

MGF-400105
Bemotrizinol (BEMT)

2.7.2 Summary of Clinical Pharmacokinetic Studies

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2.7.2.1 Background and Overview

The product development process for BEMT followed the FDA guidelines outlined in *Nonprescription Sunscreen Drug Products — Safety and Effectiveness Data* (FDA 2016), *Guidance on Maximal Usage Trials for Topically Applied Active Ingredients* (FDA 2019), and several relevant ICH guidelines referenced in this submission. This approach also incorporated the agreed-upon tests, recommendations, and advice received from the FDA during a BEMT pre-IND meeting in June 2019, as well as the overall investigational plan outlined under IND 146892.

Among the completed clinical studies is a pharmacokinetic assessment of human systemic absorption of BEMT, conducted in a pivotal Maximum Usage Trial (MUsT). This trial was carried out in two parts: a 1-arm phase 2 pilot study and a 3-arm phase 3 pivotal study. An overview of the study protocol and a brief summary of the findings are presented in Table 1. Overall, the study results provided clinical evidence of the very low bioavailability of BEMT 6% when applied at maximum topical usage levels. Further details are provided in the following sections.

Table 1 Studies Conducted Under Clinical Development Program for BEMT

Clinical Study	Objective	Status
BEMT Pilot Maximum Usage Trial (MUsT) Spaulding Study # BEMT-001 Part 1*	This was Part 1 of a single clinical MUsT study conducted in 2 parts (Part 1: pilot study and Part 2: pivotal study). Part 1 was an open-label, 1-arm study that had the following objectives: Primary: To explore whether Bemotrizinol (PARSOL® Shield), is absorbed into the systemic circulation from a high-penetrating sunscreen formulation including 6% BEMT when applied under maximal-use conditions. Secondary: 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. Study summary submitted under IND 146892 Serial 0008, section 1.13.8.2.1.	Complete
BEMT Pivotal Maximum Usage Trial (MUsT) Spaulding Study # BEMT-001 Part 2	This was Part 2 of a single clinical MUsT study conducted in 2 parts (Part 1: pilot study and Part 2: pivotal study). Part 2 was an open-label, randomized, 3-arm study (n =162) with the following objective: Primary: To assess the systemic absorption and pharmacokinetics of 6% BEMT from 3 market image sunscreen formulations under maximal-use conditions. Study summary and report submitted under IND 146892 Serial 0011, section 5.3.3.1.	Complete

2.7.2.2 Summary of Results of Individual Studies

2.7.4.2.1. Pilot phase 1 study (BEMT-001 Part 1)

This was an open-label, 1-arm trial to determine if BEMT reaches quantifiable plasma concentrations after multiple-doses of one market-image sunscreen formulation containing 6% BEMT applied to 14 healthy adult participants. The single market-image formulation used was BEMT (PARSOL® Shield) 6%, with suitable solubilizers designated Formulation SU-E-101413-70: Sunscreen oil with 10% ethyl alcohol as penetration enhancer.

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Test participants demographics were as follows: of the 14 participants enrolled, 9 (64.3%) were White, and 5 (35.7%) were Black or African American, and most participants were not Hispanic or Latino (85.7%). The Fitzpatrick skin type assessments on Day –1 were IV (8 participants, 57%), III (5, 36%), and V (1, 7%).

Thirteen of 14 participants completed the dosing phase with one discontinued before Day 4 dosing. A total of 299 plasma samples collected and analyzed showed 13 samples (4.3%) with quantifiable BEMT, 9 (3.0%) as not reportable (NR) per the laboratory's standard operating procedure for lack of internal standard reproducibility after multiple assays, and 277 (92.6%) were BLQ (<0.5 ng/mL). In 7 (50%) participants BEMT was BLQ; in the remaining participants, 13 of 154 samples were quantifiable and the maximum number of quantifiable concentrations per participant was 1, 2, and 5 on Day 1, Day 4, and overall, respectively. All samples after 82 hours had BLQ BEMT concentrations. The small number (13/299; 4.3%) of quantifiable plasma samples precluded calculation of meaningful PK parameters for C_{max} and T_{max} on Days 1 and 4, and of C_{2h} and C_{trough} ; a plasma steady state could not be defined.

The test formulation was well tolerated with a low incidence of adverse events reported in 8 of 14 participants (57.1%), consisting primarily of mild skin irritation; the discontinued participant showed moderate severity erythema and urticaria (AEs were skin reactions: welts, erythema, and/or skin irritation on upper arms, abdomen, and/or lower back; moderate in severity; evidence of BEMT increased absorption did not occur as the participant had only 1 quantifiable BEMT concentration after 3 days' dosing.

The background and outcomes for this pilot MUsT were published recently (D'Ruiz et al. 2023). Preliminary clinical pharmacokinetic evaluation of Bemotrizinol - A new sunscreen active ingredient being considered for inclusion under FDA's over-the-counter (OTC) sunscreen monograph. DOI: <https://doi.org/10.1016/j.yrtph.2023.105344>).

A tabular summary of the phase 1 pilot MUsT study BEMT-001 is presented in Table 2.

Table 2 Summary of the phase 1 pilot MUsT study BEMT-001 (Part 1)

Clinical Study	Objective	Summary
BEMT Pilot Maximum Usage Trial (MUsT) Spaulding Study # BEMT-001 Part 1*	This was Part 1 of a single clinical MUsT study conducted in 2 parts (Part 1: pilot study and Part 2: pivotal study). Part 1 was an open-label, 1-arm study that had the following objectives: Primary: Assess whether Bemotrizinol (PARSOL® Shield), is absorbed into the systemic circulation from a high-penetrating sunscreen formulation including 6% BEMT when applied under maximal-use conditions. Secondary: 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.	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.

2.7.4.2.2. Pivotal Phase 3 Study (BEMT-001 Part 2)

Based on the Pilot study results and FDA comments, the study drug formulations were modified to remove the excipient butyloctyl salicylate and substitute BEMT compatible excipients while retaining the market image representation of each complete formulation. The study drug formulations were selected after an exhaustive market analysis search for BEMT containing sunscreen formulations. The Market Survey search for sunscreen products with a claimed sun protection factor between 1 and 100 identified 68,226 products listed globally (2019 and 2020). Of these identified products, 5,419 (7.94%) were found to contain BEMT as one of the UV absorbers present in the formulations. Like the first IVPT formulations, a completed second in vitro percutaneous permeation test with the modified formulations confirmed a low BEMT permeation and penetration.

The protocol and pivotal study for Part 2 incorporates findings and information gathered in the Part 1 Pilot study to assess if BEMT 6% is absorbed into systemic circulation after maximum topical applications to study participants for pharmacokinetic assessments. The study design was a 3-arm phase 3 clinical PK study with 162 healthy adults aged at least 18 years, and after informed consent was given, 54 each were assigned randomly to one of the 3 open-label treatments: T2 = BEMT 6% oil + penetration enhancer; T3 = BEMT 6% Oil-Water; T4 = BEMT 6% Water-Oil representing market image sunscreen formulations.

The pivotal clinical MUSt was conducted with a diverse American population-representative panel of 162 human participants exposed to maximal topical applications of 3 different market-like sunscreen formulations. These were identified after an exhaustive global market survey yielding over 68,000 finished products, among which were over 5400 targeted sunscreen products containing BEMT and were the foundation for selecting and formulating the study drug products for the MUSt. To ensure balanced and diverse representation of all subpopulations most likely to use products with BEMT in the future, a statistical factorial approach was used with respect to the following factors and subgroups: sex (female, male), age (18-40, 41-60, and 60+ years), and race (Group 1: Black or African Americans; Group 2: Hispanic or Latin Americans, Asians, Native Hawaiians, American Indians, Alaska Natives; and Group 3: White Americans).

As in the pilot phase the pivotal phase participants remained in-clinic for four days receiving 4 daily applications at 0, 2, 4, and 6 hours to 75% of body surface area each with 2 mg formulation/cm² of skin; 27.75 grams mean weight of study drug was applied per subject and application, which contained 1.66 grams BEMT for 6.66 g BEMT per day (111 mg/kg b.wt./day). Specific times of study drug applications and the blood sample times after first daily dose are shown in Table 3.

Table 3 Pivotal phase dose application and blood sample times

Study Drug Application: hours after 1st Dose		Blood Sample Times: hours after 1st Dose
Day1	0, 2, 4, 6	-0.5, 2, 4, 8, 12
2	24, 26, 28, 30	23.5, 28, 32
3	48, 50, 52, 54	47.5, 52, 56
4	72, 74, 76, 78 (last dose)	71.5, 74, 76, 78, 80, 82, 84, 86
5	None	96

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Each of the 162 participants completed the study and thereby delivered 23 plasma samples over 5 days constituting 3722 plasma samples. The BEMT LLOQ was validated at 0.1 ng/mL plasma.

The participants ranged in age from 21 to 82 years with a median of 51 years. Demographic characteristics well represented the American population across the study arms. Subjects had a mean age of 49.7 years (range: 21-82 years), mean weight of 77.16 kg, and a mean BMI of 26.67 kg/m². Approximately equal percentages of male (49.4%) and female (50.6%) subjects were enrolled. Subjects were predominantly White (61.1%) or Black or African American (30.2%). Most subjects were not Hispanic or Latino (76.5%). However, to ensure balanced representation of all subpopulations most likely to use products with BEMT in the future, a factorial approach was used with respect to the following factors and subgroups: sex (female, male), age (18-40, 41-60, and 60+ years), and race (Group 1: Black or African Americans; Group 2: Hispanic or Latin Americans, Asians, Native Hawaiians, American Indians, Alaska Natives; and Group 3: White Americans). A summary of the demographic and baseline characteristics for the Part 2 pivotal MUSt is presented in Table 4.

Table 4 Demographic and Baseline Characteristics – Part 2 Pivotal MUSt (BEMT-001)

Demographic Type	BEMT 6% oil (Without BOS) (N = 54)	BEMT 6% O/W (N = 54)	BEMT 6% W/O (N = 54)	Overall (N = 162)
Sex, n (%)				
Female	28 (51.9)	29 (53.7)	25 (46.3)	82 (50.6)
Male	26 (48.1)	25 (46.3)	29 (53.7)	80 (49.4)
Age (years)				
n	54	54	54	162
Min, Max	23, 82	28, 75	21, 72	21, 82
Race, n (%)				
American Indian or Alaska Native	0	1 (1.9)	1 (1.9)	2 (1.2)
Asian	2 (3.7)	0	0	2 (1.2)
Black or African American	16 (29.6)	16 (29.6)	17 (31.5)	49 (30.2)
Native Hawaiian or Other Pacific Islander	0	1 (1.9)	0	1 (0.6)
White	32 (59.3)	33 (61.1)	34 (63.0)	99 (61.1) 3
Multiple	2 (3.7)	0	1 (1.9)	(1.9)
Unknown	2 (3.7)	3 (5.6)	1 (1.9)	6 (3.7)
Ethnicity, n (%)				
Hispanic or Latino	10 (18.5)	13 (24.1)	15 (27.8)	38 (23.5)
Not Hispanic or Latino	44 (81.5)	41 (75.9)	39 (72.2)	124 (76.5)

Abbreviations: BOS, butyloctyl salicylate; Max, maximum; Min, minimum; O/W, oil-in-water; SD, standard deviation; W/O, water-in-oil.

The denominator for percentages is based on the number of subjects in the safety population in each treatment and overall, with data for the given characteristic.

Treatment is Bemotrizinol (BEMT), PARSOL® Shield, 6%, with suitable solubilizers, applied 4 times daily for 4 days as either a sunscreen oil with 10% alcohol as penetration enhancer (BEMT 6% oil without BOS), an oil-in-water emulsion (BEMT 6% O/W), or a water-in-oil cream emulsion (BEMT 6% W/O).

The study drug formulations were well tolerated throughout the study and all participants completed the full study. In the 162 participants 49 (30.2%) had at least 1 TEAE (treatment-emergent adverse event) related to treatment totaling 111 TEAEs. Skin and subcutaneous tissue disorders accounted for 39 (24.1%) of these events; the remaining events were fewer in numbers by event.

Plasma sample analysis showed that BEMT was relatively poorly absorbed across the treatment site skin and had a low bioavailability in each treatment group as apparent in

Figure 1. Most of the quantifiable samples had concentrations between 0.100 and 0.500 ng/mL. A relatively small percentage of samples (2.6%-3.4% per treatment and 3.0% Overall) had concentrations greater than or equal to 0.5 ng/mL, the regulatory threshold. The quantifiable samples appeared distributed into 2 groups: 0.503 to 5.91 ng/mL and 10.5 to 17.4 ng/mL, with only 4 samples in the group with concentrations greater than 5.91 ng/mL:

- 10.5 ng/mL at 56 hours (Day 3) for Subject 1-1136 (BEMT 6% O/W)
- 13.0 ng/mL at 82 hours (Day 4) for Subject 1-1100 (BEMT 6% O/W)
- 16.1 ng/mL at 56 hours (Day 3) for Subject 1-1028 (BEMT 6% W/O)
- 17.4 ng/mL at 82 hours (Day 4) for Subject 1-1158 (BEMT 6% oil [without BOS])

Although none of these 4 concentrations appeared reliable given the preceding and subsequent concentrations in the individual subject profiles, these 4 data points were included in the data set. It is notable that these 4 highest sample BEMT concentrations occur in 2 pairs of samples taken on the same days. It can not be ruled out that these unusually high BEMT concentrations might be attributed to a non-systematic contamination of plasma samples during PK sample collection, despite utmost care had been taken to prevent contamination on the collection site of the elbow. Details regarding how the PK sample collection site was protected, can be found in [section 2.7.2.5](#) Appendix. Briefly, the antecubital areas were covered bilaterally by wrapping multiple layers of 2-inch self-adhesive covering (Coban) on top of a gauze underneath the Coban during the clinical phase, including product administration. The product was not applied to the covered areas. For each PK sample collection, the covering was removed, the draw site was cleaned with an alcohol wipe before the draw took place. After the draw, the area was recovered with new gauze and self-adhesive covering.

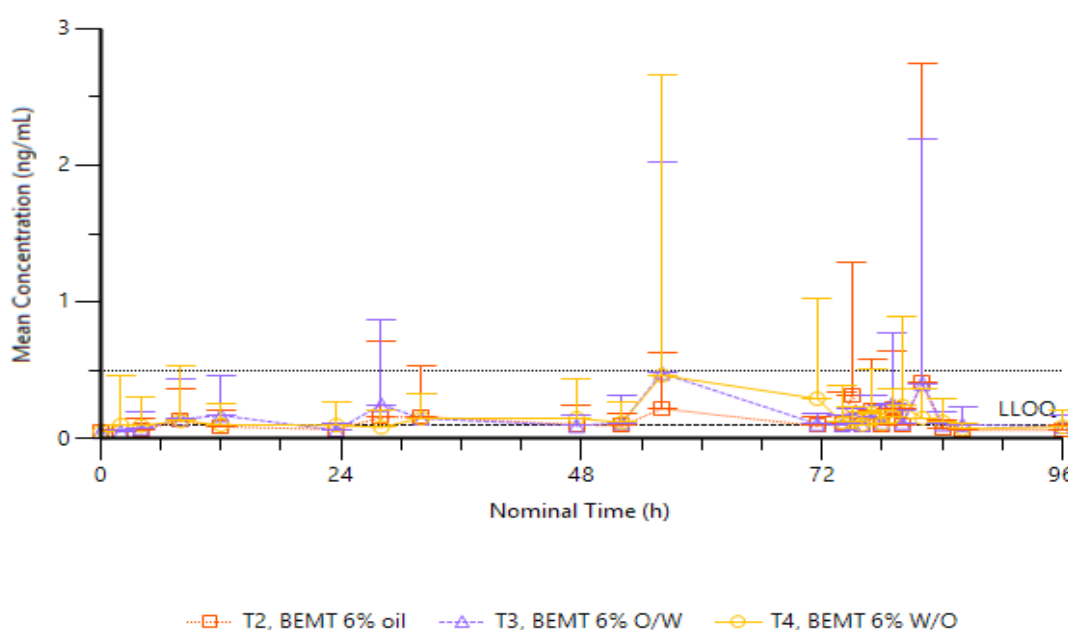


Figure 1 Number of subjects treated was 55, 53, and 54 for T2, T3, and T4, respectively. Concentrations below the lower limit of quantitation (ie, <0.100 ng/mL) were set to 0.050 ng/mL for figures. Standard deviation bars are only shown in 1 direction for a more legible display. Dashed line = lower limit of quantitation (LLOQ). Dotted line = 0.5 ng/mL, the maximum steady-state

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concentration expected to support a generally recognized as safe and effective (GRASE) determination for a sunscreen ingredient (Nonprescription Sunscreen Drug Products— Safety and Effectiveness Data, Food and Drug Administration, November 2016).

Summarized plasma concentration and estimated PK parameter results are:

- 70% of samples were below the LLOQ of 0.1 ng BEMT/mL plasma (BLQ).
- 97% of samples did not exceed FDA's threshold of 0.5ng/mL.
- Evidence was sparse, due to few quantifiable plasma results, for BEMT accumulation or steady-state BEMT concentrations above FDA's plasma threshold of 0.5 ng/mL, or the LLOQ of 0.1 ng/mL.
- Observation revealed 3, 4, and 4 pairs of consecutive concentrations >0.5 ng/mL, each in different participants in the 3 study arms. These 11 occurrences represent 0.47% to 0.66% of all samples measured per treatment group (next table and [Section 2.5.8.2](#)).
- The data are indicative of a poorly soluble, poorly absorbed compound and consistent with its low bioavailability and its physical-chemical characteristics.

The distribution of the BEMT concentration results for individual samples per treatment are shown in [Table 5](#).

Table 5 Summary Frequency of BEMT Concentration Results in the Pivotal MUsT

Formulation		< 0.1 ng/mL (BLQ)	> 0.1, <0.5 ng/mL	> 0.5 ng/mL	Consecutive Concentrations ≥0.5 ng/mL ¹	Total no. Samples Analyzed
BEMT 6% + 10% Ethanol	No.	924	341	32	3 pairs	1265
	%	73	27	1.5	0.47	
BEMT 6% Water-Oil	No.	791	451	42	4 pairs	1242
	%	64	36	3.3	0.64	
BEMT 6% Oil-Water	No.	866	353	39	4 pairs	1219
	%	71	29	3.1	0.66	
1. Only pairs of consecutive concentrations >0.5 ng/mL were seen in the individual plasma results. Each pair was in separate individuals; % values are calculated for 6, 8, and 8 samples.						

These summary data highlight the particularly low frequency of plasma concentrations exceeding 0.5 ng/mL across all treatment arms, with a slightly higher frequency of results above 0.1 ng/mL, and a high frequency of samples falling below the LLOQ. Additionally, the scarcity of sequential samples with BEMT concentrations above 0.5 ng/mL is evident (see section 2.5.8.2 for further details).

The mean plasma BEMT concentration-time profile (plotted on a semi-log scale) for all data points after Day 1 applications is shown in [Figure 2](#). Notably, the data reflect the rarity and inconsistency of measurable concentrations above the LLOQ, with an absence of sustained or consecutive measurable concentrations.

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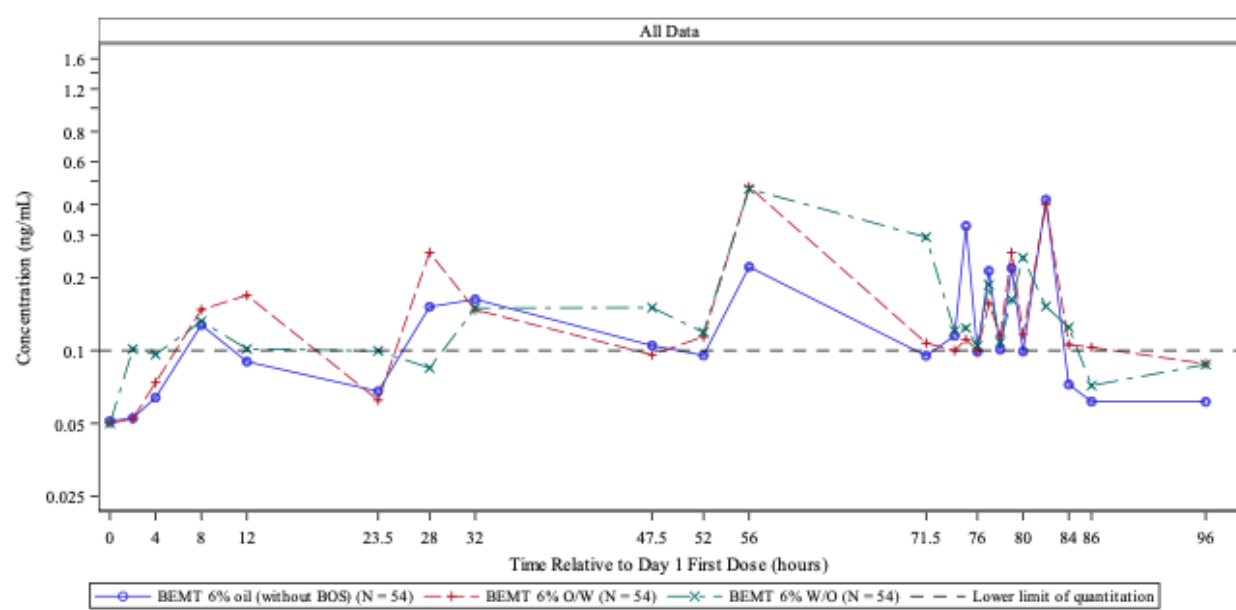


Figure 2 Mean plasma BEMT concentration-time profile (semi-log scale) for all data points after Day 1 (BEMT-001 Part 2)

Although 40% of subjects had at least one positive sample, these accounted for only 3% of the total, meaning 97% of samples showed no detectable levels of BEMT. Specifically, only 113 samples (3%) from 67 subjects exceeded 0.5 ng/mL out of a total of 3,722 samples. A detailed analysis was conducted on subjects with plasma BEMT concentrations higher than 0.5 ng/mL to determine possible contributing factors (Table 6 and Table 7).

Table 6 MUSt Subject Numbers with Frequency of plasma BEMT ≥ 0.5 ng/mL

113 samples (3%) with >0.5ng/mL out of 3722 samples analyzed					
		T2 Oil formulation	T3 O/W	T4 W/O	Total
No. of Samples >0.5ng/ml (% of 113)		32 (1.5%)	42 (3.3)	39 (3.1)	113
No. of Subjects affected (% of group)		22 (42%)	22 (42%)	23 (42%)	67
No. values >0.5 in one subject (none >6)	1	16	10	12	
	2	3	9	8	
	3	2	2	1	
	4	1	0	1	
	5	0	1	1	
Consecutive sample-timed concentrations		3 pairs	4 pairs	4 pairs	

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Table 7 Consecutive Formulation Samples Concentration > 0.5 ng/mL

Formulation		< 0.1 ng/mL (BLQ)	> 0.1 <0.5 ng/mL	≥ 0.5 ng/mL	Consecutive Concentrations ≥0.5 ng/mL ¹	Total no. Samples Analyzed
BEMT 6% + 10% Ethanol	No.	924	341	32	3 pairs	1265
	%	73	27	1.5	0.47	
BEMT 6% Water-Oil	No.	791	451	42	4 pairs	1242
	%	64	36	3.3	0.64	
BEMT 6% Oil-Water	No.	866	353	39	4 pairs	1219
	%	71	29	3.1	0.66	
1. Only pairs of consecutive concentrations >0.5 ng/mL were seen in the individual plasma results. Each pair was in separate individuals: % values are calculated for 6, 8, and 8 samples.						

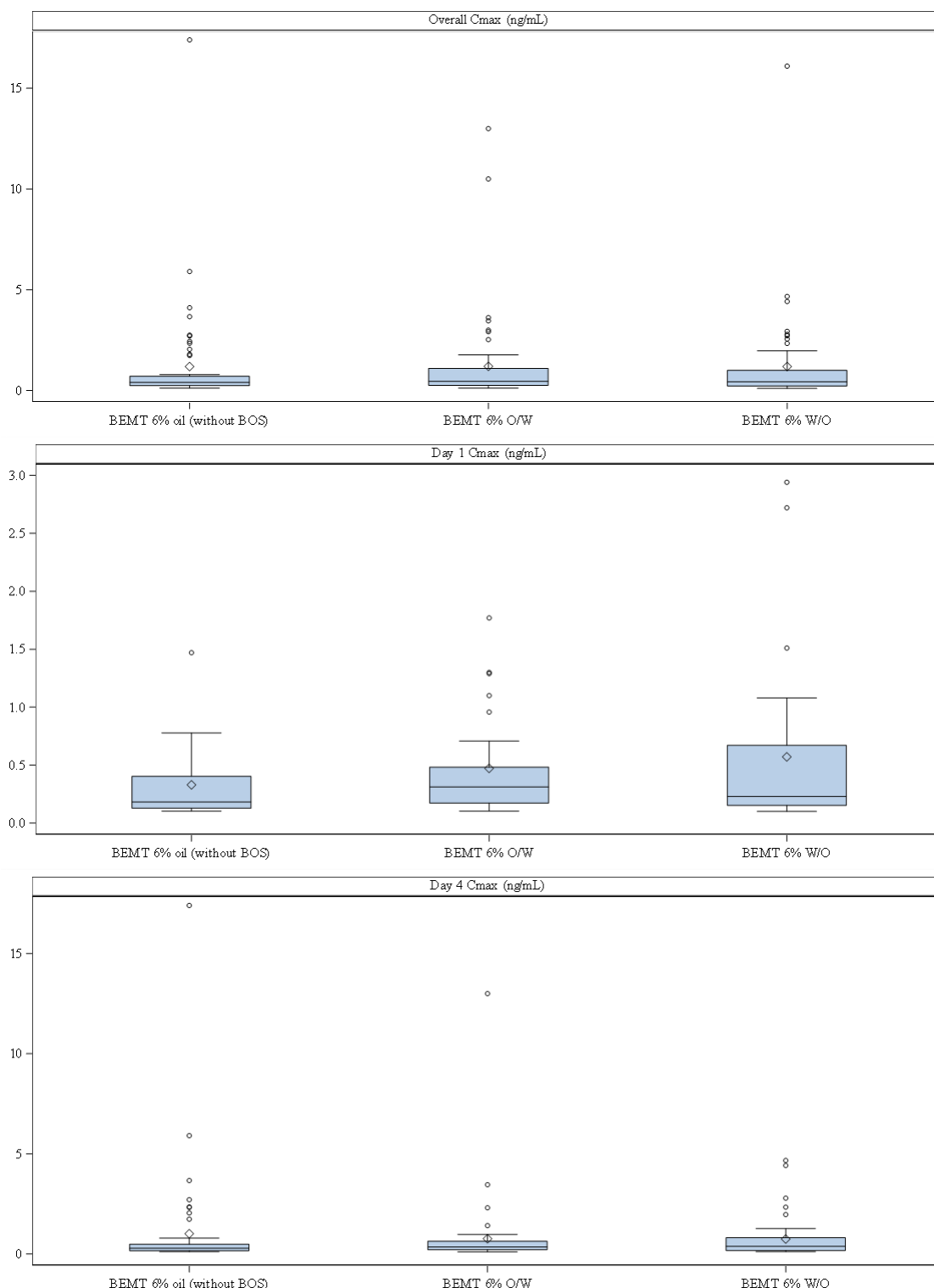
A review of the data suggests that the study design, intended to maximize passive diffusion, likely contributed to the higher observed values. Other key observations include:

- The results align with the excessive dosing regimen over the 4-day period, showing no significant bioavailability or absorption.
- Samples with a concentration > 0.5 ng/mL did not follow a consistent timing pattern, indicating random absorption events rather than systematic exposure.
- BEMT concentrations > 0.5 ng/mL were scattered across the study, with no evidence of systematic errors, contamination, or significant percutaneous absorption. Positive sequences were rare and occurred only in isolated pairs from different individuals.
- The number of samples above 0.5 ng/mL was similar across treatment groups (T2: 32, T3: 42, T4: 39), with affected subjects evenly distributed (22 or 23 per group).
- Samples exceeding 0.5 ng/mL were scattered across (sampling and analysis) time points and study days, with only 3-4 consecutive positive samples per group.
- Although one subject had five positive samples, concentrations were low and not representative of the broader population.
- Extensive contamination control measures minimized risk. The low number of positive samples relative to the total suggests minimal BEMT absorption, consistent with the pharmacokinetic analysis of 162 participants. Fewer than 50% of subjects in each treatment group had measurable BEMT, with overall low concentrations. Despite a high %CV in geometric mean C_{max}, only a slight increase in mean BEMT concentrations was observed from Day 1 to Day 4 across all groups.

Boxplots of the Overall, Day 1, and Day 4 C_{max} values from the primary analysis (all data, PK parameter population) are shown in [Figure 3](#). These boxplots show that mean and median C_{max} values were similar across the 3 treatments, and that a small number of subjects in each treatment had high C_{max} values that were outliers as noted above.

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Figure 3 Boxplots of Plasma Bemotrizinol Overall, Day 1, and Day 4 C_{max} for All Data, Primary Analysis – Part 2 (PK Parameter Population)



Abbreviations: BEMT, Bemotrizinol; BOS, butyloctyl salicylate; CV%, percent coefficient of variation; O/W, oil in water; PK, pharmacokinetic; W/O, water-in-oil.

Treatment was BEMT 6%, applied 4 times per day for 4 days, as either an oil (BEMT 6% oil [without BOS]), an O/W emulsion (BEMT 6% O/W), or a W/O cream emulsion (BEMT 6% W/O).

The box extends from quartile 1 (Q1) to quartile 3 (Q3). The whiskers extend from the minimum to the maximum values within the fence boundaries, calculated as $(Q1 - 1.5 \times [Q3 - Q1])$ and $(Q3 + 1.5 \times [Q3 - Q1])$. Outlier values that fall beyond the fence boundaries are plotted as separate symbols. The bar within the box represents the median and the diamond represents the arithmetic mean.

The primary PK analysis was consistent with the statistical analysis plan (Version 2.0).

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The results estimated for C_{max} , T_{max} and AUC values by treatment group are summarized in Table 8.

Table 8 Pivotal MUsT results estimated for C_{max} , T_{max} and AUC values by treatment group

Treatment Day	Primary Analysis Parameter ^{1,2,3}	BEMT 6% oil [n=52]	BEMT 6% O/W [n=53]	BEMT 6% W/O [n=52]
Overall ⁴	C_{max} (ng/mL)	0.5160 (160.9) [n=52]	0.5709 (148.0) [n=53]	0.5604 (158.5) [n=52]
	T_{max} (hr)	75.004 (3.92, 84.00) [n=52]	73.919 (8.00, 96.02) [n=53]	71.506 (1.92, 84.02) [n=52]
Day 1	C_{max} (ng/mL)	0.2383 (90.0) [n=22]	0.3412 (93.8) [n=27]	0.3157 (134.9) [n=24]
	T_{max} (h)	8.007 (1.92, 23.50) [n=22]	8.010 (1.92, 23.50) [n=27]	12.003 (1.92, 23.51) [n=24]
	AUC ₀₋₂₄ h*ng/mL	3.822 (94.2) (n=7)	6.611 (62.7) (n=6)	2.971 (90.1) (n=10)
	AUC _{last} h*ng/mL	1.278 (190.8) (n=22)	1.803 (189.4) (n=27)	2.222 (132.5) (n=24)
Day 4	C_{max} (ng/mL)	0.3784 (162.2) [n=49]	0.3856 (115.6) [n=48]	0.4410 (122.9) [n=45]
	T_{max} (h)	5.002 (0.00, 24.00) [n=49]	7.003 (0.00, 24.02) [n=48]	7.001 (0.00, 24.02) [n=45]
	AUC ₀₋₂₄ h*ng/mL	4.504 (62.2) (n=9)	4.512 (25.7) (n=19)	5.978 (40.1) (n=13)
	AUC _{last} h*ng/mL	1.595 (139.7) (n=24)	2.201 (134.6) (n=48)	2.285 (112) (n=45)
C_{max} and AUC parameters are presented as geometric mean (geometric CV%) by treatment. T_{max} is presented as median (minimum, maximum). - BLQ concentrations set to "missing". - The PK parameters are considered estimations as they are poorly substantiated due to the large number of missing plasma values (below LLOQ) and absence of consistent or consecutive measurable values. - A relative bioavailability assessment of the primary and secondary analysis results did not indicate a statistically significant difference between the treatments (the 90% CIs included 100% in all of the C_{max}, half of the AUC₀₋₂₄ and most of the AUC_{0-last} comparisons).				

An insufficient number of plasma concentration results precluded the calculation of AUC₀₋₂₄ for more than 60% of the subjects. However, it was estimated for approximately 11% to 19% of subjects on Day 1 and approximately 17% to 36% on Day 4. Similar to the plasma concentration parameter (C_{max}), plasma AUC_{last} was highly variable, with a geometric coefficient of variation (CV%) ranging from 112% to 191%. The geometric mean AUC_{last} was only slightly higher on Day 4 compared to Day 1 for each treatment. The terminal elimination coefficient (λ_z) and elimination half-life ($t_{1/2}$) could only be calculated for 2 or 3 individuals per treatment group (not shown). For secondary analysis, Day 1 BLQ values before the first drug application were set to zero, and all subsequent BLQ values were set to one-half of the

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LLOQ (0.05 ng/mL). Data from all subjects (PK concentration population) were included, with 4 unreliable concentrations excluded. Data not shown.

Although these parameters should be regarded as estimations with limited substantiation, given the scarcity of quantifiable plasma concentrations, they still serve as crucial indicators of the extremely low bioavailability of BEMT 6% applied at “worst case” maximum topical applications. Furthermore, a statistical assessment of the primary and secondary PK analysis of relative BEMT bioavailability across the three treatments demonstrated that the 90% CIs included 100% in all comparisons for both C_{max} and AUC_{0-last} . This indicates no substantial differences between treatments (source: CSR 11.4.1.3. Plasma Bioavailability Analysis of Bemotrizinol).

Overall, in plasma samples BEMT concentrations were above LLOQ in 31% (1169) of the 3722 plasma samples collected and analyzed from the 54 individuals in each of the three study arms; only 3% (113) of all samples had BEMT concentrations at or above a 0.5ng/mL threshold. Five of 162 subjects did not have any quantifiable BEMT concentrations in any of their 22 plasma samples.

Evidence was sparse, and due to the limited number of quantifiable plasma results, the estimations for BEMT accumulation or steady-state concentrations above the FDA’s plasma threshold of 0.5 ng/mL or the LLOQ of 0.1 ng/mL were poorly substantiated. Nonetheless, the data remain pivotal in demonstrating the very low bioavailability of BEMT 6% when applied at unreasonably high maximum topical doses (6.66 g/d; 111 mg/kg b.wt./d). These findings support the conclusion that there is no concern for human safety in the topical use of BEMT 6% in sunscreens.

Additionally, the low amount of BEMT absorption into systemic circulation further supports its sustained sun protection efficacy after topical application, as the active ingredient remains primarily on the skin where it can effectively absorb UV radiation without raising concerns about systemic exposure.

A tabular summary of the phase 3 pivotal MUSt study BEMT-001 is presented in [Table 9](#).

Table 9 Summary of PK Protocol No. BEMT-001 – Part 2 (Phase 3 pivotal MUSt study)

Study	Status	Summary
BEMT-001 - Ultraviolet Filter Bemotrizinol (BEMT): Clinical Pharmacokinetics Evaluation in a Topical Maximum Usage Trial (MUSt) - Protocol No. BEMT-001 – Part 2 (Phase 3 pivotal MUSt study)	Completed	Absorption of BEMT after topical applications of BEMT 6% sunscreen oil with 10% ethanol as penetration enhancer, BEMT 6% O/W emulsion, and BEMT 6% W/O cream emulsion applied 4 times per day for 4 days to 162 healthy subjects was limited, despite a more sensitive analytical method, with only 31.4% of the PK samples (1169/3722) having quantifiable concentrations (i.e., ≥ 0.100 ng/mL). Five (3.1%) of the 162 subjects had no quantifiable concentrations. For all treatments, geometric mean C_{max} tended to be higher on Day 4 than on Day 1, suggesting drug accumulation; however, geometric mean C_{max} values on Day 4 were below the 0.5 ng/mL threshold for all treatments. Only 7 subjects had sufficient data to estimate $t_{1/2}$. While a small number (3.0%) of BEMT samples analyzed in the pivotal study had concentrations ≥ 0.500 ng/mL, geometric mean C_{max} did not exceed 0.500 ng/mL on Day 1 or Day 4. The AUC_{0-24} could not be calculated for more than 60% of the subjects, although it could be estimated for

		approximately 11% to 19% of subjects on Day 1 and approximately 17% to 36% on Day 4. Bioavailability of BEMT was not different across the formulations based on statistical comparisons of C_{max}, AUC_{0-24}, and AUC_{0-last} on Days 1 and 4. Elimination rate $t_{1/2}$ found for 7 (2, 3, 2 per group) individuals & plasma steady state AUC above 0.5ng/mL was seen rarely in the participants. Evidence was sparse due to few quantifiable plasma results for BEMT accumulation or steady-state BEMT concentrations above FDA's plasma threshold of 0.5 ng/mL, or the LLOQ of 0.1 ng/mL. Consecutive samples with BEMT >0.5 ng/mL occurred in 3, 4, and 4 pairs of BEMT results in different individuals of each treatment group. BEMT is poorly soluble and poorly absorbed as seen from its low bioavailability in the MUsT with its exaggerated topical dosing regimen. Subjects had a mean age of 49.7 years (range: 21-82 years), mean weight of 77.16 kg, and a mean BMI of 26.67 kg/m². Approximately equal percentages of male (49.4%) and female (50.6%) subjects were enrolled. Subjects were predominantly White (61.1%) or Black or African American (30.2%). Most subjects were not Hispanic or Latino (76.5%). However, to ensure balanced representation of all subpopulations most likely to use products with BEMT in the future, an experimental approach was used for recruitment into the following factors and subgroups: sex (female, male), age (18-40, 41-60, and 60+ years), and race (Group 1: Black or African Americans; Group 2: Hispanic or Latin Americans, Asians, Native Hawaiians, American Indians, Alaska Natives; and Group 3: White Americans). From a safety perspective, topical applications of BEMT 6% sunscreen oil with 10% ethanol as penetration enhancer, BEMT 6% O/W emulsion, and BEMT 6% W/O cream emulsion applied 4 times per day for 4 days were safe and generally well tolerated.
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2.7.2.3 Comparison and Analyses of Results Across Studies

Not applicable

2.7.2.4 Special Studies

Not applicable

2.7.2.5 Appendix

Clinical practice regarding product application and the protection of PK sample collection site

The application did include 4 times per day, without showering or washing the product off in between applications – showering did not occur until the next morning. To re-outline the application process, male subjects wore shorts, female subjects wore shorts and chest covering such as a sports bra or swimsuit top. Subjects also wore eye coverings during the application process. Application of the product included the torso/neck areas anteriorly and posteriorly avoiding the covered antecubital areas and the hands – application went to the point of the wrist, bilateral lower extremities anteriorly and posteriorly to the point of the ankles – product was not applied to the feet, and face application included the cheeks and forehead to the hairline while avoiding the periorbital and perioral regions. Subjects were instructed to not touch the areas of application.

MGF-400105

Bemotrizinol (BEMT)

During the clinical phase, including the product administration, the antecubital areas were covered bilaterally with gauze and self-adhesive covering to avoid contamination. The product was not applied to the covered areas. The antecubital areas were covered bilaterally with 2-inch Coban (3M™ Coban™ Self-Adherent Wrap) with 1-2 4"x4" folded gauze underneath the Coban. The site was wrapped with multiple layers (typically 2-3 layers of Coban, as exemplified in [Figure 4](#)). At the time of the PK sample draw, the Coban and gauze were removed from the draw site and disposed of. The staff member drawing the blood cleaned the draw site thoroughly with an alcohol pad. The draw site is allowed to dry prior to introduction of the needle. The staff member drew the blood at the timepoint and then passed the draw tube off to our PK sample processing staff members so they can begin the processing steps such as centrifuge, splitting and freezing. During the draw process, the staff member drawing the blood changes gloves between subjects. Also, those processing PK samples did not have direct contact with the subject's skin. At the completion of the draw, the antecubital area was wrapped with new Coban and gauze.



Figure 4 Exemplified coverage of the antecubital area with 2-inch Coban and gauze