar Ultraviolet Simulators. J. Invest Dermatol, 53, 192.

19.0 PROTOCOL APPROVAL

19.1. SPONSOR APPROVAL

I have read the foregoing clinical trial protocol entitled "Evaluation of Topically Applied Bemotrizinol for Human Photoallergic Potential" and approve the clinical trial protocol for use in this clinical trial.

12/21/2021

Rolf Schtitz, PhD — Date
Senior Scientist II
Study Director, Personal Care
Sponsor Representative

19.2. PRINCIPAL INVESTIGATOR ACCEPTANCE

I have read the foregoing clinical trial protocol entitled "Evaluation of Topically Applied Bemotrizinol for Human Photoallergic Potential" and I agree to conduct the clinical trial in compliance with the clinical trial protocol approved by the Sponsor.

Gladys Digitally Date: 2022.01.04 09:05:2

Gladys Osis, MT — Date
Manager, Photobiology
Principal Investigator

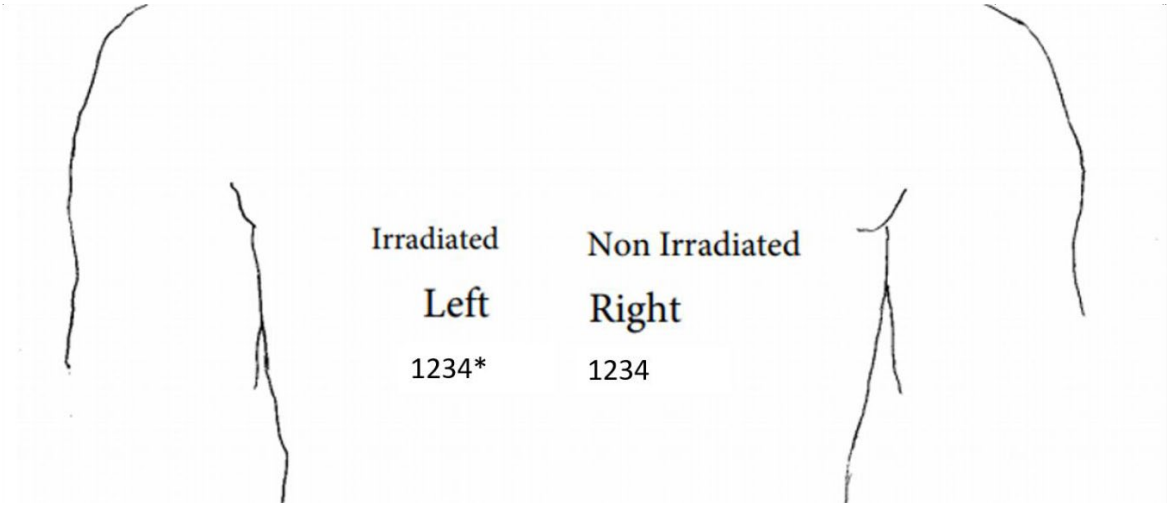
19.3. SUB-INVESTIGATOR ACCEPTANCE

I have read the foregoing clinical trial protocol entitled "Evaluation of Topically Applied Bemotrizinol for Human Photoallergic Potential" and I agree to conduct the clinical trial in compliance with the clinical trial protocol approved by the Sponsor.

Winston Moy, Digitally signed by Winston Moy, M.D.
DN: cn=Winston Moy, M.D., o=Eurofins CRL Inc, ou, email=winston.moy@crlresearchlabs.com, c=US Date: 2022.01.03 14:10:21 -05'00'

Winston Moy, MD — Date
Diplomate, American Board of Dermatology
Sub-Investigator

Appendix I – Body Map



Appendix II – Quantitative Compositions of Investigational Products

Phase	trade name	INCI	SU E 101413 85	SU E 101413 91	SU E 101413 82
			Sunscreen oil with 6% BEMT (PARSOL® Shield) and 10% ethanol as penetration enhancer	Sunscreen oil vehicle with 10% ethanol as penetration enhancer without BEMT	Dispersion of 6% BEMT (PARSOL® Shield) in petrolatum
A	PARSOL® Shield	BIS-ETHYLHEXYLOXYPHENOL METHOXYPHENYL TRIAZINE;	6.0		6.0
A	Finsolv TN	C12-15 ALKYL BENZOATE;	20.0	20.0	
A	Cetiol CC	DICAPRYLYL CARBONATE;	15.0	15.0	
A	X-Tend 226	PHENETHYL BENZOATE;	5.0	5.0	
A	Myritol 318	CAPRYLIC/CAPRIC TRIGLYCERIDE;	30.0	30.0	
A	Isopropyl Myristate	ISOPROPYL MYRISTATE;	14.0	20.0	
B	Ethanol abs.	ALCOHOL;	10.0	10.0	
B	Vaselinum album	VASELINUM ALBUM			94.0
Total:			**100.0**	**100.0**	**100.0**