INVESTIGATOR'S BROCHURE

INVESTIGATIONAL PRODUCT	**Bemotrizinol (BEMT)**
FDA IND #	**146892**
TRADE NAME (OPTIONAL)	**PARSOL® SHIELD**
GENERIC/CHEMICAL NAME	2,4-Bis[(4-(2-ethyl-hexyloxy)-2hydroxy-phenyl]-6-(4-methoxyphenyl)-(1,3,5 triazine) CAS No. 187393-00-6
EDITION NUMBER	04
RELEASE DATE	13 February 2022
REPLACES (EDITION NUMBER) DATE	Edition 03, 27 October 2020
SPONSOR/ADDRESS	DSM Nutritional Products, LLC 45 Waterview Boulevard Parsippany, NJ 07054-1298

ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BEMT	Bemotrizinol
BLQ	Below the limit of analytical quantification
CRF	Case Report Form
CRO	Contract Research Organization
DART	Developmental and Reproduction Testing
e.g.	for example
EU	European Union
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IP	Investigational Product
ISF	Investigator Site File
LD_{50}	Acute Median Lethal dose for 50% of dosed animals
LLOQ	Lower limit of analytical quantification
LOEL	Lowest Observed Effect Level
LOQ	Limit of analytical quantification
MED	Minimal Erythemal Dose
MOS	Margin of Safety; the ratio of an animal no-effect dosage to an estimated human systemic exposure
MTD	Maximum tolerated dose
NO(A)EL	No Observable (Adverse) Effect Level
OTC	Over the counter
OECD	Organization for European Co-operation and Development
p.o.	"per os" - administered via the mouth into the stomach
SAE	Serious Adverse Event
SCCS	Scientific Committee on Consumer Safety
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TG	Test Guideline
TMF	Trial master file
US FDA	United States Food and Drug Administration
UVA:	Ultraviolet light (radiation) in the wavelength range 315 to 400 nm
UVB:	Ultraviolet light (radiation) in the wavelength range 280 to 315 nm
UVR	Ultraviolet radiation
vs.	versus

TABLE OF CONTENTS

1

1.14.4.1 SUMMARY

The investigational product, 6% Bemotrizinol (BEMT), will be applied topically to subjects enrolled in four clinical studies as either a market image sunscreen formulation or in petrolatum as a 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).

Four independent clinical trials will be conducted at two separate clinical research facilities and will evaluate the pharmacokinetic (PK) uptake and systemic exposure from a maximal dermal dosing (MUsT) protocol and separately dermal safety (3 studies) of the UV filter active ingredient Bemotrizinol (BEMT) at 6% in various representative formulations. The study protocols are as follows:

- Ultraviolet Filter Bemotrizinol: Clinical Pharmacokinetics Evaluation in a Topical Maximum Usage Trial (MUsT) (BEMT-001 Part 2)
- Evaluation of Topically Applied Bemotrizinol for Human Photoallergic Potential (DSM PA 2020).
- Evaluation of Topically Applied Bemotrizinol for Human Phototoxic Potential (DSM PT 2020).
- Evaluation of Bemotrizinol in Human Repeated Insult Patch Test (HRIPT) and Cumulative Irritation Test (DSM RIPT 2020).

A total of 472 subjects will be enrolled in the 4 clinical trials associated with this IB. 162 subjects will be enrolled in Part 2 of the protocol BEMT-001. This will be an FDA Phase 3 (pivotal) MUsT study consisting of three arms with 54 subjects per arm, to achieve a minimum of 150 completers (50 completers in each arm) as recommended by FDA for this study phase. The anticipated total number of subjects that would be enrolled in the three dermal Phase 2 safety studies identified in this investigator's brochure (IB) is approximately 310 (50 in Photoallergy, 35 in Phototoxicity and 190 in HRIPT and 35 in Cumulative Irritation). As indicated in this IB, the exposure and testing of these subjects with BEMT at 6% in sunscreen formulations should be of very low risk for adverse clinical effects as demonstrated by a review of the existing body of scientific data which exists for BEMT, and the excipients proposed to be used in the test formulations. All four clinical trial protocols, test product formulations and Informed Consent Forms (ICFs) have been reviewed and approved by the Institutional Review Board (IRB) Advarra, 6100 Merriweather Dr., Suite 600, Columbia, Maryland, 21044 and all four study protocols have been registered with clinicaltrials.gov.

The MUsT Part 2 (Protocol BEMT-001) will be conducted, as was Part 1, at Spaulding Clinical Research, LLC, 525 South Silverbrook Dr, West Bend, Wisconsin, 53095 and is an open-label, randomized, 3-arm pivotal study in 162 healthy adult subjects with the objective to assess the systemic absorption and pharmacokinetics of BEMT from 3 market

image sunscreen formulations under maximal-use conditions. Based on results of MUsT Protocol Part 1 pilot phase study, FDA has set forth their recommendations that are incorporated into the pivotal phase design. Existing information database of nonclinical and clinical test results with BEMT substantiate the human safety of 6% BEMT as will be used in the topical exposures of the MUsT protocol.

The three dermal (FDA Phase 2) safety studies will be conducted at Eurofins | CRL, Inc., 371 Hoes Lane, Suite 100, Piscataway, New Jersey 08854; the anticipated total number of subjects that would be enrolled is approximately 310 (50 in Photoallergy, 35 in Phototoxicity and 190 in HRIPT and 35 in Cumulative Irritation). The protocols associated with these studies were previously submitted to FDA and amended per FDA recommendations under IND No. 146892. Based upon the existing preclinical and clinical data associated with BEMT, the exposure and testing of these subjects with BEMT at 6% in sunscreen formulations should be considered to present very low risk for adverse clinical effects. The results from the MUsT pivotal study together with these dermal safety studies with BEMT are expected to adequately support an FDA determination for BEMT to be judged as Generally Recognized as Safe and Effective (GRASE).

All BEMT clinical trials will be conducted under FDA investigational new drug (IND) No. 146892 and have been registered with ClinicalTrials.gov.

1 INTRODUCTION

Sunscreens are topically applied products that protect the skin from the sun's damaging ultraviolet (UV) radiation. Sunscreens work by absorbing or reflecting ultraviolet (UV) radiation to help protect against UV-induced skin cancers - as well as sunburns and signs of aging (Watson et al., 2016; CDC, 2020; and AAD, 2020). Bemotrizinol (BEMT) is a photostable broad-spectrum sunscreen filter which efficiently contributes to UVB and UVA protection across the full range of application forms at low concentrations. BEMT has been approved globally as a sunscreen active ingredient at concentrations up to 10% since 2000 and is currently marketed by DSM Nutritional Products, LLC (“DSM”) under the tradename PARSOL® Shield.

In the United States BEMT is not approved as an active OTC sunscreen ingredient but is currently subject to a Food and Drug Administration (FDA) Proposed Sunscreen Order (PSO) that was issued on November 13, 2014. Under the PSO, FDA has indicated that BEMT is eligible to be considered for inclusion on the OTC sunscreen monograph at a maximum concentration of 10%, pending the submission of additional data needed to support a generally recognized as safe and effective (GRASE) determination and permit its listing on the Sunscreen Monograph.

BEMT at a maximum concentration of 6% is being sponsored by DSM for inclusion under FDA’s OTC Sunscreen Monograph. As part of the safety evaluation for sunscreen products, FDA requests that the human systemic absorption of sunscreen ingredients be assessed through the conduct of a Maximum Usage Trial (MUsT) in humans (DHHS 2019). In addition, FDA also requires that human dermal safety studies be conducted,

which usually include dermal irritation and cumulative irritation patch testing, dermal sensitization patch testing, dermal phototoxicity testing, and dermal photoallergenicity testing (FDA 2016).

A market survey of BEMT-containing formulations and in vitro permeation test (IVPT) results were utilized to identify and select the "market image" sunscreen formulations and dosage forms that will be evaluated in all BEMT clinical trials. The BEMT test dosage forms proposed for all FDA-required clinical trials contain excipients (inactive ingredients) that are commonly used in sunscreen and topical drug products throughout the world, including the US; are present at levels that are recognized as safe for human topical use; and are technically suitable, given BEMT's physical chemical properties and solubility profile.

It is anticipated that the results of the clinical studies conducted on BEMT, together with the findings of other available and planned non-clinical toxicity studies, will allow FDA to estimate a safety margin (MOS) for systemic exposure to BEMT. It is also expected that the observed safe human exposure level will be well below the exposure level that causes toxicity in animals as reflected in the large MOS.

1.1 Background

BEMT is being reviewed by the Food and Drug Administration (FDA or Agency) for inclusion under the OTC Sunscreen Monograph. As part of the review process, FDA recommends that specific data regarding the safety and effectiveness of topical sunscreen actives are needed to determine whether a nonprescription (OTC) sunscreen active ingredient is generally recognized as safe and effective (GRASE) (FDA 2016).

The FDA requirements for topical sunscreen products stipulate that human pharmacokinetic testing with maximal dermal dosing (MUsT) protocols be followed to evaluate the systemic exposures with the drug ingredient. Additionally, according to 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.

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 2000. 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, indicated the following about BEMT:

- no adverse effects from maximal single oral and topical applications,
- absence of genotoxic effects with or without UV irradiation,
- it is not a photoirritant topically and is not a skin contact sensitizer with or without UV irradiation,
- is not photocarcinogenic in mice and is photoprotective for UV-induced dermal carcinogenicity,
- did not reveal adverse effects in any aspect of the full developmental and reproductive cycle of rodents and rabbits,
- not interactive with any aspects of the endocrine system,
- no adverse effects or target organs revealed after subchronic or chronic dermal and oral dosing.

A series of recent in vitro study results for local tolerance by skin irritation and sensitization and bacterial mutagenicity sponsored by DSM did not reveal adverse effects or a predicted difference from the legacy test results. A recent nonclinical PK study in rats dosed at 1000 mg/kg/d once or daily for 20 days indicated maximum plasma BEMT concentrations of only about 3 ng/ml a concentration plateau around 1.5 ng/ml without an increasing and with a linear return to pre-dosing conditions. A single daily dose for a 5-d or 28-day oral gavage test up to 1500 mg/kg/d to mice indicated 14-d and 28-d BEMT systemic exposures below 10 ng/ml and an absence of adverse effects in any dose group.

These study results support concluding that the DSM form of BEMT (PARSOL Shield) is equivalent to the historical test substances that were considered as a USP grade drug substance.

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.

Clinical controlled 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.

1.1.1 Basis for Selection of Drug Product Formulations

Details regarding the formulations and dosage forms to be used in the clinical studies are presented Section 2.2. General background information on the selection process for the investigational drug product formulations to be used is presented below.

The formulations and dosage forms to be used in the clinical studies were selected based on FDA guideline regarding the selection of market image sunscreen formulations and the results of standard design in vitro percutaneous penetration testing (IVPT) with human skin membranes. The formulation with the highest percutaneous penetration in the IVPT was used in the pilot clinical PK study (BEMT-001) and will also be used in the subsequent dermal safety testing and pivotal MUsT. The pivotal MUsT protocol is a phase 3 test and will also use two additional 6% BEMT formulations with larger subject panels for the 3-arm study design that has been previously reviewed and agreed to by FDA. The test dosage forms to be used for the pivotal MUsT Part 2 or the dermal safety tests each contain excipients (inactive ingredients) that are commonly used in sunscreen and topical drug products throughout the world, including the US; are present at levels that are recognized as safe for human topical use; and are technically suitable, given BEMT's physical chemical properties and solubility profile.

Two sequential IVPTs have been conducted. In the first test (IES 2020), five formulations representing "market image" dosage forms with 6% BEMT and commonly used and safe inactive ingredients for sunscreens were used. Based on FDA recommendation, the formulation chosen for evaluation in the MUsT pilot phase was the one identified from the IVPT that demonstrated the highest skin absorption with a permeation enhancer. While the 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 inactive sunscreen ingredient with good solubility, viscosity, and permittivity attributes for BEMT.

Upon FDA recommendation, a second IVPT (BASF, 2022) 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 butyloctyl salicylate influencing the dermal penetration/absorption of BEMT, butyloctyl salicylate was removed from all formulations to be used in all further clinical trials, including the pivotal MUsT. Hence, to maintain "linkage" between the human bioavailability and pharm-tox data, the formulation shown to have the highest in vivo absorption, expected to be the Sunscreen oil formulation (i.e., SU E 101413 85), was also incorporated into the dermal safety testing protocols. Below is a summary of the formulations and dosage forms to be used in the clinical trials.

In the Pivotal (FDA Phase 3) MUsT (BEMT-001 Part 2) the following formulations will be used:

- BEMT, PARSOL® Shield, 6%, with suitable solubilizers, Formulation SU-E-101413-85: Sunscreen oil with 10% alcohol as penetration enhancer
- BEMT, PARSOL® Shield, 6%, with suitable solubilizers; Formulation SU-E-101413-87: Oil-in-water (O/W) emulsion

- BEMT, PARSOL® Shield, 6%, with suitable solubilizers, Formulation SU-E-101413-89: Water-in-oil (W/O) cream emulsion

In the dermal safety protocols, the following formulations will be used:

- SU E 101413 85: Sunscreen oil with 6% BEMT (PARSOL® Shield) and 10% ethanol as penetration enhancer
- SU E 101413 91: Sunscreen oil vehicle (without active) and 10% ethanol as penetration enhancer
- SU-E-101413-82: Dispersion of 6% BEMT (PARSOL® Shield) in petrolatum
    - Notes:
        - The use of the formulation with 6% BEMT in a single solvent/dispersing agent (SU-E-101413-82) is intended to exclude potential cross-reactivities that could result in unexpected false positive findings from the inactive ingredients used in the sunscreen oil formulation. Petrolatum was found to be a suitable and common excipient (listed on FDA's inactive ingredient database) for UV filters tested in human dermal safety studies.
        - A control without active will also be used in parallel: Petrolatum vehicle SU-E-101413-83

1.1.1.1 Results from BEMT Pilot MUsT (BEMT-001 Part 1)

The following findings from the Pilot Part 1 (FDA Phase 1) MUsT study (NCT04355286) were used to modify the Part 2 Pivotal (FDA Phase 3) MUsT protocol BEMT-001:

- Absorption of 6% BEMT after topical administration was very limited, with only 4.3% of the PK samples (13/299) having concentrations equal to or higher than the LLOQ of 0.5 ng/mL.
- Seven of 14 subjects (50%) had a total of 13 quantifiable concentrations above the FDA threshold (i.e., >0.5 ng/mL), with values of 0.56 to 2.29 ng/mL. Overall, Cmax was 0.55 (0.72) ng/mL (mean, (SD); secondary analysis).
- There was no evidence of BEMT accumulation or steady-state BEMT concentrations above 0.5 ng/mL.
- Overall, 8 of 14 subjects (57.1%) reported at least 1 TEAE. Of the 8 subjects with TEAEs, 7 subjects (50.0%) reported TEAEs that were considered mild in severity and 1 subject (7.1%) reported TEAEs considered moderate in severity. One subject reported TEAEs of erythema and urticaria that were moderate in severity and led to discontinuation from the study. No severe TEAEs, serious AEs, or deaths were reported.
- Overall, topical applications of 6% BEMT in sunscreen oil with suitable solubilizers and 10% alcohol as penetration enhancer applied 4 times daily for 4 days were safe and well tolerated by the healthy adult male and female subjects in this study.

1.1.2 Pivotal MUsT Study (BEMT-001 Part 2)

The Part 2 Pivotal MUsT is an open-label, randomized, 3-arm study in 162 healthy adult subjects with the following primary objective:

- To assess the systemic absorption and pharmacokinetics of BEMT from 3 market image sunscreen formulations under maximal-use conditions.

A total of 162 subjects will be enrolled in Part 2 of BEMT-001 (54 subjects per study drug formulation arm) to achieve a minimum of 150 completers (50 completers in each arm) as recommended by FDA for this study phase. The Part 2 test panels will include adequate representation of male and female subjects, subjects of all ages including a sufficient number of elderly subjects, and subjects of different races.

As in Part 1, approximately 2 mg of sunscreen formulation per 1 cm^2 of body surface will be applied topically 4 times per day for 4 days (every 2 hours for 6 hours) to at least 75% of the body surface area. Each application will be prepared by a pharmacist according to the randomization schedule and the body surface area of the randomly assigned subject calculated using the Du Bois method. The weight of study drug will be measured and recorded both before and after dosing for each subject. Subjects will be in swim wear during dosing and will be confined to the CRU during the study.

PK blood samples of about 10 mL per sample will be collected for the determination of BEMT plasma concentrations atthe following time points (relative to the initial dose on Day 1):

	Dosing (hour relative from first dose)	Blood sampling (hour relative from first dose)
Day 1	0, 2, 4, 6	0 (within 30 minutes before first application), 2, 4, 8, 12
Day 2	24, 26, 28, 30	23.5, 28, 32
Day 3	48, 50, 52, 54	47.5, 52, 56
Day 4	72, 74, 76, 78 (last)	71.5, 74, 75, 76, 77, 78, 79, 80, 82, 84, 86
Day 5	–	96

The duration of participation will be approximately 50 days, including a 45-day screening period, a 4-day treatment period (Days 1-4), and subjects leaving the CRU on Day 5. On Day 12, End-of-Study activities will be completed. The Pivotal MUsT plasma samples will be analyzed for BEMT with the analytical method modified from the Part 1 pilot study LOQ of 0.5 ng BEMT/mL as validated recently to a lower limit of BEMT quantification (LLOQ) of 0.1 ng/mL.

1.1.3 Dermal Safety Tests

Below is a brief overview of the objectives and purpose for each dermal study. All clinical trials will be conducted in compliance with the specific clinical trial protocol, applicable Good Clinical Practices, and applicable regulatory requirement(s). 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.

In the photoallergy and phototoxicity studies we intend to test a concentration of 6% BEMT, which will be the maximal concentration nominated for the OTC Sunscreen monograph. The photoallergy and phototoxicity tests will follow FDA's general recommendations for photoallergy and phototoxicity testing contained in their S10 Photosafety Evaluation of Pharmaceuticals Guidance for Industry. (FDA 2015). The Human Repeat Insult Test (HRIPT) is a commonly executed method for determining the potential of an investigational product to elicit dermal irritation and/or induce sensitization. HRIPT testing presents exaggerated use conditions, exceeding typical exposure conditions for topical products, to determine sensitization potential in low-risk investigational products (FDA 2015).

Each of the Dermal Safety tests will be conducted at Eurofins | CRL, Inc., 371 Hoes Lane, Suite 100, Piscataway, New Jersey 08854 (CRL Study Number: CRLNJ2020-0494). For the phototoxicity and photoallergy studies, the CRL Principal Investigator will be Gladys Osis, MT Manager, Photobiology, the Sub-Investigator, Winston Moy, MD, Diplomate, American Board of Dermatology. For the HRIPT and Cumulative Irritation test the CRL Principal Investigator will be Samantha Poweski, Manager, Advanced Clinical Services, the Sub-investigator Winston Moy, MD, Diplomate, American Board of Dermatology.

The Institutional Review Board (IRB) (Advarra, 6100 Merriweather Dr., Suite 600, Columbia, MD 21044; 410-884-2000) has reviewed and approved each of the clinical trial protocols, investigational test product formulas, and assocaited Informed Consent Forms (ICF) in accordance with Title 21 of the Code of Federal Regulations (CFR), Parts 50 and 56.

Before entry into a clinical trial, all subjects must give voluntary written consent to participate by signing the ICF. 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. 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.

In each of the dermal safety studies the following skin-site 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 outsidethe irradiated area will be scored and recorded.

Dermal site reaction gradings:

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

1.1.3.1 Photoallergy Study (DSM PA 2020)

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.

The primary endpoint of this clinical trial is to evaluate the potential of a test material to produce a photoallergic response. As such, 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 6% bemotrizinol is generally recognized as safe and effective (GRASE) for use under FDA OTC sunscreen drug monograph (FDA 2016).

Up to 50 subjects will be enrolled in the study in an attempt to complete with 45 subjects. Attempts will be made to stratify the study population for sex, age and race. Approximately 0.15 g of each investigational product or vehicle controls will be applied to the fabric portion of separate patches with occlusive strips; an un-dosed patch will also be used. 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. In the challenge phase, the sites will be irradiated with a dose of 10 J/cm^2 of UVA light (320–400 nm) using cut-off filters to block UVB wavelength 290-320 nanometers.

This clinical trial will require subject involvement for 20 days for 4 weeks in a 6-weekperiod. 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.

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 thenon-irradiated site and the subjects will be discontinued by the Principal Investigator fromthe study. The dermal response will be followed up until resolution or until the end of the study.

1.1.3.2 Phototoxicity Study: DSM PT 2020

Photodermatitis is a form of contact dermatitis characterized by an eczematous reaction confined to light-exposed skin sites. When such a skin response develops after a single test material exposure coupled with ultraviolet light irradiation, it is considered a phototoxic effect analogous to a primary irritant effect observed independent of light exposure. Phototoxicity implies a non-immunologic state in which a photosensitizing molecule absorbs quantities of light in the UVB (290-320 nm) and UVA (320-400 nm) regions (Api et al 2008). A phototoxic effect on the skin clinically resembles a severe sunburn (Api et al 2008). Phototoxicity testing is performed clinically via photopatch testing.

Phototoxicity testing presents minimal risk of causing skin irritation, or the potential benefit of the material warrants the testing (McNamee 2008). 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 (McNamee 2008).

The primary endpoint of this clinical trial is to evaluate the potential of a test material to produce a phototoxic response. This clinical trial will assess the phototoxic potential of a test material, compared to a vehicle control and a negative control. 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 phototoxic 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 (6%) is generally recognized as safe and effective (GRASE) for OTC topical drug sunscreen use following FDA's nonprescription sunscreen drug products safety and effectiveness data guidelines (FDA 2016).

Up to 35 subjects will be enrolled in the study in order to complete with 30 subjects. Attempts will be made to stratify the study population for sex, age and race. This clinical trial will require subject involvement for 5 consecutive days. Subjects will report to the clinical site on Day 1 for informed consent, verification of enrollment criteria, dermal grading, MED irradiation and application of approximately 0.15 g of the investigational products and vehicle control under occlusive patches; an un-dosed negative control patch will also be used. 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 approximately at 24 hours or 48 hours after patch application. An additional 72 hours visit, following irradiation, will be scheduled to follow up any dermal response at 24 or 48 hours.

For evaluation of phototoxicity, the sites are irradiated with 0.5 of the subject's MED (full spectrum wavelengths UVB 290–320 nm and UVA 320-400 nm) followed by 5 J/cm^2 UVA (320-400 nm) using cut-off filters to block UVB wavelength 290-320 nanometers.

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 thenon-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.

1.1.3.3 HRIPT and Cumulative Irritation Study: DSM RIPT 2020

HRIPT presents minimal to no risk of causing skin sensitization, or the potential benefit of the material warrants the testing (McNamee et al. 2008). HRIPT risks include dermal irritation and skin sensitizations, which may present as erythema, edema, papules, vesicular eruption, or other effects of irritation or sensitizations on or around the test site (McNamee et al. 2008). Reactions to the tape adhesive may also be observed (US DHHS 2018).

The primary endpoints of this clinical trial are to determine the potential of a test material to elicit dermal irritation or to induce sensitization following repeated patch applications and in a subset of subjects to determine the cumulative irritation potential of a test

material applied topically over a 21-day period. The first objective of this study is to determine the potential of 6% bemotrizinol (BEMT) either in a basic sunscreen oil formulation (SU E 101413 85) or as dispersion in petrolatum (SU-E-101413-82) to elicit dermal irritation and induce sensitization following repeated patch application. The second objective of this study is to determine the cumulative irritation potential of 6% bemotrizinol (BEMT) either in a basic sunscreen oil formulation (SU E 101413 85) or as dispersion in petrolatum (SU-E-101413-82) topically applied to the skin of human subjects over a consecutive 21-day period.

The cumulative irritation endpoint is assessed by repeated daily patch applications intended to represent continuous daily use of the test ingredient, 6% BEMT, with observation of test site skin responses for indications of increasing adverse response to the test article. Available clinical and nonclinical test results indicate BEMT is without a cumulative skin irritation potential.

The purpose of this clinical trial is to evaluate the safety of the investigational products. In the present dermal sensitization patch testing study, a concentration of 6% BEMT will be used, which will be the maximal concentration nominated for the OTC sunscreen monograph.

This clinical trial will require subject involvement for approximately 6 weeks. Approximately 225 subjects (190 for RIPT and 35 for Cumulative Irritation) will be enrolled in this clinical trial. Attempts will be made to stratify the study population for sex, age and race. Subjects will report to the laboratory on Day 1 for informed consent, verification of enrolment criteria, dermal grading, and application of about 0.2 g of the investigational products, vehicle controls, saline control, or an un-dosed negative control patch under occlusive conditions. Subjects will return three times a week for three weeks for the duration of the Induction Phase for dermal evaluations and patch applications. The subset of subjects also participating in the cumulative irritation portion of the study will return every day, including weekends, for three weeks for dermal applications and evaluations.

1.2 Application Number

IND number: 146892. Note: BEMT safety and regulatory information previously submitted to FDA is contained in OTC Docket Number FDA-2005-N-0453.

1.3 Rational for Conducting Research on the Drug Substance

The results of these investigations along with other existing and planned studies will support an FDA determination that BEMT (6%) is generally regarded as safe and effective (GRASE). Such a determination will permit FDA to include BEMT (6% max.) as an active ingredient for sunscreen use under FDA's monograph for Sunscreen Drug Products for OTC Human Use (21 CFR Part 352).

2 PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION

2.1 Active Ingredient

2.1.1 Established Name (USAN:INN)

Bemotrizinol (BEMT)

2.1.2 Chemical Names

CAS Registry Number: 187393-00-6

UNII-PWZ1720CBH

Bis-ethylhexyloxyphenol Methoxyphenyl Triazine

2,4-Bis[(4-(2-ethyl-hexyloxy)-2hydroxy-phenyl]-6-(4-methoxyphenyl)-(1,3,5 triazine)

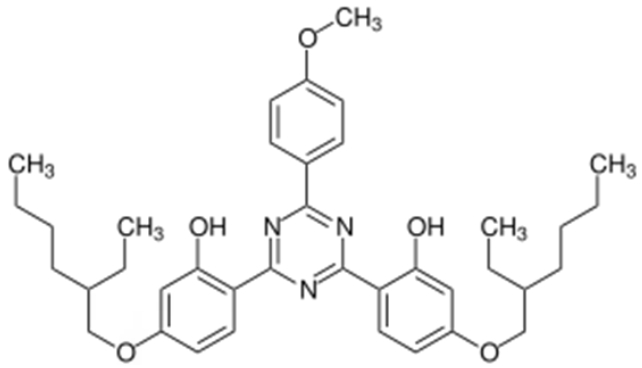
5-(2-ethylhexoxy)-2-[4-[4-(2-ethylhexoxy)-2-hydroxyphenyl]-6-(4-methoxyphenyl)-1,3,5-triazin-2-yl]phenol

2.1.3 Marketed Trade Names

PARSOL® Shield

TINOSORB® S

2.1.4 Chemical Structure

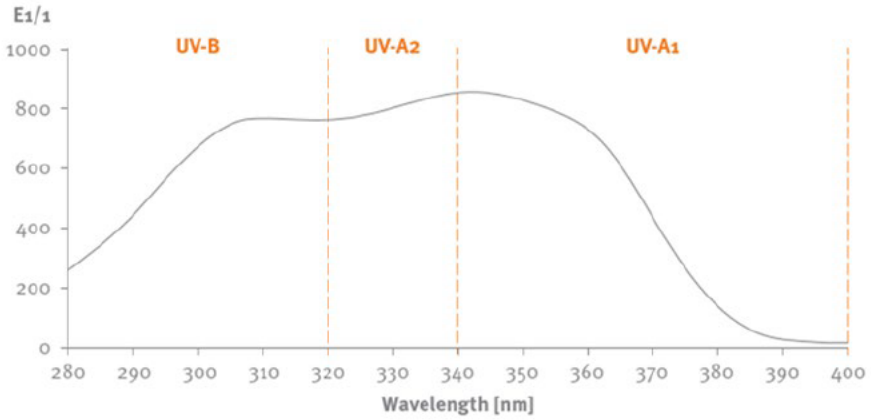


2.1.5 Pharmacological Class and Indication

Broad-spectrum UVA and UVB filter intended for use as a topical sunscreen active ingredient (maximum concentration 6%) under FDA's Sunscreen monograph for Drug Products for OTC Human Use (21 CFR Part 352). Indication: helps prevent sunburn and others allowed per: 21 CFR

§ 352.52 - Labelling of sunscreen drug products (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=352.52).

2.1.6 UV Absorption Spectrum



2.2 Formulations and Dosage Forms to be Used

The following investigational products will be used in Part 2 of the human PK Maximum Usage Trial (MUsT) or as listed for each of the identified dermal safety testing study protocols. The basis for selection of the drug product components has been set forth in the above section 1.1.1.

2.2.1 Pivotal MUsT (BEMT-001 Part 2)

In the Pivotal MUsT the following formulations will be used:

BEMT-001 Part 2 Pivotal Study at Spaulding Wisconsin

Sponsor Identification
Formulation SU-E-101413-85: BEMT, PARSOL Shield, 6%, with suitable solubilizers, Sunscreen oil with 10% alcohol as penetration enhancer
Formulation SU-E-101413-87: BEMT, PARSOL Shield, 6%, with suitable solubilizers; oil-in-water (O/W) emulsion
Formulation SU-E-101413-89: BEMT, PARSOL Shield, 6%, with suitable solubilizers, water-in-oil (W/O) cream emulsion.

2.2.2 Dermal Safety Tests at CRL-New Jersey

Dosing formulations used in each of the dermal safety protocols are summarized below.

2.2.2.1 Photoallergy Study: DSM PA 2020

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 enhancerwithout BEMT (BEMT replaced by Isopropylmyristate)	CRLNJ2020-0495-02
SU-E-101413-82: Dispersion of 6% BEMT (PARSOL® Shield) in petrolatum	CRLNJ2020-0495-03

2.2.2.2 Phototoxicity Study: DSM PT 2020

Sponsor Identification	CRL Identification Number
SU E 101413 85: Sunscreen oil with 6% BEMT (PARSOL® Shield) and 10% ethanol as penetration enhancer	CRLNJ2020-0494-01
SU E 101413 91: Sunscreen oil vehicle with 10% ethanol as penetration enhancerwithout BEMT (BEMT replaced by Isopropylmyristate)	CRLNJ2020-0494-02
SU-E-101413-82: Dispersion of 6% BEMT (PARSOL® Shield) in petrolatum	CRLNJ2020-0494-03
SU-E-101413-83: Petrolatum vehicle	CRLNJ2020-0494-04

2.2.2.3 HRIPT and Cumulative Irritation Study: DSM RIPT 2020

Sponsor Identification	CRL Identification Number
SU E 101413 85: Sunscreen oil with 6% BEMT (PARSOL® Shield) and 10% ethanol as penetration enhancer	CRLNJ2020-0493-01
SU E 101413 91: Sunscreen oil vehicle with 10% ethanol as penetration enhancerwithout BEMT (BEMT replaced by Isopropylmyristate)	CRLNJ2020-0493-02

SU-E-101413-82: Dispersion of 6% BEMT (PARSOL® Shield) in petrolatum	CRLNJ2020-0493-03
SU-E-101413-83: Petrolatum vehicle	CRLNJ2020-0493-04

Note: The vehicle controls (SU E 101413 91 and SU-E-101413-83), 0.9% saline and empty patches as negative control will be used for the HRIPT and Cumulative Irritation portion of the study. The 0.1% Sodium Laurel Sulfate (SLS) will only be used for the Cumulative Irritation portion of the study.

2.2.3 Inactive Ingredients (Excipients) for MUsT and Dermal Safety Tests

The BEMT test dosage forms to be used in all these FDA-required clinical trials contain excipients (inactive ingredients) that are commonly used in sunscreen and topical drug products throughout the world, including the US; are present at levels that are recognized as safe for human topical use; and are technically suitable, given BEMT's physical chemical properties and solubility profile.

Table 1 provides a summary of the inactive ingredients in the dosage forms that will be evaluated in each of these clinical studies. Based on the recognized safe use levels that are equal to or higher than their concentration in the Drug Product Formulations, each excipient and formulation are considered safe for use in the proposed MUsT protocol at the maximum application rates required for this study design. The Dermal Safety tests will use a formulation maximum application of 0.2 grams, which is well within the recognized safe use concentration cited in the table.

Table 1. Summary of Inactive Ingredients Contained in Formulations to be Evaluated in the BEMT Clinical Studies

Inactive Ingredient	CAS #	Function	Max. Conc. (w/w%)	Formulation Number Used in	UNII	Safety Reviews and Listings
C12-C15 Alkyl benzoate	68411-27-8	Emollient	15.0	SU-E-101413-70 SU-E-101413-73 SU-E-101413-74	N4F51K239A	Safe for use up to 59% CIR 2012; USP43-NF38 - 5609
Caprylic/Capric Triglyceride	65381-09-1 73398-61-5	Emollient	30.0	SU-E-101413-70	C9H2L21V7U	Safe for use up to 95.6% CIR 2018; USP43-NF38 - 6177
Isopropyl myristate	110-27-0	Emollient	9.00	SU-E-101413-70	0RE8K4LNJS	Listed for Topical use: FDA Inactive drug ingredients listed at max concentration of 92.38% w/w (spray aerosol); Safe up to 77.3%. CIR 2015; USP43-NF38 - 5839

Inactive Ingredient	CAS #	Function	Max. Conc. (w/w%)	Formulation Number Used in	UNII	Safety Reviews and Listings
Dicaprylyl carbonate	1680-31-5	Emollient	10.0	SU-E-101413-70 SU-E-101413-73 SU-E-101413-74	609A3V1SUA	CIR Review: 12/06/2016; safe up to 34.5% CIR 2017
Potassium Cetyl Phosphate	84861-79-0 17026-85-6 19035-79-1 90506-45-9 (generic)	Emollient	2.5	SU-E-101413-73 SU-E-101413-74	03KCY6P7UT	Safe up to 8.3%, CIR 2019
Ethanol (Alcohol)	64-17-5	Skin penetration enhancer	10.0	SU-E-101413-70	3K9958V90M	Listed for Topical use: FDA Inactive drug ingredients listed; max. concentration of 15%w/w (cream) and 41.3%w/v (spray); CIR 2008; USP43-NF38 - 6133
Butyloctyl salicylate	190085-41-7	Emollient	10.0	SU-E-101413-70 SU-E-101413-73 SU-E-101413-74	2EH13UN8D3	Listed for Topical use: FDA Inactive drug ingredients listed; Safe for use up to 35.9% in leave on CIR 2019
Stearyl alcohol	67762270	Co-emulsifier	2.5	SU-E-101413-73 SU-E-101413-74	2DMT128M1S	Safe up to 50%, CIR 1985; USP43-NF38 - 6072
Acrylates/C10-30 Alkyl Acrylate Crosspolymer	9007-20-9	Film Former	0.10	SU-E-101413-73 SU-E-101413-74	59TL3WG5CO	Safe up to 25%, CIR 2018
Phenoxyethanol, Ethylhexylglycerin	122-99-6 70445-33-9	Preservative	1.0	SU-E-101413-73 SU-E-101413-74	HIE492ZZ3T 147D247K3P	Safe up to 1% CIR 2013; FDA Inactive drug ingredients listed; USP43-NF38 - 5925
Phenethyl Benzoate	94-47-3	Emollient	5.0	SU-E-101413-70 SU-E-101413-73 SU-E-101413-74	0C143929GK	GRAS listed at 21 CFR 172.515 as synthetic flavoring substances and adjuvants, FDA Food Substances; no hazard classifications, ECHA Dossier
Xanthan Gum	11138-66-2	Yield Polymer	0.15	SU-E-101413-73 SU-E-101413-74	TTV12P4NEE	Safe up to 3 to 5%, CIR 2016 ; 2.85% max use in FDA drug ingredients listed; USP43-NF38 - 6103

Inactive Ingredient	CAS #	Function	Max. Conc. (w/w%)	Formulation Number Used in	UNII	Safety Reviews and Listings
Aqua	7732-18-5	Carrier	42.60	SU-E-101413-73 SU-E-101413-74	059QF0KO0R	USP43-NF38 - 6218
Aqua, Sodium Hydroxide	7732-18-5 1310-73-2	pH adjuster	0.15	SU-E-101413-73 SU-E-101413-74	059QF0KO0R 55X04QC32I	Safe up to 6.9%, CIR 2015; 3.2% max topical conc. in FDA drug inactive ingredients list; USP43-NF38 - 6018
Polyglyceryl-2 dipolyhydroxy-stearate	144470-58-6	Emulsifier	4.00	SU-E-101413-74	9229XJ4V12	Slight eye irritant; weak skin sensitizer at 10% to G. pig; 10% was compatible on human skin in vivo. Not classified as hazardous. NICNAS 2000
Hydrogenated castor oil	8001-79-4	Thickener-oil phase	1.50	SU-E-101413-74	D5340Y2I9G	FDA Inactive Ingredient for Approved Drug Products, 20% for IV injection, topical 1.9%. FDA Inactive drug ingredients listed, MSDS and CoA, USP43-NF38 - 5691
Polyglyceryl-3 diisostearate	66082-42-6	Emulsifier	2.00	SU-E-101413-74	46P231IQV8	Leave-on safe use up to 39% (lipcare) CIR 2016; USP/NF listed, USP43-NF38 - 5948
Microcristallina cera (Microcrystalline wax)	63231-60-7 / 64742-42-3	Thickener-oil phase	1.50	SU-E-101413-74	XOF597Q3KY	30% in topical ointments, FDA Inactive drug ingredients listed, USP43-NF38 - 6101
Magnesium stearate	557-04-0	Thickener-oil phase	0.50	SU-E-101413-74	70097M6I30	Safe in leave-on up to 10% CIR 2019; USP43-NF38 - 5864
Magnesium sulfate	10034-99-8	Bulking agent	1.00	SU-E-101413-74	DE08037SAB	Safe in leave-on up to 11% CIR 2018; USP43-NF38 - 2726
Vaselinum album (Petrolatum)	8009-03-8	Dispersant	100	SU E 101413 82 SU E 101413 83	4T6H12BN9U	Listed for topical use: Inactive Ingredient Search for Approved Drug Products (fda.gov)

Inactive Ingredient	CAS #	Function	Max. Conc. (w/w%)	Formulation Number Used in	UNII	Safety Reviews and Listings
						Max. Daily safe Exposure: cream: 4.2g, ointment: 5.99g. Daily use of 0.2 g in Clinical Safety tests is safe.

2.2.4 Compositions of Dosage Forms to be Used

The composition of the dosage forms to be used in each study are provided below.

2.2.4.1 MUsT Pivotal Dosage Forms

Table 2. Part 2 (Pivotal) Sunscreen Oil with 10% Ethanol as Skin Penetration Enhancer (SU-E-101413-85) with 6% Bemotrizinol (PARSOL® Shield)

Component Chemical/ USAN /INCI Name	Component Trade Name	Function	CAS #	UNII	Conc. (w/w%)
					(b) (4)

Table 3. Part 2 (Pivotal) Oil-in-water (O/W) emulsion (SU-E-101413-87) with 6% Bemotrizinol (PARSOL® Shield) and AMPHISOL® K

Component Chemical / USAN / INCI Name	Component Trade Name	Function	CAS #	UNII	Conc. (w/w%)
[redacted]					(b) (4)

Table 4. Part 2 (Pivotal) Water-in-oil (W/O) cream emulsion (SU E 101413-89)

Component Chemical / USAN / INCI Name	Component Trade Name	Function	CAS #	UNII	Conc. (w/w%)
					(b) (4)

2.2.4.2 Photoallergy Study (DSM PA 2020) Formulation

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 penetrationenhancer	Sunscreen oil vehiclewith 10% ethanol as penetration enhancerwithout BEMT	Dispersion of 6% BEMT (PARSOL® Shield) in petrolatum
					(b) (4)
Total:			**100.0**	**100.0**	**100.0**

2.2.4.3 Photoxicity Study (DSM PT 2020) Formulation

Phase	trade name	INCI	SU E 101413 85	SU E 101413 91	SU E 101413 82	SU E 101413 83
			Sunscreen oil with 6% BEMT (PARSOL® Shield) and 10% ethanol as penetrationenhancer	Sunscreen oil vehicle with 10% ethanol as penetration enhancer without BEMT	Dispersion of 6% BEMT (PARSOL® Shield) in petrolatum	Petrolatum
[redacted] (b) (4)						
Total:			**100.0**	**100.0**	**100.0**	**100.0**

2.2.4.4 Human Repeated Insult Patch Test (HRIPT) and Cumulative Irritation Test (DSM RIPT 2020) Formulations

Phase	Trade Name	INCI	SU E 101413 85	SU E 101413 91	SU E 101413 82	SU E 101413 83
			Sunscreen oil with6% 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	Petrolatum
(b) (4)						
Total:			**100.0**	**100.0**	**100.0**	**100.0**

2.2.5 Instructions for the Storage and Handling of the Dosage Forms

2.2.5.1 MUsT Pivotal BEMT-001 Part 2

The test product dosage formulation will be packaged and labeled in bulk form into 5.0 L HDPE bottles with a wide neck opening. The dosage forms should be stored at room temperature conditions (4°C – 50°C) as indicated on the bulk container label. The product will be dispensed on the day of application directly from the bulk container into the containers from which it will be dispensed to the subjects.

The Pharmacy Unit will dispense the investigational dosage form via weigh boats, beakers or syringes, depending on the product. In Part 2 the cream will involve the use of weigh boats, syringes will be weighed before and after application. Each weigh boat, beaker or syringe to be used will be labeled by the Pharmacy with bar-coded labels. The labels will include the protocol number, the subject number, day and timepoint and a barcode which links all of these data points into the study database. Copies of the bulk drug draft labels, together with the labels to be used by the Pharmacy for dispensing the investigational dosage forms are provided in Appendix 1.

2.2.5.2 Dermal Safety Tests

The test product dosage formulation will be packaged and labeled in bulk form into appropriate HDPE bottles with a wide neck opening. Following test material volumes will be separately filled for each test formulation:

- RIPT/Cumulative Irritation: 2 L
- PT: 250 mL
- PA: 1 L

The dosage forms should be stored at room temperature conditions (4°C – 50°C) as indicated on the bulk container label. The product will be dispensed – on the day of application – directly from the bulk container to the containers from which it will be dispensed to the subjects.

Copies of the bulk drug draft labels, together with the labels to be used by the Pharmacy for dispensing the investigational dosage forms are provided in Appendix 1.

3 BEMT NONCLINICAL STUDIES

Summarized in the following sections are information and results from the non-clinical and clinical testing of bemotrizinol (BEMT) as recently conducted under this IND or from legacy studies taken from a publicly available Time and Extent document and the associated clinical and non-clinical study reports submitted to the US FDA Docket no 2005-N-0453 (CIBA 2000).

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, indicated the following about BEMT:

- no adverse effects from maximal single oral and topical applications,
- absence of genotoxic effects with or without UV irradiation,
- it is not a photoirritant topically and is not a skin contact sensitizer with or without UV irradiation,
- is not photocarcinogenic in mice and is photoprotective for UV-induced dermal carcinogenicity,
- did not reveal adverse effects in any aspect of the full developmental and reproductive cycle of rodents and rabbits,
- not interactive with any aspects of the endocrine system,
- no adverse effects or target organs revealed after subchronic or chronic dermal and oral dosing.

A series of recent in vitro study results for local tolerance by skin irritation and sensitization and bacterial mutagenicity sponsored by DSM did not reveal adverse effects or a predicted difference from the legacy test results. A recent nonclinical PK study in rats dosed at 1000 mg/kg/d once or daily for 20 days indicated maximum plasma BEMT concentrations of only about 3 ng/ml a concentration plateau around 1.5 ng/ml without an increasing and with a linear return to pre-dosing conditions. A single daily dose for a 5-d or 28-day oral gavage test up to 1500 mg/kg/d to mice indicated 14-d and 28-d BEMT systemic exposures below 10 ng/ml and an absence of adverse effects in any dose group.

These study results support concluding that the DSM form of BEMT (PARSOL Shield) is equivalent to the historical test substances that were considered as a USP grade drug substance.

Based on these *in silico* predictions and the *in vivo* results with bemotrizinol, it is concluded to be without concern for its absorption, accumulation systemically, or for biotransformation metabolically or by UV irradiation to metabolites or moieties of relevance for secondary effects of exposure to bemotrizinol.

3.1 Nonclinical pharmacology

Specific studies to assess nonclinical pharmacological effects of bemotrizinol have not been conducted. Bemotrizinol is intended for topical application as a UV light absorber from which pharmacological action or effects are not an intended effect of the substance. The completed non-clinical toxicity studies did not reveal outcomes indicative of any pharmacological effects.

3.2 Pharmacokinetics and product metabolism in animals

3.2.1 In Vitro Percutaneous Permeation Test (IVPT) with Human Skin Membranes

A first IVPT was performed under GLP and following OECD Guideline no. 428 (2004) with consideration of the Guidance Notes on Dermal Absorption No. 156 from OECD (2011) and determined the in-vitro dermal absorption of [14C]-bemotrizinol in five different cosmetic formulations, each at a concentration of 6% (w/w) BEMT applied on human skin membranes. The primary use of the results is selection of the dosing formulations to use in the human Maximum Usage Trial (MUsT). The five sunscreen formulations included 2 oil-based sprays, with and without 10% alcohol, 2 oil-in-water emulsions without and with a penetration enhancer, and a water-in-oil cream emulsion, each applied at nominal 2 mg/ cm^2 of skin to groups of flow-through diffusion cells exposed for 24h.

Penetration of radiolabeled test item through the membranes was below the limit of quantification (LOQ; 0.1%) in all groups throughout the exposure period so the cumulative LOQ values were used as a worst-case penetration amount; a flux rate could not be estimated. The total skin permeation results were 1.35 % and 0.85 % for the oil formulations (A1 and A2, respectively), 0.34 % and 1.07 % for the oil in water emulsions (Formulations A3 and A4, respectively), and 0.67 % for the water in oil emulsion (Formulation A5). The overall total absorbed dose by dermal permeation of BEMT did not differentiate the formulations tested and was 0.34-1.35 % of the applied dose. The oil formulation (A1) without alcohol was at a maximum of 1.35 $\pm$ 0.7% of applied dose amongst all tested formulas. (Hassler 2019).

Upon FDA recommendation, a second IVPT (Project No. BASF Study 10B0377/21B110) 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 0.08% to 0.57% of applied dose, which is below the skin permeation seen in the first IVPT study formulations (0.34 to 1.34% of applied dose).

However, to rule out any possibility of butyloctyl salicylate influencing the dermal penetration/absorption of BEMT, butyloctyl salicylate was removed from all formulations to be used in the pivotal MUsT. Three arms will be used for the pivotal MUsT, one arm for each of the 3 different formulation types used in the IVPT: the sunscreen oil with penetration enhancer, the oil-in-water (O/W) emulsion, and the water-in-oil (W/O) cream. The O/W emulsion containing skin penetration enhancer did not show a measurable increase in skin permeation of BEMT under the IVPT conditions. Most relevant to market formulations and maximizing exposure from absorbed dose is the sunscreen oil formulation plus ethanol as skin penetration enhancer expected to represent a likely “worst case” potential for percutaneous permeation of BEMT as indicated by results of the IVPT.

3.2.2 In vitro percutaneous permeation study with 6% BEMT in a Cosmetic Oil formulation applied to rat skin membranes

The in vitro percutaneous permeation study with rat skin membranes showed rat skin as 6-times more permeable to BEMT than was human skin membranes under the same test paradigm. This differentiation is relevant to the assessment of rat plasma concentrations observed in the 2-year dermal carcinogenicity study with rats, their comparison to the plasma concentrations in the chronic dermal minipig study, and their interpretation in reference to the requested additional systemic carcinogenicity study.

3.2.3 In-silico Evaluation for Metabolism and Metabolites

An *in-silico* evaluation of bemotrizinol with Meteor Nexus, a software tool for estimation of metabolism or metabolic products by recognized physiological pathways (Lhasa Ltd., Meteor Nexus: 3.1.0, Nexus: 2.2.1), was run under both “plausible” outcomes, the lowest constraints on expectations, and the higher confidence expectations termed “probable” outcomes. The principal biotransformation products resulted mainly from phase I processes of oxidative demethylation, hydroxylation of terminal alkyl groups, and phase II processes, mainly glucuronidation of aromatic alcohols. Neither of these constraint conditions suggested that biotransformation to moieties or metabolites of concern should be expected.

In vivo dosing of rats by either oral or dermal application have been conducted and by both routes of exposure revealed only very low absorption, no accumulation and rapid and complete elimination as the unchanged parent molecule. Study details are presented in the next summaries.

3.2.4 In vivo Single Oral Dosing ADME

The oral bioavailability of BEMT was evaluated in a GLP-compliant study following OECD TG 417. Groups of 4 male and 4 female rats were each given a single oral dose of 50 mg [^{14}C]-bemotrizinol /kg to investigate systemic exposure, tissue distribution and metabolite profiles and excretion. An additional group of 9 male and 9 female rats were each given a single oral dose of 50 mg [^{14}C]-bemotrizinol/kg and samples taken for a time course kinetics in blood and plasma over 24-hour after dosing.

After the single oral dose of radio-labeled test article, excretion was rapid and extensive in both male and female rats. Urinary excretion accounted for mean totals of 0.1 % and 0.2% of the dose and fecal excretion accounted for mean totals of 94% and 97% of the dose for males and females, respectively. The only component found in the fecal extracts was identified as parent bemotrizinol and represented 100% of the dose excreted in feces of all rats. Residues in tissues accounted for <0.01 % of the dose in total in both males and females and were not associated with any specific tissues. The radioactivity remaining in the residual carcass accounted for 0.3% of the dose for males and 0.1% for females.

The total recoveries of administered radioactivity were approximately 95% for males and 97% for females. The concentration of radioactivity in blood and plasma was below the limit of detection at all time points up to 24 hours after dosing. The mean limits of

detection were <0.038 µg/g and <0.019 µg/g in blood and plasma, respectively. Following a single oral dose the absorption of [^{14}C]-bemotrizinol was very low and the substance is considered as not orally bioavailable after single oral dose (Silcock 2002a).

3.2.5 In vivo pharmacokinetics after 21-day oral gavage dosing

In a GLP compliant study, three groups of Wistar Han rats received BEMT, referred to as DNP-038124, in PEG 400 by oral gavage (10 mL/kg body wt.) in a single dose or in successive daily doses on each of 20 days, with the objective to demonstrate the BEMT systemic pharmacokinetic parameters at the 1000 mg/kg bwt/day, which is the NOAEL for key legacy studies with BEMT.

A single oral gavage dose with 1000 mg/kg/day did not result in quantifiable BEMT plasma concentrations at any of the collection times, all were BLQ, except one sample at the 30h (0.506 ng/ml) and two samples at the 48h sample time (0.579, 0.572 ng/ml.

A second group of 8 rats dosed at 1000 mg/kg by oral gavage once daily on each of 20 consecutive days showed plasma mean concentrations in a narrow range of 1.72 ng/mL to 2.81 ng/mL over 48 hours following the last administration of BEMT. A clear relationship between concentration and time of collection was not found and the mean plasma concentrations and C_{max} were each about 2.8 ng/mL. Unscheduled observations of the animals at blood sampling days were of soft feces noted on 9 of the 10 sampling days.

A third group of four male rats each received a daily oral dose of BEMT at 1000 mg/kg/day for 20 days with plasma sample collection at 24 hours after doses on days 1, 2, 4, 7, 10, 14, 18, and 20. Unscheduled observations of these animals at blood sampling days showed soft feces on 9 of the 11 sampling days and on day 17, “wet red material around mouth” for one animal of the group. The plasma concentration of BEMT appeared to increase to a BEMT maximum concentration of approximately 1.45 ng/mL 24 hours after the last dose, could be quantified in plasma for at least 168 hours (7 days), and showed a linear concentration decrease to below 0.5 ng/ml by 264 hours after the last dose.

Rat whole blood samples were also taken at terminal sampling times in each study group and analyzed for their BEMT concentrations. These whole blood sample results were consistent with those results from plasma analysis thereby indicating plasma is fully representative for systemic concentrations of BEMT in these studies.

It was concluded that the systemic availability of BEMT was not quantifiable after a single oral gavage dose at 1000 mg/kg bwt/day; after 20 days of single daily doses rat plasma reached maximum concentrations of only about 3 ng/ml with a plateau around 1.5 ng/mL but without an increasing trend; BEMT remained quantifiable (0.55 ng/ml) until 168 hours (7 days) after a 20-day dosing period suggesting a slow elimination phase; a very limited systemic bioavailability and a linear return to pre-dosing conditions were seen in the rat after repeated dosing with a NOAEL dosage.

3.2.6 In vivo Single Dermal Dosing ADME

The dermal bioavailability of BEMT was evaluated in a GLP-compliant study following OECD TG 427. A representative sunscreen formulation, containing 4% bemotrizinol, was by dermal dosing used to investigate dermal absorption of labelled test article applied at 2 different dose volumes to the male rat. Either 50 µl or 20 µl of each formulated dose was applied to 10 cm^2 of shaved skin per rat, corresponding to doses of 2 mg and 0.8 mg bemotrizinol per rat. These applications were designed to simulate potential human dermal exposure to the formulation during normal use.

After dermal exposure to 2 mg [^{14}C]- bemotrizinol formulation for 6-hours, a mean of about 90% of the applied radioactivity was washed from the skin surface using soap solution and water. About 2.0% of the dose remained associated with the application site following the 6-hour skin-wash and some of this was available for absorption. The residue associated with the application site declined slightly at later time-points. The amount of dose absorbed was 0.2% after 6- and 24-hours. The absorbed dose was not associated with any specific tissues.

After dermal exposure to 0.8 mg [^{14}C]-bemotrizinol formulation for 6-hours, a mean of approximately 96% of the applied radioactivity was washed from the skin surface using soap solution and water. About 2.1 % of the dose remained associated with the application site and some of this was available for absorption. The residue associated with the application site declined slightly at later time-points and the amount of dose absorbed after 6 and 24 hours was 0.1% - 0.4%. The absorbed dose was not associated with any specific tissues. The study results indicated that dermal absorption of bemotrizinol was very low and the substance is not readily bioavailable after dermal application. (Silcock 2002b)

3.2.7 Absorption with Chronic Topical Dosing

Prolonged (39 weeks) dermal dosing of minipigs with maximum achievable doses of bemotrizinol suspended in PEG 400 vehicle was GLP-compliant and followed a standard test guidance of European Agency for Evaluation of Medicinal Products. Three groups of four male and four female Göttingen minipigs received once daily cutaneous application of the test article suspended in the vehicle (PEG 400) at constant dose volume of 2.5 mL/kg body weight/day on closely clipped dorsal skin. The dose-levels used were 250, 500 and 1250 mg bemotrizinol /kg body wt/day and the treatments were continued for 39 weeks. The high dose of 1250 mg/kg/day was the highest technically achievable dose based on the physical characteristics (viscosity, density, rheology) of test article in the PEG 400 vehicle that allowed accurate and reproducible preparation and application of the dosages. A control group of four males and four females received the PEG 400 vehicle during the dosing period.

Results of each of the standard study parameters for dosed animals were not different from the control group animals and macroscopic and microscopic observations did not indicate any test item related changes. Plasma concentrations of bemotrizinol in samples at weeks 13 and 26 and before terminal sacrifice were detected but did not show a clear

relationship to dose level or duration of dosing. The repeated topical application of high doses of bemotrizinol did not induce a consistent or clear systemic exposure concentration and the absence of systemic or local topical adverse effects or target organs could not be associated with the test item dosages. A NOEL of 1250 mg/kg body wt/day is indicated in this pivotal non-clinical test. (Haag 2006)

3.2.8 Conclusions

Based on the *in-silico* predictions and the *in vivo* results with bemotrizinol as summarized above, the substance did not show meaningful systemic exposure via absorption, accumulation was not indicated, and biotransformation to metabolites or moieties of relevance for secondary effects of exposure to bemotrizinol are not indicated.

3.3 Non-clinical Toxicology Testing

In the following summary table are details of the additional legacy tests and results as available from records in the FDA Docket No 2005-N-0453.

Results Summary for Legacy Studies in FDA Docket No 2005-N-0453 with Test Article Bemotrizinol (BEMT)								
Type of Study	Species and Strain	Method of Dosing	Duration of Dosing	Doses (a.i. = BEMT)	With GLP	Results / Findings	Laboratory Study No.	Report Location
Single Dose Toxicity								
Acute Dermal Toxicity	Rat, Wistar	Dermal, semi-occlusive	1 day	2000 mg/kg at 4 ml/kg body weight	yes	LD_{50} >2000 mg/kg	RCC No. 651420, 1997	
Acute Oral Toxicity	Rat, Wistar	oral, gavage	1 day	2000 mg/kg at 10 ml/kg body weight	yes	LD_{50} >2000 mg/kg	RCC No. 651407, 1997	
Repeat Dose Toxicity								
14-Day Oral Gavage Dose Range Finding	Rat, Wistar	oral, gavage	14 days	0 (PEG 400) 50, 200, 800 or 2000 mg/kg at10 ml/kg body weight	no	Test item related effects did not occur in any group	RCC No. 667530, 1998	
13-Week Oral Gavage	Rat, Wistar	oral, gavage	90 days	0 (PEG 400), 100, 500, 1000 mg/kg	yes	Seven deaths, not test item related, during the study. Gamma globulin fraction decreased 21-22% in high dose males and 30% in high dose females. Urinalysis showed increased output and decreased specific gravity in high dose males	RCC No. 667541, 1998	

Results Summary for Legacy Studies in FDA Docket No 2005-N-0453 with Test Article Bemotrizinol (BEMT)								
Type of Study	Species and Strain	Method of Dosing	Duration of Dosing	Doses (a.i. = BEMT)	With GLP	Results / Findings	Laboratory Study No.	Report Location
						and in mid and high dose females. **NOEL 1000 mg/kg/day**		
14-Day Dermal-Dose Range Finder	Rat, Wistar Han	Dermal, un-occluded	14 days	1000 at 2.5 ml/kg body wt/d; about 6 mg a.i./cm² daily	no; data under QAU audit	Mortality or test item-related effects did not occur during the study. Dermal scabs in 1 dosed male; cutaneous desquamation in 1control and most of the dosed females were observed.	CIT No. 25455 TSR, 2003	
13-Week Dermal	Rat, Wistar Han	Dermal, un-occluded	90 days	0 (PEG 400), 250, 500, 1000 mg/kg/d in 2.5 ml/kg bwt/d; approx. 1.5, 5, 6 mg a.i./cm² daily	yes	Each study parameter, including behavioral responses, estrous cycle and microscopic pathology changes, did not show dose or treatment-related effects. Plasma mean results for the two high dose groups were about 10 ng a.i./ml or less, most results were below 2 ng/ml (LOQ). **NOAEL: 1000 mg/kg/day**.	CIT No. 25378 TCN, 2006	
39-Week-Dermal	Göttingen minipig	Dermal, un-occluded	9 months	0 (PEG 400), 100, 500, 1250 mg/kg/d as 10%, 20%, 50% a.i./day; 2.5 mL/kg body wt/d; approx. 7, 14, 35 mg a.i./cm²/day	yes	Up to highest achievable dosage, dose site without macro- and microscopic signs of test article intolerance or observable tumors. Systemic toxicity did not occur based on clinical signs,	CIT No. 25384 TCR, 2003	

Results Summary for Legacy Studies in FDA Docket No 2005-N-0453 with Test Article Bemotrizinol (BEMT)								
Type of Study	Species and Strain	Method of Dosing	Duration of Dosing	Doses (a.i. = BEMT)	With GLP	Results / Findings	Laboratory Study No.	Report Location
						hematology, clinical chemistry, ophthalmology endpoints. Plasma showed test item in all dose groups (LOQ = 2ng/ml), but at levels below 16 ng/ml (only 4 values exceeded 10ng/ml) and without relationship to sex, dose levels or weeks of exposure. **NOEL 1250 mg/kg/day**		
Genotoxicity								
Ames Mutation Assay	*Salmonella* TA98; TA100; TA 1535 & TA1537; *E. coli* WP2uvrA	BEMT in DMSO; plate incorporated and pre-incubation	1h incubation; 48h for plates	33, 100, 333, 1000, 2500 & 5000 µg/plate with and without rat-S9 mix	yes	Negative for base-pair and frame-shift mutations.	CCR No 582800, 1997 and 618300, 1998	
In vitro CHO Chromosome Aberration Assay	Chinese Hamster V79 cells	BEMT in acetone	4, 18, or 28 hours	Doses 3.3 up to 210 µg/ml with and without rat-S9 mix	yes	Structural chromosome aberrations or polyploidy did not occur	CCR No 597700, 1998	
In vivo Mouse Micronucleus Test	Mouse, Swiss Ico: OF1 (IOPS Caw)	Intraperitoneal injection	24 hours	0 (corn oil), 500, 1000, or 2000 mg/kg bwt	yes	Damage to chromosomes or mitotic apparatus of bone marrow cells did not occur	CIT No. 25608 MAS, 2003	

Results Summary for Legacy Studies in FDA Docket No 2005-N-0453 with Test Article Bemotrizinol (BEMT)								
Type of Study	Species and Strain	Method of Dosing	Duration of Dosing	Doses (a.i. = BEMT)	With GLP	Results / Findings	Laboratory Study No.	Report Location
In vivo Unscheduled DNA Synthesis Assay	Rat, Fischer	oral gavage	4 h or 16 h in vivo; hepatocytes in vitro	1000 or 2000 mg a.i./kg body wt.; Vehicle (0.5% w/v carboxymethyl-cellulose in distilled water)	yes	A proliferative effect in rat liver or genotoxic activity did not occur	Institute Pasteur de Lille Study No. FSR-IPL 040012, 2004	
Carcinogenicity								
Lifetime Carcinogenicity	Rat, Wistar Han	Dermal, unoccluded	104 weeks	0, 0 (PEG 400),100, 500 or 1000 mg/kg in 2.5 mL/kg body wt/day; about 1, 5 or 10 mg a.i./cm²/d	yes	At the highest technically achievable dosage survival was not adversely affected. Chronic moderate skin irritation expressed as topical scabs limited mainly to the mid- and high-dose-treated sites, and at higher incidence in males than females indicated the MTD was achieved; a related tumor response did not occur. Plasma analysis (LOQ 2 ng/ml) for BEMT showed similarly low concentrations across the groups. Neoplastic and non-neoplastic tumors occurred but their incidences were not related to the test item. **BEMT is not a dermal carcinogen in rats.**	CIT No. 25382 TCR, 2006	
Reproductive and Developmental Toxicity								

Results Summary for Legacy Studies in FDA Docket No 2005-N-0453 with Test Article Bemotrizinol (BEMT)								
Type of Study	Species and Strain	Method of Dosing	Duration of Dosing	Doses (a.i. = BEMT)	With GLP	Results / Findings	Laboratory Study No.	Report Location
Segment I- Fertility and Reproduction	Rat, Crj:CD® (SD)IGS SPF	Oral, gavage	Males- 53 days Females- 55 days max.	0 (PEG 400), 100, 300, or 1000 in 10mL/kg bw	yes	Test article-related effects did not occur in any parameter.	Hashima Laboratory No. 300721, 2002a	
Segment II - Developmental Oral Gavage	Rat, Wistar	Oral, gavage	Gestation day 6 thru 17	0 (PEG 400), 100, 300, 1000	yes	The observed changes in BEMT-treated vs control groups were not attributed to the test article or did not exceed the historical control ranges. **Maternal & Fetal NOAEL 1000 mg/kg/day**	RCC No. 681491, 1998	
Segment II Developmental Study	Rabbit, Hra:NZW	Oral, gavage	Gestation day 6 thru 19	0 (CMC-Tween 80), 100, 300, or 1000 at 10 ml/kg bw	yes	Test article related effects did not occur in any group. **NOAEL 1000 mg/kg/day**	Charles River No 203-014, 2005	
Segment III Reproduction	Rat, Crj:CD® (SD)IGS SPF)	Oral, gavage	Parent dams: gestation day 6 thru lactation day 20 d; F1 & F2 animals not dosed	0 (PEG 400), 100, 300, or 1000 at 10mL/kg bw	yes	Test article-related effects did not occur in any endpoint for material parameters or for pre- and post-natal development parameters. **NOEAL 1000 mg/kg/day**	Hashima Laboratory No. 300721, 2002b	
Local tolerance								

Results Summary for Legacy Studies in FDA Docket No 2005-N-0453 with Test Article Bemotrizinol (BEMT)								
Type of Study	Species and Strain	Method of Dosing	Duration of Dosing	Doses (a.i. = BEMT)	With GLP	Results / Findings	Laboratory Study No.	Report Location
Skin Irritation	Rabbit, New Zealand White	semi-occlusive	4 hours	0.5 g test article; moistened, bi-distilled water to 6cm² per rabbit	yes	Not irritant	RCC No 651431, 1997	
Eye Irritation	Rabbit, New Zealand White	instilled, not rinsed	72 hours	0.1 g test article	yes	Not irritant	RCC No 651442, 1997	
Dermal Sensitization	Guinea pig, Himalayan Spotted	Intradermal; Topical, occlusive patch	7 + 1 day; 1 day	3% (w/v) in PEG 400; 30% BEMT to 4 cm² topical induction & challenge (50 mg a.i./cm²)	yes	Not a skin contact sensitizer	RCC No 651453, 1997	
Endocrine Effect Testing								
Estrogen Receptor Competitive Binding Assay	Rat, Alpk: APfSD (Wistar) immature uteri cytosol	co-incubation in vitro	17 hours	Ten-fold dilution steps: $5x10^{-10}$ to $5x10^{-4}$ Molar	no	Binding affinity or competitive inhibition to binding did not occur.	CTL Study No. 024529, 2001	
Androgen Receptor Competitive Binding Assay	Rat, Alpk: APfSD (Wistar) immature prostate cytosol	co-incubation in vitro	17 hours	Ten-fold dilution steps: $5x10^{-10}$ to $5x10^{-4}$ Molar	no	Binding affinity or competitive inhibition to binding did not occur.	CTL Study No. 024530, 2001	
Uterotrophic Assay	Rat, Alpk: APfSD (Wistar) immature	subcutaneous injection	3 days	0 (arachis oil), 250, 500, 1000 mg/kg body wt/day	no	Estrogenic effects or inhibition of uterine maturation did not occur	CTL Study No. ZR1601, 2002	
Other Toxicity Studies: Photosafety testing								

Results Summary for Legacy Studies in FDA Docket No 2005-N-0453 with Test Article Bemotrizinol (BEMT)								
Type of Study	Species and Strain	Method of Dosing	Duration of Dosing	Doses (a.i. = BEMT)	With GLP	Results / Findings	Laboratory Study No.	Report Location
Photomutagenicity Ames Assay	*S. typhimurium* TA 102 and *E. coli* WP2	Irradiation, 10 or 40 seconds	UV B/A at 4/80 mJ/cm² for TA102; 1/20 mJ/cm² for WP2	33, 100, 333, 1000, 2500 & 5000 µg/plate	yes	Not a photomutagenic effector	RCC-CCR Nos. 704428 and 689354, 1998	
Photogenotoxicity: Chromosomal Aberration Assay	Chinese Hamster V79 cells	Irradiation:	UV B/A at 200/22 or 300/33 mJ/cm²	6.25, 12.5, 25.0, 100.0 µg/ml	yes	Not a photoclastogenic effector	RCC-CCR No 615904, 1998	
Phototoxicity	Guinea pig, Dunkin Hartley albino	Skin sites pretreated with DMSO; Topically applied by spatula; Irradiation UVA 20 J/cm²	30 minutes + irradiation time	0 (PEG 400), 10, 15, 25 and 30%.	yes	Not phototoxic	RCC No 651475, 1997	
Photoallergenicity	Guinea pig, Dunkin Hartley albino	Irradiation; Intradermal, Topically via spatula	Induction: 1.8 J/cm² UV-B + 10 J/cm² UV-A. Challenge: 10 J/cm² UV-A	Induction: 0.1 ml 30% a.i. in PEG 400 intradermally; then 4 topically by 0.0125 ml/cm² of 10, 15, 25, and 30%; Challenge at same doses	yes	Not a photoallergenic effector	RCC No 651497, 1997	

Results Summary for Legacy Studies in FDA Docket No 2005-N-0453 with Test Article Bemotrizinol (BEMT)								
Type of Study	Species and Strain	Method of Dosing	Duration of Dosing	Doses (a.i. = BEMT)	With GLP	Results / Findings	Laboratory Study No.	Report Location
13-week Dermal Phototoxicity (Dose Range Study)	Mice, Hairless Crl:SKH1-hrBR	BEMT in 'hydrated, hydrophilic Base Ointment' to 25 cm^2 skin once, before or after daily Irradiation	13 weeks, 5 days / week 600 or 1200 RBU	Dosed as % a.i./d: 2.5, 5.0, 10, or 20 in 100 µl/mouse once daily at 0.1, 0.2, 0.4, or 0.8 mg a.i./cm^2 skin, respectively.	yes	All dosages and exposures were without adverse effects.	CRL No 203-006, 2003	
12-Month Dermal Photocarcinogenicity	Mice, Hairless Crl:SKH1-hrBR	BEMT in 'hydrated, hydrophilic Base Ointment' to 25 cm^2 skin once, before or after daily Irradiation	40 weeks, 5 days / week 600 or 1200 RBU	0, vehicle, 50 mg (5%) ai at 0.1 mg/cm^2, or 200 mg (20%) a.i. /g formulation. at 0.8 mg/cm^2/UV radiation at 600 or 1200 RBU	yes	The photocarcinogenic response was delayed by BEMT, showing a protective effective against photo-co-carcinogenesis.	CRL No 203-006, 2005	

DSM-Sponsored In vitro and In vivo Studies with Bemotrizinol (a.i., BEMT)								
Type of Study	Species and Strain	Method of Dosing	Duration of Dosing	Doses (a.i. = BEMT)	With GLP	Results / Findings	Study No.	Report Location
Local tolerance studies								
Skin irritation	Human skin model EPISKIN-SM™	a.i. applied to pre-moistened tissue directly	15 min	About 10 mg	yes	Mean tissue viability 92% vs control; Positive control (SDS) mean viability 27%; BEMT did not cause color interference. Not irritant	WIL Study 512975, 2016	
Direct Peptide Reactivity Assay	Synthetic peptides containing cysteine (SPCC) or lysine (SPCL)	direct volume addition to peptide solutions	24 hours	50 µl or 250µl of a.i. 100 mM stock solution (104.1 mg a.i. in 1658 µl acetone) with SPCC or SPCL, respectively	yes	Percent SPCC depletion for BEMT was 0.6% ± 1.1% in cysteine assay. Lysine assay was rejected. BEMT was not reactive but at reduced reliability.	CRL Study 517122, 2017	
Skin sensitization potential	KeratinoSens™ assay: ARE-Nrf2 luciferase reporter assay	50 µl of a.i. suspension on 10,000 cells/ well	48 hours	25 mM a.i. suspension in DMSO; a.i. dosed at 0.12-250 µM (2-fold dilution steps)	yes	Interpretable luminescence data were obtained as cell viability was >70% at all doses (97-116%). No luciferase induction of >1.5-fold was observed at any of the doses up to 250 µM; solubility limits were <1000 µM. Guideline not met for conclusive result.	WIL Study 512976, 2016	
Mutagenicity								

Bacteria reverse mutation assay	Salmonella typhimurium (TA1535, TA1537, TA98 and TA100) & E. coli (WP2uvrA)	Admix with top agar	48 hours	1st assay: 5.4 to 512 µg/plate ± 10% (v/v) S9-mix in all strains. 2nd assay: 87 to 878 µg/plate ± 10% (v/v) S9-mix in all strains.	yes	Not mutagenic with or without metabolic activation		
Repeat dose								
5-day and 28-day oral gavage	CByB6F1 Hybrid (non-transgenic littermate) mice	oral gavage; BEMT suspension in PEG 400	Once daily consecutively for 5-days & then 28 days	5-d: 0, 500, 750, 1000, 1500 mg/kg/d (10 mL/kg body wt) 28-d: 0, 500, 1000, 1500	yes	5d: no adverse effects in any group 28d: no adverse effects in any group; adrenal gland wt significant increase but not related to BEMT; Plasma BEMT exposures below 10 ng/ml were not dose, time or sex-related	Charles River Labs Study 20209876, 2021	

3.3.1 Conclusions for Safe Use in the proposed human studies

From completed nonclinical safety testing results, BEMT up to 10% has been shown to be safe for use in human topically applied products for all age groups. Based on physical-chemical characteristics of the bemotrizinol molecule that can limit the reliable preparation of useful formulations, the current recommended use concentration is 6% BEMT for use in topically applied products. At this lower concentration each of the summarized studies and conclusions remain relevant and applicable to this safety assessment.

A safety assessment of 6% BEMT used in human topically applied products was conducted and is summarized below using a margin of safety (MOS) calculation for the estimated human exposures compared to the hazard indications from non-clinical testing. The NOAEL of 1000 mg/kg/d is based on the outcome of a series of oral gavage tests in rats and is used in the MOS calculation shown in Table 2, which is the comparison of exposures from usual daily uses of sunscreen products versus that from the FDA-specified amounts to be used in the MUsT protocol. This type of test, referred to as a maximal use PK (pharmacokinetic) trial, is designed to demonstrate the in vivo bioavailability of a topically applied pharmaceutical ingredient when used at a maximal exposure (FDA 2019). As shown, the MUsT exposures to BEMT are about 6 times higher than that from the usual daily sunscreen use.

Considering that a MOS of 100 indicates proposed human exposures are safely above any indicated hazards reported in non-clinical testing, application of 6% BEMT in either a usual daily sunscreen usage or in the MUsT protocol is 10 to 5 times above the safety threshold. The much lower dose concentrations (0.15 to .02 g) to be used in the human clinical dermal safety protocols discussed above are clearly within the estimated safety margins.

Table 2. Margin of Safety Calculation for 6% BEMT

Margin of Safety Calculation for 6% BEMT in Usual Daily Use in Finished Sunscreens vs. MUsT FDA design

Parameter	**Usual Daily Sunscreen Use (EU SCCS[a])**	**MUsT FDA Protocol [b] (FDA 2019)**
Body weight (B)	60 kg	60 kg
Formulation applied/day (A)	18 g	105 g
Skin surface area treated (C)	17,500 cm^2	13,125 cm^2
Total BEMT applied (6%A) = (D)	1080 mg/d	6300 mg/d
Skin absorption [c] (R)	0.36% of applied	0.36%
Skin area dosage (D/C)	0.062 mg a.i./cm^2	0.48 mg a.i./cm^2
Systemic daily exposure (D x R)	5.72 mg a.i.	33.39 mg a.i.
Systemic daily dosage (DxR)/B	0.0954 mg/kg bwt.	0.556mg/kg bwt.
Margin of Safety [d]	**10,482**	**556**

a. *European Union, Scientific Committee on Consumer Safety, Notes of Guidance 2018.*
b. *Formulation applied 4x daily at 2 mg/cm^2 on 75% skin surface area: a.i.= BEMT*
c. *From the in vitro human skin permeation test; mean (0.19) +SD (0.17) (BASF 10B0377-21B110, 2022).*
d. *[Rat oral 1000 mg/kg/d] ÷ [Human systemic daily dose].*

In the MUsT protocol and in the dermal safety studies, the BEMT active ingredient is expected to be without concern for its safe use in the planned clinical studies.

4 EFFECTS ON HUMANS

Clinical safety testing of BEMT in two short studies, previously submitted to FDA under a time and extent application (TEA), with relatively small panels of volunteers did not demonstrate adverse events (AEs) related to the topical applications used to assess local tolerance for skin irritation and sensitization, without or with UV radiation exposures. The local tolerance of BEMT, without and with, UV irradiation of skin sites exposed to prospective sunscreen formulations can be without concerns for adverse effects.

Systemic metabolism is not expected, the molecule is photo-stable to high irradiance, pharmacologic effects have not been reported to have occurred and are not predicted by non-clinical test results, indicating BEMT is of very low concern for its clinical safety.

A 20-years' long history of global use of BEMT in consumer sunscreen-containing products has shown the active ingredient to have relatively few noticeable or reported concern for its skin tolerance, consumer avoidance, or regulatory authorities' concern for BEMT's continued safety or for limiting its market availability to use in consumer products.

Potential adverse effects could include signs for local skin irritation or cumulative intolerance, although such events have not been reported to date. Compromised or ectopic skin may exhibit signs of intolerance or allergenic reactions as indicated by the only published case report associated with BEMT in a sunscreen formulation (Luna-Bastante et al. 2019).

A Margin of Safety of 346 is estimated for the MUsT design's exceptionally high daily exposures and indicates acceptable risk for human subjects

4.1 Pharmacokinetics and product metabolism in humans

Bemotrizinol has been used in one recent controlled clinical study to evaluate pharmacokinetics (PK), systemic distribution or metabolism, which is a pilot phase (Part 1) MUsT protocol and will be followed by Part 2 as supported by this IB.

A single clinical study with the ultraviolet filter Bemotrizinol (BEMT) is being conducted in 2 parts (Part 1: pilot study; Part 2: pivotal study) to evaluate the clinical pharmacokinetics in a Topical Maximum Usage Trial (MUsT). Only Part 1 is completed and presented here. There was no evidence of BEMT accumulation or steady-state BEMT concentrations above 0.5 ng/mL. Part 1 was an open-label, 1-arm study in 14 healthy

adult subjects with the following objectives: Primary objective was to explore whether the active component, bemotrizinol (BEMT), was absorbed from a high-penetrating sunscreen formulation including 6% BEMT into the systemic circulation when applied under maximal-use conditions. Secondary objective was to obtain information needed for a successful pivotal study such as preliminary pharmacokinetic (PK) data, validation of study and analytical procedures, and the number of subjects needed.

Pharmacokinetics: Blood samples (N = 22 per subject) were collected for the determination of BEMT plasma concentrations at the following time points (within ±5 minutes from the nominal time while confined):

	Dosing (hour relative from first dose)	**Blood sampling (hour relative from first dose)**
Day 1	0, 2, 4, 6	–0.5, 2, 4, 8, 12
Day 2	24, 26, 28, 30	23.5, 28, 32
Day 3	48, 50, 52, 54	47.5, 52, 56
Day 4	72, 74, 76, 78 (last)	71.5, 74, 76, 78, 80, 82, 84, 86
Days 5, 8, and 12	–	96, 168 (±4), 264 (±4)

NOTE: When a time point corresponded with sunscreen application, the PK sample was collected before sunscreen application.

The PK parameters for plasma BEMT (i.e., C_{max}, T_{max}, C_{2h}, C_{trough}, $AUC_{0\text{-}24h}$, λ_z, C_{max}, and $t_{1/2}$) were selected based on an FDA guidance and published MUsT results (DHHS 2019, Matta et al 2019). The time interval for the overall PK parameters was 0 to 264 hours or, if the subject terminated early, the time of the last sample.

Absorption of BEMT after topical administration was very limited, with only 4.3% of the PK samples (13/299) having quantifiable concentrations equal to or higher than the lower limit of quantification (i.e., ≥0.5 ng/mL). Thirteen of the 14 subjects completed the PK sample collection; 1 subject (1010) discontinued on Day 4. Of the 299 samples analyzed, 13 (4.3%) were quantifiable, 9 (3.0%) were not reportable (NR; per the laboratory's standard operating procedure for lack of internal standard reproducibility after multiple assays), and the remainder (92.6%) were BLQ (i.e., <0.5 ng/mL) (Table 1). Systemic absorption of BEMT was limited: of the 14 subjects, 7 (50%) had no quantifiable concentrations, and the maximum number of quantifiable concentrations per subject was 1, 2, and 5 on Day 1, Day 4, and overall, respectively. All samples after 82 hours had BLQ concentrations.

Based on the completed non-clinical testing and a single human PK study in 12 subjects, a very low systemic uptake and only limited plasma concentrations and distribution are predicted for topically applied BEMT. If systemic uptake does occur during usual topical product use, as in the clinical safety studies, or as resulting from high exposures during the MUsT protocol, in silico models predict BEMT metabolism by the usual elimination phase 1 and phase 2 pathways and in vivo short-term animal studies suggest direct elimination of parent molecule without apparent accumulation.

4.2 Safety and Efficacy

Clinical controlled testing in two short studies with relatively small panels of volunteers did not demonstrate adverse events (AEs) related to the topical applications used to assess local tolerance for skin irritation and sensitization, without or with UV radiation exposures. Clinical pharmacokinetics and dynamics have not been determined with any completed controlled clinical trials. The local tolerance of BEMT, without and with, UV irradiation of skin sites exposed to prospective sunscreen formulations is expected to be without concern for using the high topical exposures required during a MUsT protocol.

Bemotrizinol efficacy as a UV light absorbing molecule has been demonstrated by in vitro test systems showing its stability under high UV irradiation and its effective skin protection potential by SPF (sun protection factor) testing. In vivo efficacy of BEMT has been substantiated with controlled clinical SPF testing and by standard clinical efficacy tests for UV protection from formulated sunscreen products containing BEMT.

4.2.1 Clinical Safety

4.2.1.1 Phototoxicity in Humans

Phototoxicity was assessed with a panel of 26 human volunteers given a single application of 10% bemotrizinol in an oil in water lotion and then irradiated with 16 J/cm^2 UVA and UVB at 0.75 times an individual's minimal erythema dose (MED). Only one adverse reaction was reported and was determined not to be related to BEMT treatment. On average, the irradiated test-material treated sites exhibited lower skin reactions than the irradiated sites for vehicle or saline applications. Phototoxic or skin irritation responses did not occur in any of the volunteers. (Parisse 1998a)

4.2.1.2 Photosensitization in Humans

Photosensitization potential of bemotrizinol was determined with a repeated insult patch test protocol using 33 human volunteers given twice-weekly applications of 10% bemotrizinol in an oil/water lotion and irradiation with two times the volunteer's MED for UVA and UVB during the 3-week induction phase. On study week 6, a 24-hr application of the challenge dose was followed by 16 J/cm^2 UVA and UVB at 0.75 times an individual's MED. On average, the irradiated test-material treated sites exhibited lower skin reactions than the irradiated sites for vehicle or saline applications. Photosensitization or sensitization responses did not occur in any of the volunteers. (Parisse 1998b)

4.2.1.3 Controlled Safety Testing with Formulated Sunscreen Products

A Time and Extent Application and a follow-up eligibility submission by CIBA Specialty Chemicals to US FDA (CIBA 2000), reported that 32 individual sunscreen formulations containing up to 7.5% BEMT and other UV filters (not disclosed) were tested in separate studies using a total of 1250 subjects given a single dose by patch application. Although mild skin irritation events related to treatment were reported, they could not be attributed to BEMT directly because other active UV filters were included in the treatments. Severe

adverse events or effects did not occur. (Docket FDA-2005-N-0453; Tab V.C.1.1a thru 1.19a)

4.2.1.3.1 Summary of Safety Information Obtained from BEMT-001 Pilot Study

Information obtained from the MUsT Part 1 Pilot study (BEMT-001) includes the following:

4.2.1.3.1.1 Adverse Events

There were no serious adverse events (SAEs) reported in the Pilot MUsT Study (BEMT-001). Overall, 8 of 14 subjects (57.1%) reported at least 1 TEAE in the pilot MUsT study (BEMT-001). Of these, 5 subjects (35.7%) reported TEAEs that were considered related to study drug. The most commonly reported TEAE was skin irritation (28.6% of subjects) followed by dry skin, increased lacrimation, and skin laceration (2 subjects each, 14.3%). All other TEAEs were reported by 1 subject (7.1%) each. The TEAEs considered related to study drug were skin irritation (4 subjects, 28.6%) and dry skin, erythema, pruritus, erythematous rash, urticaria, increased lacrimation, constipation, and rhinorrhea (1 subject each, 7.1%). Of the 8 subjects with TEAEs, 7 subjects (50.0%) reported TEAEs that were considered mild in severity and 1 subject (7.1%) reported TEAEs considered moderate in severity. One subject reported TEAEs of erythema and urticaria that were moderate in severity and led to discontinuation from the study (discussed later in this section). No severe TEAEs, serious AEs, or deaths were reported. All TEAEs resolved by the end of the study

An adverse event (AE) incidence table for the BEMT-001 Part 1 (pilot) study is presented in Table 3 below.

*Table 3 **AE Incidence Summary Associated with Pilot (Part 1) MUsT Study***

MedDRA System Organ Class Preferred Term	**Study BEMT - 001 (Pilot MUsT) BEMT 6% oil (N=14)**	**Severity**	**Relationship**
Number of AEs	36	30 – Mild 6 - Moderate	10 – Not Related 26 - Related
Skin and subcutaneous tissue disorders, n (%)	5 (35.7)	Mild	
• Skin irritation	4 (28.6)	Mild	Related
• Dry skin	2 (14.3)	Mild	1 Not related 1 Related
• Ecchymosis	1 (7.1)	Mild	Not related
• Erythema	1 (7.1)	Moderate	Related
• Pruritus	1 (7.1)	Mild	Related

MedDRA System Organ Class Preferred Term	Study BEMT - 001 (Pilot MUsT) BEMT 6% oil (N=14)	Severity	Relationship
• Rash erythematous	1 (7.1)	Mild	Related
• Urticaria	1 (7.1)	Moderate	Related
General disorders and administration site conditions, n (%)	3 (21.4)	Mild	3 Not related
• Fatigue	1 (7.1)	Mild	Not related
• Vessel puncture site bruise	1 (7.1)	Mild	Not related
• Vessel puncture site pain	1 (7.1)	Mild	Not related
Eye disorders, n (%)	2 (14.3)	Mild	
• Lacrimation increased	2 (14.3)	Mild	1 Not related 1 Related
Injury, poisoning and procedural complications, n (%)	2 (14.3)	Mild	Not related
• Skin laceration	2 (14.3)	Mild	Not related
Gastrointestinal disorders, n (%)	1 (7.1)	Mild	Not related
• Constipation	1 (7.1)	Mild	Not related
Nervous system disorders, n (%)	1 (7.1)	Mild	Not related
• Headache	1 (7.1)	Mild	Not related
Respiratory, thoracic and mediastinal disorders, n (%)	1 (7.1)	Mild	Related
• Rhinorrhea	1 (7.1)	Mild	Related

4.2.1.3.1.2 Subjects Who Dropped Out During the Course of the Part 1 Investigation in Association with Any Adverse Experience, Whether Or Not Thought To Be Drug Related

One subject (#1010) was dropped from the pilot MUsT due to treatment emergent adverse events (TREAs) of erythema and urticaria. Subject 1010 (58-year-old White female) received BEMT 6% oil topical application 4 times daily on Days 1 through 3. On Day 3, approximately 1 hour after the third application, the subject reported TEAEs of skin irritation of the lower back and abdomen that were considered mild in severity, probably related to study drug, and resolved within approximately 18 hours of onset. On Day 4, approximately 17 hours after the fourth application on Day 3, on physical examination, the subject was observed to have erythema and welts confluent on the abdomen and all 4 extremities, and approximately 2 hours later, the subject was observed to have skin irritation of the abdomen and lower back that were considered clinically significant. The events were documented as TEAEs of erythema of the upper arms, abdomen, and lower back and TEAEs of urticaria of the upper arms, lower back, and abdomen that were

considered moderate in severity and probably related to study drug. The TEAEs led to study drug withdrawal and study discontinuation on Day 4. The TEAE of erythema of the upper arms and the TEAE of urticaria of the upper arms resolved within 9 hours of onset. The TEAEs of erythema of the abdomen and lower back and TEAEs of urticaria of the abdomen and lower back resolved within 7 days of onset. Also, on Day 4, approximately 1 day after the last application, the subject reported a TEAE of dry skin of the upper arms that was considered mild in severity, probably related to study drug, and resolved within approximately 8 days of onset. The subject did not receive any treatment for the TEAEs of erythema, urticaria, or dry skin. In addition, the subject did not report any relevant medical history.

4.2.1.4 Publicly Reported Adverse Events

Bemotrizinol has been sold and used in commercial skin care products, including sunscreen formulations, since 2000 when it was approved by the European Commission as safe for use in sunscreens and cosmetic products. Subsequently, BEMT was found to be safe for use by Regulatory Agencies and Competent Authorities in markets of most other countries or regions, except in the United States where the demands and data requirements of the notification and approval process were prohibitive. In the various countries in which BEMT has been notified none have refused or rejected the registration and the product continues to be approved for use in commercial consumer products.

Being widely sold in global markets since 2000 has brought BEMT into regular use in topically applied consumer cosmetic and related sunscreen and skin care products. A recent (May 24, 2020) search of Australia's Therapeutic Goods Administration (TGA) Database of Adverse Event Notifications - medicines for the years 1999-2020 using bemotrizinol as the key search phrase showed that only 16 sunscreen medicines containing bemotrizinol, together with other sunscreen active ingredients, were submitted to the TGA database as case reports of a patient's signs or symptoms that were classified as MedDRA reaction terms or adverse events (see Appendix 2). Source: https://apps.tga.gov.au/PROD/DAEN/daen-report.aspx.

From the 16 medicines containing BEMT found in the database, there were about 40 adverse events identified where the case reporter considered there to be an association of the medicine to the adverse event; however, the TGA database interpretation guide cautions that the presence of an adverse event report does not mean that the medicine is the cause of the adverse event. Further, it should be noted that each patient presented in a case report may have experienced or demonstrated more than one reaction that is included in the total number of adverse events reported, so the total number of adverse events will be greater than the number of cases.

A summary of the events recorded for BEMT during the time period 1999-2020 are presented in Table 4. The adverse events were grouped together in the summary and one patient may have had multiple adverse events; thus, the range is 39-42 cases.

Table 4. Summary of TGA Adverse Event Notification Data for BEMT (Years 1999-2020). Source: https://apps.tga.gov.au/PROD/DAEN/daen-report.aspx

MedDRA system organ class[i]	MedDRA reaction term[ii]	Number of cases[iii]	Number of cases with a single suspected medicine[iv]	Number of cases where death was a reported outcome[v]
Injury, poisoning and procedural complications	Sunburn	20	20	0
General disorders and administration site conditions	Therapeutic product ineffective	13	13	0
General disorders and administration site conditions	Drug ineffective	7	7	0
Product issues	Product quality issue	6	6	0
Skin and subcutaneous tissue disorders	Rash	5	5	0
Skin and subcutaneous tissue disorders	Blister	5	5	0
Immune system disorders	Hypersensitivity	3	3	0
Skin and subcutaneous tissue disorders	Dermatitis contact	3	3	0
Skin and subcutaneous tissue disorders	Urticaria	2	2	0
Injury, poisoning and procedural complications	Burns second degree	1	1	0
Eye disorders	Eye pruritus	1	1	0
General disorders and administration site conditions	Pain	1	1	0
Nervous system disorders	Burning sensation	1	1	0
Skin and subcutaneous tissue disorders	Erythema	1	1	0
Eye disorders	Eye pain	1	1	0
Skin and subcutaneous tissue disorders	Acne cosmetica	1	1	0
Infections and infestations	Eyelid infection	1	1	0
Skin and subcutaneous tissue disorders	Pruritus	1	1	0
Skin and subcutaneous tissue disorders	Skin irritation	1	1	0
Skin and subcutaneous tissue disorders	Rash pruritic	1	1	0

A review of the listed reports for these 39-40 cases as shown in Appendix 2 and summarized in Table 4 for the 16 medicines indicated that all are related to finished sunscreen products commercially available in Australia and the affected individuals represented ages of less than 1 year up to 99 years. As noted in the Table 4, each of the adverse effects or complaints are categorized as “suspected to be related to the medicine”, which is in all cases a complete sunscreen product, and not bemotrizinol specifically. Each of the medicines listed in the reports contain at least three other UV filter active ingredients in addition to bemotrizinol, plus any included but not listed, inactive formulation excipients.

Because systematic diagnostic patch testing of the specific UV filters or ingredients in the 16 medicines was not disclosed to have been done or any results reported, none of these adverse event reports can be used to implicate bemotrizinol as the direct causative agent. Further, all other available testing results with BEMT and the safe use concentrations for the selected excipients in the MUsT formulations, did not show adverse topical effects or intolerance, and do not indicate concerns for a clinical trial using maximum topical exposures to our proposed formulations.

A slight contrast to these adverse event listings was presented by a recent search of the open scientific literature via PubMed that did reveal only one case report of adverse reactions on human skin (Luna-Bastante et al. 2019).

In this event, a 39-year-old non-atopic female presented with eyelid eczema and two-years history of pruritic erythematous scaly plaques in both periorbital skin regions. Patch testing in the subject with the Spanish Contact Dermatitis Standard Baseline series, the two suspect cosmetic formulations, and then their individual ingredients tested separately revealed positive skin reactions to two ingredients in the sunscreen: *Scutellaria baicalensis* root extract and Tinosorb® S. In their systematic approach the authors also used the ingredients found positive in the subject to patch test 16 healthy controls, none of which showed positive reactions to the ingredients. The subject was treated with topical medications that resolved the lesions and advised to avoid cosmetics containing the two ingredients.

4.2.2 Clinical Efficacy

4.2.2.1 UV Absorption Efficacy for SPF Determination

Bemotrizinol is proven to be an effective UV light absorbing ingredient as substantiated in testing by standard clinical designs used to evaluate finished sunscreen products that contained other UV Filer active ingredients along with BEMT. Some in silico tools, or calculators, are available that will estimate the UV SPF of a formulation based on the specific UV filter(s) added to a mixture. It is well established that BEMT is an effective UV light absorber in the UVA and UVB wavelengths ranges.

4.2.3 Safety and Risks Indicated by Clinical Experience

Bemotrizinol is intended for topical application in sunscreen formulations to prevent sunburn to the skin. The safety of BEMT predicted by non-clinical testing has been substantiated by the absence of published case reports for adverse skin or systemic effects or serious impairments following its use by consumers. The Expert Review of BEMT for safety and efficacy done in compliance with other country's regulatory requirements has supported the registration and listing of BEMT as safe for consumer use. Most importantly, subsequent withdrawal or cancellation of any BEMT registration has not been seen.

Bemotrizinol is not easily absorbed across the skin or from parenteral exposures and systemic exposures are predicted to be very low, unlikely to be metabolized and is rapidly eliminated as the parent molecule. The high stability of BEMT to UV irradiation indicates photo-degradation products or reactive moieties are not expected to occur on or in human skin after topical applications.

The clinical safety in usage is clearly supported by the absence of notable risks and relatively few adverse effects in its' nearly 20 years of continuous use in topically applied consumer products.

Companies using BEMT in their marketed sunscreen formulations have not reported to DSM any notified complaints or adverse experiences with BEMT in their products. This is consistent with the absence of adverse effects in controlled clinical testing for skin irritation and sensitization with and without UV irradiation and with the very low

frequency of only one published case report of human adverse events from use of BEMT in commercially available consumer products.

4.3 Marketing and registration experiences

BEMT has globally been used as a broad-spectrum UV filter in consumer sunscreen products since 2000. BEMT is currently marketed throughout the world as PARSOL SHIELD® and Tinosorb S®. Table 5 provides a summary of maximum concentration of BEMT currently permitted to be used in sunscreen and personal care cosmetic products internationally. The sponsor is not aware of any withdrawals.

Table 5. Maximum Concentration (%) of BEMT Currently Permitted for Use in Sunscreen Products by Country/Region

EU	Canada	MERCOSUR	Australia	China	Korea	ASEAN
10.0%	6.0%	10.0%	10.0%	10.0%	10.0%	10.0%

Since BEMT is not currently marketed for sunscreen use in the United States, a global market survey of BEMT-containing formulations was performed using a commercially available database (MINTEL SOLUTIONS, GNPD - Global New Products Database) to identify the number and types of products, dosage forms and formulations that exist for BEMT-based sunscreens outside of the United States. The results of the survey were also used to inform and substantiate our selection of the test formulations used in our IVPT and proposed MUsT studies. As part of our market survey methodology, we searched the full GNPD database but limited the product search criteria by defining a cluster of personal care products that claim to have a sun protection factor between 1 and 100, without limiting the publication year. These criteria returned 68,226 products listed globally and published in 2019 and 2020 in the full database. Of these returned products, 5,419 (7.94%) were found to contain BEMT as one of the UV absorbers present in the formulation (Table 6).

Table 6. Number of BEMT-based Sunscreen Products Marketed Globally (non-US)

	Ingredient / Search String	GNPD Global Hits (Total)	GNPD Global Hits (as % of Total)
Code	Search: Personal Care products with SPF from 1-100 that include	68226	100
	BEMT / Bemotrizinol	5419	7.94

5 SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

A total of 162 subjects will be enrolled in Part 2 Pivotal MUsT (54 subjects per study drug formulation arm) to achieve a minimum of 150 completers (50 completers in each arm) as recommended by FDA for this study phase. The anticipated total number of subjects that would be enrolled in the three dermal safety studies identified in this IB is approximately 310 (50 in Photoallergy, 35 in Phototoxicity and 190 in HRIPT and 35 in

Cumulative Irritation). A total of 472 subjects will be enrolled in the 4 clinical trials associated with this IB.

The exposure and testing of these subjects with BEMT at 6% in sunscreen formulations should be considered to be of very low risk for adverse clinical effects as discussed here.

Bemotrizinol is a photostable broad-spectrum UV filter that at low concentrations efficiently contributes to UVB and UVA protection across the full range of topical application forms (Herzog et al. 2004). The photosafety of BEMT has been substantiated by the outcomes of standard in vitro and in vivo non-clinical and in clinical controlled studies. In the completed non-clinical and clinical studies BEMT was well tolerated on the skin, did not show irritation or contact sensitization without and with UV irradiation, is not interactive with key endocrine effect modulators, and it did not adversely affect any aspect of the full reproduction and development cycle in rats. Bemotrizinol is not genotoxic or mutagenic based on results of in vitro and in vivo testing, and in representative animal models dosed chronically, BEMT was not a dermal carcinogen or photo-carcinogen.

Clinical safety testing of BEMT in two short studies with relatively small panels of volunteers did not demonstrate adverse events (AEs) for topical applications used to assess local tolerance for skin irritation and sensitization without or with UV radiation exposures. The local tolerance of BEMT, without and with, UV irradiation of skin sites exposed to prospective sunscreen formulations is considered to be without concerns for adverse effects.

A 20-years' long history of global use of BEMT in consumer sunscreen-containing products has shown the active ingredient to be without noticeable concern for its skin tolerance, consumer avoidance, or regulatory authorities' concern for BEMT's continued safety or limiting its market availability to use in consumer products.

As reviewed in the foregoing sections BEMT is of very low bioavailability by transdermal absorption, physiological metabolism and photo-degradation have not been shown to occur, and given its use topically, would not lead to systemic overdose or pharmacological signs of excessive intake. Likewise, oral ingestion of BEMT, without associated excipients, would not be expected to show clinical adverse effects.

The sunscreen formulations' ingredients (excipients) to be used in the proposed clinical testing paradigms have been selected for their compatibility with BEMT and for their recognized safety in use for human cosmetics and in formulated drug products. Concerns for adverse effects (AE) are expected to be low. However, two inactive ingredients (potassium cetyl phosphate magnesium stearate) contained in each of the emulsion formulas to be applied during part 2 of the study may cause eye irritation. As such, a standardized approach for applying formulations to the face along with appropriate eye protection and onsite procedures for eyewash care have been included in the study protocol. This also includes eye irritation assessment in safety/adverse event skin evaluations.

As indicated in section 4.2.1.4, potential adverse effects could include signs for local skin irritation or cumulative intolerance. Compromised or ectopic skin may exhibit signs of intolerance or allergenic reactions as indicated by the only published case report associated with BEMT in a sunscreen formulation. (Luna-Bastante et al. 2019)

Safety Data sheets for each of the excipients to be used the test dosage forms have been provided to the 2 Clinical Research Laboratories under a separate transmission.

6 APPENDIX 1

6.1 Draft Labeling per the requirements of 21 CFR 312.6(a)

6.1.1 Pivotal 6% MUsT (BEMT-001 Part 2) Labels

6.1.1.1 Part 1 (BEMT-001) Draft Bulk Label

Below is a copy of the draft bulk label of the investigational MUsT dosage form: Sunscreen oil SU-E-101413-70.

SU E 101413 70 – sunscreen oil with skin penetration enhancer (batch 005)

Caution: New Drug--Limited by Federal law to investigational use.

IND number: 146892

Protocol number: BEMT-001

Active Ingredients: Bemotrizinol 6% **Purpose:** Sunscreen

Inactive Ingredients: [redacted] (b) (4)

Storage conditions: Ambient

Expiry date: 02. December 2020 when stored in an unopened container

Total amount: [redacted] (b) (4)

DSM Nutritional Products Ltd, Wurmisweg 576, 4303 Kaiseraugst, Switzerland

6.1.1.2 Proposed Part 2 Draft Bulk Labels:

Test Formulation SU E 101413 85

SU-E-101413-85 batch 22015OEV – sunscreen oil with skin penetration enhancer

Caution: New Drug--Limited by Federal law to investigational use.

IND number: *146892*

Protocol number: BEMT-001

Active Ingredients: Bemotrizinol 6% **Purpose:** Sunscreen

Inactive Ingredients: (b) (4)

Storage conditions: ambient

Expiry date: 03.12.2022 when stored in an unopened container

Total amount: (b) (4)

DSM Nutritional Products Ltd, Wurmisweg 576, 4303 Kaiseraugst, Switzerland

Test Formulation SU E 101413 87:

SU E 101413 87 batch 22010OEV – O/W emulsion without penetration enhancer

Caution: New Drug--Limited by Federal law to investigational use.

IND number: *146892*

Protocol number: BEMT-001

Active Ingredients: Bemotrizinol 6% **Purpose:** Sunscreen

Inactive Ingredients: (b) (4)

Storage conditions: ambient

Expiry date: 31.07.2022 when stored in an unopened container

Total amount: (b) (4)

DSM Nutritional Products Ltd, Wurmisweg 576, 4303 Kaiseraugst, Switzerland

Test Formulation SU E 101413-89:

SU E 101413 89 batch 22017OEV – W/O emulsion without penetration enhancer

Caution: New Drug--Limited by Federal law to investigational use.

IND number: *146892*

Protocol number: BEMT-001

Active Ingredients: Bemotrizinol 6% **Purpose:** Sunscreen

Inactive Ingredients: (b) (4)

(b) (4)

Storage conditions: ambient

Expiry date: 07.08.2022 when stored in an unopened container

Total amount: (b) (4)

DSM Nutritional Products Ltd, Wurmisweg 576, 4303 Kaiseraugst, Switzerland

Draft Dosage Form Labels

The test products will be dispensed by the Pharmacy – on the day of application – directly from the bulk container to the containers from which it will be dispensed to the subjects. This will either be weigh boats or syringes depending on the product. Copies of the draft label to be used by the Pharmacy are provided below. Bar code labels will be used and will include the protocol number, the subject number, day and timepoint and a barcode which links all of these data points into the study database.

6.1.2 Dermal Safety Studies

Test Formulation SU E 101413 82 batch -004

RIPT/Cum. Irritation: CRLNJ2020-0493:

SU E 101413 82 batch -004 – formulation with petrolatum

Caution: New Drug--Limited by Federal law to investigational use.

IND number: *146892*

RIPT/Cum. Irritation: CRLNJ2020-0493

Active Ingredients: Bemotrizinol 6% **Purpose:** Sunscreen

Inactive Ingredients: PETROLATUM

Storage conditions: ambient

Expiry date: 28.11.2022 when stored in an unopened container

Total amount: (b) (4)

DSM Nutritional Products Ltd, Wurmisweg 576, 4303 Kaiseraugst, Switzerland

Test Formulation SU E 101413 82 batch -004

PT (Phototoxicity): CRLNJ2020-0494:

SU E 101413 82 batch -004 – formulation with petrolatum

Caution: New Drug--Limited by Federal law to investigational use.

IND number: *146892*

PT (Phototoxicity): CRLNJ2020-0494

Active Ingredients: Bemotrizinol 6% **Purpose:** Sunscreen

Inactive Ingredients: PETROLATUM

Storage conditions: ambient

Expiry date: 28.11.2022 when stored in an unopened container

Total amount: (b) (4)

DSM Nutritional Products Ltd, Wurmisweg 576, 4303 Kaiseraugst, Switzerland

Test Formulation SU E 101413 82 batch -004

PA (Photoallergenicity): CRLNJ2020-0495:

SU E 101413 82 batch -004 – formulation with petrolatum

Caution: New Drug--Limited by Federal law to investigational use.

IND number: *146892*

PA (Photoallergenicity): CRLNJ2020-0495

Active Ingredients: Bemotrizinol 6% **Purpose:** Sunscreen

Inactive Ingredients: PETROLATUM

Storage conditions: ambient

Expiry date: 28.11.2022 when stored in an unopened container

Total amount: (b) (4)

DSM Nutritional Products Ltd, Wurmisweg 576, 4303 Kaiseraugst, Switzerland

Test Formulation SU E 101413 85 batch -004

RIPT/Cum. Irritation: CRLNJ2020-0493:

SU E 101413 85 batch -004 – sunscreen oil with skin penetration enhancer

Caution: New Drug--Limited by Federal law to investigational use.

IND number: *146892*

RIPT/Cum. Irritation: CRLNJ2020-0493

Active Ingredients: Bemotrizinol 6% **Purpose:** Sunscreen

Inactive Ingredients: [redacted]

Storage conditions: ambient

Expiry date: 01.12.2022 when stored in an unopened container

Total amount: [redacted]

DSM Nutritional Products Ltd, Wurmisweg 576, 4303 Kaiseraugst, Switzerland

Test Formulation SU E 101413 85 batch -004

PT (Phototoxicity): CRLNJ2020-0494:

SU E 101413 85 batch -004 – sunscreen oil with skin penetration enhancer

Caution: New Drug--Limited by Federal law to investigational use.

IND number: *146892*

PT (Phototoxicity): CRLNJ2020-0494

Active Ingredients: Bemotrizinol 6% **Purpose:** Sunscreen

Inactive Ingredients: [redacted]

Storage conditions: ambient

Expiry date: 01.12.2022 when stored in an unopened container

Total amount: [redacted]

DSM Nutritional Products Ltd, Wurmisweg 576, 4303 Kaiseraugst, Switzerland

Test Formulation SU E 101413 85 batch -004

PA (Photoallergenicity): CRLNJ2020-0495:

SU E 101413 85 batch -004 – sunscreen oil with skin penetration enhancer

Caution: New Drug--Limited by Federal law to investigational use.

IND number: *146892*

PA (Photoallergenicity): CRLNJ2020-0495

Active Ingredients: Bemotrizinol 6% **Purpose:** Sunscreen

Inactive Ingredients: (b) (4)

Storage conditions: ambient

Expiry date: 01.12.2022 when stored in an unopened container

Total amount: (b) (4)

DSM Nutritional Products Ltd, Wurmisweg 576, 4303 Kaiseraugst, Switzerland

Test Formulation SU E 101413 83 batch -002

RIPT/Cum. Irritation: CRLNJ2020-0493:

SU E 101413 83 batch -002 – formulation with petrolatum

Caution: New Drug--Limited by Federal law to investigational use.

IND number: *146892*

RIPT/Cum. Irritation: CRLNJ2020-0493

Active Ingredients: 0% **Purpose:** Sunscreen

Inactive Ingredients: PETROLATUM

Storage conditions: ambient

Expiry date: 14.10.2022 when stored in an unopened container

Total amount: (b) (4)

DSM Nutritional Products Ltd, Wurmisweg 576, 4303 Kaiseraugst, Switzerland

Test Formulation SU E 101413 83 batch -002

PT (Phototoxicity): CRLNJ2020-0494:

SU E 101413 83 batch -002 – formulation with petrolatum

Caution: New Drug--Limited by Federal law to investigational use.

IND number: *146892*

PT (Phototoxicity): CRLNJ2020-0494

Active Ingredients: 0% **Purpose:** Sunscreen

Inactive Ingredients: PETROLATUM

Storage conditions: ambient

Expiry date: 14.10.2022 when stored in an unopened container

Total amount: (b) (4)

DSM Nutritional Products Ltd, Wurmisweg 576, 4303 Kaiseraugst, Switzerland

Test Formulation SU E 101413 91 batch -001

RIPT/Cum. Irritation: CRLNJ2020-0493:

SU E 101413 91 batch -001 – sunscreen oil with skin penetration enhancer

Caution: New Drug--Limited by Federal law to investigational use.

IND number: *146892*

RIPT/Cum. Irritation: CRLNJ2020-0493

Active Ingredients: 0% **Purpose:** Sunscreen

Inactive Ingredients: (b) (4)

Storage conditions: ambient

Expiry date: 10.10.2022 when stored in an unopened container

Total amount: (b) (4)

DSM Nutritional Products Ltd, Wurmisweg 576, 4303 Kaiseraugst, Switzerland

Test Formulation SU E 101413 91 batch -001

PT (Phototoxicity): CRLNJ2020-0494:

SU E 101413 91 batch -001 – sunscreen oil with skin penetration enhancer

Caution: New Drug--Limited by Federal law to investigational use.

IND number: *146892*

PT (Phototoxicity): CRLNJ2020-0494

Active Ingredients: 0% **Purpose:** Sunscreen

Inactive Ingredients: (b) (4)

Storage conditions: ambient

Expiry date: 10.10.2022 when stored in an unopened container

Total amount: (b) (4)

DSM Nutritional Products Ltd, Wurmisweg 576, 4303 Kaiseraugst, Switzerland

Test Formulation SU E 101413 91 batch -001

PA (Photoallergenicity): CRLNJ2020-0495:

SU E 101413 91 batch -001 – sunscreen oil with skin penetration enhancer

Caution: New Drug--Limited by Federal law to investigational use.

IND number: *146892*

PA (Photoallergenicity): CRLNJ2020-0495

Active Ingredients: 0% **Purpose:** Sunscreen

Inactive Ingredients: [redacted] (b) (4)

Storage conditions: ambient

Expiry date: 10.05.2022 when stored in an unopened container

Total amount: [redacted] (b) (4)

DSM Nutritional Products Ltd, Wurmisweg 576, 4303 Kaiseraugst, Switzerland

7 APPENDIX 2

7.1 TGA Database of Adverse Events Notification – BEMT Report

Australian Government
Department of Health
Therapeutic Goods Administration

Database of Adverse Event Notifications - medicines

Medicine summary

You searched for the following **16 medicines** between **01/01/1999 – 01/02/2020**:

- B3-T Superfluid Sunscreen SPF50+ AUST L 239432 (bemotrizinol; butyl methoxydibenzoylmethane; homosalate; methylene bis-benzotriazolyl tetramethylbutylphenol; octocrylene; octyl salicylate; titanium dioxide; zinc oxide)
- Banana Boat Baby SPF50+ Roll On Sunscreen (octocrylene; 4-methylbenzylidene camphor; butyl methoxydibenzoylmethane; bemotrizinol)
- Banana Boat Everyday Sensitive SPF50+ Sunscreen Lotion AUST L 196375 (4-methylbenzylidene camphor; bemotrizinol; butyl methoxydibenzoylmethane; octocrylene)
- Banana Boat Kids SPF50+ sunscreen (octocrylene; 4-methylbenzylidene camphor; butyl methoxydibenzoylmethane; bemotrizinol)
- Banana Boat Kids SPF50+ Sunscreen Lotion Spray (pump) Aust L 196668 (4-methylbenzylidene camphor; bemotrizinol; butyl methoxydibenzoylmethane; octocrylene)
- Banana Boat Ultra SPF50+ (4-methylbenzylidene camphor; bemotrizinol; butyl methoxydibenzoylmethane; octocrylene)
- Cancer Council Active Dry Touch Sunscreen SPF50+ Lotion - AUST L 207979 (octocrylene; 4-methylbenzylidene camphor; butyl methoxydibenzoylmethane; bemotrizinol)
- Cancer Council Australia Kids Sunscreen SPF50+ (4-methylbenzylidene camphor; bemotrizinol; methylene bis-benzotriazolyl tetramethylbutylphenol; zinc oxide)
- Nivea Sun Protect & Moisture Moisturising Sunscreen Lotion SPF50 AUST L 270877 (octyl salicylate; homosalate; octocrylene; butyl methoxydibenzoylmethane; bemotrizinol)
- NIVEA Sun Ultra Beach Sunscreen Spray SPF50+ AUST L 234687 (octyl salicylate; homosalate; octocrylene; butyl methoxydibenzoylmethane; bemotrizinol)
- SunActive SPF 50+ Face Cream - AUST L 212693 (octyl methoxycinnamate; octyl salicylate; octocrylene; butyl methoxydibenzoylmethane; diethylamino hydroxybenzoyl hexyl benzoate; bemotrizinol)
- SUNSENSE Junior - AUST L 220952 (octyl methoxycinnamate; octyl salicylate; titanium dioxide; diethylamino hydroxybenzoyl hexyl benzoate; bemotrizinol)

- Ultra UV Protective Daily Moisturiser SPF 30 Mattifying - AUSTL 251012 (octyl methoxycinnamate; octocrylene; phenylbenzimidazole sulfonic acid; butyl methoxydibenzoylmethane; bemotrizinol)
- Ultra UV Protective Daily Moisturiser SPF 30 Mattifying AUST L 251012 (octyl methoxycinnamate; octocrylene; phenylbenzimidazole sulfonic acid; butyl methoxydibenzoylmethane; bemotrizinol)
- Ultra UV Protective Daily Moisturiser SPF30 Hydrating - AUST L 236265 (octyl methoxycinnamate; octocrylene; phenylbenzimidazole sulfonic acid; butyl methoxydibenzoylmethane; bemotrizinol)
- Ultra UV Protective Daily Moisturiser SPF50+ - AUST L 237094 (octyl methoxycinnamate; octocrylene; phenylbenzimidazole sulfonic acid; butyl methoxydibenzoylmethane; bemotrizinol)

Important information

The TGA uses adverse event reports to identify when a safety issue may be present. An adverse event report does not mean that the medicine is the cause of the adverse event. If you are experiencing an adverse event, or think you may be experiencing one, please seek advice from a health professional as soon as possible. The TGA strongly advises people taking prescription medicines not to change their medication regime without prior consultation with a health professional.

About the Database of Adverse Event Notifications (DAEN) - medicines

- The DAEN - medicines contains information from reports of adverse events that the TGA has received in relation to medicines including vaccines used in Australia.
- The DAEN - medicines does not contain all known safety information about a particular medicine. Please do not make an assessment about the safety of a medicine based on the information in the DAEN - medicines.

The TGA medicine safety monitoring program

More information about the DAEN - medicines and the TGA medicines safety monitoring program is available at:

- About the DAEN - medicines <http://www.tga.gov.au/safety/daen-about.htm>
- Medicines safety <http://www.tga.gov.au/safety/information-medicines.htm>

You are encouraged to report an adverse event suspected of being related to a medicine used in Australia. Reports of adverse events in relation to medicines and vaccines can be reported using the 'blue card' reporting form, by phone and online <http://www.tga.gov.au/safety/problem.htm>.

Other useful sources of information on Australian medicines

More information about a medicine is available from the Product Information (PI) <http://www.tga.gov.au/hp/information-medicines-pi.htm> and Consumer Medicine Information (CMI) <http://www.tga.gov.au/consumers/information-medicines-cmi.htm> leaflet or the labelling of the medicine. Australian Public Assessment Report for Prescription Medicines (AusPARs) <http://www.tga.gov.au/industry/pm-auspar.htm> for some prescription medicines, are also available from the TGA website. <http://www.tga.gov.au>
Your health professional can also provide help and assistance on how to use medicines.
Information on medicines used in Australia is available from NPS MedicineWise <http://www.nps.org.au/>.

About the release of this information

While reasonable care is taken to ensure that the information is an accurate record of the adverse events reported to the TGA, the TGA does not guarantee or warrant the accuracy, reliability, completeness or currency of the information or its usefulness in achieving any purpose.
To the fullest extent permitted by law, including but not limited to section 61A of the Therapeutic Goods Act 1989, the TGA will not be liable for any loss, damage, cost or expense incurred in or arising by reason of any person relying on this information.

Results

Number of reports (cases): 40

(Multiple adverse events have been reported for some patients)

Number of cases with a single suspected medicine: 40

(The TGA thinks there is a possibility that the medicine caused the adverse event)

Number of cases where death was a reported outcome: 0

(These reports of death may or may not have been a result of taking a medicine)

MedDRA system organ class[i]	MedDRA reaction term[ii]	Number of cases[iii]	Number of cases with a single suspected medicine[iv]	Number of cases where death was a reported outcome[v]
Injury, poisoning and procedural complications	Sunburn	20	20	0
General disorders and administration site conditions	Therapeutic product ineffective	13	13	0
General disorders and administration site conditions	Drug ineffective	7	7	0
Product issues	Product quality issue	6	6	0
Skin and subcutaneous tissue disorders	Rash	5	5	0
Skin and subcutaneous tissue disorders	Blister	5	5	0
Immune system disorders	Hypersensitivity	3	3	0
Skin and subcutaneous tissue disorders	Dermatitis contact	3	3	0
Skin and subcutaneous tissue disorders	Urticaria	2	2	0
Injury, poisoning and procedural complications	Burns second degree	1	1	0
Eye disorders	Eye pruritus	1	1	0
General disorders and administration site conditions	Pain	1	1	0
Nervous system disorders	Burning sensation	1	1	0
Skin and subcutaneous tissue disorders	Erythema	1	1	0
Eye disorders	Eye pain	1	1	0
Skin and subcutaneous tissue disorders	Acne cosmetica	1	1	0
Infections and infestations	Eyelid infection	1	1	0
Skin and subcutaneous tissue disorders	Pruritus	1	1	0
Skin and subcutaneous tissue disorders	Skin irritation	1	1	0
Skin and subcutaneous tissue disorders	Rash pruritic	1	1	0

Footnotes

[i] A description of what, in general terms, was affected by the adverse event, as described by the Medical Dictionary for Regulatory Activities MedDRA (for example 'cardiac disorders')

[ii] A description of the adverse event as defined by MedDRA; these adverse events are grouped by system organ class. You can use the MedlinePlus medical dictionary <http://www.nlm.nih.gov/medlineplus/mplusdictionary.html> to look up terms.

[iii] The number of cases for which each type of adverse event was reported

[iv] Results show where a medicine is the only medicine suspected to be related to the adverse event

[v] These reports of death may or may not have been the result of taking a medicine

8 REFERENCES

8.1 Citations Not Part of the FDA Docket 2005-N-0453

AAD 2020. American Academy of Dermatology. Skin Cancer Incidence rates: https://www.aad.org/media/stats-skin-cancer; Last accessed May 4, 2020

Api AM, Vey M. Implementation of the dermal sensitization Quantitative Risk Assessment (QRA) for fragrance ingredients. Regul Toxicol Pharmacol. 2008;52(1):53-61.

Ashby J., Tinwell H., Plautz J., Twomey K., and Lefevre P.A. 2001. Lack of Binding to Isolated Estrogen or Androgen Receptors, and Inactivity in the Immature Rat Uterotrophic Assay, of the Ultraviolet Sunscreen Filters Tinosorb□M-Active and Tinosorb□S. Reg Tox Pharmacol 34: 287-291.

CDC 2020. Centers for Disease Control and Prevention. Melanoma of the Skin Statistics: https://www.cdc.gov/cancer/skin/statistics/index.htm; Last accessed May 4, 2020

Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. Nutrition. 1989;5(5):303-311.

DHHS 2019. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Guidance for Industry: Maximal Usage Trials for Topical Active Ingredients Being Considered for Inclusion in an Over-The-Counter Monograph: Study Elements and Considerations, May 2019. https://www.fda.gov/media/125080/download. Last accessed May 5, 2020

FDA 2015. Food & Drug Administration, HHS. 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

FDA 2016. Nonprescription Sunscreen Drug Products — Safety and Effectiveness Data Guidance for Industry. FDA, Center for Drug Evaluation and Research (CDER) November 2016. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM473464.pdf

CIBA 2000. TINOSORB® S: Bis-Ethylhexyloxyphenol methoxyphenyltriazine (BEMT): Next Generation UV Filter for Sun Protection. Information package, Attachment 2, submitted as Citizen's Petition under US Food and Drug Administration Time and Extent Application, Docket No. 78N-0038. Ciba Specialty Chemicals Corp. 5 September 2005. The currently available Public Docket number is 2005N-0446 and FDA-2005-N-0453-003 available at https://www.regulations.gov/document?D=FDA-2005-N-0453-0003.

CRL 2017. In Chemico Determination of the Skin Sensitization Potential of DNP-038124 using the Direct Peptide Reactivity Assay (DPRA). Charles River Laboratories Den Bosch BV; Study Number 517122. 29 March 2017.

DSM (2019). In silico metabolism of bemotrizinol by Meteor Nexus (v.3.1.0) with maximum likelihood probable. Reported 18 January 2019.

EU SCCS 2018. The SCCS Notes of Guidance for the testing of cosmetic ingredients and their safety evaluation, 10th revision, SCCS/1602/18; October 2018. Available at https://ec.europa.eu/health/sites/health/files/scientific_committees/consumer_safety/docs/sccs_o_224.pdf

FDA 2019. Maximal Usage Trials for Topical Active Ingredients Being Considered for Inclusion in an Over-The-Counter Monograph: Study Elements and Considerations. Guidance for Industry. FDA, Center for Drug Evaluation and Research; Clinical Pharmacology/ Over-The-Counter (OTC). Final guidance, May 2019. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM608356.pdf

Hassler, S. (2019). DNP-038124 - In vitro Dermal Absorption of [^{14}C]DNP-038124 in Different Cosmetic Formulations at a Concentration of 6% (w/w) on Human Skin Membranes. Innovative Environmental Services (IES) Ltd Study No. 20190089 ; December 11, 2019.

Herzog, B, Hueglin, D., Borsos E, et al. 2004. New UV absorbers for cosmetic sunscreens- a breakthrough for the photoprotection of human skin. CHIMIA International Journal for Chemistry 58 (7-8). 554-559.

Luna-Bastante L., Gatica-Ortega M-E, Pastor-Nieto M-A, Vergara-de-la-Campa L, Gómez-Dorado B, Alonso-Naranjo L., Pérez-Hortet C. 2019. Allergic contact dermatitis to Tinosorb S, Scutellaria baicalensis, and other emerging allergens in cosmetics Contact Dermatitis- Contact Points; 26 December 2019. DOI link: https://doi.org/10.1111/COD.13460

McNamee PM, Api AM, Basketter DA, et al. A review of critical factors in the conduct and interpretation of the human repeat insult patch test. Regul Toxicol Pharmacol. 2008;52(1):24-34.

Second IVPT (Project No. BASF Study 10B0377/21B110): 14C-BEMT in Different Cosmetic Formulations - Study of Penetration through Human Skin In Vitro. OECD Guideline for the testing of chemicals no. 428. BASF SE, Germany, 2021.

Therapeutic Goods Administration (TGA), Australia; database of adverse event notifications-medicines. Summary of adverse events reported as of 25 February 2020; accessed 24 May 2020. http://apps.tga.gov.au/PROD/DAEN/daen-report.aspx (TGA_daen_medicines sum-table)

Therapeutic Goods Administration (TGA), Australia; database of adverse event notifications-medicines. Summary of adverse events reported as of 25 February 2020; accessed 25 May 2020. http://apps.tga.gov.au/PROD/DAEN/daen-report.aspx (TGA_daen-listed_reports)

US DHHS 2018. 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.

Watson eta. 2106. Watson M, Holman DM, Maguire-Eisen M. Ultraviolet Radiation Exposure and Its Impact on Skin Cancer Risk. Semin Oncol Nurs. 2016;32(3):241-254. doi:10.1016/j.soncn.2016.05.005

WIL Research 2016a. *In vitro* skin irritation with DNP-038124 using a human skin model. WIL Research Europe B.V.; Study number 207420_512975; 25 May 2016.

WIL Research 2016b. Evaluation of *in vitro* skin sensitization potential of DNP-038124 with the KeratinoSens™ assay. WIL Research Europe B.V.; Study number 207420_512976; 29 June 2016.

WIL Research 2016c. Evaluation of the mutagenic activity of DNP-038124 in the Salmonella typhimurium reverse mutation assay and the Escherichia coli reverse mutation assay. WIL Research Europe B.V.; Study number 207420_512974; 27 May 2016.

8.2 Citations Available on FDA Docket 2005-N-0453

Individual studies referenced to section 4.3.

Bibliographic Citation	Testing Laboratory Location
Arcelin, G. (1997a). Acute dermal toxicity study with CGF-C-1607 in rats. RCC Project 651420.	RCC Group, Itingen, Switzerland
Arcelin, G. (1997b). Acute oral toxicity study with CGF-C-1607 in rats. RCC Project 651407.	RCC Group, Itingen, Switzerland
Arcelin, G. (1997c). Contact hypersensitivity to CGF-C-1607 in albino guinea pigs maximization-test. A.5	RCC Group, Itingen, Switzerland
Arcelin, G. (1997d). Determination of photoallergenicity with CGF-C-1607 in albino guinea pigs (including information about allergenicity, photoirritation, and irritation). RCC Project 651497 A7	RCC Group, Itingen, Switzerland
Arcelin, G. (1997e). Determination of phototoxicity with CGF-C-1607 in albino guinea pigs. RCC Project 651475. A 6	RCC Group, Itingen, Switzerland
Braun, W.H. (1997a). Primary skin irritation study with CGF-C-1607 in rabbits (4-hour semi-occlusive application). RCC Project 651431.	RCC Group, Itingen, Switzerland
Braun, W.H. (1997b). Primary eye irritation study with CGF-C-1607 in rabbits. RCC Project 651442.	RCC Group, Itingen, Switzerland
Becker, H. and Biedermann, K. (1998). Prenatal toxicity study with CGF-C-1607 in the rat. RCC Project 681491. A 14	RCC Group, Itingen, Switzerland
Czich, A. (1998a). *In vitro* chromosome aberration assay in Chinese hamster V79 cells with CGF-C1607. RCC-CCR Project 597700. Project ID of contracting institute RCC 672017 A 19	RCC Group, Itingen, Switzerland
Czich, A. (1998b). Chromosome aberration assay *in vitro:* photomutagenicity in Chinese hamster V79 cells with CGF-C-1607. Project ID of contracting institute RCC 701853. (Tab.III.A.23)	RCC Group, Itingen, Switzerland

Bibliographic Citation	Testing Laboratory Location
Gaou, I. 2003a. Preliminary 2-Week toxicity study by cutaneous route in rats. CIT Study Number 25455 TSR. (Tab.III.A.9)	CIT Laboratories, Evreux, France
Gaou, I. 2003b. 13-Week toxicity study by cutaneous route in rats with FAT 70'884. CIT Study Number 25378 TCR. (Tab.III.A.11)	CIT Laboratories, Evreux, France
Gaou, I. 2006.Carcinogenicity study by cutaneous route in rats. CIT Study Number 25382 TCR. (Tab III.A.12)	CIT Laboratories, Evreux, France
Haag, V. (2006). 39-week toxicity study by cutanoeus route in Gottingen minipigs with FAT 70'884. CIT Study number 25384 TCN. (Tab.III.A.27)	CIT Laboratories, Evreux, France
Haddouk, H. (2003). Bone marrow micronucleus test by intraperitoneal route in mice with test item FAT 70'884/B. CIT Study number 25608 MAS (Tab.III.A.20)	CIT Laboratories, Evreux, France
Hamann, H-J., Schmid, H., Luetkemeier, H., Biedermann, K., and Chevalier, H-J. (1998). 13-Week oral toxicity (gavage) study with CGF-C-1607 in the rat. RCC Project 667541. (Tab.III.A.10)	RCC Group, Itingen, Switzerland
Hoberman, A. and Foss, J. (2005). Oral (stomach tube) developmental toxicity study of Tinosorb S in rabbits. Charles River Discovery and Developmental Services, Argus Division. Study protocol number 203-014. (Tab.III.A.15)	Charles River Laboratories, Horsham, PA, USA
Learn, D., Sambuco, C., and Forbes, D. (2003a). Topical evaluation of the protective potential of Tinosorb M, Tinosorb MBBT and Tinosorb S against ultraviolet radiation (uvr) induced cutaneous inflammation in hairless mice: a Sun Protection Factor (SPF)-like evaluation. Charles River Discovery and Developmental Services, Argus Division. Study protocol number 203-018. (Tab.III.A.24)	Charles River Laboratories, Horsham, PA, USA
Learn, D., Sambuco, C., and Forbes, D. (2003b). Thirteen-week topical range-finding study of Tinosorb M, Tinosorb MBBT and Tinosorb S in hairless mice, with or without simulated sunlight. Charles River Discovery and Developmental Services, Argus Division. Study protocol number 203-006. (Tab.III.A.25)	Charles River Laboratories, Horsham, PA, USA
Learn, D., Sambuco, C., and Forbes, D. (2005). Twelve-month topical study to determine the influence of Tinosorb S on Photocarcinogenesis in hairless mice. Argus Research, Charles River Laboratories, Study number 203-008. (Tab.III.A.26)	Charles River Laboratories, Horsham, PA, USA
Lefevre, P. A. (2001a). CGF-C2089 and CGF-C1607: Androgen competitive binding assay. Central Toxicology Laboratory Study No. 024530. (Tab.III.A.17)	Central Toxicology Laboratory, Macclesfield, Cheshire, UK
Lefevre, P. A. (2001b). CGF-C2089 and CGF-C1607: Estrogen competitive binding assay. Central Toxicology Laboratory Study No. 024529. (Tab.III.A.17)	Central Toxicology Laboratory, Macclesfield, Cheshire, UK
Nesslany, F. (2004). In vivo/in *vitro* Unscheduled DNA (UDS) synthesis assay in rat hepatocytes with FAT 70'884/C. Institute Pasteur de Lille; study number FSR-IPL 040012. (Tab.III.A.21)	Institute Pasteur de Lille; Lille, France
Ota, T. (2002a). Study for effects of oral administration of RM-60 on fertility and early embryonic development to implantation in rats. Hashima Laboratory, Nihon Bioresearch, Inc., Hashima, Gifu, Japan; Study No. 100721. (Tab.III.A.13)	Nihon Bioresearch, Inc., Hashima, Gifu, Japan

Bibliographic Citation	Testing Laboratory Location
Ota, T. (2002b). Study on effects of oral administration of RM-60 on pre- and postnatal development, including maternal function, in rats. Hashima Laboratory, Nihon Bioresearch, Inc., Hashima, Gifu, Japan; Study No. 300721. (Tab.III.A.16)	Nihon Bioresearch, Inc., Hashima, Gifu, Japan
Parisse, A.J. (1998a). Evaluation of human photoallergy by repeated insult patch test. HTR Project No. 100243B. Sponsor Number CGF-C-1607/7.	Hill Top Research, Inc.; East Brunswick, NJ, USA
Parisse, A.J. (1998b). Evaluation of phototoxicity in humans. HTR Project No. 100243A. Sponsor Number CGF-C-1607/7.	Hill Top Research, Inc.; East Brunswick, NJ, USA
Schmid, H., Luetkemeier, H., and Wilson, J. (1998) 14-Day dose range-finding (gavage) study with CGF-C-1607 in the rat. RCC Project 667530. (Tab.III.A.8)	RCC Group, Itingen, Switzerland
Silcock, R. 2002a. CGF-C1607: Metabolic fate following oral administration to rats. Central Toxicology Laboratory Study No. UR0698. (Tab.III.A.28_29)	Central Toxicology Laboratory, Macclesfield, Cheshire, UK
Silcock, R. 2002b. CGF-C1607: Metabolic fate following *in vivo* dermal administration to rats. Central Toxicology Laboratory Study No. UR0722. (Tab.III.A.28_29)	Central Toxicology Laboratory, Macclesfield, Cheshire, UK
Twomey, K. (2002). CGF-C-1607: Uterotrophic Assay in immature rats. Central Toxicology Laboratory Study No. ZR1601. (Tab.III.A.17)	Central Toxicology Laboratory, Macclesfield, Cheshire, UK
Watkinson, A.C. (1998). *In vitro* human skin penetration and distribution of the UV absorber CGF-C1607. An-eX Analytical Services, Ltd. Report Number CSC/8/98. (Tab.IV.A.1)	An-eX analytical services ltd.; Cardiff, UK
Wollny, H. (1997). *Salmonella* typhimurium reverse mutation assay with CGF-C-1607. CCR Project 582800. Project ID of the contracting institute- RCC 651508. (Tab.III.A.18)	RCC Group, Itingen, Switzerland
Wollny, H. (1998a). *Escherichia coli* reverse mutation assay with CGF-C1607. CCR Project 618300; RCC project 704428. (Tab.III.A.18)	RCC Group, Itingen, Switzerland
Wollny, H.E. (1998b). Photomutagenicity in a *Salmonella* typhimurium and *Escherichia* coli reverse mutation assay with CGF-C-1607. RCC-CCR Project 609003. Project ID of the contracting institute RCC 689354. (Tab.III.A.22	RCC Group, Itingen, Switzerland