

2.2 Introduction to the Summary Documents

DSM is sponsoring a Tier 1 Over the Counter (OTC) Monograph Order Request (OMOR) for a Generally Recognized as Safe and Effective (GRASE) determination for Bemotrizinol (BEMT) 6% as a new sunscreen active ingredient under FDA's OTC Monograph M020: Sunscreen Drug Products for OTC Human Use (21 CFR Part 352).

The Quality sections of this OMOR (Modules 3 and [2.3](#)) provide descriptive characteristics of BEMT, including its synthesis, chemistry, and chemical properties that support its use as an OTC drug substance. The Chemistry, Manufacturing, and Controls (CMC) procedures document steps related to starting materials, excipients, intermediates, stability, purification, and residual materials, ensuring that the final drug substance, the API, consistently meets the specifications of the draft USP Monograph for Bemotrizinol and the label parameters. The control, reduction, and elimination of impurities from the synthesis of the starting material to the API are successfully demonstrated, ensuring no carryover of impurities and compliance with the draft USP Monograph for Bemotrizinol. A forced degradation study further confirmed the extreme stability of the API. DSM only places BEMT into commerce as a safe and effective UV filter; it does not sell or market any finished drug sunscreen products containing BEMT.

Also included in Module 3 is a series of "market image" OTC sunscreen drug products containing BEMT 6% that were used in several controlled clinical safety and efficacy studies conducted under the FDA-agreed protocols to meet safety and efficacy requirements. These market-image sunscreen formulations contained only the investigational drug substance Bemotrizinol and were not intended for commercial sale. They were designed to represent the found in the U.S. sunscreen market, addressing the "worst case" scenario regarding dermal absorption. These representative OTC sunscreen drug products ensured that the clinical test results would accurately reflect typical consumer use of future sunscreen products containing BEMT.

The nonclinical safety of BEMT is supported by legacy pharmacokinetic and toxicology test results submitted in 2005 and 2006 under a TEA as referenced in [Module 1.4](#). The nonclinical data gaps identified by the FDA have been addressed to enhance the safety profile of BEMT, following FDA recommendations and aligned with the FDA's 2016 Guidance for Industry on Nonprescription Sunscreen Drug Products - Safety and Effectiveness Data. The only remaining component is the systemic carcinogenicity study, which is proposed to be conducted using a transgenic mouse model. We are currently seeking a waiver for this study and have included the relevant information in this OMOR submission to support the waiver request ([Module 1.12.5](#)).

Pharmacokinetic results from repeated oral and dermal dosing in rats, as well as plasma concentration profiles from long-term dermal and oral dosing, indicate that BEMT has low systemic bioavailability, particularly via oral routes, with dermal dosing resulting in slightly higher systemic exposure at comparable doses. In vitro percutaneous penetration studies of 6% BEMT across human skin membranes consistently showed absorption below 1% of the applied dose from various drug product formulations, including those containing skin penetration enhancers and different dosage forms.

The nonclinical test results support the conclusions that BEMT poses no concern for target organ effects, carcinogenicity, tumorigenicity, genotoxicity, reproductive systems effects, or behavioral modifications. In none of the 12 completed repeat dose pivotal studies did any BEMT dose-related adverse effect appear, even at the highest doses, which were either the maximum tolerated or achievable for the dose formulation or test system. The absence of hormonal modulation, immunotoxicity or suppression, and lack of metabolism of BEMT into human specific metabolites further corroborate the safety of 6% BEMT for human topical use.

Clinical pharmacokinetics of 6% BEMT in healthy subjects from a phase 3 pivotal MUsT topical study, using 'market image' sunscreen formulations, showed that plasma steady-state concentrations did not reach 0.5 ng/mL (LLOQ 0.1 ng/mL). Only 3% (113/3722) of samples were above 0.5 ng/mL, likely due to the low transcutaneous absorption of BEMT, even under the excessively high topical application conditions used in the study. The pilot MUsT was an open-label, 1-arm, 4-day trial designed to assess whether BEMT reaches quantifiable plasma concentrations after multiple applications of a market image sunscreen formulation containing 6% BEMT and 10% ethanol as a permeation enhancer. The formulation followed FDA's 2016 Sunscreen GRASE safety and 2019 MUsT design guidance, aiming to provide clinical insight into BEMT's systemic absorption and evaluate trial design and instrumentation performance.

Results showed BEMT rarely exceeded the plasma threshold, with no evidence of accumulation or steady-state concentrations above 0.5 ng/mL. Adverse events were few and mild. The study provided essential data for a successful pivotal trial, including preliminary pharmacokinetic (PK) data, validation of procedures, and subject requirements, while demonstrating that maximal topical applications did not result in significant systemic exposure.

As discussed in [Module 2.7.4.2.2](#), the small number of positive samples at the limit of quantitation (0.5 ng/mL) is likely attributable to the protocol's design, which aimed to maximize absorption by driving passive diffusion. The overall low bioavailability observed supports our request for a waiver of the systemic carcinogenicity study.

In the four clinical dermal safety tests, 6% BEMT did not elicit signs or reactions indicating skin irritation, sensitization, phototoxicity or photoallergenicity in any of the subjects completing the studies. The few non-completers were lost to follow-up or discontinued for reasons not related to the BEMT test formulation.

Efficacy testing for sunburn protection in two independent clinical SPF studies demonstrated that BEMT, at concentrations of 1.0 to 4.5%, provides SPF values above 2, thereby effectively protecting skin from UV irradiation delivered by spectral solar simulations. A concentration-related increase in the SPF values was observed. While combinations with other sunscreen actives from FDA's OTC sunscreen monograph were not within the scope of FDA's GRASE determination guidelines ([Nonprescription Sunscreen Drug Products – Safety and Effectiveness Data | FDA](#)), the absence of clinical adverse over 24 years of use in sun protection products worldwide supports the safe use of BEMT.

Clinical testing demonstrated the topical safety of BEMT 6% under controlled protocols, providing effective protection against solar irradiation to prevent sunburn, and showing very low systemic exposure to BEMT even at exaggerated topical dosing. The comprehensive data from nonclinical and clinical studies, and the absence of documented clinical adverse events during 24 years of commercial use in sunscreen and sun protection products world-wide, supports the conclusion that BEMT 6% is a safe and effective UV filter that will play a meaningful role in the sunscreen monograph.

We have not conducted, nor are we aware of, any negative safety or efficacy study outcomes that would counter the safety and effectiveness of Bemotrizinol for use as an OTC monograph-listed sunscreen ingredient.

A table of all the nonclinical and clinical studies included in this Tier 1 OMOR follows.

Table 1 Summary Table of All Safety and Efficacy Studies in Submission (Also cross-referenced in [Module 1.4](#))

Study Type	Study Report Title ¹	Study Number	Location
Nonclinical Pharmacokinetics	<i>Dermal (topical) application is the intended route for human use</i>		
In vitro skin permeation- rat skin	DNP-038124 - In vitro Dermal Absorption of [¹⁴ C]DNP-038124 in a Cosmetic Oil Formulation (SU E 101413 62) at a Concentration of 6% (w/w) on Rat Skin Membranes	IES 2019090	4.4.4.2 2019090
Human skin in vitro	DNP-0138124- In vitro dermal absorption of ¹⁴ C-DNP-038124 in different cosmetic formulations at a concentration of 6% (w/w) on human skin membranes	IES 20190089	4.4.4.2 2019089
Human skin in vitro	¹⁴ C-BEMT in different cosmetic formulations- Study of penetration through human skin in vitro	BASF 10B0377/21B110	4.2.2.2 10B0377/21B110
Bioanalytic plasma method Mice	Validation of an UHPLC-MS/MS assay for the determination of DNP-038124 concentrations in mouse plasma	CRL 00825013	4.2.2.2 00825013
Bioanalytic plasma method Rat	Validation of an UHPLC-MS/MS assay for the determination of DNP-038124 concentrations in rat plasma	CRL 00825015	4.2.2.2 00825015
Bioanalytic plasma method Rat	Determination of FAT 70'884/C in rat plasma; method development & validation: rat dermal 90d study	CIT 25378_TCR	4.2.2.3 25378 TCR
Bioanalytic plasma method Minipig	Validation of the analytical method in minipig plasma	CIT 25384 TCN	4.2.2.3 5384 TCN
Single dose dermal rat	CGF-C1607: Metabolic fate following in vivo dermal application in rats	CTL UR0722	4.2.2.2 UR0722
Single dose oral rat	CGF-C1607: Metabolic fate following oral administration in rats	CTL UR0698	4.2.2.2 UR0698
Repeat dose dermal	DNP-038124: A single and 21-day repeated dose dermal study in Wistar Han rats	CRL 00825024	4.2.2.2 00825024
Repeat dose oral	DNP-038124: A single and repeated oral dose non-radiolabeled pharmacokinetic study in rats	CRL 00825016	4.2.2.2 00825016

Study Type	Study Report Title ¹	Study Number	Location
Metabolism, in vitro incubation	In vitro investigations of the metabolic profile of Bemotrizinol by incubation of human hepatocytes and S9 fractions with ¹⁴ C-Bemotrizinol	DSM RD-00068522	4.2.2.4 RD-00068522
Nonclinical Toxicology			
Acute dermal	Acute dermal toxicity study with CGF-C1607 in rats	RCC 651420	4.2.3 651420
Acute oral	Acute oral toxicity study with CGF-C1607 in rats	RCC 651407	4.2.3 651407
<u>Repeat dosing</u> Dose range finding	Preliminary 2-week toxicity study by cutaneous route in rats	CIT 25455 TSR	4.2.3 25455 TSR
	2-Week preliminary toxicity study by cutaneous route in Goettingen minipigs	CIT 25383 TSN	4.2.3 25383 TSN
	A GLP 5-day and 28-day study of DNP-038124 by oral gavage administration in mice	CRL 20209876	4.2.3 20209876
	14-Day dose range-finding (gavage) study with CGF-C-1607 in the rat	RCC No. 667530	4.2.3 667530
<u>Pivotal repeat dosing</u>	13-Week toxicity study by cutaneous route in rats (2 volumes)	CIT 25378 TCR	4.2.3 25378 TCR
	39-Week toxicity study by cutaneous route in Goettingen minipigs	CIT 25384 TCN	4.2.3 25384 TCN
	13-Week oral toxicity (gavage) study with CGF-C-1607 in the rat (4 volumes)	RCC 667541	4.2.3 667541
<u>Genotoxicity in vitro</u>	Salmonella typhimurium reverse mutation assay with CGF-C-1607	RCC-CCR 582800	4.2.3 582800
	Escherichia coli reverse mutation assay with CGF-C-1607	RCC-CCR 618300	4.2.3 618300
	Evaluation of the mutagenic activity of DNP-038124 in the Salmonella typhimurium reverse mutation assay and the Escherichia coli reverse mutation assay	WIL 512974	4.2.3 512947

Study Type	Study Report Title ¹	Study Number	Location
	In vitro chromosome aberration assay in Chinese hamster V79 cells with CGF-C-1607	CCR 597700	4.2.3 597700
Genotoxicity in vivo	Bone marrow micronucleus test by intraperitoneal route in mice	CIT 25608 MAS	4.2.3 25608 MAS
	Measurement of unscheduled DNA synthesis (UDS) in rat hepatocytes using an in vivo procedure with test compound FAT 70'884/C	FSR-IPL 040012	4.2.3 FSR-IPL 040012
Carcinogenicity	Carcinogenicity study by cutaneous route in rats (12 volumes)	CIT 25382 TCR	4.2.3 25382 TCR
<u>Reproductive & Developmental toxicity</u> dose range finding	Dose range-finding prenatal toxicity study with CGF-C-1607 in the rat	RCC 681480	4.2.3 681480
	Oral (stomach tube) dosage-range developmental toxicity study of Tinosorb S (FAT 70'884) in rabbits	CRL-Argus 203-014P	4.2.3 203-014P
Pivotal DART	Study for effects of oral administration of RM-60 on fertility and early embryonic development to implantation in rats	Nihon 100721	4.2.3.1 100721
	Prenatal toxicity study with CGF-C-1607 in the rat	RCC 681491	4.2.3 681491
	Oral (stomach tube) developmental toxicity study of Tinosorb S (FAT 70'884) in rabbits	CRL-Argus 203-014	4.2.3. 203-014
	Study for effects of oral administration of RM-60 on pre- and postnatal development, including maternal function, in rats	Nihon 300721	4.2.3 300721
<u>Local Tolerance</u> In vitro	In vitro skin irritation test with DNP-038124 using an human skin model	WIL 512975	4.2.3 512975
	Evaluation of skin sensitization potential of DNP-038124 with the Keratinosens TM assay	WIL 512976	4.2.3 512976
	<i>In chemico</i> determination of the skin sensitization potential of DNP-038124 using the Direct Peptide Reactivity Assay (DRPA)	CRL 517122	4.2.3 517122

Study Type	Study Report Title ¹	Study Number	Location
In vivo	Primary skin irritation study with CGF-C-1607 in rabbits	RCC 651431	4.2.3 651431
	Primary eye irritation study with CGF-C-1607 in rabbits	RCC 651442	4.2.3 651442
	Contact hypersensitivity to CGF-C-1607 in albino Guinea pigs- Maximization test	RCC 651453	4.2.3 651453
<u>Other Toxicity Studies</u> <u>Endocrine system tests</u>	In vitro: Estrogen competitive binding assay	CTL 024529	4.2.3 024529
	In vitro: Androgen competitive binding assay	CTL 024530	4.2.3 024530
	In vivo: CGF-C-1607 Uterotrophic assay in immature rats	CTL zr1601	4.2.3 zr1601
Phototoxicity tests	In vitro: Photomutagenicity in a Salmonella typhimurium and Escherichia coli assay with CGF-C-1607	RCC-CCR 609003	4.2.3 609003
	Chromosome aberration assay in vitro: Photomutagenicity in Chinese hamster V79 cells with CGF-C-1607	RCC-CCR 615904	4.2.3 615904
	Determination of phototoxicity with CGF-C.1607 in albino Guinea pigs	RCC 651475 (2 volumes)	4.2.3 651475
	Determination of phototoxicity with CGF-C.1607 in albino Guinea pigs (including information about allergenicity, photoirritation and irritation)	RCC 651497	4.2.3 651497
Repeat topical dose	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	CR-Argus 203-018	4.2.3 203-018
	13-Week topical range-finding study of Tinosorb M, Tinosorb MBBT, and Tinosorb S in hairless mice, with or without simulated sunlight	CR-Argus 203-006	4.2.3 203-006

Study Type	Study Report Title ¹	Study Number	Location
Photo-co-carcinogenicity	Twelve-month topical study to determine the influence of Tinosorb S (FAT 70'884) on photocarcinogenesis in hairless mice	CR-Argus 203-008	4.2.3 203-008
Clinical Studies			
Bioanalytical methods	Validation of an UHPLC-MS/MS assay for the determination of DNP-038124 concentrations in human plasma	CRL 00825020	5.3.1 00825020
	Validation of an UHPLC-MS/MS assay for the determination of DNP-038124 concentrations in K ₂ EDTA human plasma (low range)	CRL 00825023	5.3.1 00825023
In vivo PK (MUsT)	Ultraviolet filter Bemotrizinol (BEMT): Clinical pharmacokinetics evaluation in a topical maximum usage trial (MUsT)	Spaulding BEMT-001	5.3.3 BEMT-001
<u>Controlled Clinical Safety</u>	Evaluation of phototoxicity in humans	HTR 100243A	5.4 HTR 100243A
	Evaluation of human photoallergy by repeated insult patch test	HTR 100243B	5.4 HTR 100243B
	Evaluation of Bemotrizinol in human repeated insult patch test (HRIPT) and Cumulative irritation	CRLNJ2020-0493	5.3.5 CRLNJ2020-0493
	Evaluation of topically applied Bemotrizinol for human phototoxic potential	CRLNJ2020-0494	5.3.5 CRLNJ2020-0494
	Evaluation of topically applied Bemotrizinol for human photoallergic potential	CRLNJ2020-0495	5.3.5 CRLNJ2020-0495
<u>Efficacy</u>	In vivo determination of sun protection factor	Schrader HP-22-0682-1	5.3.5 HP-22-0682-1
	Evaluation of a sun protection product according to the FDA Document: Labelling and effective testing; Sunscreen drug products for Over-the-Counter Use, June 2011	Eurofins PC2022-0231	5.3.5 PC2022-0231
Post-Market Experience	Luna-Bastante L. et al. Contact Dermatitis- Contact Points; 26 December 2019: Allergic contact dermatitis to Tinosorb	doi:10.1111/cod.13460	5.4 Luna-Bastante L et al.

Study Type	Study Report Title ¹	Study Number	Location
<i>Case report</i>	<i>S. Scutellaria baicalensis</i> as well as other emerging allergens in cosmetics		
<i>Case report</i>	Suzuki K., et al. Contact Dermatitis. 2022 Jul;87(1):108-110. Allergic contact dermatitis caused by dimethicodiethylbenzylmalonate (polysilicone-15, Parsol SLX) and bis-ethylhexyloxyphenol methoxyphenyl triazine (Tinosorb S) in sunscreen cream	doi: 10.1111/cod.14112	5.4 Suzuki K. et al.
1. Bemotrizinol as the used test material is also referred to as CGF-C-1607, FAT 70'884, RM-60, or DNP-038124			