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Clinical Study Protocol

CCP-020 (Diacerein 1%) Topical Ointment

Sponsor Protocol No.CCP-020-103

TKL Study No. DS106217

# A Randomized, Controlled Study to Evaluate the Sensitizing Potential of CCP-020 (Diacerein 1%) Topical Ointment in Healthy Subjects Using a Repeat Insult Patch Test Design

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|---|---|
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# Synopsis

| | |
|---|---|
| **Study Title:** | A Randomized, Controlled Study to Evaluate the Sensitizing Potential of CCP-020 (Diacerein 1%) Topical Ointment in Healthy Subjects Using a Repeat Insult Patch Test Design |
| **TKL Study Number:** | DS106217 |
| **Sponsor Protocol Number:** | CCP-020-103 |
| **Sponsor:** | Castle Creek Pharmaceuticals, LLC |
| **Development Phase:** | 1 |
| **Study Objectives:** | To evaluate the sensitization potential of CCP-020 (Diacerein 1%) Topical Ointment on normal skin. |
| **Study Design:** | Single center, randomized, controlled, evaluator blinded, within-subject comparison study. |
| **Planned Sample Size:** | 200 evaluable subjects |
| **Study Population:** | Healthy adult males and females volunteer subjects |
| **Investigational Products:** | CCP-020 (Diacerein 1%) Topical Ointment, approximately 0.2 mL, applied topically under occlusive patch conditions to the infrascapular area of the back, 3 times weekly for 3 weeks (9 applications) during the Induction Phase, and one time at Challenge (10 times in total).<br>Vehicle, approximately 0.2 mL, applied topically under occlusive patch conditions to the infrascapular area of the back, 3 times weekly for 3 weeks (9 applications) during the Induction Phase, and one time at Challenge (10 times in total). |
| **Concurrent Controls:** | A solution of 0.9% saline, approximately 0.2 mL applied topically under occlusive patch conditions to the infrascapular area of the back, 3 times weekly for 3 weeks (9 applications) during the Induction Phase, and one time at Challenge (10 times in total) will serve as a negative irritant control. |
| **Efficacy Evaluation Criteria:** | Not Applicable |
| **Safety Evaluation Criteria:** | 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 patch are to be rated for all AEs. |
| **Statistical Methods:** | Cumulative irritancy during Induction will be quantified using the mean and total cumulative irritancy scores received during the Induction Phase (9 readings). This parameter will be tested pairwise for product differences using analysis of variance (subject, product).<br>A narrative description of reactions in the Challenge and Rechallenge Phases will be provided together with the opinion of the Investigator as to whether such reactions are felt to be indicative of contact sensitization. |
| **Number of Study Centers:** | Single center |

## Signature page

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

**TKL Study number:** **DS106217**

**Sponsor protocol number:** **CCP-020-103**

The signatures of the representatives on 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:**

**Sponsor**

## Signature page for the Principal Investigator

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

**TKL Study number:** **DS106217**

**Sponsor protocol number:** **CCP-020-103**

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.

[redacted]

## Investigators and study administrative structure

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# List of Abbreviations

| | |
|---|---|
| ACD | Allergic Contact Dermatitis |
| AE | Adverse Event |
| ANOVA | Analysis Of Variance |
| CII | Cumulative Irritancy Index |
| 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 Harmonization |
| IL | Interleukin |
| IP | Investigational Product |
| IRB | Institutional Review Board |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MU | Make-up Patch |
| N9G | No 9$^{th}$ Grading |
| NF | National Formulary |
| NP | Not Patched |
| NSAID | Non-steroidal anti-inflammatory drug |
| OA | Osteoarthritis |
| OTC | Over-The-Counter |
| PI | Principal Investigator |
| PMD | Primary Medical Doctor |
| RIPT | Repeated Insult Patch Test |
| 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 |

# 1. INTRODUCTION

This study investigates the sensitization potential of CCP-020 (Diacerein 1%) Topical Ointment under standardized conditions compared with an inert control (normal saline). Because CCP-020 (Diacerein 1%) Topical Ointment is formulated for topical use, it is necessary to determine the potential of this product to cause sensitization after repeated topical application to the skin.

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

## 1.1. Background Information

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 irritation potential of CCP-020 (Diacerein 1%) topical ointment.

## 1.2. Rationale for the Study

This study is intended to determine the contact sensitization (allergic) potential of topically applied CCP-020 (Diacerein 1%) topical ointment treatment on normal skin in healthy volunteers.

# 2. STUDY OBJECTIVES

The primary objective of this study will be to determine the potential of CCP-020 (Diacerein 1%) topical ointment to induce sensitization by repeated topical application to the healthy skin of humans under controlled conditions.

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

# 3. INVESTIGATIONAL PLAN

## 3.1. Study Design

This will be a randomized, single-center, controlled, evaluator-blinded, within-subject comparison study of the investigational products (IPs) (CCP-020 [Diacerein 1%] topical ointment and vehicle) and negative irritant control under occlusive conditions in healthy volunteer subjects. All subjects will have fields designated for the IP patches and the negative irritant control patch at 3 randomly assigned, adjacent sites, for the purpose of determining sensitization potential.

During the Induction Phase of the study, the IPs and negative irritant control will be applied to adjacent sites on the infrascapular area of the back. Evaluation of dermal reactions at the application sites will be assessed clinically using a visual scale that rates the degree of erythema, edema, and other signs of cutaneous irritation (see Section 3.5.5).

Following the Induction Phase, subjects will have a 10 to 14-day Rest Period, after which they will enter the Challenge Phase, which consists of one 48-hour patch application to a naïve site on the opposite side of the back. Observations based on the grading from Table 3 at the naïve site during Challenge Phase and the patterns of reactivity during the Induction Phase will provide a basis for an interpretation of contact sensitization (see Section 3.5.5). Notations on the appearance of the skin will be made using the scoring system presented in Tables 4 and 5.

If a cutaneous response observed in the Challenge Phase indicates possible sensitization (grade 3 of higher from Table 3), and/or at the discretion of the Investigator, a Rechallenge will occur (see Section 3.5.1). A narrative description of reactions in the Challenge and Rechallenge Phases will be reported together with the opinion of the Investigator as to whether such reactions are felt to be indicative of contact sensitization.

A total of 10 patch applications will be made over a period of approximately 6-8 weeks.

## 3.2. Discussion of Design

Allergic contact dermatitis (ACD), also referred to as dermal sensitization, is a delayed-type hypersensitivity reaction induced by small reactive chemicals (haptens).[2] It is a T-cell-mediated skin inflammatory systemic reaction, caused by repeated skin exposure to contact allergens. Erythema, edema, and occasionally papules and vesicles characterize the clinical appearance of this reaction. The ACD inflammatory skin reaction occurs as a delayed response (24-48 hours or longer) after contact with a sensitizing chemical.

In pharmaceutical and cosmetic industries it is mandatory to identify chemicals that are potential ACD inducers before they become a part of a new product.[2] Substances that come into contact with human skin need to be evaluated for their propensity to irritate and/or sensitize. Once an appropriate pre-clinical safety evaluation has been performed, a reproducible, standardized, quantitative patch evaluation procedure must be used to demonstrate that a particular material can be applied safely to human skin without significant risk of adverse reactions.[3]

Repeated insult patch test (RIPT) evaluation is a predictive patch study that can detect weak sensitizers that require multiple applications to induce a T-cell-mediated (Type IV) immune response sufficient to cause an allergic reaction. Irritant reactions may also be detected using this evaluation method, although this is not the primary purpose of this procedure.

The human RIPT study design is based on the Modified Draize procedure, and is an accepted standard methodology used for assessment of skin sensitization.[4, 5]

The IPs in the study will be CCP-020 (Diacerein 1%) topical ointment and Vehicle**.** The negative irritant control field will be 0.9% saline, 0.2 mL, applied topically under occlusive conditions.

## 3.3. Study Population

### 3.3.1. Subject Population

A sufficient number of subjects will be enrolled in order to provide 200 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) on Day 1 prior to randomization 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. Is of any Fitzpatrick Skin Type or race, providing the skin pigmentation will allow discernment of erythema (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 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;
2. 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;
3. 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);
4. 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);
5. Is unwilling or unable to refrain from the use of sunscreens, cosmetics, creams, ointments, lotions or similar products on the back during the study;
6. Has psoriasis and/or active atopic dermatitis/eczema;
7. 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;
8. Is a female who is pregnant, plan to become pregnant during the study, or is breast feeding a child;
9. 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;
10. Has received treatment for any type of internal cancer within 5 years prior to study entry;
11. Has a history of, or are currently being treated for skin cancer and/or hepatitis;
12. Has a history of, or is currently being treated for, insulin dependent diabetes;
13. Has any condition that might compromise study results;
14. Currently or expect to sunbathe or use tanning salons during the study;
15. Is currently participating in any clinical testing;
16. Has any known sensitivity to adhesives; and/or
17. 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 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.

Individual patches may be discontinued if a reaction of a grade of 3 or greater (see Section 3.5.5 for examples of values using additive grades from Tables 3 and Table 4) occurs at any point during the study. Further patch applications of that product on that individual subject will be terminated. A "not patched" (NP) symbol and a score of 3 will be assigned for all subsequent days.

If a reaction is observed in any induction evaluation, a change in site location for the remaining applications in the Induction Phase will take place for that particular patch. See Section 3.5.5 for interpretations of scores.

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 of 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 primary medical doctor (PMD). The specific AE in question will be recorded on the appropriate CRF.

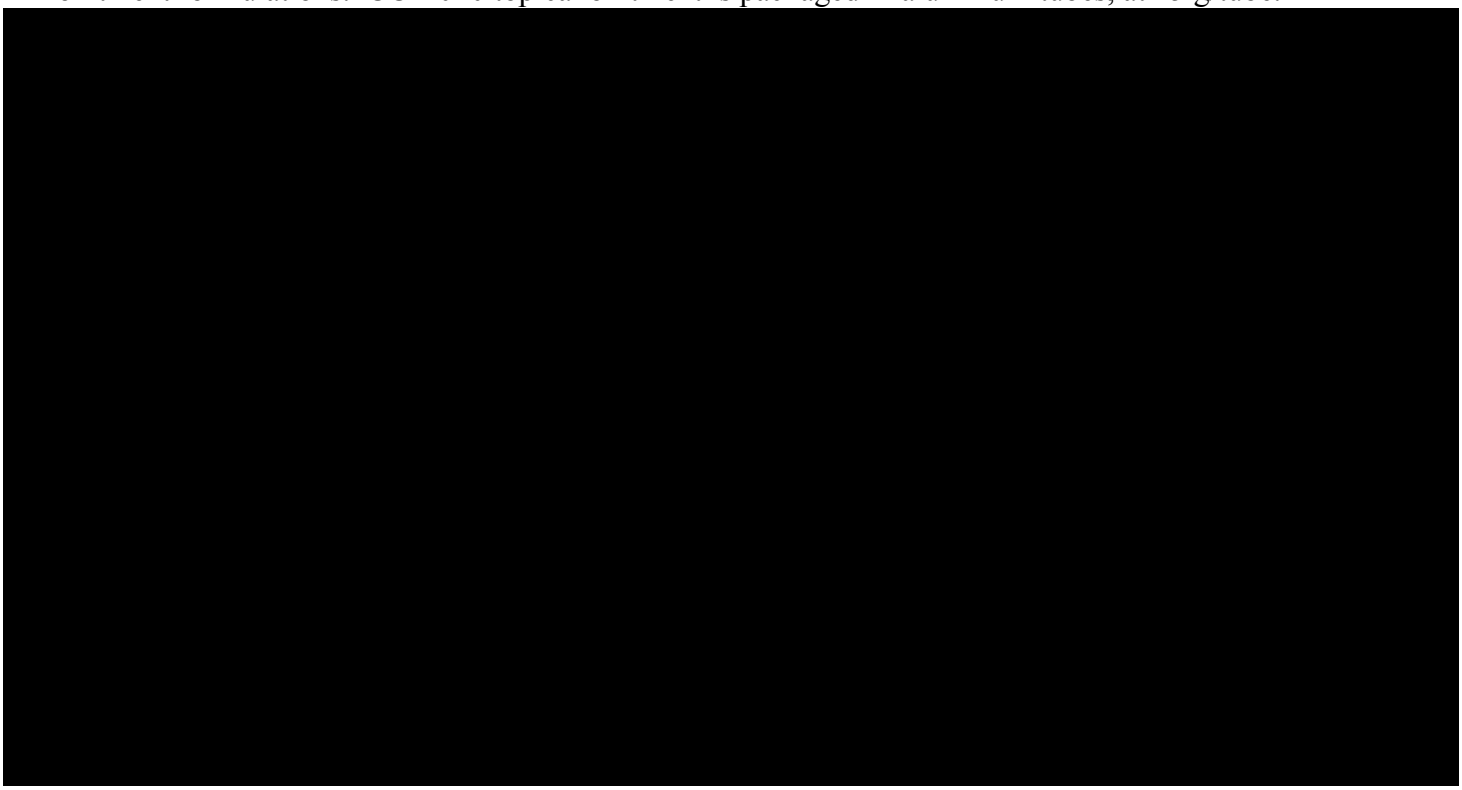
## 3.4. Treatments

### 3.4.1. Investigational Product and Controls

**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 ointment formulations. CCP-020 topical ointment is packaged in aluminum tubes, at 25 g/tube.



CCP-020 topical ointment and vehicle 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:

[redacted]

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.

The IPs will be dispensed via Eppendorf® Combitips onto separate occlusive patches at approximately 0.2 mL per patch applied 3 times weekly for 3 weeks (9 applications) during the Induction Phase, and one time at Challenge (10 times in total).

**Control**

A commercially available solution of 0.9% saline for topical administration (e.g., from Medline Industries Inc. (RDI30296)), applied 3 times weekly for 3 weeks (9 applications) during the Induction Phase, and one time at Challenge (10 times in total).

Eppendorf® Combitips will be used to apply 0.2 mL of the saline solution to its designated occlusive patch.

### 3.4.2. Description of Investigational Products

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

### 3.4.3. Description of Patch Conditions

CCP-020 (Diacerein 1%) topical ointment, vehicle, and negative irritant control will be evaluated under occlusive patch conditions by means of application to a 2 x 2 cm Webril® pad. The patches will be secured with nonporous Blenderm tape and hypoallergenic paper tape 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 form (ICF) will be assigned a screening number. If the subject meets all of the inclusion and none of the exclusion criteria, and successfully completes the screening procedures, they will be enrolled in the study. Upon enrollment, each subject will be assigned a unique subject number and receive a randomization code, indicating application placement of the study materials. Each subject in this study will serve as his or her own control. All subjects will receive the IPs and control products at adjacent application sites.

The IPs (CCP-020 [Diacerein 1%] topical ointment and vehicle) and study control (saline) will be assigned in a randomized sequence to test Sites 1 through 3 using a set of independent 3-by-3 Latin squares. The same study material will be applied to the same test site throughout the study.

#### 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 not perform the evaluation of skin responses. Investigative personnel who are involved in the preparation/application and removal of the treatments will be unblinded. The trained evaluator who will be evaluating skin responses will be blinded to IPs and control 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 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);
- Use of sunbeds or sunlamps or deliberate exposure of the test sites to natural sunlight or to other sources of ultraviolet (UV) light;
- Participation in any other clinical study;
- Soaking of test areas; and/or
- 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.

If individual patches become dislodged or are misplaced, such that continuous contact with the skin has been interrupted, then patching at that site must be discontinued for the remainder of the study and that patch site will be considered not complete. If all patches become dislodged, the subject will be discontinued from further participation in the study.

## 3.5. Visit Schedule and Assessments

### 3.5.1. Study Procedures and Visit Schedule

**Screening**

At Screening, the subjects will receive any necessary written and verbal information, and the informed consent of each subject will be obtained. Demographic data (including Fitzpatrick skin

type) will be recorded, a medical history will be taken, and previous and concomitant medications will be reviewed. Eligibility will be determined by review of the inclusion/exclusion criteria.

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

Prior to randomization, women of childbearing potential will be administered a UPT. If the subject fulfills all of the inclusion and none of the exclusion criteria, he/she will be allowed participation in the study. A Baseline evaluation of the patch sites will be performed 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. Subjects will receive a unique randomization number, which determines the application scheme of the study materials for that individual subject.

A set of 3 patches will be prepared in accordance with the randomization scheme on either the left or right side of the infrascapular area of the subject's back during the Induction Phase and the opposite side of the infrascapular area of the subject's back during the Challenge Phase. A visual inspection of skin clarity and the side of patch application will be recorded on the CRF to ensure consistent placement of the patches at subsequent visits. 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. The distance between the patches will be approximately 1 cm. The numbering of the test sites will remain the same throughout the study. A surgical marker will be used to draw lines to indicate the 3 site locations for compliance purposes. All patches will be affixed to the test sites on the intact skin of the infrascapular area of the subject's back by investigative personnel.

CCP-020 (Diacerein 1%) topical ointment and vehicle will be applied in the amount of 0.2 mL to a 2 cm x 2 cm Webril® patch pad via Eppendorf® Combitips and then applied to the subject's skin surface as soon as possible following product application. The sterile 0.9% saline (negative

irritant control) will be applied to a 2 cm x 2 cm Webril® patch pad via pipette and then applied to the subject's skin surface. All 3 products will be evaluated under occlusive patch conditions by means of application to a 2 cm x 2 cm Webril® pad. The patches will be secured with hypoallergenic tape as needed.

**Induction**

The Induction Phase consists of a series of 9 applications of the study material and subsequent evaluations of the application sites. The subjects will return to the facility 3 times per week for 3 consecutive weeks at 48 – 72 (± 4) hour intervals to have the patches removed (i.e. Mondays, Wednesdays, and Fridays for 3 consecutive weeks). Using a tissue, the evaluator will remove any remaining excess study material to avoid transference of materials between sites. The sites will be evaluated using the scoring system detailed in Section 3.5.5. Identical patches will then be applied to the same sites. A new tube of CCP-020 (Diacerein 1%) topical ointment and vehicle will be opened every 14 days due to qualified product suitability (see Section 3.5.2).

Subjects who are absent once during the 3-week, 9-patch Induction Phase will be instructed to keep the patches in place and return to the facility on their next scheduled visit. They will be scheduled to receive a make-up (MU) patch application at the last Induction visit. The MU patches will be removed 48 – 72 (±4) hours later and the sites will be graded. If subjects fail to return for removal/evaluation of the MU patch, a no ninth grading (N9G) will be recorded.

In cases where the subject misses the 9th evaluation in Induction Phase, the subject will be allowed to remove the patches by themselves in accordance with investigative personnel instructions. A telephone log will be written for any subjects that experience this situation to document the telephone conversation regarding the removal by subject.

Subjects who miss the 9$^{th}$ evaluation, but have had 9 patch applications will be considered to have completed the Induction Phase.

During Induction, the actual patch test grade is a combination of a numerical (Table 3) and letter (Table 4) grade consistent with the definitions given in the grading scales. A grade of 3 or higher to a specific study material (see Section 3.5.5 for interpretation of symbols) observed at the first or second reading of the Induction Phase would indicate the subject is pre-sensitized, and application of the product(s) in question would be discontinued. If these reactions are observed after the first or second reading of the Induction Phase, this would necessitate a change in patch location to a naïve site. A second site change to the specific study material would potentially require a patch condition change to semi-occlusive conditions for the remaining applications in the Induction Phase (see Section 3.5.6).

**Rest Period**

During the Rest Period of approximately 10-14 days, subjects will not receive any application of study materials.

**Challenge**

At the Challenge Phase, subjects who have completed the Induction Phase and the Rest Period will have identical patches applied to naïve sites. Patches will remain on the naïve sites for 48 (±1) hour to be evaluated at 30 (+ 10) minutes and 24 (± 1), 48 (± 1), and 72 (± 4) hours following patch removal (e.g., apply patch on Monday, remove patch on Wednesday, evaluate

test sites on Wednesday, Thursday, Friday, and Saturday), using the procedures described above for the Induction Phase. A possible follow-up reading may be conducted at 96 (± 4) hours for subjects with a score of 3 or higher at the 72 (± 4) hour time point.

Concomitant medications and AEs will be reviewed and recorded at the time of evaluation.

To be considered a **completed case**, a subject must have 9 applications of the study material and no fewer than 8 subsequent readings during Induction Phase and one application followed by 4 subsequent readings during the Challenge Phase. Only completed cases will be used to assess sensitization.

**Rechallenge**

A subject will be rechallenged to a specific study material if, in the opinion of the Investigator, any sign suggestive of contact sensitization (definite erythema with papules and/or edema) is observed at any of the 4 Challenge evaluations or at the Investigator's discretion for that study material.

Rechallenge patches will be applied at least 2 weeks after the end of the Challenge Phase. The study material will be applied to naïve sites on the back, in a manner similar to that used in the Challenge Phase. Rechallenge patches will remain in place for 48 (± 1) hour and patch sites will be evaluated 30 (+ 10) minutes and 24 (± 1), 48 (± 1), and 72 (± 4) hours after removal. As an example, patches will be applied on Monday and removed on Wednesday; the test sites will be evaluated on Wednesday, Thursday, Friday, and the following Saturday.

**End of Study**

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

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

- Concomitant medication
- AEs
- UPT in females of childbearing potential

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

### 3.5.2. Visit Schedule

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

**Table 2: Visit Schedule and Assessments**

| | Screening Day -21 to -1 | Induction Weeks 1-3 | Rest Weeks 4-5 | Challenge Week 6 | EOS | Rechallenge |
|---|---|---|---|---|---|---|
| Informed consent | X | | | | | |
| Demographics | X | | | | | |
| Inclusion/Exclusion | X | | | | | |
| Medical history | X | | | | | |
| UPT | | X[a] | | | X | |
| Randomization | | X[a] | | | | |
| Study treatment applications and/or removals | | X | X[b] | X | | X |
| Evaluations | | X | X[c] | X | | X |
| Make-up applications (if applicable) | | X | | | | |
| Concomitant medications | X | X | X | X | X | X |
| Adverse events | | X | X | X | X | X |

a: Day 1 only
b: Day 1 of Week 4, removal/evaluation of last Induction patch.
c: 48-72 (±4) hour evaluation of MU patch (if applicable).

**Note:** The visit schedule may be revised if necessary.

### 3.5.3. 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.

### 3.5.4. Efficacy Assessments

No efficacy will be assessed in this study.

### 3.5.5. Safety Assessments

#### 3.5.5.1. Local Tolerability Assessments

Assessment of the patch sites will be conducted by a trained evaluator once at Baseline (Day 1), 9 times during the Induction Phase, 4 times during the Challenge Phase and, if applicable, 4 times during Rechallenge. The trained evaluator will assign a grade to each site (Table 3). 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. For the purpose of statistical analysis only, each grade will correspond to a score. The following symbols and their respective numerical equivalents (see Table 3) will be used to express the response observed at the time of examination (see Table 4):

**Table 3: Response Symbols and Numerical Equivalents**

| Grade | Score* | Definition |
|---|---|---|
| 0 | 0 | No evidence of irritation |
| 1 | 1 | Minimal erythema; barely perceptible |
| 2 | 2 | Definite erythema, readily visible; or minimal edema; or minimal papular response |
| 3 | 3 | Erythema and papules |
| 4 | 3 | Definite edema |
| 5 | 3 | Erythema, edema, and papules |
| 6 | 3 | Vesicular eruption |
| 7 | 3 | Strong reaction spreading beyond test site |

*Scores are utilized only during the statistical analysis process of the study. Grades will be conducted throughout the study by the trained evaluator.

**Table 4: Effects on Superficial Layers of Skin**

| Grade | Score* | Response |
|---|---|---|
| A | 0 | Slight glazed appearance |
| C | 1 | Marked glazing |
| E | 2 | Glazing with peeling and cracking |
| F | 3 | Glazing with fissures |
| G | 3 | Film of dried serous exudate covering all or portion of the patch site |
| H | 3 | Small petechial erosions and/or scabs |

*Scores are utilized only during the statistical analysis process of the study. Grades will be conducted throughout the study by the trained evaluator.

Other notations (see Table 5) may be made in place of a score to designate particular circumstances preventing the assignment of a score or in addition to a score to identify damage to the epidermis and/or spreading of a reaction beyond the patch site.

The actual patch test grades are a combination of a numerical (Table 3) and letter (Table 4) grades consistent with the definitions given in the grading scales. However, in order to determine discontinuation of a patch site (grade > 3) and to perform statistical analyses, grades containing letter grades have to be converted to numerical equivalents. These are converted as follows: A=0, C=1, E=2 and F, G, and H =3. These equivalents are considered additive to any numerical score (e.g., 2C=2+1=3), in this case the patch site would be discontinued.

**Table 5: Other Notations**

| Notation | Definition |
|---|---|
| X | Subject absent |
| B | Burning or stinging sensation |
| PD | Patch dislodged |
| NA | Patch not applied |
| NP | No patch due to limiting irritation |
| I | Itching |
| D | Damage of the epidermis: oozing, crusting, and/or superficial erosions |
| p | Papular response |
| pv | Papulovesicular response |
| S | Spreading of reaction beyond patch site (i.e., reaction where study material did not come in contact with skin) |
| T | Tape related reaction |

Details regarding the statistical analysis of the cumulative irritation scores are provided in Section 4.6.

### 3.5.6. Criteria for Changing the Application Site or Conditions

A grade of 3 or higher to a study product (using Table 3 and Table 4) observed at the first or second reading of the Induction Phase would indicate the subject to be pre-sensitized, and application of the product in question would be discontinued.

After the second reading of the Induction Phase, reactions graded 3 or higher (using Table 3 or Table 4) require that the investigational product be applied to a naïve site under occlusive conditions. Such a change of application site may occur no more than twice during the Induction Phase for a particular product, after which applications of the product will be discontinued for that subject for the remainder of the study. Subjects requiring site changes due to irritancy in the Induction Phase will be considered evaluable for sensitization, provided that they receive a total of no fewer than 9 applications of the product.

No more than 2 changes for a given product will occur, whether the changes are to a new site under occlusive conditions (first move) or a new site under semi-occlusive conditions (second move).

Occlusive patch conditions include a Webril® cotton patch surrounded with Blenderm tape and covered with paper tape. There is no air flow under the patch. Semi-occlusive patch conditions include a Webril® cotton patch covered with paper tape, to allow air flow under the patch itself.

The 3-week period of continuous patch contact during the Induction Phase frequently results in tape-related irritation that is exacerbated by warm weather, but which occurs among some individuals irrespective of the season. Since adhesive tape is an integral part of the test article, tape-related irritation at the site will be documented as an application site reaction using the symbol "T" from Table 5. Severe tape-related irritation will require a change of application site. Mild and moderate tape related reactions will not require of a change of application site. If all sites are experiencing tape reactions, the patch sites will be discontinued and a not patched (NP) symbol will be recorded for the remainder of the study. The subject will be discontinued from the study. An AE will be recorded in order to follow through to resolution of the tape related reaction.

## 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 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 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 6.

**Table 6: 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. This will be noted in the database as "T" as indicated in Table 5 and will be considered an expected AE. When all application sites are experiencing tape reaction, the subject is discontinued and therefore be recorded as an AE. The subject will be followed up through resolution.

## 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 or pregnancy has not been previously documented (i.e., is a new occurrence) and it is thought to be related to the investigational product (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 or pregnancy 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 RIPT study design using 200 subjects is considered adequate to identify any significant safety hazard due to the potential of a topically administered dermatologic agent to induce allergenic sensitization. Individual subjects' cutaneous responses after Challenge Phase are classified as indicative of sensitization or not indicative of sensitization based on specific criteria defined in terms of an ordinal rating scale. The occurrence in this study of even a single reaction indicative of sensitization is sufficient to suggest that the test product may have the potential to cause hypersensitivity.

The statistical analyses described below will be supplemented by a comprehensive Statistical Analysis Plan (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 200 evaluable subjects conforms to industry and regulatory standards for determination of dermal sensitization potential. In the absence of any sensitization reactions, a 95% upper confidence bound on the population rate of sensitization would be 1.5%.

## 4.3. Subject Populations for Analysis

All subjects who receive treatment will be evaluable for AEs. The evaluation of sensitization will be based on all subjects who complete the Challenge Phase of the study. The analysis of cumulative irritancy will be based on all subjects who complete the Induction Phase of 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. Cumulative Irritancy

Cumulative irritancy during Induction will be quantified by means of the cumulative irritancy index (CII), defined as the mean of the total cumulative irritation scores received during the Induction Phase (9 readings). The total cumulative irritation score for each subject and product will be calculated by summing each individual's scores on each of the 9 evaluation days in the Induction Phase. Response grades will be assigned numerical scores according to Table 3 and Table 4. Once the maximum score (combined score from Table 3 and Table 4) or a 3 or greater is achieved, the remaining scores of 3 will be carried forward through all subsequent readings. No data imputations are to be made for discontinued subjects or missed evaluations.

The CII will be tested pairwise for product differences using Fisher's protected least significant differences in the context of the 2-way analysis of variance (ANOVA) including main effects of subject and product, without interaction. Pairwise differences will be tested for all products at the 5% level. Mean cumulative irritation scores will also be presented for each patch in a listing.

### 4.6.2. Analysis of Dermal Sensitization Potential

The determination of dermal sensitization potential will be based on specific scoring criteria (Table 3) derived from observations in the Challenge Phase of the study and confirmed in the Rechallenge Phase, if necessary.

Criteria specified in Section 3.5.5 may cause the continuation of a subject into the Rechallenge Phase of the study. The recurrence of a cutaneous response of 3 or greater from Table 3 at Rechallenge equivalent to or more severe than that observed at Challenge will be considered indicative of a sensitization reaction. The observation of such a response in even a single subject suggests that the test product may have the potential to cause hypersensitivity.

A narrative description of reactions in the Challenge and Rechallenge Phases will be provided together with the opinion of the Investigator as to whether such reactions are felt to be indicative of contact sensitization.

### 4.6.3. Adverse Events

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

Treatment-emergent 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, 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 SOPs. 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.
- US 21 Code of Federal Regulations 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 Castle Creek Pharmaceuticals, LLC 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 Castle Creek Pharmaceuticals, LLC 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 Castle Creek Pharmaceuticals, LLC.

## 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 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 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

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