Drug Delivery Solutions Ltd.
(Part of MC2 Therapeutics)
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Denmark

Clinical Study Protocol

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

Sponsor Protocol No. MC2-01-C9

TKL Study No. PB610818

A 4-Day, Randomized Study to Evaluate the Potential of MC2-01 Cream to Induce a Phototoxicity Skin Reaction in Healthy Subjects, Using a Controlled Photopatch Test Design

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Synopsis

Study Title:	A 4-Day, Randomized Study to Evaluate the Potential of MC2-01 Cream to Induce a Phototoxicity Skin Reaction in Healthy Subjects, Using a Controlled Photopatch Test Design
TKL Study Number:	PB610818
Sponsor Protocol Number:	MC2-01-C9
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:	To determine the potential of MC2-01 (Calcipotriene/betamethasone dipropionate 0.005/0.064 w/w%) Cream to cause a phototoxic reaction when topical application to skin is followed by light exposure.
Study Design:	On Day 1, MC2-01 Cream and MC2-01 Vehicle will each be applied to 2 sites on the infrascapular area of the back under semi-occlusive patches for approximately 24 (±2) hours. This will be the only application during the study. Minimal erythema dose (MED) irradiation will also be performed for each subject on Day 1. After patch removal on Day 2, all application sites will be evaluated, and one application site of each study product will be irradiated with 16 J/cm^2 of Ultraviolet A (UVA) followed by 0.5 times the MED of UVA/Ultraviolet B (UVB) irradiation. An additional site will also be irradiated with 16 J/cm^2 of UVA followed by 0.5 times the MED of UVA/UVB and will serve as an untreated control. On Day 3, approximately 24 hours (±4 hours) after irradiation and Day 4, approximately 48 hours (±4 hours) after irradiation, all application sites and the untreated control site will be evaluated.
Planned Sample Size:	30 evaluable subjects
Study Population:	Healthy adult male and female volunteer subjects
Investigational Products:	Each study product, MC2-01 Cream and MC2-01 Vehicle, will each be applied in an amount of 0.2 g under semi-occlusive patch conditions to 2 sites (2 cm x 2 cm each) on the infrascapular area of the back once for approximately 24 hours (±2 hours).
Control:	An untreated irradiated control site.
Efficacy Evaluation Criteria:	Not applicable
Safety Evaluation Criteria:	Phototoxic potential of the study products will be evaluated for all subjects completing the study. 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:	Selected pairwise comparisons will be performed on the mean of the Day 3 and Day 4 response scores in the context of the analyses of variance (ANOVA). Pairs to be compared are: each test sample irradiated versus non-irradiated and all pairwise comparisons of each set (MC2-01 Cream versus MC2-01 Vehicle on both the irradiated and non-irradiated sites and MC2-01 Cream versus untreated and MC2-01 Vehicle versus untreated on the irradiated sites).
Number of Study Centers:	Single Center

Signature page

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

TKL Study number: **PB610818**

Sponsor protocol number: **MC2-01-C9**

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 Studies*	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: **PB610818**

Sponsor protocol number: **MC2-01-C9**

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

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Table of Contents

Synopsis 2
Signature page 4
Signature page for the Principal Investigator 5
Investigators and study administrative structure 6
Table of Contents 7
List of Tables 10
List of Abbreviations 11
1. INTRODUCTION 12
1.1.1. The MC2-01 Cream Formulation 12
1.1.2. MC2-01 Cream – Non-clinical Data 13
1.1.3. MC2-01 Cream – Clinical Data 13
2. STUDY OBJECTIVES 15
3. INVESTIGATIONAL PLAN 16
3.1. Study Design 16
3.2. Discussion of Design 16
3.3. Study Population 16
3.3.1. Subject Population 16
3.3.2. Inclusion and Exclusion Criteria 17
3.3.3. Interruption or Discontinuation of Treatment 19
3.3.4. Withdrawals 19
3.4. Treatments 20
3.4.1. Investigational Products and Control 20
3.4.2. Description of Investigational Products 20
3.4.3. Description of Patch Conditions 20
3.4.4. Packaging/Labeling 21
3.4.5. Assignment to Treatment 21
3.4.5.1. Randomization 21
3.4.5.2. Blinding 21
3.4.6. Prior and Concomitant Therapy 22
3.4.7. Treatment Compliance 23

3.5. Visit Schedule and Assessments 23
3.5.1. Study Procedures and Visit Schedule 23
3.5.2. Visit Schedule 26
3.5.3. Definition of Minimal Erythemal Dose 27
3.5.4. Light source 27
3.5.5. Background Information 27
3.5.6. Efficacy Assessments 27
3.5.7. Safety Assessments 27
3.5.7.1. Patch Test Site Evaluations 27
3.6. Adverse Events 29
3.6.1. Method of Determining Adverse Events 29
3.6.2. Adverse Event Definitions 29
3.6.2.1. Adverse Events 29
3.6.2.2. Serious Adverse Events 30
3.6.2.3. Severity of Adverse Events 31
3.6.2.4. Relationship of Adverse Events to Study Treatments 31
3.6.3. Reporting Adverse Events 31
3.6.4. Adverse Event Follow-up 32
3.6.5. Pregnancy reporting 32
3.6.6. Expected Adverse Events 32
3.7. Instructions for Rapid Notification of Serious Adverse Events 33
3.7.1. Safety Contact person and number 33
3.7.2. Reporting Responsibility 33
3.7.3. Reporting procedures 33
3.8. Appropriateness of Safety Measurements 33
4. STATISTICAL METHODS 34
4.1. General Considerations for Data Analysis 34
4.2. Sample Size and Power Considerations 34
4.3. Subject Populations for Analysis 34
4.3.1. Background and Demographic Characteristics 34
4.3.2. Study Product/Visit Compliance 34

4.4. Prior and Concomitant Medications 34
4.5. Efficacy Evaluation 34
4.6. Safety Evaluation 35
4.6.1. Local Tolerability Assessment 35
4.6.2. Adverse Events 35
4.7. Other topics 35
4.8. Interim analyses 35
4.9. Special Methods 35
5. ADMINISTRATIVE PROCEDURES 36
5.1. Ethics and Good Clinical Practice 36
5.2. Institutional Review Board 36
5.3. Informed consent 36
5.4. Declaration of Helsinki 37
5.5. Changes in Planned Study Conduct 37
5.5.1. Protocol amendments 37
5.5.2. Other changes in study conduct 37
5.5.3. Termination or suspension of study 37
5.6. Data handling and record keeping 38
5.6.1. Recording of data 38
5.6.2. Retention of documents 38
5.7. Product handling and accountability 38
5.8. Quality control and quality assurance 39
5.8.1. Monitoring procedures 39
5.8.2. Auditing procedures 39
5.9. Confidentiality and publication policies 39
5.9.1. Disclosure and confidentiality 39
5.9.2. Communication and publication of results 40
6. REFERENCES 41

List of Tables

Table 1: Fitzpatrick Skin Types 24
Table 2: Visit Schedule and Assessments 26
Table 3: Response Scores 28
Table 4: Notations 28
Table 5: Relationship of AE to Study Drug 31

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
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
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
NSAID	Nonsteroidal Anti-Inflammatory Drug
OTC	Over-the-counter
PAD™	Polyaphron Dispersion Technique
PI	Principal Investigator
PMD	Primary Medical Doctor
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
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 cause a phototoxic 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 phototoxic reaction after topical application and irradiation 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 phototoxicity 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 phototoxic potential of MC2-01 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 single-center, randomized, double-blind, controlled, within-subject comparison study of the investigational products (IPs), MC2-01 Cream and MC2-01 Vehicle in healthy volunteer subjects. MC2-01 Cream and MC2-01 Vehicle will each be applied to 2 sites, one which will be irradiated and one which will remain non-irradiated. The irradiated and non-irradiated sites will be compared with each other and with an untreated irradiated site

A total of 4 application sites (2 cm x 2 cm each) will be marked on the subject's infrascapular region of the back: 2 sites for MC2-01 Cream and 2 sites for MC2-01 Vehicle. Each study product will be applied according to the randomization scheme in an amount of 0.2 g under semi-occlusive patch conditions once during the study.

Approximately 24 (±2) hours post study product application, the patches will be removed by study staff. The sites will then be graded for cutaneous reactions by a trained evaluator and the designated sites, including the untreated site, will be exposed to irradiation. One set (MC2-01 Cream and MC2-01 Vehicle patches) on the back will be designated for irradiation and the other set will remain non-irradiated. An additional site on the back will be marked which will receive no treatment but will receive irradiation to serve as an untreated irradiated control. The sites will be examined at approximately 24 and 48 hours post irradiation and graded for reactions. Cutaneous 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).

Safety evaluations include collection of 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 which becomes available.

This phototoxicity study is designed to detect the ability of the MC2-01 Cream and its vehicle (MC2-01 Vehicle) to cause topical skin irritation when exposed to light. Each subject is to receive applications of the IPs to 2 separate sites. One will be irradiated, and one will remain non-irradiated. An untreated site will also be irradiated. This design provides built-in controls for the test product (MC2-01 Cream and MC2-01 Vehicle) 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 30 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 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. Is 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 is 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 ultraviolet (UV) sun lamps/sunlight exposure;
19. Is currently participating in any clinical study;
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

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 case report form (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 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 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 IPs.

- 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 be applied topically, under semi-occlusive patch conditions once over a 4-day period. Each product will be applied to 2 sites (one irradiated site and one non-irradiated site) on the lower thoracic area of each subject's back for approximately 24 (±2) hours. An amount of IP sufficient to cover an area of the back approximately 2 cm x 2 cm will be applied (approximately 0.2 g).

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 patches will be secured to the skin with hypoallergenic tape (Micropore).

3.4.4. Packaging/Labeling

The study product tube 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.

For each subject, one set of patches (MC2-01 Cream and MC2-01 Vehicle) will be designated for irradiation and the other set will remain non-irradiated. In each set one application site will be assigned to MC2-01 Cream and one will be assigned to MC2-01 Vehicle according to the randomization schedule. One additional site will be assigned to serve as the untreated irradiated control.

3.4.5.2. Blinding

The treatments (IPs and control) 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 the 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.

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 to participate 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 marked on each subject's back, placing 2 sites for MC2-01 Cream and 2 sites for MC2-01 Vehicle. One set (MC2-01 Cream and MC2-01 Vehicle) will be designated for irradiation and the other set will remain non-irradiated under semi-occlusive conditions. 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 previous 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]

Day 2

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).

The clinical staff will remove the patches approximately 24 (± 2) hours after application and evaluate the application sites according to the criteria in Table 3 and Table 4 (Section 3.5.7). Evaluations will be recorded on the appropriate source document. The duration of the UVA and UVA/UVB irradiation will be calculated based on 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. The sites designated for irradiation will receive 16 J/cm^2 of UVA radiation followed by 0.5 times the MED of UVA/UVB (full spectrum) irradiation, using a filtered light source (see Section 3.5.4). One additional site (untreated) will be irradiated with 16 J/cm^2 of UVA radiation followed by 0.5 times the MED of UVA/UVB radiation, using a filtered light source and will serve as an untreated control.

In addition, AEs and concomitant medications will be reviewed and recorded, as appropriate.

Day 3

On Day 3, approximately 24 (±4) hours after irradiation (ie, approximately 48 (±4) hours following product application), all application sites (MC2-01 Cream and MC2-01 Vehicle) and the untreated control site will be evaluated. In addition, AEs and concomitant medications will be reviewed and recorded.

Day 4/End of Study

On Day 4, approximately 48 (±4) hours after irradiation (ie, approximately 72 (±4) hours following product application), all application sites (MC2-01 Cream and MC2-01 Vehicle) and the untreated control site will be evaluated.

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).

Retest

Although not all observations of erythema and edema are associated with phototoxicity, erythema and edema must be observed for a reaction to be suspected of being a positive

phototoxic reaction. An increase in the intensity of the reaction over time further supports an assessment of phototoxicity. If a reaction is observed at both the irradiated and non-irradiated product sites (ie, if contact sensitization or irritation may have occurred), the reaction upon retest must be at least one grade more intense at the irradiated site than at the non-irradiated site for the reaction to be suspected of being a phototoxicity reaction (refer to Section 3.5.7 for response grades and notations).

If it is determined by the Investigator that a retest should be performed, then the retest patches will be applied as soon as the original reactions have resolved. The Investigator will determine the patch conditions to use during the Retest (see Section 3.4.3). The study material will be applied to naive sites on the back, using appropriate patches to further discriminate a phototoxic reaction from an irritation reaction. Identical patches will be applied to sites previously unexposed to the study material. Approximately 24 (± 2) hours later one site will be irradiated with full spectrum UV light (UVA/UVB) using a filtered light source. An additional untreated site will be irradiated with UV light (UVA/UVB) using a filtered light source and serve as an untreated irradiated control. All sites will be evaluated upon patch removal at approximately 24 and 48 hours after irradiation. Concomitant medications and AEs will also be reviewed.

In some cases, the retest may be done on the individual ingredients of the products.

3.5.2. Visit Schedule

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

Table 2: Visit Schedule and Assessments

	Dosing Phase			
	Day 1 Screening*	Day 2	Day 3	Day 4 EOS
Informed consent	X			
Inclusion/Exclusion	X			
Medical history	X			
Demographic information	X			
MED irradiation/evaluation	X	X		
Randomization (if applicable)	X[a]			
Product application	X			
Patch Removal		X		
Application site evaluations	X	X	X	X
Application site and untreated control site irradiation		X		
Untreated control evaluation		X	X	X
Review of concomitant medications	X	X	X	X
Review of adverse events		X	X	X
Urine Pregnancy Test	X			X

a The treatment placement randomization will be performed on Day 1 of the study.
* Screening may take place on a separate day.

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 application 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

Assessment of the study material application sites will be done once daily, Days 1-4. Assessment of the untreated irradiated control site will be done once daily on Days 2, 3 and 4.

The symbols listed in Table 3 and their respective numerical equivalents will be used to express the response observed at the time of examination. Additional response notations are presented in Table 4. The same evaluator (where possible) should perform the assessment throughout (from Day 1 to Day 4 and Retest, if necessary) 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

If after the PI reviews the results and determines a retest is needed, the subject(s) will be retested to the product(s) to demonstrate that the results obtained are reproducible before results are interpreted as indicative of phototoxicity.

If the non-irradiated study product sites give reactions indicative of significant primary irritancy or prior sensitization, it may not be possible to make any comments about phototoxic potential. In such situations, further routine patch evaluation might be recommended.

Because of the relatively small number of subjects evaluated in this study, it will generally not be possible (except in extreme cases) to categorize a product as having mild, moderate or severe phototoxic potential.

The readings will be made under a standardized white light source. The numerical equivalent scores will be used for calculations.

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, 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/IRB reporting requirements.

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 phototoxic response to the study products. The parameter for phototoxicity will be the mean of Day 3 and 4 scores (sum of erythema and edema).

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 30 evaluable subjects conforms to industry and regulatory standards for determination of irritation 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 evaluation of phototoxicity potential of the study products will be assessed for all subjects completing the study.

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. Local Tolerability Assessment

All assigned scores during the study for subjects who complete the study will be summarized using frequency counts by treatment for Days 2, 3 and 4. Selected pairwise comparisons will be performed on the mean of the Day 3 and Day 4 response scores (sum of erythema and edema scores) in the context of the analyses of variance (ANOVA). Pairs to be compared are: each study product irradiated versus non-irradiated and all pairwise comparisons of each set (MC2-01 Cream versus MC2-01 Vehicle on both the irradiated and non-irradiated sites and MC2-01 Cream versus untreated and MC2-01 Vehicle versus untreated on the irradiated sites).

4.6.2. 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 Good Clinical Practice 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).
- 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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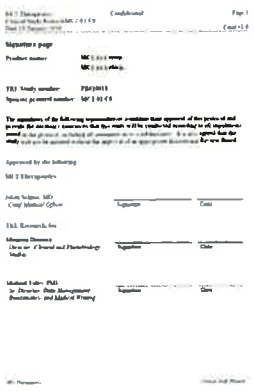

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