6 Century Drive, 2nd Floor
Parsippany, NJ 07054

Clinical Study Protocol

CCP-020 (Diacerein 1%) Topical Ointment

Sponsor Protocol No. CCP-020-104

TKL Study No. PB610317

A 4 Day, Randomized Study to Evaluate the Potential of CCP-020 (Diacerein 1%) Topical Ointment to Induce a Phototoxicity Skin Reaction in Healthy Subjects, Using a Controlled Photopatch Test

Author:	[redacted]
Document type:	Clinical Study Protocol
Development Phase:	1
Document Date:	23-October-2017
Document Status	Amendment 1
Number of Pages:	**38**

Synopsis

Study Title:	A 4 Day, Randomized Study to Evaluate the Potential of CCP-020 (Diacerein 1%) Topical Ointment to Induce a Phototoxicity Skin Reaction in Healthy Subjects, Using a Controlled Photopatch Test
TKL Study Number:	PB610317
Sponsor Protocol Number:	CCP-020-104
Sponsor:	Castle Creek Pharmaceuticals, LLC
Development Phase:	1
Study Objectives:	To determine the potential of CCP-020 (Diacerein 1%) Topical Ointment and vehicle ointment to cause irritation when topical application to skin is followed by light exposure.
Study Design:	On Day 1, CCP-020 (Diacerein 1%) Topical Ointment and vehicle ointment will each be applied to 2 sites on the lower thoracic area of the back under fully 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, CCP-020 (Diacerein 1%) Topical Ointment and vehicle ointment will be applied in an amount of 0.2 mL under 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 non-occlusive (open) 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 will be evaluated. The intensity, duration, and causal relationship to the study products 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 on each side (CCP-020 (Diacerein 1%) Topical Ointment versus vehicle ointment on both the irradiated and non-irradiated sides and CCP-020 (Diacerein 1%) Topical Ointment versus untreated and vehicle ointment versus untreated on the irradiated side).
Number of Study Centers:	Single Center
Planned Dates of Study	November 2017 – December 2017

Signature page

Product names: **CCP-020 (Diacerein 1%) Topical Ointment**
Vehicle Ointment

TKL Study number: **PB610317**

Sponsor protocol number: **CCP-020-104**

The signatures of the representatives on this and the following page 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:

Castle Creek Pharmaceuticals, LLC:

Signature page for the Principal Investigator

Product names: **CCP-020 (Diacerein 1%) Topical Ointment**

Vehicle Ointment

TKL Study number: **PB610317**

Sponsor protocol number: **CCP-020-104**

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.

Investigators and study administrative structure

Name	Affiliation / Address	Responsibility
[redacted]	[redacted]	[redacted]

Table of Contents

List of Tables

List of Abbreviations

AE	Adverse Event
ANOVA	Analysis of Variance
CFR	Code of Federal Regulations
CRF	Case Report Form
DMP	Data Management Plan
EBS	Epidermolysis bullosa simplex
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
IP	Investigational Product
IRB	Institutional Review Board
MED	Minimal Erythemal Dose
MedDRA	Medical Dictionary for Regulatory Activities
NF	National Formulary
NSAID	Nonsteroidal Anti-Inflammatory Drug
OA	Osteoarthritis
OTC	Over-the-counter
PI	Principal Investigator
PMD	Primary Medical Doctor
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOPs	Standard Operating Procedures
TKL	TKL Research, Inc.
UPT	Urine pregnancy test
USP	United States Pharmacopeia
UV	Ultraviolet
UVA	Ultraviolet A
UVB	Ultraviolet B

1. INTRODUCTION

Because CCP-020 (Diacerein 1%) Topical Ointment 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. This study investigates the phototoxic potential of CCP-020 (Diacerein 1%) Topical Ointment under standardized conditions compared with an untreated control site.

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

CCP-020 (previously developed as AC-203) is a topical ointment containing diacerein (4,5-bis[acetyloxy]-9,10-dihydro-9,10-dioxo-2-anthracene carboxylic acid; also known as diacetyl-rhein), a highly purified anthraquinone derivative, and is being developed by Castle Creek Pharmaceuticals for the treatment of epidermolysis bullosa simplex (EBS). The capsule formulation of diacerein, intended for oral use and systemic absorption, was initially approved for use in osteoarthritis (OA) in France in 1992 (as Artodar®, ART50®, or Zondar®). Since then, it has received marketing authorization in over 30 countries in Europe, South America, and Asia. It is classified as a Symptomatic Slow-Acting Drug in OA. Following oral administration of the capsule formulation, diacerein is rapidly metabolized to the deacetylated active metabolite, rhein. Similarly, diacerein in the topical formulation is hydrolyzed to rhein in the epidermis and the dermis following administration. Diacerein and rhein have been shown to inhibit the in vitro and in vivo production and activity of interleukin (IL)-1β and other proinflammatory cytokines. It has a novel mode of action that differentiates it from non-steroidal anti-inflammatory drugs (NSAIDs) and other conventional forms of drug therapy.

For the development of CCP-020, a total of 10 animal studies have been conducted with CCP-020 ointment 1%, including one skin penetration study, three acute dermal toxicity studies, one phototoxicity study, three pharmacokinetic studies, and two sub-chronic juvenile toxicity studies. CCP-020 was well-tolerated in these studies and no untoward adverse effects (AEs) were noted. To date, two clinical studies of CCP-020 have been completed in patients with epidermolysis bullosa simplex (EBS). These include a Phase one pilot study in five patients and a Phase 2, multiple-site study in 17 patients in Europe. The Phase 2 study demonstrated CCP-020 was well-tolerated and no treatment-related AEs were reported. The Investigator's Brochure should be consulted for summaries of the results of these studies.[1]

This Phase 1 study will assess the phototoxicity potential of CCP-020 (Diacerein 1%) topical ointment.

2. STUDY OBJECTIVES

The objective of this study is to determine the phototoxic potential of CCP-020 (Diacerein 1%) Topical Ointment and vehicle ointment when topical application to skin is followed by light exposure.

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

3. INVESTIGATIONAL PLAN

3.1. Study Design

This is a single-center, randomized, within-subject comparison study of CCP-020 (Diacerein 1%) Topical Ointment and vehicle ointment. CCP-020 (Diacerein 1%) Topical Ointment and vehicle ointment 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 control.

A total of 4 application sites (2 cm x 2 cm each) will be marked on the subject's lower thoracic area of the back: 2 sites on each side of the back – 2 sites for CCP-020 (Diacerein 1%) Topical Ointment and 2 sites for vehicle ointment. Each study product will be applied according to the randomization scheme in an amount of 0.2 mL under 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 side of the back will be designated for irradiation and the other side will remain non-irradiated. An additional site will be marked on the "irradiated side" of the back which will receive no treatment, but will receive irradiation to serve as an untreated irradiated control. The sites and control 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 adverse events (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 Research, Inc. 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 CCP-020 (Diacerein 1%) Topical Ointment and vehicle ointment to cause topical skin irritation when exposed to light. Each subject is to receive applications of CCP-020 (Diacerein 1%) Topical Ointment and vehicle ointment to 2 separate sites. One will be irradiated and one will remain non-irradiated. An untreated control will also be irradiated. This design provides built-in controls for the test product (CCP-020 (Diacerein 1%) Topical Ointment) 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. In the case of a female of childbearing potential, is using two acceptable forms of birth control (oral/implant/injectable/transdermal contraceptives, intrauterine device, condom with spermicide, diaphragm with spermicide, abstinence, partner's vasectomy, tubal ligation). Abstinence or vasectomies are acceptable if the female subject agrees to implement two of the other acceptable methods of birth control if her lifestyle/partner changes;
4. In the case of a female of childbearing potential, has a negative urine pregnancy test (UPT) at Day 1 and are willing to submit to a UPT at the end of study (EOS);
5. 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;
6. Has uniformly-colored skin on the lower thoracic area of the back which will allow discernment of erythema, and has Fitzpatrick Skin Types I, II, or III (see Table 1);
7. Complete a medical screening procedure; and
8. 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. 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;

4. 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);
5. Is taking medication known to cause phototoxic reactions (eg, tetracyclines, thiazides, nonsteroidal anti-inflammatory drugs [NSAIDs]);
6. 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, and others);
7. Is unwilling or unable to refrain from the use of sunscreens, cosmetics, creams, ointments, lotions or similar products on the back during the study;
8. Has psoriasis and/or active atopic dermatitis/eczema;
9. Has a known sensitivity or allergy to constituents of the materials being evaluated including diacerein, mineral oil, petrolatum, cetyl alcohol, D&C Yellow #10 and/or ethyl paraben;
10. Is a female who is pregnant, plans to become pregnant during the study, or is breast feeding a child;
11. 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;
12. Has received treatment for any type of internal cancer within 5 years prior to study entry;
13. Has a history of, or is currently being treated for skin cancer and/or hepatitis;
14. Has a history of, or is currently being treated for diabetes;
15. Has any condition that might compromise study results;
16. Is currently or expects to sunbathe or use tanning salons during the study;
17. Has a history of adverse response (eg, blistering, sun poisoning) to ultraviolet (UV) sun lamps/sunlight exposure;
18. Is currently participating in any clinical testing;
19. Has any known sensitivity to adhesives; and/or
20. Has received any investigational drug(s) within 4 weeks prior to study entry.

3.3.3. Interruption or Discontinuation of Treatment

In accordance with legal requirements and ICH-GCP guidelines, every subject or his/her legal representative 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 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 investigational products (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 primary medical doctor (PMD). The specific AE in question will be recorded on the appropriate CRF.

3.4. Treatments

3.4.1. Investigational Products and Control

Investigational Product(s):

CCP-020 Topical Ointment

CCP-020 is a topical ointment, 1% (w/w). All excipients used in the topical formulation meet United States Pharmacopeia (USP)/ National Formulary (NF) criteria and are commonly used in

The CCP-020 topical ointment and vehicle ointment will be applied topically, under 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 investigational product sufficient to cover an area of the back approximately 2 cm x 2 cm will be applied (approximately 0.2 mL).

CCP-020 topical ointment and vehicle ointment should be stored at room temperature (15°C/59°F to 30°C/86°F). 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.

Lot numbers will be given in the clinical study report.

Manufacturer:

TWi Pharmaceuticals will be responsible for the manufacturing and filling into the primary package; aluminum tubes. TWi Pharmaceuticals will be responsible to package and distribute to TKL. CCP will be responsible for final release of the product. TKL will be responsible for labeling the product upon site delivery.

Control

An untreated irradiated non-occlusive (open) 2 cm x 2 cm site will serve as a control.

3.4.2. Description of Investigational Products

The IPs (CCP-020 [Diacerein 1%] topical ointment and vehicle ointment) will be supplied in aluminum tubes for the clinical study. CCP-020 (Diacerein 1%) topical ointment and vehicle ointment were manufactured and packaged in accordance with good manufacturing practice (GMP).

3.4.3. Description of Patch Conditions

The IP and vehicle will be evaluated under occlusive patch conditions is applied to a 2 cm x 2 cm Webril pad attached to a non-porous, plastic film adhesive bandage (medical tape). The patch is secured with hypoallergenic tape (Micropore), as needed.

3.4.4. Packaging/Labeling

The study medication tube label will show at least the following:

- Protocol number
- Storage conditions
- Instructions for use
- Expiration date
- Sponsor information
- Investigational drug warning
- Space to enter lot number.

A full product description can be found in the Investigator's Brochure (IB).[1]

All study IPs should be stored at room temperature (15°C/59°F to 30°C/86°F).

3.4.5. Assignment to Treatment

3.4.5.1. Randomization

Each subject who signs an informed consent and successfully completes the screening procedures will be enrolled in the study. Upon enrollment, each subject will be assigned a unique number, which will correspond to the subject number on the 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 side of the back will be designated for irradiated sites and the other side will be for non-irradiated sites. On each side one application site will be assigned to the CCP-020 [Diacerein 1%] topical ointment and one will be assigned to the vehicle ointment according to the randomization schedule. On the irradiated side only one additional site will be assigned to the untreated irradiated control.

3.4.5.2. Blinding

Investigative personnel who are involved in the preparation/application and removal of the treatments (CCP-020 [Diacerein 1%] topical ointment and vehicle ointment) will be unblinded and will not perform the evaluation of skin responses. 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, 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, nonsteroidal anti-inflammatory drugs (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.[1]

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 burn, deeply pigmented[4,5]

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 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 consecutive, unique 3-digit subject number starting with 001, which will correspond to the subject number on the 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 on opposite sides of the back. Of the 4 sites, 2 will be designated as "irradiated sites" and 2 will be designated as "non-irradiated sites". The CCP-020 [Diacerein 1%] topical ointment and its vehicle ointment will then each be applied to its designated "irradiated site" and its "non-irradiated site" under 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 (MED) 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. 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).[2]

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.[3]

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 CRF. The timing 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 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 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 and the untreated control site will be evaluated. Adverse events and concomitant medications will be reviewed and recorded, as appropriate. A UPT will be performed for female subjects of childbearing potential.

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 16 J/cm^2 of UVA followed by ½ MED of UVB radiation using a filtered light source. An additional untreated site will be irradiated with 16 J/cm^2 of UVA followed by ½ MED of UVB radiation using a filtered light source and serve as an untreated irradiated control. All sites will

be evaluated upon patch removal and approximately 24, 48, and 72 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 randomization will be performed on Day 1 of the study.

Note: The visit schedule may be revised if necessary.

3.5.3. Definition of minimal erythemal dose

Minimal erythemal dose (MED) 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 UVB (290-320 nm) as part of its emission spectrum.[2]

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).[2] 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 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.

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

Before results are interpreted as indicative of phototoxicity, the subject(s) must first be retested to the product(s) to demonstrate that the results obtained are reproducible.

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. AEs 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;
- 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 investigational product, whether or not considered related to the medicinal investigational product.

Adverse Events will be coded using an internationally recognized 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 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.

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

"Severity" of the AE refers to the extent to which an AE affects the subject's daily activities and differs from "Serious," which is a regulatory classification.

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

- **Mild:** The symptom has a negligible effect or no impairing effect on the subject's normal function.
- **Moderate:** The symptom impairs the subject's normal function to some extent.
- **Severe:** The symptom has an obvious, significantly impairing effect on the subject's normal function.

3.6.2.4. Relationship of Adverse Events to Study Treatments

The Investigator is to classify the drug relationship of an AE according to the definitions outlined in Table 5.

Table 5: Relationship of AE to Study Drug

Association	Definition
Not related	(1) the existence of a clear alternative explanation (e.g., mechanical bleeding at surgical site) or (2) non-plausibility, e.g., the subject is struck by an automobile or cancer developing a few days after drug administration.
Unlikely	There is no medical evidence to suggest that the AE may be related to study drug usage, or there is another more probable medical explanation.
Possible	There is medical evidence to suggest that there is a reasonable possibility that the AE may be related to study drug usage. However, other medical explanations cannot be excluded as a possible cause.
Probable	There is strong medical evidence to suggest that the AE is related to study drug usage.
Definite	A clinical event, including laboratory test abnormality (if applicable), in which there is no uncertainty in its relationship to test drug (e.g., positive Rechallenge).

3.6.3. Reporting Adverse Events

Adverse events that occur from first dose through completion of the last study visit should be reported. All SAEs, regardless of causality, occurring from the time of informed consent until 30 days following study completion OR until 30 days after the subject's last application of study medication, whichever is longer, must be reported to TKL Clinical Safety within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). SAEs occurring after the 30-day follow-up period AND considered related to study drug must also be reported to the Sponsor.

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. The signed Informed Consent Form must document this discussion.

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.

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 around all sites. When 1 or 2 sites are experiencing severe tape related reactions, the application site will be stopped and the subject will continue on the study.

3.7. Instructions for Rapid Notification of Serious Adverse Events

3.7.1. Contact person and number

Serious adverse events must be reported immediately (i.e., not later than 24 hours after first knowledge) by e-mail with the scanned TKL SAE report form to:

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 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).

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 on each side (CCP-020 [Diacerein 1%] topical ointment versus vehicle ointment on both the irradiated and non-irradiated sides and CCP-020 [Diacerein 1%] topical ointment versus untreated and vehicle ointment versus untreated on the irradiated side).

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 AEs 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, unlikely, possible, probable, and definite).

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 Research, Inc.'s standard operating procedures. These are designed to ensure adherence to Good Clinical Practices guidelines, as described in:

- ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
- United States (US) 21 Code of Federal Regulations (CFRs) dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB/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 must explain to each subject (or legally authorized representative) 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, or his/her legally authorized representative.

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 Castle Creek Pharmaceuticals, LLC before submission to the IRB and a copy of the approved version must be provided to Castle Creek Pharmaceuticals, LLC 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 Castle Creek Pharmaceuticals, LLC 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 Castle Creek Pharmaceuticals, LLC. 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 or until the Sponsor advises to release the archives 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. Patient confidentiality will be maintained at all times and consent for this will be obtained before entry of the patient 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.

Castle Creek Pharmaceuticals, LLC 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.

6. REFERENCES

1. Investigator's Brochure. CCP-020 (Diacerein 1%) Topical Ointment. Castle Creek Pharmaceuticals, LLC. Version Number 1.0. 04 November 2016.
2. Berger DS. Specification and design of solar ultraviolet simulators. Journal of Investigational Dermatology. 1969; 53:192-199.
3. Final Monograph: 21 CFR Parts 310, 352, 700, 740. Sunscreen drug products for over-the-counter human use. Federal Register. Vol 64/No. 98/Pages: 27666-27693.
4. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. Arch.Dermatol. 1988; 124: 869-871.
5. Sachdeva S. Fitzpatrick skin typing: Applications in dermatology. Indian J Dermatol Venereol Leprol 2009;75:93-6