Drug Delivery Solutions Ltd.
(Part of MC2 Therapeutics)
C/O: Agern Allé 24-26, 2970 Hørsholm,
Denmark

Clinical Study Protocol

MC2-01 Cream (Calcipotriene/Betamethasone Dipropionate 0.005/0.064 w/w%)

Sponsor Protocol No. MC2-01-C10

TKL Study No. PB710518

A 6-Week, Randomized Study to Evaluate the Potential of MC2-01 Cream to Induce a Photoallergic Skin Reaction in Healthy Subjects, Using a Controlled Photopatch Test Design

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Synopsis

Study Title:	A 6-Week, Randomized Study to Evaluate the Potential of MC2-01 Cream to Induce a Photoallergic Skin Reaction in Healthy Subjects, Using a Controlled Photopatch Test Design
TKL Study Number:	PB710518
Sponsor Protocol Number:	MC2-01-C10
Sponsor:	Drug Delivery Solutions Ltd. (Part of MC2 Part of MC2 Therapeutics) C/O: Agern Allé 24-26, 2970 Hørsholm, Denmark
Development Phase:	1
IND Number:	127152
Study Objectives:	The primary objective of this study will be to determine the photoallergic potential of MC2-01 Cream when topical application to healthy skin is followed by light exposure. In addition, safety will be assessed by evaluation of any AEs reported during the study.
Study Design:	During the 3-week Induction Phase, MC2-01 Cream and MC2-01 Vehicle, will each be applied 2 times per week (Monday and Thursday) to 2 sites on the infrascapular area of the back under semi-occlusive patch conditions for approximately 24 hours (± 4 hours). Minimal erythema dose (MED) irradiation will also be performed for each subject on Day 1. After approximately 24 hours (± 4 hours) patches are removed, all application sites will be evaluated, and one application site of each study product will be irradiated with 2 times the subject's MED using the full Xenon lamp spectrum. All sites will be evaluated post irradiation at approximately 48 hours later when irradiated on Tuesdays and 72 hours later when irradiated on Fridays. If a subject misses an irradiation session during the Induction Phase, an additional application of study product may be applied on the Monday of the rest period (week 4) and an additional irradiation approximately 24 hours (± 4 hours) after application has occurred. At Challenge, MC2-01 Cream and MC2-01 Vehicle will each be applied once to 2 naïve sites on the infrascapular area of the back under semi-occlusive patch conditions for approximately 24 hours (± 4 hours). After patch removal, all application sites will be evaluated, and one site of each test product will be irradiated with 6 J/cm^2 of Ultraviolet A (UVA) followed by 0.5 times the subject's MED of UVA/Ultraviolet B (UVB). An additional untreated site will also be irradiated at Challenge and will serve as an untreated control. Each site, including the untreated control site, will be evaluated again at approximately 24 hours, 48 hours, and 72 hours following irradiation. A Rechallenge will be performed if a cutaneous response observed during the Challenge Phase indicates possible photosensitization or at the discretion of the Investigator.
Planned Sample Size:	50 evaluable subjects
Study Population:	Healthy adult male and female volunteer subjects
Investigational Products:	MC2-01 Cream MC2-01 Vehicle
Control:	An untreated irradiated control site.

Efficacy Evaluation Criteria:	Not applicable
Safety Evaluation Criteria:	The safety endpoints for this study are irritation responses during the Induction Phase, positive responses at Challenge (ie, reactions indicative of a sensitization response) and adverse events. All local and systemic adverse events (AEs) observed by or reported to the Investigator throughout the study will be evaluated. The intensity, duration, and causal relationship to the investigational products (IPs) are to be rated for all AEs.
Statistical Methods:	The focus of the statistical analysis will be the comparison with controls of the photoallergic response to the study products. The diagnosis of photosensitization response will be made by the Investigator based on review of the observed skin responses after Challenge. The mean score by subject and treatment, including all scores assigned during Induction, will be analyzed using Fisher's least significant differences in the analysis of variance (ANOVA) with factors subject and treatment. All pairwise comparisons will be performed: MC2-01 Cream on both the irradiated and non-irradiated sites, and MC2-01 Vehicle on both the irradiated and non-irradiated sites.
Number of Study Centers:	Single Center

Signature page

Product names: **MC2-01 Cream**
MC2-01 Vehicle

TKL Study number: **PB710518**

Sponsor protocol number: **MC2-01-C10**

The signatures of the following representatives constitute their approval of this protocol and provide the necessary assurances that this study will be conducted according to all stipulations stated in the protocol, including all statements as to confidentiality. It is also agreed that the study will not be initiated without the approval of an appropriate Institutional Review Board.

Approved by the following:

MC2 Therapeutics:

Johan Selmer, MD *Chief Medical Officer*	Johan Selmer Johan Selmer (Jan 14, 2019) Signature	Jan 14, 2019 Date

TKL Research, Inc.:

Maureen Damstra *Director, Clinical and Photobiology*	Maureen Damstra Maureen Damstra (Jan 10, 2019) Signature	Jan 10, 2019 Date
Michael Tuley, PhD *Sr. Director, Data Management, Biostatistics, and Medical Writing*	Michael Tuley, PhD Michael Tuley, PhD (Jan 10, 2019) Signature	Jan 10, 2019 Date

Signature page for the Principal Investigator

Product names: **MC2-01 Cream**
MC2-01 Vehicle

TKL Study number: **PB710518**

Sponsor protocol number: **MC2-01-C10**

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Jonathan S. Dosik, MD
Principal Investigator

Jonathan Dosik, MD
Jonathan Dosik, MD (Jan 10, 2019)
Signature

Jan 10, 2019
Date

Investigators and study administrative structure

Name	Affiliation / Address	Responsibility
MC2 Therapeutics	C/O: Agern Allé 24-26, 2970 Hørsholm, Denmark	Sponsor
TKL Research, Inc.	TKL Research, Inc. One Promenade Blvd., Suite 1101/1201 Fair Lawn, NJ 07410	CRO
Lærke K. Kyhl, MD	MC2 Therapeutics C/O: Agern Allé 24-26, 2970 Hørsholm, Denmark ☎ +45 29246928 e-mail: lky@mc2therapeutics.com	Senior Medical Adviser
Birgitte Vestbjerg	MC2 Therapeutics C/O: Agern Allé 24-26, 2970 Hørsholm, Denmark ☎ +45 20772575 e-mail:bve@mc2therapeutics.com	Director Clinical Operation
Jonathan S. Dosik, MD	TKL Research, Inc. One Promenade Blvd., Suite 1201 Fair Lawn, NJ 07410 ☎ (201) 587-0500, ext. 2562 🗐 (201) 773-7371 e-mail: jdosik@tklresearch.com	Principal Investigator
Michael Tuley, PhD	TKL Research, Inc. One Promenade Blvd., Suite 1201 Fair Lawn, NJ 07410 ☎ (201) 587-0500, ext. 2608 🗐 (551) 497-6696 e-mail: mtuley@tklresearch.com	Senior Director, Biostatistics and Data Management
Maureen Damstra	TKL Research, Inc. One Promenade Boulevard, Suite 1201 Fair Lawn, NJ 07410 ☎ (201) 587-0500, ext.2229 🗐 (201) 773-7371 e-mail: mdamstra@tklresearch.com	Director of Clinical Studies
Kathy Oneglia	TKL Research, Inc. 1 Promenade Boulevard, Suite 1201 Fairlawn, NJ 07410 ☎ (201) 587-0500, ext.2526 🗐 (201) 773-7371 e-mail: koneglia@tklresearch.com	Associate Clinical Research Coordinator
Allyson Marshall, PhD	TKL Research, Inc. One Promenade Blvd., Suite 1201 Fair Lawn, NJ 07410 ☎ (201) 587-0500, ext. 2522 🗐 (201) 296-66660 e-mail: amarshall@tklresearch.com	Sr. Medical Writer

Table of Contents

List of Tables

List of Abbreviations

AE	Adverse Event
ANOVA	Analysis of Variance
API	Active Pharmaceutical Ingredients
B17P	Betamethasone 17-Propionate
BDP	Betamethasone Dipropionate
CAL	Calcipotriene, Anhydrate
CFR	Code of Federal Regulations
CRF	Case Report Form
DMP	Data Management Plan
EEC	European Ethics Committee
EOS	End of Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigational Brochure
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IEC	International Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine Device
IUS	Intrauterine System
MC2-01	Calcipotriene/Betamethasone Dipropionate 0.005/0.064 w/w%
MED	Minimal Erythemal Dose
MedDRA	Medical Dictionary for Regulatory Activities
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OTC	Over-the-counter
PAD™	Polyaphron Dispersion Technique
PI	Principal Investigator
PMD	Primary Medical Doctor
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOPs	Standard Operating Procedures
TEAE	Treatment-emergent Adverse Event
TKL	TKL Research, Inc.
UBC	United BioSource Corporation
UPT	Urine pregnancy test
US	United States
UV	Ultraviolet
UVA	Ultraviolet A
UVB	Ultraviolet B

1. INTRODUCTION

This study evaluates the potential of MC2-01 (Calcipotriene/betamethasone dipropionate 0.005/0.064 w/w%) Cream to induce a photoallergic skin reaction using a controlled photopatch test design. Because MC2-01 Cream is formulated for topical use and has shown to absorb light within the range of natural sunlight (290-400 nm), it is necessary to determine the potential of this product to cause a photoallergic reaction after application to the skin.

The study will be conducted in compliance with Food and Drug Administration (FDA) regulations, the ethical principles of the Declaration of Helsinki concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964 and amendments 2013), the International Conference on Harmonization (ICH) – Good Clinical Practice (GCP) Guidelines as currently amended, and all applicable standard operating procedures (SOPs) of TKL Research, Inc. (TKL).

1.1. Background Information

MC2-01 Cream contains two active pharmaceutical ingredients (APIs): the vitamin D3 analogue calcipotriene 0.005% as anhydrate (CAL) and the glucocorticosteroid betamethasone 0.064% as betamethasone dipropionate (BDP). Use of the combination of vitamin D and corticosteroids for the treatment of plaque psoriasis has proven very effective and safe both for acute treatment and for long-term maintenance therapy.[1,2] This combination is today approved in different formulation worldwide, including an ointment, a gel-topical suspension and a foam, under different brand names. A combination of CAL/BDP is recommended by both European guidelines[3-5], the Canadian Dermatology Association[6], and by the American Academy of Dermatology[7] as a first line treatment of mild to moderate plaque psoriasis.[8]

This Phase I study will assess the photosensitization potential of MC2-01 Cream.

1.1.1. The MC2-01 Cream Formulation

The currently marketed products of this drug combination are restricted to non-aqueous oil-based formulations that are sticky and inconvenient to many patients[9], as it has not previously been possible to co-formulate CAL and BDP in an aqueous formulation due to very different pH requirements for long-term stability of the two compounds.

The MC2-01 Cream is an aqueous formulation designed for patient-friendly treatment of psoriasis vulgaris. The cream has been developed using the Polyaphron Dispersion Technique™ (PAD™) Technology which protects the drug substances from degrading during storage. The MC2-01 Cream is easy to apply, and the cosmetic appearance is that of a white, easily-spreadable cream that absorbs completely into the skin a few minutes after application.

The concentrations of CAL and BDP in the MC2-01 cream are identical to the concentrations in already-marketed CAL/BDP medicinal products, which have been found to be efficacious and safe.[8]

1.1.2. MC2-01 Cream – Non-clinical Data

The safety profiles of topical applied CAL and BDP has, in numerous preclinical studies, been found benign. The systemic absorption of CAL and BDP through intact skin of rats, minipigs, and humans from the marketed products is very small. The main adverse local effects identified in non-clinical toxicology studies with topical products containing CAL and BDP are skin irritation due to the CAL component and skin atrophy due to the BDP component.

In vitro skin penetration studies comparing MC2-01 Cream with the marketed Daivobet® Ointment (in US marketed as Taclonex® Ointment) and Daivobet® Gel (in US marketed as Taclonex® Topical Suspension) indicate that the transdermal penetration of CAL and BDP from the MC2-01 Cream is in the same range as that seen with Daivobet® Ointment and Daivobet® Gel.

A 4-week local tolerance study conducted with MC2-01 Cream in minipigs showed that this formulation was well tolerated and without systemic effects. There was no obvious difference with respect to the local skin tolerance between MC2-01 Cream and the reference Daivobet® Gel.

In an 8-week study in minipigs, the toxicological profile, safety, as well as the pharmacokinetic profile of MC2-01 Cream and Daivobet® Ointment was investigated after daily applications on 10% of the surface area of the animals. None of the animals showed signs of systemic toxicity, and the study showed that the MC2-01 Cream had a higher local tolerance compared to Daivobet® Ointment. Very few samples had quantifiable plasma concentrations of the parent compounds BDP and CAL. The majority of animals had measurable levels of the BDP metabolite betamethasone 17-propionate (B17P), and the pre-dose plasma levels of B17P at Day 22 were essentially similar between the two treatment groups.[8]

1.1.3. MC2-01 Cream – Clinical Data

The marketed formulations of the CAL/BDP combination are known as efficacious and safe drugs for the treatment of plaque psoriasis. According to the USPI for Taclonex® Topical Suspension, only a limited number of adverse reactions has been reported. There were no adverse reactions reported that occurred in ≥1% of subjects treated with Taclonex® Topical Suspension and at a rate higher than in subjects treated with vehicle. Similar safety profiles are reported with Taclonex® Ointment and Enstilar® Foam.

Available data on MC2-01 cream suggest that MC2-01 cream displays a similar safety profile as the approved CAL/BDP topical products. A Phase 3 trial with MC2-01 cream has been completed. The Phase 3 trial including 794 subjects was a randomized, investigator-blind, multicentre, vehicle and comparator controlled, parallel-group, 3-arm trial, designed to show therapeutic non-inferiority of MC2-01 cream to Taclonex® Suspension in subjects with mild-to-moderate psoriasis vulgaris. The primary objective of demonstration of non-inferiority of MC2-021 compared to Taclonex® Suspension was met. The PGA treatment success was higher in the MC2-01 cream group (40.1% of subjects achieved treatment success; 95% CI 34.5, 45.6) compared with the active comparator group (24.0% of subjects achieved treatment success; 95% CI 19.0, 29.0). A subsequent post hoc analysis of treatment efficacy of MC2-01 cream compared to active comparator was performed on the PGA and other disease activity measures based on

the ITT population. The PGA treatment success rate was found to be statistically significantly higher in the MC2-01 cream group compared to the active comparator at Weeks 4 (24.18 vs. 12.9, p=0.0001), Week 6 (32.95 vs. 20.16, p<0.0001), and Week 8 (37.38 vs. 22.75 p<0.0001). Similar statistical superiority of MC2-01 cream over Taclonex® Suspension was demonstrated for the modified PASI score (excluding the face).

The type and incidence of AEs were as expected based on the known safety profile as the marketed products containing CAL/BDP at identical concentrations (w/w 0.005%/0.064%). The incidence of treatment emergent adverse events (TEAEs), related TEAEs, and lesional and lesional/perilesional AEs was low and comparable between MC2-01 cream and Taclonex® Suspension. TEAEs were most frequently reported in the SOC "infections and infestations" but with no difference in incidence between MC2-01 cream, Taclonex® Suspension, and vehicle. Furthermore, most of these TEAEs were judged not to be related to trial medication. Also, the incidence of TEAEs related to "General disorders and administration site reactions" were low and similar between the three trial arms. Finally, the trial did not indicate a significant effect of MC2-01 cream or Taclonex® Suspension on calcium homeostasis.

2. STUDY OBJECTIVES

The primary objective of this study will be to determine the photoallergic potential of MC2-01 Cream when topical application to healthy skin is followed by light exposure.

In addition, safety will be assessed by evaluation of any AEs reported during the study.

3. INVESTIGATIONAL PLAN

3.1. Study Design

This will be a randomized, double-blind, single-center, controlled, within-subject comparison study of the investigational products (IPs), MC2-01 Cream, MC2-01 Vehicle, and an untreated irradiated control site in healthy volunteer subjects. A total of 8 application sites (2 cm x 2 cm each) will be marked on the subject's back and distributed so that 4 sites are on one side of the back for induction, and 4 sites are on the other side for challenge patches. The IPs will be applied in two sets. One set of patches on the back will be designated for irradiation after approximately 24 hours (± 4 hours) of study product application and the other set will remain non-irradiated. An additional site will be marked on the back during Challenge. The site will receive no treatment but will be irradiated at Challenge to serve as an untreated irradiated control.

A defined area (approximately 50 cm^2) on the infrascapular region of each subject's back will be irradiated to determine the minimal erythemal dose (MED) of ultraviolet (UV) light.

During the 3-week Induction Phase of the study, 0.2 g of each study product will be applied to 2 sites twice each week (Monday and Thursday) for approximately 24 hours (± 4 hours) under semi-occlusive patch conditions (6 applications). After patch removal, all application sites will be evaluated, and one application site of each study product will be irradiated with 2 times the subject's MED using the full Xenon lamp spectrum. The sites will be evaluated by a trained evaluator. All sites will be reevaluated post irradiation, at approximately 48 hours later when irradiated on Tuesdays and at approximately 72 hours later when irradiated on Fridays except when irradiated on the last Friday of the Induction Phase or after the last make-up visit (if required), the sites will not be evaluated because these readings are not used for determination of photosensitization and any response will have subsided by Monday. These procedures will be performed each week for 3 weeks of the Induction Phase. Dermal reactions at the application sites will be evaluated using a visual scale that rates the degree of erythema, edema, and other signs of cutaneous irritation (see Table 3 and Table 4).

At the end of the Induction Phase, the subjects will enter a Rest Period of 10-17 days and then a Challenge Phase. One application/irradiation session may be missed during the Induction Phase. If a subject misses an irradiation session during the Induction Phase, an additional application/irradiation session will be scheduled the Monday of rest period (week 4).

At Challenge, each study product will be applied in an amount of 0.2 g to 2 naive sites once for approximately 24 hours (±4 hours) under semi-occlusive patches. After 24 hours (±4 hour) of product application, all sites will be evaluated, and one application site of each product and the additional untreated site will be irradiated. The sites will be examined for dermal reactions at approximately 24 hours (±4 hours), 48 hours (±4 hours), and 72 hours (±4 hours) post-irradiation. A Rechallenge should be performed if a cutaneous response observed during the Challenge Phase indicates possible photosensitization or at the discretion of the Investigator.

The safety endpoints for this study are irritation responses during the Induction Phase, positive responses at Challenge (ie, reactions indicative of a sensitization response) and AEs.

3.2. Discussion of Design

Results are interpreted according to working criteria which are based upon published works, as well as the clinical experience of TKL. These working criteria are periodically reviewed and amended subject to new information that becomes available.

This photoallergy study is designed to detect the ability of the MC2-01 Cream and MC2-01 Vehicle to cause photoallergic skin reactions when exposed to sunlight. Each subject is to receive applications of the MC2-01 Cream and MC2-01 Vehicle to 2 separate sites. One will be irradiated, and one will remain non-irradiated. An untreated site will also be irradiated at Challenge. This design provides built-in controls for the test product (MC2-01 Cream) under both irradiated and non-irradiated conditions.

3.3. Study Population

3.3.1. Subject Population

A sufficient number of subjects will be enrolled in order to provide 50 completed subjects evaluable for analysis; an individual subject will be allowed to participate in the study one time only.

A rationale for the choice of sample size is provided in Section 4.2 of this protocol.

3.3.2. Inclusion and Exclusion Criteria

Inclusion Criteria

A subject will be considered eligible for participation in the study if all of the following inclusion criteria are satisfied prior to randomization:

1. Is a healthy male or female (to be confirmed by medical history);
2. Is 18 years of age or older;
3. Agree not to participate in any clinical or patch test studies at Day 1 through study completion;
4. Females of childbearing potential must use a highly effective method of contraception (ie, a method with a failure rate of less than 1% per year when used consistently and correctly) for one month prior to Screening and until the end of study (EOS) visit has been performed. Highly effective contraception is defined as follows:
    a. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibitor of ovulation (oral, injectable, implantable, transdermal, intravaginal)
    b. Intrauterine device (IUD)
    c. Intrauterine hormone-releasing system (IUS)
    d. Bilateral tubal occlusion
    e. Vasectomized partner (Provided that is the sole sexual partner of the subject and that the vasectomized partner has received medical assessment of the surgical success)

f. Sexual abstinence (if in line with the preferred and usual lifestyle of the subject and defined as refraining from heterosexual intercourse during the entire period of the trial

*Periodic methods of abstinence (e.g. calendar, ovulation, symptothermal, post ovulation methods) are not accepted methods of contraception).

5. In the case of a female of childbearing potential, has a negative urine pregnancy test (UPT) on Day 1 prior to randomization and are willing to submit to a UPT at the EOS;
6. In the case of a female of non-childbearing potential, has had a hysterectomy or is postmenopausal (at least 1 year with no menses prior to enrollment);
7. Is free of any systemic or dermatological disorder, which, in the opinion of the Investigator, will interfere with the study results or increase the risk of AEs;
8. Has uniformly-colored skin on the infrascapular region of the back which will allow discernment of erythema, and has Fitzpatrick Skin Types I, II, or III (see Table 1);
9. Complete a medical screening procedure; and
10. Read, understand, and sign an informed consent.

Exclusion criteria

A subject who has any of the following will be excluded from the study:

1. Has a history of photosensitivity or photoallergy;
2. Has any visible skin disease at the application site which, in the opinion of the Investigator, will interfere with the evaluation of the test site reaction;
3. Current or past history of hypercalcemia, vitamin D toxicity, severe renal insufficiency, or severe hepatic disorders;
4. Is using systemic/topical corticosteroids within 3 weeks prior to and/or during the study, or systemic/topical antihistamines 72 hours prior to and during the study;
5. Is not willing to refrain from using systemic/topical anti-inflammatory analgesics such as aspirin (81 mg daily aspirin will be allowed), Aleve, Motrin, Advil, or Nuprin for 72 hours prior to and during the study (occasional use of acetaminophen will be permitted);
6. Are taking medication known to cause phototoxic reactions (eg, tetracyclines, thiazides, nonsteroidal anti-inflammatory drugs [NSAIDS]);
7. Is using medication which, in the opinion of the Investigator, will interfere with the study results (e.g. anti-inflammatory medications, antipsychotics, anticonvulsants with potential pain relief effects, immunomodulatory medications);
8. Is unwilling or unable to refrain from the use of sunscreens, cosmetics, creams, ointments, lotions or similar products on the back during the study;
9. Has psoriasis and/or active atopic dermatitis/eczema;
10. Has a known sensitivity or allergy to constituents of the materials being evaluated;

11. Is a female who is pregnant, plans to become pregnant during the study, or is breast feeding a child;
12. Has damaged skin in or around the test sites, including sunburn, excessively deep tans, uneven skin tones, tattoos, scars, excessive hair, numerous freckles, or other disfigurations of the test site;
13. Has received treatment for any type of internal cancer within 5 years prior to study entry;
14. Has a history of, or are currently being treated for skin cancer and/or hepatitis;
15. Has a history of, or is currently being treated for diabetes;
16. Has any condition that might compromise study results;
17. Is expected to sunbathe or use tanning salons during the study;
18. Has a history of adverse response (eg, blistering, sun poisoning) to UV sun lamps/sunlight exposure;
19. Is currently participating in any clinical testing;
20. Has any known sensitivity to adhesives; and/or
21. Has received any investigational drug(s) within 28 days from Day 1.

3.3.3. Interruption or Discontinuation of Treatment

A reaction of at least moderate erythema (2) accompanied with mild, but definite edema (1) to a study product observed after the first patch application/irradiation sequence of the Induction Phase may indicate the subject to be pre-sensitized and may cause the discontinuation of the subject from the study.

After the second reading of the Induction Phase, either of the following conditions will require that the study product be applied to a naïve patch site under open patch conditions:

- Reaction of >50% “p” or “p” with no erythema, mild but definite erythema, moderate or severe erythema; or “D” (see Table 3 and Table 4);
- Any reaction of definite erythema (mild, moderate or severe) with definite edema.

Study product may not be relocated more than twice.

If the reactions noted above occur on an irradiation day during the Induction Phase, the sites will not be able to be irradiated. Patches will be relocated at the subject’s next visit.

The 3 weeks of continuous patch contact during the Induction Phase frequently results in tape-related irritation that is exacerbated by warm weather, but which occurs among some individuals irrespective of the season. Tape-related irritation will not be graded as a photosensitivity response at the patch site but will be noted separately on the case report form (CRF). Severe tape-related irritation will necessitate a change in the application site. As above, the application site will only be changed twice and then the subject must be discontinued.

One application/irradiation session may be missed during the Induction Phase. In case of a missed application/irradiation, an additional application/irradiation during Week 4 must be

performed. In this case, no evaluation will be required following irradiation. Only one missed patch application or irradiation is allowed. A subject must be discontinued and considered not complete if more than one application or irradiation is missed.

In accordance with legal requirements and ICH-GCP guidelines, every subject has the right to refuse further participation in the study at any time and without providing reasons (see also Section 5.3). A subject's participation is to be terminated immediately upon his/her request. The Investigator should seek to obtain the reason and record this on the CRF.

If at the time of refusal, a study product has already been administered, the subject should be advised on follow-up safety investigations. If a subject withdraws from the study, all efforts will be made to complete a final evaluation if possible. Subjects experiencing an AE will be followed until the AE is resolved, a reasonable explanation is provided for the event, or the subject is referred to his/her own primary medical doctor (PMD). The specific AE in question will be recorded on the appropriate CRF.

If a subject develops a serious adverse event (SAE), his/her termination from the study will be considered by the Investigator. Similarly, if the subject develops conditions over the course of the study which would have excluded his/her entry in the study according to the safety-related medical exclusion criteria, he/she must be withdrawn immediately.

The subject may be withdrawn from the study at any time at the discretion of the Investigator for medical reasons and/or due to non-adherence to the treatment scheme and other duties stipulated in the study protocol. The reasons are to be documented on the CRF.

In addition, the Sponsor retains the right to end the study at any time if the study cannot be carried out as agreed upon in the protocol. In case of premature termination or suspension of the study, the Sponsor's study manager will promptly inform the Investigator/institutions and regulatory authorities of the termination or suspension and the reason for that. It is the responsibility of the Principal Investigator (PI) to notify the Institutional Review Board (IRB) in the case of premature termination/suspension.

3.3.4. Withdrawals

The following medical and other reasons justify a premature termination (by subject or Investigator) of any of the study PI.

- Adverse Event/Serious Adverse Event
- Death
- Protocol Violation (e.g. non-compliance)
- Investigator Judgment
- Pregnancy
- Lost to Follow-up
- Withdrawal by Subject
- Study Terminated by Sponsor

- Other

If a subject withdraws from the study, all efforts will be made to complete a final evaluation, if possible. Subjects discontinued for having experienced an AE will be followed until the AE is resolved, a reasonable explanation is provided for the event, or the subject is referred to his/her own PMD. The specific AE in question will be recorded on the appropriate CRF.

3.4. Treatments

3.4.1. Investigational Products and Control

Investigational Products:

MC2-01 Cream

MC2-01 cream contains 0.005% w/w CAL (as anhydrate) and 0.064% w/w% BDP and is filled in sealed, collapsible aluminum tubes as primary packaging material. The MC2-01 cream formulation contains 70% oil and 30% aqueous external phase at approximately neural pH. The oil fully solubilizes the drug substances and provides semi-occlusiveness important for skin penetration, while the aqueous external phase contributes to the skin feel. The cosmetic appearance is a white easily spreadable cream with high oil content that absorbs completely into the skin within few minutes of application.[8]

MC2-01 Vehicle

MC2-01 Vehicle contains no active components.

MC2-01 Cream and MC2-01 Vehicle will each be applied in an amount of 0.2 g to 2 sites (2 cm x 2 cm) on the infrascapular area of the subjects' backs for 24 hours (±4 hours) under semi-occlusive patch conditions (Webril®). The patches will be secured to the skin with airtight nonporous Blenderm® tape. This will be repeated twice each week during the 3-week Induction Phase, once on Monday during rest week 4 as applicable (if a subject misses a visit and doesn't apply the IPs) and once at Challenge. One application site of each study product will be irradiated and the other will remain non-irradiated.

Lot numbers will be given in the clinical study report.

Manufacturer: DPT Laboratories, Ltd.

307 E. Josephine St.

San Antonio, Texas 78215

Control

An untreated irradiated site will serve as a control.

3.4.2. Description of Investigational Products

The IPs (MC2-01 Cream and MC2-01 Vehicle) will be supplied in collapsible aluminum tubes for the clinical study. MC2-01 Cream and MC2-01 Vehicle were manufactured and packaged in accordance with good manufacturing practice (GMP).

3.4.3. Description of Patch Conditions

Material evaluated under semi-occlusive patch conditions is applied to a 2 cm x 2 cm Webril® pad. The pad is affixed to the skin with hypoallergenic tape (Micropore).

Material evaluated under open (non-occlusive) conditions is applied directly to a 2 cm x 2 cm area of the skin, which is then loosely covered by gauze secured on 2 sides with Micropore tape.

3.4.4. Packaging/Labeling

The study product tubes labels will contain, at a minimum, the following information:

- Name and address of the Sponsor
- Protocol number
- Name and address of manufacturer
- Date of manufacture
- Lot / batch number
- Tube contents
- Storage conditions
- Caution statements:
  - "New Drug – Limited by Federal Law to Investigational Use"
  - "Flammable"
  - "Keep out of reach of children"

A full product description can be found in the Investigator's Brochure (IB).[8]

MC2-01 Cream and MC2-01 Vehicle must be stored at 2°-8°C (36°-46°F) in a temperature-controlled cabinet at the clinical site. MC2-01 will not be dispensed to individual subjects during this clinical study but may be stored at temperatures below 25°C (77°F) during the product application visits. The PI will be responsible for the suitable storage of the IPs in compliance with the storage instructions and must restrict access to the investigative personnel only.

3.4.5. Assignment to Treatment

3.4.5.1. Randomization

Each subject who signs an informed consent form (ICF) will be assigned a screening number. If the subject meets all of the inclusion and none of the exclusion criteria, and successfully completes the screening procedures, they will be enrolled in the study. Upon enrollment, each subject will be assigned a unique subject number and receive a randomization code, indicating application placement of the study materials. Each subject in this study will serve as his or her own control. All subjects will receive MC2-01 Cream and MC2-01 Vehicle at adjacent application sites, i.e. study product placement on the left side will be the same as on the right side.

The MC2-01 Cream and MC2-01 Vehicle will be assigned in a randomized sequence to the test sites. The same study material will be applied to the same test site throughout the Induction Phase and to a naïve site at Challenge and Rechallenge Phases (if applicable).

3.4.5.2. Blinding

The treatments (MC2-01 Cream and MC2-01 Vehicle) will not be blinded to investigative personnel involved in the preparation/application and removal of treatments.

Investigative personnel who are involved in the preparation/application and removal of the treatments will be unblinded and will not perform the evaluation of skin responses. The subjects and the trained evaluator who will be evaluating skin responses will be blinded to IPs and the treatment allocation; however, because of the demarcations/skin coloration remaining on the skin following patch removal, complete blinding of the evaluators cannot be completely assured.

Investigative personnel who are blinded, including the Investigator and trained evaluator involved in the evaluation of responses, will remain blinded during the course of the study until Database Lock and finalization of the Statistical Analysis Plan (SAP).

In the event of an emergency, if possible, the Investigator or designee will contact the Sponsor with notification of the intent to unblind the treatment codes prior to the actual unblinding. If it is not possible to notify the Sponsor prior to the unblinding, the Investigator or designee will contact the Sponsor immediately following the unblinding procedure and follow with a written notification to document the exact manner in which the code was broken and the justification for the unblinding. The Investigator will communicate the treatment identification to only the investigative personnel who require the information to manage the emergency. Unblinding will happen on site at TKL.

3.4.6. Prior and Concomitant Therapy

All medications, including over the counter (OTC) drugs and vitamins, taken within 28 days prior to the start of the study will be recorded at Screening. Thereafter, a record of all medications taken during the course of the study will be made. Information regarding the total daily dose, route of administration, start and discontinuation dates, and indication are to be captured on the subject's CRF.

The following prohibitions will apply for the duration of the study:

- There will be no use of systemic/topical anti-inflammatory analgesics which in the opinion of the investigative personnel will interfere with the study results, including anti-inflammatory medications such as aspirin (81 mg aspirin will be allowed at the discretion of the Investigator), Aleve, Motrin, Advil, or Nuprin for 72 hours prior to and during the study (occasional use of acetaminophen will be permitted);
- There will be no use of systemic/topical corticosteroids within 3 weeks prior to and/or during the study;
- There will be no use of systemic/topical antihistamines 72 hours prior to and during the study;

- There will be no use of medication known to cause phototoxic reactions (e.g., tetracyclines, thiazides, NSAIDs);
- There will be no use of medication which, in the opinion of the Investigator, will interfere with the study results (e.g. anti-inflammatory medications, antipsychotics, anticonvulsants with potential pain relief effects, immunomodulatory medications, and others);
- There will be no use of sunbeds or sunlamps or deliberate exposure of the test sites to natural sunlight or to other sources of UV light;
- There will be no participation in any other clinical study;
- There will be no soaking of test areas; and/or
- There will be no application of any product to the test areas.

The use of or change in the dose of any and all concomitant medication, either prescription or OTC, during the study will be recorded. The reason for use or change of dose of a concomitant therapy may need to be reported as an AE. Therapies (medication and non-medication therapies) not restricted by the protocol may be used. Non-prohibited chronic therapies being used at Baseline may be continued.

All topical or systemic medication listed in the exclusion criteria are prohibited during this study.

See the IB for information about possible drug-drug interactions.[8]

3.4.7. Treatment Compliance

All patches will be applied and removed by investigative personnel. Whereas bathing will be allowed (low tub bath/frontal showers), the patched areas are not to be soaked and are to be kept as dry as possible, per the instructions to be given to each subject. Subjects will be instructed to contact the Investigator before starting any medication, including OTC remedies. In the case of an emergency treatment, the Investigator must be informed as soon as possible. A trained, experienced evaluator will assess study compliance.

Records of patch applications and visit schedule compliance will be recorded on the subjects' CRFs.

If individual patches become dislodged or are misplaced, such that continuous contact with the skin has been interrupted, the subject will be discontinued from further participation in the study.

3.5. Visit Schedule and Assessments

3.5.1. Study Procedures and Visit Schedule

Screening

At Screening, the subjects will receive any necessary written and verbal information, and the informed consent of each subject will be obtained. Demographic data (including Fitzpatrick skin type) will be recorded, a medical history will be taken, and previous and concomitant medications will be reviewed. Eligibility will be determined by review of the inclusion/exclusion criteria.

- Any written and verbal information
- Informed consent
- Demographics
- Previous/concomitant medication
- Review of inclusion and exclusion criteria
- Medical history (including lifestyle and habits)
- Evaluation of application site area

Table 1: Fitzpatrick Skin Types

I	Always burns easily, never tans
II	Always burns easily, tans minimally
III	Burns moderately, tans gradually
IV	Burns minimally, always tans well
V	Rarely burns, tans very well
VI	Never burns, deeply pigmented[10, 11]

Day 1

On Day 1, all subjects will be questioned regarding the entry criteria and female subjects of childbearing potential will undergo a UPT. If the subject fulfills all of the inclusion and none of the exclusion criteria, he/she will be allowed participation in the study. Concomitant medications and AEs will be reviewed and recorded at this visit.

Upon enrollment, each subject will be assigned a unique subject number and receive a randomization code, indicating application placement of the study products.

A baseline evaluation of the patch sites will be performed immediately prior to application of the patches to ensure that no conditions, markings, or coloration of the skin will interfere with interpretation of the study results.

A total of 4 application sites (2 cm x 2 cm each) will be planned on each subject's back. Prior to patching, sites will be marked with site numbers. The distance between the patches will be no less than one centimeter. The numbering of the test sites will remain the same throughout the study. The sites will be marked with an indelible, surgical marker.

Minimal Erythema Dose Determination

On Day 1, subjects will have an area of skin on their back, approximately 50 cm^2, divided into 6 equal sites marked with a surgical marker. The duration of UVA/UVB irradiation for minimal

erythema dose (MED) exposure will be calculated based on subjects' Fitzpatrick Skin Type and the output of the solar simulator. The solar simulator output will be measured prior to each irradiation. Details of the UV irradiation including output of the simulator, time of exposure, equipment used, and staff performing irradiations will be documented. Each of the sites will be irradiated with full spectrum UV light (UVA/UVB), with each exposure differing from the next by a factor of 1.25 (ie, each irradiated site will be exposed to a 25% greater dose of UV irradiation than the previous site).[12]

The areas involved in MED determination will be different from the study product application sites. Evaluation of the exposed sites will be performed on Day 2.[12]

On Day 2, a trained evaluator will examine the 6 irradiated sites and determine the MED for each subject. To determine the MED the sites are read and scored by the trained evaluator for the presence of erythema. There will be a main evaluator for the study; a backup evaluator will also be assigned in the event that an emergency occurs, and the main evaluator is unable to attend the study visit. The lowest exposure dose of the 6 irradiated sub-sites showing an erythema response is selected as the minimal erythema dose (see Section 3.5.7 for scoring scale).

Induction

The Induction Phase consists of a series of 6 patch applications of the study products (twice a week [Monday and Thursday] and subsequent irradiation [Tuesday and Friday] and evaluations of the patch test sites [Thursday and Monday]) over a 3-week Induction Phase.

Under semi-occlusive conditions, 0.2 g of each study product, MC2-01 Cream and MC2-01 Vehicle will be applied to two Webril® patches. The patches will then be applied to their assigned sites on the back for Induction for 24 hours (±4 hours). This process will be repeated twice each week (Mondays and Thursdays) during the 3-week Induction Phase. The patches will be secured to the skin with airtight nonporous Blenderm® tape. The same study product will be applied to the same test site throughout the Induction Phase.

Application sites will be evaluated immediately prior to study product application.

After 24 hours (±4 hours) of study product application (eg, Tuesday and Friday), all patches will be removed. The sites will be evaluated using the scoring system detailed in Section 3.5.7.1. One set of patches will be assigned for irradiation and the other will remain non-irradiated, ie, only one application site of each study product will receive irradiation. On all Tuesdays and Fridays, the sites designated for irradiation will be irradiated with 2 times the subject's MED using the full Xenon lamp spectrum.

Adverse events and concomitant medications will be reviewed at each visit and recorded as applicable.

One application/irradiation session may be missed during the Induction Phase. If a subject misses an irradiation session during the Induction Phase, an additional application/irradiation session will be scheduled the Monday of rest period (week 4).

Rest Period (Weeks 4 and 5)

During the Rest Period of approximately 10-17 days, subjects will not receive any application of study materials. An additional application of study product may be applied on the Monday of the

rest period (week 4) if the subject misses an irradiation session during the Induction Phase of the study.

Challenge (Week 6)

On Day 1 of the Challenge Phase, subjects who have completed the Induction Phase and the Rest Period will have study product applications to naïve sites in the same manner as applied during the Induction. As in the Induction Phase, 0.2 g of MC2-01 Cream and MC2-01 Vehicle will each be applied to 4 assigned sites for Challenge for approximately 24 hours (±4 hours) under semi-occlusive patch conditions. A baseline evaluation of the naïve sites will be performed immediately prior to application of the patches to ensure that no conditions, markings, or coloration of the skin will interfere with interpretation of the study results. The clinical staff will then remove the patches and a trained evaluator will evaluate the test sites. The designated sites and an additional untreated site will be irradiated with 6 J/cm^2 of UVA (320-400 nm) followed by 0.5 times the MED of UVA/UVB (full-spectrum) irradiation, obtained by using a filtered light source (see Section 3.5.4). Each site will be evaluated again at approximately 24 hours (±4 hours), 48 hours (±4 hours), and 72 hours (±4 hours) post irradiation.

Adverse events and concomitant medications will be reviewed at each visit and recorded as applicable. A UPT will be performed for female subjects of childbearing potential at the last study visit (if rechallenge is not required).

Rechallenge

A Rechallenge should be performed if a cutaneous response observed during the Challenge Phase indicates possible photosensitization or at the discretion of the Investigator. If it is determined by the Investigator that a Rechallenge should be performed, the Rechallenge patches will be applied as soon as Challenge reactions have resolved. Just as in the Challenge procedure 0.2 g of each study product MC2-01 Cream and MC2-01 Vehicle will each be applied to 4 naïve sites for approximately 24 hours (±4 hours) using appropriate patches to further discriminate a photosensitization reaction from an irritation reaction. A baseline evaluation of the naïve sites will be performed immediately prior to application of the patches to ensure that no conditions, markings, or coloration of the skin will interfere with interpretation of the study results. Approximately twenty-four (24) hours (±4 hours) after study product application, the clinical staff will remove the patches and a trained evaluator will evaluate the test sites. One site of each product and an additional untreated site will be irradiated with full spectrum UV light (UVA/UVB) using a filtered light source. All sites (irradiated and non-irradiated) will be graded for dermal reactions at approximately 24 hours (±4 hours), 48 hours (±4 hours), and 72 hours (±4 hours) following irradiation. Concomitant medications and AEs will also be reviewed. A UPT will be performed for female subjects of childbearing potential at the last study visit.

End of Study

At the EOS, all patches will be removed as described above, and the final evaluations of the test sites will be made.

An EOS examination will be conducted and consist of the following:

- Concomitant medication

- AEs
- UPT in females of childbearing potential

Concomitant medications and AEs will be reviewed and recorded during the whole study. For a detailed listing of scheduled study time points refer to the Visit Schedule and Assessments (Table 2).

3.5.2. Visit Schedule

A summary of the visit schedule and assessments is presented in Table 2.

Table 2: Visit Schedule and Assessments

Treatment Period	**Screening**	**Day 1[a] (M)**	**Induction (Weeks 1-3)**				**Rest (Weeks 4-5)**	**Challenge (Week 6)**				
Study Days			**M 8, 15**	**Tu 2, 9, 16**	**Th 4, 11, 18**	**F 5. 12, 19**		**M 36**	**Tu 37**	**W 38**	**Th 39**	**F 40**
Informed consent	X											
Inclusion/Exclusion	X	X										
Medical history	X											
Demographic information	X											
Fitzpatrick Skin Typing	X											
UPT		X										X
MED irradiation/evaluation		X[b]		X[c]								
Randomization		X										
Product application		X	X		X			X				
Application site evaluations		X	X	X	X	X[d]		X	X	X	X	X
Application site irradiation				X		X[d]			X			
Untreated control site irradiation									X			
Make-up evaluation/ application							X[e]					
Make-up evaluation/ irradiation							X[e]					
Review of concomitant medications	X	X	X	X	X	X	X[f]	X	X	X	X	X
Review of AEs	X	X	X	X	X	X	X[f]	X	X	X	X	X

a Screening and the first day of Induction (Day 1) may take place on the same day.
b MED irradiation on Day 1.
c MED evaluation on Day 2.
d Evaluations will not be conducted after irradiation on the last Friday of the Induction Phase.
e Make-up evaluation/application and evaluation/irradiation are performed as necessary (see Section 3.5.1).
f Concomitant medications and AEs will be reviewed only for subjects who are required to return to the test facility for make-up visits during Rest Period - Week 4.

Note: The visit schedule may be revised if necessary.

3.5.3. Definition of Minimal Erythemal Dose

Minimal erythemal dose is defined as the length (in time) of light exposure required to produce a minimal erythema reaction 16 - 24 hours after irradiation using a standardized filtered UV light source that emits UVA/UVB (full spectrum) irradiation as part of its emission spectrum.[12]

3.5.4. Light source

The light source will be a Xenon Arc Solar Simulator (150 W), with UV-reflecting dichroic mirror, UVC-blocking filter, and visible/infrared blocking filter to generate a continuous emission spectrum in the UVA and UVB range (290 to 400 nm).[12] An additional filter is added during irradiation of the 6 J/cm2 of UVA (320-400 nm) to the test sites to block UVB radiation allowing only UVA irradiation of the sites. The output is measured daily prior to irradiation using a radiometer/photometer.

3.5.5. Background Information

Date of birth, gender, race, Fitzpatrick skin type (see Table 1), and a significant medical history of each subject will be recorded at Screening.

3.5.6. Efficacy Assessments

No efficacy will be assessed in this study.

3.5.7. Safety Assessments

3.5.7.1. Patch Test Site Evaluations

For both Induction and Challenge Phases, after 24 hours (±4 hours) of product application, all sites will be evaluated, and one application site of each product and the additional untreated site will be irradiated. The sites will be examined for dermal reactions at approximately 24 hours, 48 hours, and 72 hours post-irradiation.

The scores in Table 3 will be used to express the response observed at the time of examination and will be recorded on the subjects' CRFs. The score will be used for statistical analysis. Additional response notations are presented in Table 4. The same evaluator (where possible) should perform the assessment throughout (from Induction to Rechallenge) the study.

Table 3: Response Scores

Response	Symbol	Numerical Equivalent Score
Erythema		
No reaction	-	0
Mild, but definite erythema	+	1
Moderate erythema	++	2
Marked/severe erythema	+++	3
Edema		
No reaction	-	0
Mild, but definite edema	**	1
Definite edema with erosion/vesiculation	***	2

Table 4: Notations

Response/Comment	Notation
Hyperpigmentation	Hr
Hypopigmentation	Ho
Vesiculation	V
Papular response	p
Papulovesicular response	pv
Damage to epidermis: oozing, crusting, and/or superficial erosions	D
Itching	I
Spreading of reaction beyond patch study site (ie, reaction where material did not contact skin)	S
Follicular irritation with or without pustule formation (folliculitis)	f
Subject absent	X
Patch dislodged	PD
Not patched	NP
No reaction	0

The readings will be made under a standardized white light source.
The 3-week period of patch contact during the Induction Phase may result in tape-related irritation in some individuals. Tape related irritation will not be graded as an irritant response at the patch site but will be noted separately on the CRF.

The Investigator will assess the reactions seen during the Challenge Phase and determine whether the subject is photosensitized or not. The following guidelines are generally considered in this assessment. Not all observations of erythema and edema are associated with photosensitivity; only if erythema and edema are observed can a reaction be suspected of being a positive photosensitivity reaction. An increase in the intensity of the reaction over time further supports an assessment of photosensitivity. If reactions are observed at both the irradiated and non-irradiated study product sites (ie, if contact sensitization may have occurred), the reaction at the irradiated site upon Rechallenge must be at least one grade more intense than at the non-irradiated site for the reaction to be suspected of being a photosensitivity reaction (refer to Section 3.5.7.1 for response scores and notations).

3.6. Adverse Events

3.6.1. Method of Determining Adverse Events

Safety assessments will include recording AEs reported spontaneously by the subject or collected by the Investigator. Adverse events will be collected during the period from the time of the signature of the informed consent form and first trial-related activity performed until the end of the trial. Adverse events will be recorded at each visit throughout the study on the appropriate CRF. Every attempt should be made to describe the AE in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events.

Subjects should be asked whether, since the time of the last observation or visit, they had any of the following:

- Experience any changes in well-being;
- Used any new medications other than those permitted in the inclusion criteria;
- Changed medication regimens (both prescription and OTC); and/or
- Were admitted to a hospital or had any accidents.

All questions should be of a general nature and should not suggest symptoms.

When an AE is suspected, all relevant evaluations will be carried out and appropriate treatment provided. Additional follow-up will be done as necessary (Section 3.6.4) and recorded in the subject's source documents, and the results will be provided to the Sponsor.

For AE definitions and reporting requirements refer to Section 3.6.2 and Section 3.6.3.

Note: Any observed response which can be denoted using the irritation criteria summarized in Table 3 and Table 4 will not be considered an AE. Likewise, any tape-related irritation will only be noted as an AE when all patches are discontinued due to tape reaction around all sites (see Section 3.6.6).

3.6.2. Adverse Event Definitions

3.6.2.1. Adverse Events

Information about all local and systemic AEs, whether volunteered by the subject, discovered by Investigator questioning, or detected through other means, will be collected and recorded on the AE CRF and followed as appropriate.

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product (or cosmetic product), which does not necessarily have a causal relationship with this treatment. An AE can therefore, be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal IP, whether or not considered related to the medicinal IP.

Any AE that is considered related to the IP must be followed by the investigator until it is resolved or until the medical condition of the subject is stable; all relevant follow-up information will be reported to MC2 or designee. Adverse Events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Medical conditions/diseases present before starting study treatment are considered AEs only if they worsen after starting study treatment (any study procedures specified in the protocol). Any AEs occurring before starting study treatment but after signing the ICF are recorded on the Medical History/Current Medical Conditions CRF.

To the extent possible, each AE will also be described by:

1. its duration (start and end dates),
2. the severity grade (mild, moderate, severe)
3. its relationship to the study drug,
4. the action(s) taken, and
5. as relevant, the outcome.

Note: Any observed response which can be denoted using the irritation criteria summarized in Table 3 and Table 4 will not be considered an AE. Likewise, any tape-related irritation will not be noted as an AE.

The outcome of an AE will be classified as recovered, recovered with sequelae, recovering/resolving, ongoing, or death.

3.6.2.2. Serious Adverse Events

A "SAE" is any AE that:

- Results in death;
- Is life-threatening (Note: the term "life-threatening" refers to any AE that, as it occurs, puts the subject at immediate risk of death. It does not refer to an AE that hypothetically might have caused death if it were more severe).

- Results in hospitalization or prolongation of current hospitalization (not including hospitalization for a pre-existing condition that has not increased in severity or frequency from the subject's underlying medical condition prior to entry into the study).
- Is a congenital anomaly/birth defect in the offspring of a subject.
- Is another serious (important medical events) event.
- Results in persistent or significant disability/incapacity.

(Note: Important medical events may not be immediately life-threatening or result in death or hospitalization but may be considered serious when, based on the appropriate medical judgment, they may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or development of drug dependency or drug abuse.)

3.6.2.3. Severity of Adverse Events

The Investigator is to classify the severity (intensity) of an AE according to the following definitions:

- Mild – The subject was aware of the signs and symptoms, but the signs and symptoms were easily tolerated and do not interfere with daily activity.
- Moderate – The signs and symptoms were sufficient to restrict, but did not prevent, usual daily activity for the subject. The subject is still able to function.
- Severe – The subject was unable to perform usual daily activity.

The maximum intensity of an AE (mild, moderate, or severe) will be assessed taking into account the possible range of intensity of the symptom(s).

3.6.2.4. Relationship of Adverse Events to Study Treatments

The Investigator is responsible to assess the relationship of an AE to the IP treatment using good clinical judgment and definitions outlined in Table 5.

Table 5: Relationship of AE to Study Drug

Association	Definition
Not related	The AE is clearly explained by another cause not related to the IP administration; the temporal relationship of the AE to IP administration makes a causal relationship unlikely, or, concomitant medication, therapeutics interventions, or underlying condition provide a sufficient explanation for the observed AE
Possibly Related	The AE and administration of IP are temporally related, but the AE can be explained equally well by causes other than the IP administration
Probably Related	The AE and use of IP are temporally related, and the AE is more likely explained by IP administration than by other causes
Definitely Related	The AE and IP administration are related in time, and a direct association can be demonstrated. Concomitant medication, therapeutics interventions, or underlying conditions do not provide a sufficient explanation for the observed AE

3.6.3. Reporting Adverse Events

Adverse events that occur from the time of informed consent through completion of the last study visit should be reported.

Every attempt should be made to describe the AE in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

Any SAEs occurring in a subject receiving study drug must be reported to the Sponsor within 24 hours of the site being informed of the event, even if the event does not appear to be drug-related. The report must be made by sending a completed SAE Report form to the Sponsor. Any pertinent follow-up information should be provided in a similar manner. Contact information is provided in Section 3.7.1.

3.6.4. Adverse Event Follow-up

Any ongoing AE at the time of study completion or withdrawal will be followed until the AE is resolved or the subject is referred to his/her own PMD. The Investigator and the Sponsor will decide if longer follow-up is appropriate on a case-by-case basis. Subjects who experience any clinically significant AE will remain under medical supervision until the Investigator or the Sponsor's Medical Monitor deems the AE to be resolved, stabilized, or no longer serious enough to warrant follow-up.

3.6.5. Pregnancy reporting

Prior to study enrollment, females of childbearing potential must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy.

A UPT will be performed on all females of childbearing potential at Day 1 (day of first patch application) and EOS. All women of childbearing potential will receive a UPT prior to the first study drug administration and the study drug must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive any study drug and must not be enrolled in the study.

Pregnancy follow-up should be reported to the IRB within 24 hours of first knowledge on a Pregnancy Report Form. Follow up will describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects.

3.6.6. Expected Adverse Events

Any observed response in the patch test area that can be denoted using the irritation criteria summarized in Table 3 and Table 4 will not be considered an AE.

Tape related reactions will only be recorded as AEs when the subject is discontinued due to tape reaction.

3.7. Instructions for Rapid Notification of Serious Adverse Events

3.7.1. Safety Contact person and number

Serious adverse events and pregnancies must be reported immediately (i.e., not later than 24 hours after first knowledge). The SAE or pregnancy report should be e-mailed or faxed to United BioSource Corporation (UBC) using the following e-mail or fax-number:

Email: EUSafety@ubc.com

Fax: +41 225 964 446

3.7.2. Reporting Responsibility

Any death, SAE, pregnancy, (see Section 3.6), or unusual frequency of AEs, must be reported immediately (i.e., not later than 24 hours after first learning of its occurrence) to the Sponsor's study manager by the Investigator, even if the event(s) appear to be unrelated to study treatment. Follow-up information about a previously reported SAE or pregnancy must also be reported to the Sponsor within 24 hours of receiving it. If the SAE has not been previously documented (i.e., is a new occurrence) and it is thought to be related to the IP (or therapy), the Sponsor may contact the Investigator to obtain further information. If warranted, an investigator alert may be issued to inform all Investigators involved in any study with the same product (or therapy) that this SAE has been reported.

The IRB should also be notified of SAEs or pregnancies and of any follow-up information in writing, as is practical, and depending on local regulations.

3.7.3. Reporting procedures

For each SAE, the Investigator will complete a SAE Report Form in English and assess the relationship of each SAE to study treatment. The completed form(s) should be sent by e-mail to

the Sponsor within 24 hours of first knowledge of the SAE (as outlined in Section 3.7.1 and Section 3.7.2). The initial SAE should be reported immediately, even if only preliminary information is available. Follow-up information should be sent by the same Investigator, restating the date of the original report. Either a new SAE form is sent (stating that it is a follow-up), or the original one is resent (with the new information highlighted and a new date provided). The follow-up should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or discontinued study participation. The form confirmation will be retained.

Pregnancy follow-up (as outlined in Section 3.6.5) should be reported to the IRB within 24 hours of first knowledge on a Pregnancy Report Form. Follow up will describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects.

3.8. Appropriateness of Safety Measurements

The safety assessments in the study are standard safety measures in clinical trials.

4. STATISTICAL METHODS

4.1. General Considerations for Data Analysis

The focus of the statistical analysis will be the comparison with controls of the photoallergic response to the study products. The diagnosis of photosensitization response will be made by the Investigator based on review of the observed skin responses after Challenge.

The mean score by subject and treatment, including all scores assigned during Induction, will be analyzed in the analysis of variance with factors subject and treatment. All pairwise treatment comparisons will be performed.

The statistical analyses described below will be supplemented by a comprehensive SAP which will be finalized before the database is locked. Any changes to the statistical plans will be described and justified in the final report.

All statistical processing will be performed using the SAS® system (version 9.2 or higher). No interim or subgroup analyses are planned.

4.2. Sample Size and Power Considerations

The sample size of 50 evaluable subjects conforms to industry and regulatory standards for determination of irritation/sensitization when topical application to skin is followed by light exposure.

4.3. Subject Populations for Analysis

All subjects who receive treatment will be evaluable for AEs. The analysis of local tolerability (photoirritation) will be based off all subjects who complete the Induction Phase of the study. Subjects who completed Induction are those who have received at least 6 applications/irradiation of study products, and at least 11 subsequent evaluations during Induction. The evaluation of photosensitization will be based on all subjects who complete the Challenge Phase of the study. Subjects who completed Challenge are those who have received at least 6 applications/irradiation of study products, and at least 11 subsequent evaluations during Induction, completed the Rest Phase and have received one application of study products at Challenge, subsequent irradiation and complete the 3 post-irradiation evaluations for that product.

4.3.1. Background and Demographic Characteristics

Descriptive statistics will be used to summarize demographic characteristics (age, gender, Fitzpatrick skin type, and race) and background characteristics for the randomized subject population. Past/coexistent medical history information for all randomized subjects will be presented in a by-subject listing.

4.3.2. Study Product/Visit Compliance

Descriptive statistics will be used to summarize study product compliance for the randomized subject population.

4.4. Prior and Concomitant Medications

Prior and concomitant medication information for all randomized subjects will be presented in a by-subject listing.

4.5. Efficacy Evaluation

This section is not applicable to this study.

4.6. Safety Evaluation

4.6.1. Assessment of Responses

All assigned scores during Induction and Challenge will be summarized by frequency counts by time point and treatment. The incidence of reactions will be summarized by frequency counts for each treatment. The mean score by subject and treatment, including all scores assigned during Induction, will be analyzed using Fisher's least significant differences in the analysis of variance (ANOVA) with factors subject and treatment. All pairwise comparisons will be performed: MC2-01 Cream on both the irradiated and non-irradiated sites, and MC2-01 Vehicle on both the irradiated and non-irradiated sites.

4.6.2. Photosensitivity

The determination of dermal photosensitization potential will be made by the Investigator based on specific scoring criteria derived from observations in the Challenge Phase of the study and confirmed in the Rechallenge Phase, if necessary. The incidence of photosensitization reactions will be summarized by frequency counts for each treatment. If photosensitization occurs, the 95% confidence interval for the proportion of subjects with photosensitization for each product will be calculated. Photosensitivity will not be determined by statistical methods.

4.6.3. Adverse Events

Adverse events will be summarized as an overall incidence of at least one event, incidence within body systems only, incidence by body system and preferred term, and by highest severity. Each subject will contribute only once (e.g., the first occurrence) to each of the rates, regardless of the number of occurrences (events) the subject experiences.

Treatment-emergent adverse events (TEAEs) will be summarized and tabulated by the system organ class and preferred term, by severity (mild, moderate, severe) and by relationship to study product (not related, possibly related, probably related, and definitely related).

Treatment-emergent will be defined as any AE with an onset date on or after the first study product administration date. Any event with a missing onset date will be included as a treatment-emergent AE.

Deaths and SAEs will be listed by subject.

4.7. Other topics

There are no other topics being evaluated.

4.8. Interim analyses

No interim analyses are anticipated.

4.9. Special Methods

This section is not applicable for this protocol.

5. ADMINISTRATIVE PROCEDURES

5.1. Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and in accordance with TKL's SOPs. These are designed to ensure adherence to GCP guidelines, as described in:

- ICH Harmonized Tripartite Guidelines for GCP 1996. Directive 91/507/European Ethics Committee (EEC), The Rules Governing Medicinal Products in the European Community.
- United States (US) 21 Code of Federal Regulations (CFR) dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB/International Ethics Committee (IEC)/EEC regulations).
- Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964 and amendments).

The PI agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP that it conforms to.

5.2. Institutional Review Board

Before implementing this study, the protocol, the ICF and other information to subjects, must be reviewed by a properly constituted IRB. A signed and dated statement that the protocol and informed consent have been approved by the IRB must be given to Sponsor before study initiation. This committee must also approve any amendments to the protocol, other than administrative ones, and a signed and dated statement of approval must be sent to the Sponsor prior to initiation of the amendment procedures. The name and occupation of the chairman and the members of the IRB must also be supplied to Sponsor.

5.3. Informed consent

The Investigator or designee must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and he/she should be given a copy of the signed document. No subject can enter the study before informed consent has been obtained from him/her.

The ICF is considered to be part of the protocol and must be submitted by the PI with it for IRB approval. Any changes to the proposed ICF suggested by the PI must be agreed to by Sponsor before submission to the IRB and a copy of the approved version must be provided to Sponsor after IRB approval.

5.4. Declaration of Helsinki

The PI must conduct the study in accordance with the laws and regulations of the country in which the study is conducted, as outlined in the Declaration of Helsinki.

5.5. Changes in Planned Study Conduct

5.5.1. Protocol amendments

With the exception of changes in the visit schedule and/or administrative changes, any changes or additions to this clinical study protocol require a written protocol amendment that must be approved by Sponsor and the PI before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, require additional approval by the appropriate IRB. A copy of the written approval of the IRB, which becomes part of the protocol, must be given to Sponsor. Examples of amendments requiring such approval are:

1. an increase in study product dosage or duration of product exposure of subjects,
2. a significant change in the study design (e.g., addition or deletion of a control group),
3. an increase in the number of invasive procedures to which subjects are exposed, and
4. addition or deletion of a test procedure for safety monitoring.

These requirements for approval should in no way prevent any immediate action from being taken by the Investigator or the Sponsor in the interests of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt to be necessary by the Investigator and is implemented by him/her for safety reasons the study Sponsor should be notified, and the IRB should be informed within 10 working days.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval, but the IRB must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB approval that can be treated as administrative amendments include:

1. changes in the staff used to monitor studies, and
2. minor changes in the packaging or labeling of the study product.

5.5.2. Other changes in study conduct

Deviations from the planned study conduct are not permitted; any unforeseen changes in study conduct must be reported to the Sponsor and noted in the final clinical study report.

5.5.3. Termination or suspension of study

Both the Sponsor and the PI reserve the right to terminate or suspend the study at any time. If study termination is necessary, the procedures will be arranged on an individual study basis after review and consultation by both parties. It is the responsibility of the PI to notify the IRB of the

termination/suspension and the reason(s). In terminating the study, the Sponsor and the PI will ensure that adequate consideration is given to the protection of the subjects' interests.

5.6. Data handling and record keeping

5.6.1. Recording of data

Case report forms will be designed to identify each subject by subject entry number and, where appropriate, subject's initials, the product being evaluated, and the results observed. All entries to the CRFs must be made as instructed by the study Sponsor at study initiation. Data on subjects collected on CRFs during the study will be documented in an anonymous fashion, and the subject will only be identified by the subject number, and by his/her initials, if also required. If, as an exception, it is necessary for safety or regulatory reasons to identify the subject, both the study Sponsor and the PI are bound to keep this information confidential.

The PI must sign the designated page(s) of the CRFs, thereby stating that he/she takes responsibility for the accuracy of the data in the entire case record book. All records will be kept in conformance to applicable national laws and regulations.

The original signed ICF will be attached to each subject's file. When the study treatment is completed, the ICF will be kept in the appropriate file folder; otherwise a note indicating where the records can be located will be made.

5.6.2. Retention of documents

Storage is maintained for 5 years at either the TKL facility at One Promenade Blvd. Suite 1101/1201, Fair Lawn, NJ 07410 in a secured room accessible only to TKL employees, or at an offsite location that provides a secure environment with burglar/fire alarm systems, camera detection, and controlled temperature and humidity. Originals or copies of the CRFs, source documents, correspondence, IRB documents, study reports, etc. will be available for the Sponsor's review on the premises of TKL or at a secure location off-site. All database management activities can be found in the data management plan (DMP).

5.7. Product handling and accountability

All product supplies are to be used only for this clinical study and not for any other purpose. Study product supplies must be kept in an appropriate, secure area (e.g., locked cabinet) and stored according to the conditions specified on the product labels.

The PI or a designee must maintain a full record of the shipment and application of study product in a product accountability ledger. This log must be kept current and should contain the following information:

- identification of the subject to whom the study product was dispensed,
- date(s) of the study product dispensed to the subject, and
- initials of the study site representative(s) dispensing study product.

The inventory must be available for inspection by the study monitor. A product-inventory and storage-facility inspection will be conducted at appropriate time intervals throughout the clinical investigation, depending on enrollment and the length of the study. Any discrepancy and/or deficiency must be accounted for by the PI or his/her designee.

The PI must not destroy any product labels, or any partly used or unused product supply. At the conclusion of the study and, as appropriate, during the course of the study, all study product supplies, including partially used or empty containers, must be returned according to the designation of the Sponsor. Any missing supplies will be indicated on the inventory; the original inventory list will be retained in the PI's records for this clinical study.

5.8. Quality control and quality assurance

5.8.1. Monitoring procedures

During the study, the Sponsor may visit the site regularly to check the completeness of subject records, the accuracy of entries on the CRFs, the adherence to the protocol and to ICH-GCP guidelines, the progress of enrollment, and also to ensure that study product is being stored, dispensed and accounted for according to specifications. Key investigative personnel will be available to assist the field monitor during these visits.

The data required by the protocol must be recorded on the appropriate CRFs. The CRFs and any source documents will be available to the study monitor who will perform a 100% data check (comparison of the data recorded in the CRF with those in the source documents). The CRFs and source data will also be available for an audit by the Sponsor or the FDA at any time.

The Investigator will give the monitor access to relevant clinical records, to confirm their consistency with the CRF entries. No information in these records about the identity of the subjects will leave the study center. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

5.8.2. Auditing procedures

In addition to the routine monitoring procedures, a study center may be audited in depth for study quality assurance by the Sponsor, an external auditor on behalf of the Sponsor, and/or by regulatory authorities. This audit may include a review of all source documents, drug records, and original CRFs the study site used in this study. Subject confidentiality will be maintained at all times and consent for this will be obtained before entry of the subject into the clinical study (see Section 5.3). If an inspection is requested by a regulatory authority, the PI must immediately inform the study Sponsor that this request has been made.

5.9. Confidentiality and publication policies

5.9.1. Disclosure and confidentiality

By signing the protocol, the PI agrees to keep all information provided by the Sponsor in strict confidence and to request similar confidentiality from his/her staff and the IRB. Study documents provided by the Sponsor (protocols, IBs, CRFs and other material) will be stored

appropriately to ensure their confidentiality. The information provided by the Sponsor to the PI may not be disclosed to others without direct written authorization from the Sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the study.

5.9.2. Communication and publication of results

Any formal presentation or publication of data from this study will be considered as a joint publication by the Investigator(s) and appropriate Sponsor personnel. Authorship will be determined by mutual agreement.

Sponsor must receive copies of any intended communication in advance of publication (at least 15 working days for an abstract or oral presentation and 45 working days for a journal submission). The Sponsor will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information is not being inadvertently divulged and provide any relevant supplementary information.

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