CLINICAL STUDY PROTOCOL
CCP-020 (DIACEREIN 1% STERILE OINTMENT)
CCP-020-101

A Multi-center Study to Evaluate the Pharmacokinetics of Diacerein and Rhein and the Safety of Diacerein after Maximum Use, Topical Administration of CCP-020 (Diacerein 1% ointment) to Patients with Epidermolysis Bullosa (EB)

[redacted]

Confidentiality Statement

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for Diacerein 1% Ointment. I have read the CCP-020-101 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

STUDY CONTACT INFORMATION

Table 1: Emergency Contact Information

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Table 1: Emergency Contact Information (Continued)

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

2. SYNOPSIS

Name of Sponsor/Company:
Castle Creek Pharmaceuticals, LLC

Name of Investigational Product:
CCP-020 (diacerein 1% ointment)

Name of Active Ingredient:
Diacerein

Title of Study:
A Multi-center Study to Evaluate the Pharmacokinetics of Diacerein and Rhein and the Safety of Diacerein after Maximum Use, Topical Administration of CCP-020 (Diacerein 1% ointment) to Patients with Epidermolysis Bullosa (EB)

Studied period (years):	**Phase of development:** I
Estimated date first patient enrolled: March 2018 Estimated date last patient completed: November 2018	

Objectives:

Primary:

- The primary objective of the study is to descriptively characterize the single-dose and steady-state pharmacokinetics (PK) of diacerein (if quantifiable) and its active metabolite, rhein, after topical application of CCP-020 (diacerein 1% ointment) under maximum use conditions in adolescent and adult patients with EB, and in infants/children with EB.

Secondary:

- The secondary objective of the study is to assess the safety and tolerability of single-dose and steady-state topical application of CCP-020 (diacerein 1% ointment) in patients with EB.

Methodology:

The study is designed as an open label, single period study in approximately 16-20 patients with EB ranging in age from infants/children (ages 6 months – 11 years, inclusive) and adolescents/adults (ages 12 and up) with at least 8-10 subjects between the aged 6 months to 11 years, inclusive (infants/children). The study will be conducted in two cohorts as follows:

1. 8-10 adolescent and adult patients with EB (aged 12 and older)
    a. EBS subjects: lesions encompassing ≥ 2% BSA for study entry. Diacerein application area to be ≥ 5% BSA and include lesioned and non-lesioned skin (if lesions account for less than 5% BSA); however, topical administration must be ≤30% BSA.
    b. DEB/JEB subjects: lesions encompassing ≥ 2% BSA for study entry. Diacerein application area to be ≥ 5% BSA and include lesioned and non-lesioned skin (if lesions account for less than 5% BSA); however, topical administration must be ≤30% BSA.
2. 8-10 infants/children with EB (aged 6 months to 11 years, inclusive)
    a. EBS subjects: lesions encompassing ≥ 2% BSA for study entry. Diacerein application area to be ≥ 5% BSA and include lesioned and non-lesioned skin (if

lesions account for less than 5% BSA); however, topical administration must be ≤30% BSA.

b. DEB/JEB subjects: lesions encompassing ≥ 2% BSA for study entry. Diacerein application area to be ≥ 5% BSA and include lesioned and non-lesioned skin (if lesions account for less than 5% BSA); however, topical administration must be ≤30% BSA.

NOTE: 1% BSA is defined as the area of the subject's hand held flat, including the thumb and fingers held together

NOTE: No more than 4-5 DEB/JEB patients (50% of the cohort) may be enrolled into the cohort. DEB/JEB patients will not be eligible for the open-label extension study.

For adolescent/adult patients with EB (Cohort 1):

Eligible, consented (assented and/or consent via guardian) adolescent and adult patients aged 12 and up with EB lesions encompassing ≥ 2% BSA will be enrolled in the study. On Day 1, the total surface area of all available areas for application will be quantified and recorded. The area(s) surrounding the lesion/lesions, will be marked (with a marker) encompassing no less than a total of 5% BSA (across all lesions, total) and separate paper body charts will be completed documenting the application area. The area(s) encompassing no less than 5% BSA will be defined as the application area(s) and will remain fixed over the course of the 10 Day treatment period. On Day 1, the topical dose of CCP-020 will be applied by study staff followed by blood sampling for plasma analysis of diacerein and rhein through 8 hours post-application. PK samples will be collected at pre-dose, 0.5, 1, 2, 3, 4, 6, and 8 hours post-dose on Days 1 and 10. Trough PK samples will be collected on any two available days from Day 3 through Day 9. Patients will be discharged from the study site on Day 1 and will continue applications to the entire application area for 9 days at home at the same time each day. For the trough sample visits between Days 3 and 9, CCP-020 will be applied after the blood draw. The application area should be left uncovered for at least one-hour post-application, after which it is acceptable to apply non-absorbent bandages consistent with standard of care. On Day 10, patients will return to the study site for a pre-dose blood sample and application of CCP-020 to the application area followed by blood sampling for plasma analysis of diacerein and rhein.

For infant/child patients with EB (Cohort 2):

Eligible, assented (consented via guardian) infant/child patients aged 6 months to 11 years, inclusive with EB lesions encompassing ≥ 2% BSA will be enrolled in the study. On Day 1, the total surface area of all available areas for application will be quantified and recorded. The area(s) surrounding the lesion/lesions, will be marked (with a marker) encompassing no less than a total of 5% BSA (across all lesions, total) and separate paper body charts will be completed documenting the application area. The area(s) encompassing no less than 5% BSA will be defined as the application area(s) and will remain fixed over the course of the 10 Day treatment period. On Day 1, the topical dose of CCP-020 will be applied by study staff followed by blood sampling for plasma analysis of diacerein and rhein through 8 hours post-application. PK samples will be collected at pre-dose, 1, 2, 4, 6, and 8 hours post-dose on Days 1 and 10. Trough samples for Days 3-9 will **not** be required for this cohort. Patients will be discharged from the study site on Day 1 and will continue applications to the entire application area for 9 days at home at the same time each day. The application area should be left uncovered for at least one-hour post-application, after which it is acceptable to apply non-absorbent bandages consistent with standard of care. On Day 10, patients will return to the study site for a pre-dose blood sample and application of CCP-020 to the application area followed by blood sampling for plasma analysis of diacerein and rhein. For sites participating in the United States (US), children under the age of 4 are prohibited from participating due to regulatory restrictions.

For both cohorts, on Days 1 and 10, void-volume catheters will be placed to obviate multiple needle sticks in blood sampling.

Safety will be monitored throughout the study by repeated clinical and laboratory evaluations.

The clinic/study site will attempt to contact subjects using their standard procedures approximately 14 days after the last study drug application to determine if any adverse events (AEs) have occurred since the last dose of study drug. Subjects who terminate the study early will be contacted if the Principal Investigator (PI) deems necessary.

EB (excluding DEB/JEB) patients that complete this study or receive at least one dose of study drug will be eligible for consideration to enroll an open-label extension study conducted under a separate protocol.

Number of patients (planned):

- 8-10 adolescent/adult patients with EB
- 8-10 infant/child patients with EB

Diagnosis and main criteria for inclusion:

Inclusion criteria:

1. Subject/caregiver is able to comprehend and willing to sign an Informed Consent and/or Assent Form.
2. Subject is male or female, at least 12 years of age (Cohort 1) or at least 6 months of age to 11 years, inclusive (Cohort 2) at screening. **US only**: subjects must be at least 4 years of age to 11 years, inclusive (Cohort 2)
3. The subject must weigh at least 9 kg (19.8 lbs) at Screening.
4. Subject has a documented genetic mutation consistent with EB. A blood or saliva sample will be collected for genetic confirmation if no documented gene mutation data is available. diagnosis of EB (EBS, DEB, JEB).
5. Subject has EB lesions on ≥ 2% body surface area (BSA) and the EB lesions are in the following body areas:
    a. Localized: plantar and/or palmar areas
    b. Generalized: arms, legs, torso, hands and feet.
6. Subject/caregiver agrees to not apply any other topical products to the application area during the treatment period
7. If the subject is a woman of childbearing potential, she has a negative urine pregnancy test and agrees to use an approved effective method of birth control, as defined by this protocol, for the duration of the study.
8. Subject is non-pregnant, non-lactating and is not planning for pregnancy during the study period
9. Subject is in good general health and free of any known disease state or physical condition which, in the investigator's opinion, which exposes the subject to an unacceptable risk by study participation.
10. Subject is willing and able to follow all study instructions and to attend all study visits.

Exclusion criteria:

1. Subject has EB lesions where drug will be applied that are infected (i.e., EB lesions that require anti-microbial therapy to treat an infection)

2. Subject has used any diacerein containing product within 1 month prior to Visit 1
3. Subject has used systemic immunotherapy or cytotoxic chemotherapy within 60 days prior to dosing.
4. Subject has used systemic steroidal therapy or has used topical steroidal therapy on the EB lesions in the application area within 14 days prior to dosing (Note: inhaled, nasal sprays, and ophthalmic products containing steroids are allowed)
5. Subject has evidence of a systemic infection or has used systemic antibiotics within 7 days prior to dosing
6. Subject has used any systemic diuretics or cardiac glycosides or any systemic product that, in the opinion of the investigator, might put the subject at undue risk by study participation or interferes with the study medication application or the study assessments within 30 days prior to dosing
7. Subject has a current malignancy, or a history of treatment for a malignancy within 2 years prior to dosing (Note: does not include non-melanoma skin cancer)
8. Subject currently has diabetes mellitus (HbA1c ≥6.5%) Note: controlled diabetes (HbA1c < 6.5%) is also considered exclusionary
9. Subject has a history of cardiac, hepatic (ALT and or AST >2x ULN, Total bilirubin >1.5x ULN at Visit 1), or renal disease (eGFR<30 ml/min/1.73 m^2 [MDRD-adults ≥18, Bedside Schwartz – children <18]) that, in the opinion of the investigator, might put the subject at undue risk by study participation or interferes with the study medication application of the study assessments
10. Subject has an active non-EB skin disease (e.g., psoriasis, atopic dermatitis, eczema, sun damage, etc.), or condition (e.g., sunburn) that, in the opinion of the investigator, would put the subject at undue risk by study participation or would interfere with the study medication application or the study assessments
11. Subject has a history of sensitivity to any of the ingredients in the study medication
12. Subject has participated in an investigational drug trial in which administration of an investigational study medication occurred within 30 days prior to dosing

Investigational product, dosage and mode of administration:

Diacerein 1% Ointment administered topically

Duration of treatment:

10 Days; EB (excluding DEB/JEB) patients that complete this study or receive at least one dose of study drug will be eligible for an open-label extension study conducted under a separate protocol.

Reference therapy, dosage and mode of administration:

None

Criteria for evaluation:

Pharmacokinetics:

Concentrations of diacerein (if measurable) and rhein in plasma will be determined after each treatment using validated bioanalytical methods. Relevant plasma PK parameters for diacerein (if possible) and rhein will be calculated using standard non-compartmental methodology. All non-compartmental analyses will be performed based on actual sample collection times using Phoenix WinNonlin (version 6.3 or later). Pharmacokinetic parameters (Cmax, tmax and AUC), if available, will be summarized using descriptive statistics.

Safety:

Adverse events will be collected and evaluated as they occur throughout the study. Safety assessments, including physical examinations, application site assessment, vital signs assessments, and clinical laboratory tests, will be performed at select time points.

Statistical methods:

Analysis Populations:

Pharmacokinetic Evaluable Population: The PK Evaluable Population will comprise all subjects receiving at least one dose of CCP-020 who have sufficient ($\geq$ 4 quantifiable concentrations) plasma concentration data to calculate PK parameters for rhein and if possible, diacerein.

Pharmacokinetic Concentration Population: The PK Concentration Population will comprise all subjects receiving at least one dose of CCP-020 who have at least one quantifiable plasma concentration for rhein and if possible, diacerein. Safety Population: The safety population will consist of all subjects who receive any amount of study drug.

Pharmacokinetic Analysis:

Summaries of plasma concentration will be based on PK Concentration Population. Individual and mean graphs of plasma diacerein (if measurable) and rhein concentrations versus time after single dose and multiple dose of CCP-020 will be constructed and displayed for relevant treatment comparisons, as data permit.

Plasma concentrations of diacerein and rhein will be summarized by Cohort and EB type using descriptive statistics (sample size, mean, median, coefficient of variation [CV%], standard deviation [SD], minimum, and maximum). Corresponding by-subject data listings will be tabulated. The summary statistics for each scheduled time will only be reported when at least 50% of subjects have quantifiable concentrations.

Summaries of plasmas PK parameters will be based on PK Evaluable Population. Derived plasma PK parameters (Cmax, tmax and AUC), if available, for diacerein and rhein will be summarized by Cohort and EB type using descriptive statistics (sample size, arithmetic mean, CV%, SD of the arithmetic mean, median, minimum, and maximum). Geometric mean and geometric CV will also be provided for Cmax and AUC. Corresponding by-subject data listings will be tabulated.

Safety Analysis:

The number and percentage of subjects reporting any treatment-emergent AE will be tabulated by system organ class and preferred term for each Cohort and EB type (coded using Medical Dictionary for Regulatory Activities). Treatment-emergent AEs will be further classified by maximum severity and relationship to treatment.

Physical examinations, vital signs, application site assessment, and clinical laboratory test data (observed and change from baseline) will be summarized using appropriate descriptive statistics.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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REPRESENTATIVES FROM CASTLE CREEK PHARMACEUTICALS

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and in accordance with the principles that have their origin in the Declaration of Helsinki.

[redacted]

[redacted]

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
BSA	Body Surface Area
°C	Degrees Celsius
CBD	Cannabidiol
CMH	Cochran-Mantel-Haenszel
CR	Clinically Relevant
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
EB	Epidermolysis Bullosa
EBS	Epidermolysis Bullosa Simplex
e.g.	For Example, (Latin; exempla gratia)
EC	Ethics Committee
CRF	Case Report Form
EDC	Electronic Data Capture
DEB	Dystrophic Epidermolysis Bullosa
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
G	Gram
GCP	Good Clinical Practice
HCG	Human Chorionic Gonadotrophin
HIPAA	Health Insurance Portability and Accountability Act of 1996
Hg	Mercury
IB	Investigator's Brochure
ICF	Informed Consent Form

Table 2: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
ICH	International Conference on Harmonization
i.e.	That Is (Latin; id est)
IGA	Investigator's Global Assessment
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-To-Treat
JEB	Junctional Epidermolysis Bullosa
LOCF	Last Observation Carried Forward
LSA	Lesion Surface Area
MedDRA	Medical Dictionary for Regulatory Activities
Ml	Milliliter
Mm	Millimeter
µMol	Micro-molar
NCR	Not Clinically Relevant
OTC	Over-The-Counter
PK	Pharmacokinetic
PP	Per Protocol
SAE	Serious Adverse Event
SI	Subject Identifier
SOP	Standard Operation Procedure
TEAE	Treatment Emergent Adverse Event
US	United States
WOCBP	Women of childbearing potential

5. INTRODUCTION

Epidermolysis bullosa simplex (EBS) is a rare, genetic skin disease characterized by fragility of the skin and mucous membranes resulting in painful blisters and erosions after minor trauma, and is associated with significant morbidity and mortality[1,2]. EBS is both a pediatric and an adult disease that tends to affect younger patients most severely. Most patients with EBS have 10% to 30% of body surface area (BSA) affected by blisters, although there can be wide variations. EBS frequently has palmar and plantar involvement, which can significantly affect patients' mobility and quality of life. In addition to blistering and skin infections, patients suffer from pain and severe, continuous itching. There are currently no approved treatments for EBS.

The simplex form is 1 of 3 major types of EB and is classified by skin blister development in the basal epidermis[3]. Those born with EB are often called "Butterfly Children" because, as the analogy goes, their skin is as fragile as the wings of a butterfly. The prevalence of inherited EB in the US is estimated to be approximately 11 per million live births according to the National Epidermolysis Bullosa Registry in the US; there are around 20 new EB cases per 1 million live births, of which approximately 92% are EBS[4].

Diacerein 1% Ointment 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 for the treatment of 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 dermis following administration. Diacerein and rhein have been shown to inhibit the in vitro and in vivo production and activity of interleukin-1β (IL-1β) and other pro-inflammatory 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.

IL-1β is a pro-inflammatory cytokine that has been linked to a number of inflammatory and autoimmune diseases, including rheumatoid arthritis (RA), OA, hemophilic arthropathy, gouty arthritis, type 2 diabetes mellitus (T2DM), diabetic nephropathy (DN), and EBS. In vitro and in vivo animal studies have shown that both diacerein and its active metabolite rhein inhibit the production and activity of pro-inflammatory and pro-catabolic cytokines such as IL-1 and IL6, and the expression of inducible nitric oxide synthase (iNOS) and tumor necrosis factor-α (TNF-α).

Prior to the first application of diacerein in a phase 1 EBS treatment study, a single topical application of 50 mg Diacerein 1% Cream was applied to the skin of a patient with EBS[5]. The amount of rhein detected in the patient's urine was 2.4% of the amount detected in the urine after oral administration of the same dose. Pharmacokinetic (PK) analysis of rhein was performed in 2 patients with EBS from the phase 2 trial described below. Serum and urine samples were collected immediately following 4 weeks of administration of Diacerein 1% Cream to 3% of these patients BSA. The highest level of rhein in urine was 39.9 ng/ml and the highest level of rhein in serum was 20.1 ng/ml. This serum level represents less than 1% of the serum level

detectable after oral administration of a single dose of 50 mg diacerein.6 These data suggest that upon topical administration, diacerein reaches circulation in the form of rhein and is excreted as rhein. Additionally, the most commonly reported adverse effects after oral administration, such as diarrhea, nausea, and vomiting, occur at only higher systemic concentrations, which should not be achieved following topical administration.

Phase 1 and phase 2 studies of Diacerein 1% Cream for treatment of EBS have been successfully completed. Both studies were conducted in Europe under Dr. Johann Bauer as principal investigator.

A phase 1 clinical pilot study of topical Diacerein 1% Cream to reduce blistering in patients with EBS-DM (generalized severe type) was completed in 2012 and its results were published in 2013. Five patients with EBS-DM initially applied Diacerein 1% Cream underneath both armpits in the first 6-week open-label phase. Then, each participant received Diacerein 1% Cream for one armpit and placebo for the other in a second, randomized, placebo-controlled 6-week phase 2. Time to loss of efficacy (defined as halving of the effect observed in phase 1) was chosen as the primary endpoint. Results showed a statistically significant reduction of blisters within the first 2 weeks of the open-label phase 1. In phase 2, there was no loss of efficacy in both the treated and placebo groups.

A phase 2 clinical study was completed in 2015. This was a placebo-controlled, randomized, and double-blinded crossover study of 17 randomized and treated patients, ages 4 to 19, diagnosed with generalized severe EBS[6]. A 4-week treatment period and a three month follow-up period was performed in both Year 1 and Year 2 of the study, with a cross over of groups (placebo and diacerein) between years. During the 4 week treatment period, patients or their caregivers applied 3 finger-tip units of Diacerein 1% Cream or placebo onto a pre defined skin area. Three percent of the total BSA was chosen, together with the patients, with the pre-requisite that significant numbers of blisters were present at Time 0.

The results of these studies suggest that topical diacerein has the potential to down-regulate the activity of IL-1β and reduce the inflammatory effects in the skin of patients with EBS. The favorable product profile of diacerein, an anti-IL-1β small molecule, provides a rationale for investigating the clinical utility in reducing the frequency or preventing of blister formation in patients with EBS.

Detailed information about the phase 1 and phase 2 study designs and results are presented in the Diacerein 1% Ointment Investigator's Brochure.

A global randomized, double-blind, phase 2 study comparing the efficacy of diacerein 1% ointment to placebo in treating patients with EBS is ongoing. A phase 2, open-label extension study evaluating the long term safety of diacerein 1% ointment in treating patients with EBS is ongoing.

This study is an open-label, phase 1 study evaluating the pharmacokinetics of Diacerein 1% Ointment in patients with EB. EB (excluding DEB/JEB) patients that complete this study or receive at least one dose of study drug will be eligible for an open-label extension study conducted under a separate protocol.

5.1. Rationale For Use of Patients With All Forms of EB in Maximal Use PK Study

Epidermolysis bullosa (EB) is cluster of inherited disorders defined by skin blistering, structural defects and abnormal disruption of the epidermis or epidermal–dermal junction in response to minor mechanical trauma. The primary pathophysiologic factor in all types of EB is skin blisters and disruption of normal function as a permeability barrier. The outermost part of the skin, epidermis, is composed of stratified layers of flattened cells that overlies a basal layer composed of columnar cells arranged perpendicularly. This epidermal layer provides a barrier to environmental pathogens and insults and regulates the amount of water and electrolytes released from the body into the atmosphere through transepidermal water loss (TEWL), and is perturbed due to the presence of blistering. The normal permeability barrier resides in the stratum corneum, a resilient layer composed of corneocytes and stratum corneum intercellular lipids, and this layer is physically separated from underlying structural skin elements when blistering occurs. The main EB types can be classified according to extent of body surface area involvement, as well as related histopathophysiology. EB simplex (EBS) is characterized by fragility and blistering caused by mutations in keratin intermediate filaments of basal keratinocytes. Such mutations lead to a conformational change and an increased self-aggregation of the protein. The presence of aggregates in the cytoplasm as a result of stress may subsequently lead to the disintegration and collapse of the IF network. EBS can affect the majority of the skin in early years or may be as little as 5% of body surface area (BSA) in adulthood. Dystrophic EB (DEB) is defined is due to defects in type VII collagen. Clinically, patients suffer from blistering of the skin and mucous membranes upon minor trauma, resulting in an impaired life quality due to pain and pruritus. Patients with DEB may have 80% or more of their BSA affected by disease.

Based on mechanistic studies and clinical observation, it is likely that inflammatory cytokines including IL-1β are also involved in the pathogenesis of various types of EB. There is evidence that both EB simplex as well as dystrophic EB pathology is the result of elevated levels of cytokines.

Therefore, a clinical strategy that seeks to reduce the levels of inflammatory molecules is justified in both EBS as well as DEB. To this end, inclusion of patients with DEB in a PK study that allows follow up may provide some clues as to diacerein autoinflammatory priorities in these patients while at the same time allowing for enrollment of patients with more extensive skin involvement to help with requirement for maximal skin involvement.

In order to assess the possibility of diacerein and rhein to be absorbed through skin under maximum use conditions, the sponsor proposes applying diacerein ointment to all types of EB skin. While, the target indication is EBS, the blistering symptoms are similar across all major types of EB, with the major differences being that patients with dystrophic EB typically have greater body surface area involvement than those with the simplex form. The epidermal permeability barrier is disrupted in all forms of EB, and to help measure extent of topical drug absorption under maximum use conditions it is recommended that patients with all forms of EB be evaluated.

5.2. Risks and/or Benefits to Subjects

The application of study drug administered in this study is not anticipated to induce therapeutic benefit due to the short treatment duration. However, it is anticipated that continued use of the study medication (8 weeks on, 8 weeks off) will reduce the blister severity of the affected area. EB-Simplex patients who complete this study or receive at least one dose of study drug will be eligible for a long-term open label extension study (DEB/JEB patients are not be eligible for the extension due to the lack of efficacy data to support any benefit for patients in these subtypes). In addition, subjects will receive study drug at no cost during this open label PK study.

The safety monitoring practices employed by this protocol (i.e. vital signs, clinical and laboratory evaluations, and AE questioning) are adequate to protect the subjects' safety and are expected to be sufficient to detect all treatment emergent adverse events (TEAEs).

The approximate volume of blood planned for collection from each subject over the course of the study is not considered to present undue risk to the subjects. No further risk is present if additional blood is required for recheck of safety laboratory tests, as deemed necessary by the PI.

An indirect health benefit to the EB subjects enrolled in this trial is the medical testing received at screening and during the study as outlined in this protocol, will be provided at no cost to the subject.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

The primary objective of the study is to descriptively characterize the single-dose and steady-state pharmacokinetics (PK) of diacerein (if quantifiable) and its active metabolite, rhein, after topical application of CCP-020 (diacerein 1% ointment) under maximum use conditions in adolescent and adult patients with EB, and in infants/children with EB.

6.2. Secondary Objectives

The secondary objective of the study is to assess the safety and tolerability of single-dose and steady-state topical application of CCP-020 (diacerein 1% ointment) in patients with EB.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is an open label, single period study in 16 to 20 patients with EB consisting of infants/children (ages 6 months – 11 years, inclusive) and adolescents/adults (ages 12 and up) with at least 6 subjects between the aged 6 months to 11 years, inclusive (infants/children). The study will consist of two cohorts as follows:

1. 8-10 adolescent and adult patients with EB (aged 12 and older)
    a. Lesions encompassing ≥ 2% BSA for study entry. Diacerein application area to be ≥ 5% BSA and include lesioned and non-lesioned skin (if lesions account for less than 5% BSA); however, topical administration must be ≤30% BSA.
2. 8-10 infants/children with EB (aged 6 months to 11 years, inclusive)
    a. Lesions encompassing ≥ 2% BSA for study entry. Diacerein application area to be ≥ 5% BSA and include lesioned and non-lesioned skin (if lesions account for less than 5% BSA); however, topical administration must be ≤30% BSA.

For adolescent/adult patients with EB (Cohort 1):

Eligible, consented (assented and/or consent via guardian) adolescent and adult patients aged 12 and up with EB lesions encompassing ≥ 2% BSA will be enrolled in the study. On Day 1, the total surface area of all available areas for application will be quantified and recorded. The area(s) surrounding the lesion/lesions, will be marked (with a marker) encompassing no less than a total of 5% BSA (across all lesions, total) and separate paper body charts will be completed documenting the application area. The area(s) encompassing no less than 5% BSA will be defined as the application area(s) and will remain fixed over the course of the 10 Day treatment period. On Day 1, the topical dose of CCP-020 will be applied by study staff followed by blood sampling for plasma analysis of diacerein and rhein through 8 hours post-application. PK samples will be collected at pre-dose, 0.5, 1, 2, 3, 4, 6, and 8 hours post-dose on Days 1 and 10. Trough PK samples will be collected on any two available days from Day 3 through Day 9. Patients will be discharged from the study site on Day 1 and will continue applications to the entire application area for 9 days at home at the same time each day. For the trough sample visits between Days 3 and 9, CCP-020 will be applied after the blood draw. The application area should be left uncovered for at least one-hour post-application, after which it is acceptable to apply non-absorbent bandages consistent with standard of care. On Day 10, patients will return to the study site for a pre-dose blood sample and application of CCP-020 to the application area followed by blood sampling for plasma analysis of diacerein and rhein.

For infant/child patients with EB (Cohort 2):

Eligible, assented (consented via guardian) infant/child patients aged 6 months to 11 years, inclusive with EB lesions encompassing ≥ 2% BSA will be enrolled in the study. On Day 1, the total surface area of all available areas for application will be quantified and recorded. The area(s) surrounding the lesion/lesions, will be marked (with a marker) encompassing no less than a total of 5% BSA (across all lesions, total) and separate paper body charts will be completed documenting the application area. The area(s) encompassing no less than 5% BSA will be defined as the application area(s) and will remain fixed over the course of the 10 Day treatment

period. On Day 1, the topical dose of CCP-020 will be applied by study staff followed by blood sampling for plasma analysis of diacerein and rhein through 8 hours post-application. PK samples will be collected at pre-dose, 1, 2, 4, 6, and 8 hours post-dose on Days 1 and 10. Trough samples for Days 3-9 will not be required for this cohort. Patients will be discharged from the study site on Day 1 and will continue applications to the entire application area for 9 days at home at the same time each day. The application area should be left uncovered for at least one-hour post-application, after which it is acceptable to apply non-absorbent bandages consistent with standard of care. On Day 10, patients will return to the study site for a pre-dose blood sample and application of CCP-020 to the application area followed by blood sampling for plasma analysis of diacerein and rhein. For sites participating in the United States (US), children under the age of 4 are prohibited from participating due to regulatory restrictions.

Safety will be monitored throughout the study by repeated clinical, and laboratory evaluations.

The clinic/study site will attempt to contact subjects using their standard procedures approximately 14 days after the last study drug application to determine if any adverse events (AEs) have occurred since the last dose of study drug. Subjects who terminate the study early will be contacted if the Principal Investigator (PI) deems necessary.

Subjects (excluding DEB/JEB) that complete this study or receive at least one application of study medication will be eligible for an open-label extension study with CCP-020 treatment conducted under a separate protocol.

7.2. Number of Subjects

The study will enroll 8-10 adolescent/adult patients with EB and 8-10 infant/child patients with EB. The intention is to obtain a full complement of PK samples (on Day 1 and Day 10) on at least 8 patients with no patients replaced. However, additional patients may be enrolled to achieve this; up to 10 patients per cohort, if is deemed necessary as determined by the Sponsor.

Only 50% of each cohort (e.g. 4-5 patients) may contain the EB subtypes of DEB and JEB. For sites participating in the United States (US), children under the age of 4 are prohibited from participating due to regulatory restrictions.

7.3. Treatment Assignment

All subjects will be dosed open label with CCP-020 (Diacerein 1% ointment).

7.4. Dose Adjustment Criteria

Subjects/caregivers should not modify the study drug application procedure or frequency.

7.4.1. Safety Criteria for Adjustment or Stopping Doses

If any significant study drug intolerance or safety issue occurs the investigator or designee may direct the subject/caregiver to discontinue use of the product and withdraw from the study.

Moderate-to-severe diarrhea has been observed in some patients administered oral diacerein for the treatment of osteoarthritis:

- Moderate diarrhea: 5-10 watery stools per day
- Severe diarrhea: >10 watery stools per day

Study medication applications should be discontinued if the subject experiences moderate or severe diarrhea.

Study medication should also be discontinued if the subject experiences any instance of diarrhea with bleeding and there is no clear medical rationale for the occurrence.

The diarrhea must be reported as an adverse event in the CRF. These subjects should be withdrawn from the study.

Subjects/caregivers should not make study medication applications to infected EBS lesions. Infected EBS lesions should be managed following the investigator's routine practice. The infection must be reported as an adverse event in the CRF.

7.4.2. Pharmacokinetic Criteria for Adjustment or Stopping Doses

There are no PK criteria for adjusting the dose in this study. If the site staff is unable to place the collection catheter or cannot obtain the samples required for the study, the subject will be terminated from the study.

7.5. Criteria for Study Termination

The study may be discontinued at the discretion of Castle Creek Pharmaceuticals, LLC. Some examples of reasons for discontinuation are the occurrence of the following:

- Increased frequency, severity or duration of known AEs
- Medical, regulatory or ethical reasons affecting the continued performance of the study

Figure 1: Study Design

Cohort 1 (adolescents and adults)

CCP-020 (Diacerein 1% Ointment) Application

Screening	Day 1	Day 3 - Day 9	Day 10
	PK Blood Sampling Times		
	Pre-dose, 0.5, 1, 2, 3, 4, 6, and 8 hours post-dose	Pre – Dose (Samples to be collected on any two days prior to CCP-020 application)	Pre-dose, 0.5, 1, 2, 3, 4, 6, and 8 hours post-dose

Cohort 2 (infants and children*)

CCP-020 (Diacerein 1% Ointment) Application

Screening	Day 1	Day 3 - Day 9	Day 10
	PK Blood Sampling Times		
	Pre-dose, 1, 2, 4, 6, and 8 hours post-dose	None	Pre-dose, 1, 2, 4, 6, and 8 hours post-dose

*Children in the US under the age of 4 are prohibited from participating in this study

Table 3: Schedule of Assessments

Assessment	Screening	Application				Follow Up
Study Day	**-42**	**1**	**3-9**[1]	**3-9**[1]	**10**	**24**
Informed Consent/Assent	X					
Inclusion/ Exclusion	X	X				
Genotyping Sample	X[2]					
Medical History	X					
Identify Application Area	X	X				
Vital Signs	X	X			X	
Physical Exam	X					
CCP-020 Application		X	X	X	X	
CCP-020 Application Diary		X	X	X	X	
Pharmacokinetics						
Full Sampling		X[3]			X[3]	
Trough Samples			X[4]	X[4]		
Safety						
Adverse Events[5]		X	X	X	X	X[6]
Urine Pregnancy Test[7]	X	X			X	
Urinalysis	X				X	
Lab Tests	X	X[8]			X	
Body Weight	X				X	

[1] Visit is eligible to be performed at the subject's home (Cohort 1)
[2] Only if the subject does not have documented genotype confirming EB
[3] Samples drawn at pre-dose and 0.5, 1, 2, 3, 4, 6 and 8 hours post-dose for Cohort 1; pre-dose, 1, 2, 4, 6, and 8 for Cohort 2.
[4] Trough PK samples will be collected on any two available days from Day 3 through Day 9 for Cohort 1 only
[5] At each visit the Investigator should examine the lesions being treated for any adverse events specific to treatment
[6] Phone call only
[7] For WOCBP only
[8] If Day 1 is within 7 days of Screening, labs do not need to be repeated

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

1. Subject/caregiver is able to comprehend and willing to sign an Informed Consent and/or Assent Form.
2. Subject is male or female at least 12 years of age (Cohort 1) or at least 6 months of age to 11 years, inclusive (Cohort 2) at screening. **US only**: subjects must be at least 4 years of age to 11 years, inclusive (Cohort 2) at time of consent.
3. The subject must weigh at least 9 kg (19.8 lbs) at Screening.
4. Subject has a documented genetic mutation consistent with EB. A blood or saliva sample will be collected for genetic confirmation if no documented gene mutation data is available.
5. Subject has EB lesions on ≥ 2% body surface area (BSA) and the EB lesions are in the following body areas:
    a. Localized: plantar and/or palmar areas
    b. Generalized: arms, legs, torso, hands and feet.
6. Subject/caregiver agrees to not apply any other topical products to the application area during the treatment period
7. If the subject is a woman of childbearing potential, she has a negative urine pregnancy test and agrees to use an approved effective method of birth control, as defined by this protocol, for the duration of the study.
8. Subject is non-pregnant, non-lactating and is not planning for pregnancy during the study period
9. Subject is in good general health and free of any known disease state or physical condition which, in the investigator's opinion, which exposes the subject to an unacceptable risk by study participation.
10. Subject is willing and able to follow all study instructions and to attend all study visits.

8.2. Subject Exclusion Criteria

1. Subject has EB lesions where drug will be applied that are infected (i.e., EB lesions that require anti-microbial therapy to treat an infection)
2. Subject has used any diacerein containing product within 1 month prior to Visit 1
3. Subject has used systemic immunotherapy or cytotoxic chemotherapy within 60 days prior to dosing.
4. Subject has used systemic steroidal therapy or has used topical steroidal therapy on the EB lesions in the application area within 14 days prior to dosing (Note: inhaled, nasal sprays, and ophthalmic products containing steroids are allowed)

5. Subject has evidence of a systemic infection or has used systemic antibiotics within 7 days prior to dosing
6. Subject has used any systemic diuretics or cardiac glycosides or any systemic product that, in the opinion of the investigator, might put the subject at undue risk by study participation or interferes with the study medication application or the study assessments within 30 days prior to dosing
7. Subject has a current malignancy, or a history of treatment for a malignancy within 2 years prior to dosing (Note: does not include non-melanoma skin cancer)
8. Subject currently has diabetes mellitus (HbA1c ≥6.5%) Note: controlled diabetes (HbA1c < 6.5%) is also considered exclusionary
9. Subject has a history of cardiac, hepatic (ALT and or AST >2x ULN, Total bilirubin >1.5x ULN at Visit 1), or renal disease (eGFR<30 ml/min/1.73 m2 [MDRD-adults ≥18, Bedside Schwartz – children <18]) that, in the opinion of the investigator, might put the subject at undue risk by study participation or interferes with the study medication application of the study assessments
10. Subject has an active non-EB skin disease (e.g., psoriasis, atopic dermatitis, eczema, sun damage, etc.), or condition (e.g., sunburn) that, in the opinion of the investigator, would put the subject at undue risk by study participation or would interfere with the study medication application or the study assessments
11. Subject has a history of sensitivity to any of the ingredients in the study medication
12. Subject has participated in an investigational drug trial in which administration of an investigational study medication occurred within 30 days prior to dosing

8.3. Subject Withdrawal Criteria

Subjects/caregiver will be informed that the subjects are free to withdraw from the study at any time and for any reason.

The investigator may remove a subject from the study if, in the investigator's opinion, it is not in the best interest of the subject to continue the study.

Examples of other reasons subjects may be discontinued from the study are:

- A change in compliance with an inclusion or exclusion criterion
- Occurrence of AEs
- Occurrence of pregnancy
- Use of a prohibited therapy
- Failure to maintain the required application frequency
- The study is discontinued by the sponsor

In case of premature discontinuation of study participation, efforts will be made to perform all final study day assessments. The date the subject is withdrawn from the study and the reason for

discontinuation will be recorded on the subject's CRFs. All withdrawn subjects with ongoing AEs will be followed as appropriate.

The investigator must immediately (within 24 hours) notify the Castle Creek Pharmaceuticals, LLC assigned study monitor of a subject discontinuation.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

The study medication must be stored in a secure area with limited access under appropriately controlled and monitored storage conditions.

Table 4: CCP-020 (Diacerein 1% Ointment)

	Investigational Product
Product Name:	Diacerein (CCP-020) 1% Ointment
Dosage Form:	Ointment
Unit Dose	Once-daily application to all EB lesions identified in the application area
Route of Administration	Topical
Physical Description	The study medication is a yellow ointment.
Manufacturer	[redacted]

9.2. Concomitant Medications

Concomitant therapies are any new or existing/ongoing therapy received from Visit 1 until discharge from the study, including therapies modified for non-medical reasons and therapies used for prophylaxis.

Concomitant therapies include drug (e.g., prescription, over-the-counter [OTC]) and non-drug (e.g., chiropractic, physical therapy, energy-based treatments [e.g. lasers, light-based therapy]) therapies. Subjects will refrain from receipt of any therapy in compliance with the inclusion/exclusion criteria. Subjects should refrain, if possible, from changing the use of any concomitant therapies during the study.

All new or modified concomitant therapies used during the study must be recorded.

Any new or modified concomitant therapy must be considered to determine if it is related to an adverse event (AE). An AE must be reported unless the therapy is modified for non-medical reasons (e.g., health insurance purposes) or it is for prophylaxis (e.g., vaccinations, topical anesthetics used during blood sampling).

9.2.1. Permitted & Prohibited therapies

A non-exhaustive list of products permitted for use are bland, non-medicated emollient/moisturizers such as:

- Emu oil
- Restore® Dimethicreme
- A&D®
- Aquaphor®
- White petroleum
- Coconut Oil

The use of bland, non-medicated emollients/moisturizers must be restricted so as not to interfere with the study medication. Therefore, emollients moisturizers may not be used in the application area 1 hour prior to the application of study medication and at any time within 6 hours after the study medication application. On Days 1 and 10, emollients/moisturizers should not be used until after the final PK draw (8 hr).

The investigator should consult with the Medical Monitor for discussion on any moisturizers or therapies in question that are not directly specified in the protocol.

Routine cleansers and cleaning products, bleach baths, and essential topical antiseptics are permitted at least 2 hours before and 6 hours after the study medication application.

A non-exhaustive list of therapies prohibited during the study are:

- CBD oil
- MediHoney
- Silvadine cream 1%
- Restore Silver contact layer and foam
- Mepilex® AG
- Acticoat
- Aquacel® AG
- SilvaSorb
- Silverlon
- Contreet
- Sunscreens

The investigator should notify the Medical Monitor immediately if any prohibited therapies are required to ensure subject safety.

9.2.2. Bandaging/Dressing Use

Bandaging is not prohibited provided the subject maintains their current bandaging routine and remains consistent throughout their participation in the study. However, subjects should be restricted from using dressings to cover the application area for the first hour after study medication application.

In general, the types of dressings to be used for the study should be minimally absorptive, non-adhesive (to the skin), not-intended to treat the wounds (i.e. antimicrobial, honey, keratin, collagen and/or impregnated dressings) and used in a manner that, based on the subject's experience, do not promote new lesion emergence.

9.3. Treatment Compliance

Each subject/caregiver will record the subject's compliance with the study medication application frequency (including time dosed) on a daily basis using a paper diary.

9.4. Randomization and Blinding

This is an open label study; no randomization or blinding is employed.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

The study medication is a yellow colored ointment and will be packaged in aluminum tubes that each contain 25 grams of sterile study medication.

A bulk supply of Diacerein 1% Ointment study medication, with one tube in each carton, will be provided to each investigational center. A sufficient supply of study medication will be provided to each site prior to the initiation of subject enrollment and replenished as needed.

10.2. Study Drug Packaging and Labeling

A bulk supply of Diacerein 1% Ointment study medication, with one tube in each carton, will be provided to each investigational center. A sufficient supply of study medication will be provided to each site prior to the initiation of subject enrollment and replenished as needed.

Each study medication carton will be labeled with a one-part label that is completed when the tube is dispensed, remains attached to the carton.

The carton label shows at least the following:

- Protocol number
- Tube number
- Study medication identity
- Investigational drug warning
- Space to enter the SI

Each study medication tube will be labeled with a two-part label. Both parts of the label are completed when the tube is dispensed, one part of the completed label remains attached to the tube, the other part (tear-off) is separated and attached to the subject's drug accountability log.

Both parts of the carton label show at least the following:

- Protocol number
- Tube number
- Study medication identity
- Storage conditions
- Instructions for use
- Sponsor information
- Investigational drug warning
- Space to enter the SI
- Space to enter the date dispensed

10.3. Study Drug Storage

Study drug must be stored between 59°F to 86°F (15°C to 30°C)

10.4. Study Drug Formulation

Table 5: Study Medication Formulation

[redacted]

10.5. Study Drug Dispensation

The amount of study drug dispensed to each subject on Day 1 will depend on the subject's % BSA of lesions identified in the application area.

Table 6: Number of Tubes of Study Drug (by %BSA)

[redacted]

Table 6: Number of Tubes of Study Drug (by %BSA) (Continued)

[redacted]

[1] Assumptions based on 23g of product will be used per tube

10.6. Study Drug Administration

The study medication is for external, topical use on the subject's EB lesions and assigned, un-involved skin only as defined by the application area.

At Study Day 1, an investigational center staff member will review the appropriate application technique with the subject/caregiver.

To perform a study medication application, the subject/caregiver should:

- Wash her/his hands before starting the application
- Apply sufficient quantity of the assigned study medication to cover all EB lesions and to uninvolved skin within the application area with a thin layer and gently rub it in
- For at least 6 hours after a study medication application, DO NOT:
  - Wash/submerge the treated EB lesions
  - Participate in any activity that might result in profuse perspiration (e.g., vigorous exercise, saunas, steam rooms, etc.).
- Follow the instructions for blister lancing management and care

- Not cover the treated area with any type of bandage or dressing for 1 hour after the application per clinical discretion of the PI
- Wash her/his hands after completing the application.

10.6.1. Application Area

EB patients that have ≥2% BSA of lesions will be instructed to apply the ointment to all designated lesions identified by the investigator. In addition, subjects that do not have at least 5% BSA will be instructed to apply the ointment to lesions as well as surrounding, uninvolved skin so that the total application is at minimum, 5% BSA not to exceed 30% BSA. This will be the "application area". The application area will be defined at Day 1 and will not change throughout the 10 day application period. The application area will be outlined using an appropriate marking tool in order to ensure the subject consistently applies the ointment to the same area each day as directed by the site staff. In addition, body charts will be kept with the site and a copy given to the patients that clearly outline the application area.

An investigational center staff member will dispense a blister lancing kit and instructions to every subject/caregiver as appropriate. The subject will be instructed to lance all EB blisters in the application area within 24 hours. Blister lancing kits and written instructions for use of the kits will be provided to each investigational center prior to the initiation of subject enrollment; however, if the subject prefers to use alternative lancing kits, this is acceptable.

EB lesions that are excluded from applications with the study medication (e.g. those exceeding 30% BSA) may be treated following the typical standard of care regimen used by the subject as long as the standard of care regimen is permitted by protocol and does not include prohibited medications.

No study drug applications should be made to infected lesions. If study medication is not applied to any EB lesions because they are infected this situation must be noted as an adverse event.

10.7. Study Drug Accountability

The investigator or designee will maintain an accurate record of the receipt of the study medications as shipped by Castle Creek Pharmaceuticals, LLC (or designee), including the date received and the condition of the study medications. One copy of this receipt will be returned to Castle Creek Pharmaceuticals, LLC when the contents of the study medication shipment have been verified and one copy maintained in the study file. In addition, an accurate study medication disposition record will be kept, specifying the amount dispensed to each subject/caregiver and the date of dispensing. This inventory record will be available for inspection at any time. At the completion of the study, the original inventory record will be available for review by Castle Creek Pharmaceuticals, LLC upon request.

10.8. Study Drug Handling and Disposal

At the completion of the study, all unused study medication will be returned to Castle Creek Pharmaceuticals, LLC (or designee) for disposal per Castle Creek Pharmaceuticals, LLC's (or designee's) written instructions.

11. PHARMACOKINETIC ASSESSMENTS

11.1. PK Blood Sample Collection

Sites will receive a laboratory manual with detailed instructions for collecting, handling, and processing PK samples. Sites will receive PK sample kits from the central laboratory.

On Day 1, the topical dose of CCP-020 will be applied by study staff followed by blood sampling for plasma analysis of diacerein and rhein through 8 hours post-application. PK samples for Cohort 1 will be collected at pre-dose, 0.5, 1, 2, 3, 4, 6, and 8 hours post-dose on Days 1 and 10 and PK samples for Cohort 2 will be collected at pre-dose, 1, 2, 4, 6, and 8 hours post-dose on Days 1 and 10. Trough PK samples will be collected on any two available days from Day 3 through Day 9 for Cohort 1 only. For the trough sample visits between Days 3 and 9 (Cohort 1), CCP-020 will be applied at the site after the blood draw. The dosing area should be left uncovered for at least one-hour post-application and then it is acceptable to apply non-absorbent bandages consistent with standard of care. On Day 10, patients will return to the study site for a pre-dose blood sample and application of CCP-020 to the application area followed by blood sampling for plasma analysis of diacerein and rhein through 8 hours post-application.

For both cohorts on Days 1 and 10, void-volume catheters will be placed to obviate multiple needle sticks in blood sampling.

Table 7: PK Blood Sample Collection Times

Cohort	**Day 1**								**Day 3-9**		**Day 10**							
Hour[1]	Pre	0.5	1	2	3	4	6	8	Pre	Pre	Pre	.5	1	2	3	4	6	8
1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
2	X		X	X		X	X	X			X		X	X		X	X	X

[1] Collection time window allowances will be included in a document separate from this protocol

11.2. Total Volume of Blood Collected

The total blood volume collected for each subject for the entire study will be compliant with WHO guidelines.

[redacted]

[redacted]

[redacted] on whether blood sample for genotyping is necessary. 4 mL is required for genotyping

11.3. Sample Analysis

Individual and mean graphs of plasma diacerein (if measurable) and rhein concentrations versus time after administration of CCP-020 will be constructed and displayed for relevant treatment comparisons, as data permit.

Plasma concentrations of diacerein and rhein will be summarized by treatment using descriptive statistics (sample size, mean, median, coefficient of variation [CV%], standard deviation [SD], minimum, and maximum). Corresponding by-subject data listings will be tabulated. The summary statistics for each scheduled time will only be reported when at least 50% of subjects have quantifiable concentrations.

Derived plasma PK parameters (Cmax, Tmax and AUC), if available, for diacerein and rhein will be summarized by treatment using descriptive statistics (sample size, arithmetic and geometric mean, CV%, SD of the arithmetic mean, median, minimum, and maximum).

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

12.1.1. Demographic/Medical History

At the timepoints specified in the Study Flow Chart, the investigator or designee will interview each subject/caregiver to obtain demographic information including date of birth, sex at birth, race and ethnicity.

Medical history information will be recorded including all medical conditions and disease states that, at Day 1:

- Are ongoing
- Require concomitant therapy
- Are, in the opinion of the investigator, relevant to the subject's study participation.

12.1.2. Vital Signs

At the timepoints specified in the Study Flow Chart, a qualified staff member will measure each subject's vital signs. The following items will be measured:

- Body temperature
- Pulse rate
- Respiration rate
- Blood pressure (systolic and diastolic) after the subject remains at rest for at least 5 minutes (to the extent that this is possible with infants/children)

12.1.3. Weight

At the timepoints specified in the study flow chart, the subject's weight will be collected.

12.1.4. Physical Examination

At the timepoints specified in the Study Flow Chart, the investigator or designee will perform a complete physical examination that will include, at a minimum, evaluation of the following body systems and organs:

- Skin
- Cardiovascular system
- Respiratory system
- Head, eyes, ears, nose and throat
- Lymph nodes
- Abdominal Exam

12.1.5. Laboratory Assessments

Sites will receive a laboratory manual with detailed instructions for collecting, handling, and processing samples. Sites will receive clinical laboratory kits from the central laboratory. Subjects will not be required to fast prior to laboratory sample collection.

12.1.5.1. Hematology

At the timepoints specified in the Study Flow Chart, the following hematology labs will be drawn:

- Hematocrit
- Hemoglobin
- Platelet count
- Red blood cell morphology
- Red blood cell count
- White blood cell count
- White blood cell differential
- % and absolute:
  - Basophils
  - Eosinophils
  - Lymphocytes
  - Monocytes
  - Neutrophils

The results of the clinical laboratory tests will be reported on the central laboratory's standard reports.

12.1.5.2. Blood Chemistry

At the timepoints specified in the Study Flow Chart, the following clinical chemistry labs will be drawn:

- Albumin
- Alkaline phosphatase (ALP)
- Alanine aminotransferase (ALT)
- Amylase
- Aspartate aminotransferase (AST)
- Blood urea nitrogen (BUN)
- Bicarbonate
- Chloride
- Creatinine
- Gamma-glutamyl transferase (GGT)
- Glucose
- HbA1c
- Lactate dehydrogenase (LDH)
- Lipase
- Potassium
- Sodium
- Total bilirubin
- Total protein
- Uric acid

The results of the clinical laboratory tests will be reported on the central laboratory's standard reports.

12.1.5.3. Urinalysis

A complete urinalysis will be performed at the timepoints listed in the schedule of assessments.

12.1.5.4. Pregnancy Screen

At the timepoints specified in the Study Flow Chart, a qualified staff member will perform a urine pregnancy test for subjects who are WOCBP. Sites will receive urine pregnancy test kits from the central laboratory.

Subjects who are WOCBP must have a negative pregnancy test result at Day 1 to be enrolled in the study.

If the result of any post-study medication application urine pregnancy test is positive, the subject will be withdrawn from the study and the subject's pregnancy will be documented and followed until completion and for at least 6 weeks after birth.

13. ADVERSE AND SERIOUS ADVERSE EVENTS

Adverse events will be monitored throughout the study and immediately reported on the appropriate AE eCRF.

13.1. Adverse events(s)

An adverse event is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

At each visit the Investigator should examine the lesions being treated for any adverse events specific to treatment. Events should be recorded on the appropriate eCRF.

Adverse events, which include clinical laboratory test variables, will be monitored and documented from the time of the first study medication application until 30 days after the subject's last study medication application.

Subject/caregivers should be instructed to report any adverse event that they experience to the Investigator. Beginning with the start of the first study medication application, investigators should make an assessment for adverse events at each visit and record the event on the appropriate adverse event eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (*e.g.*, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure.

Any medical condition already present at screening should not be reported as an adverse event unless the medical condition or signs or symptoms present at screening worsens in severity or seriousness at any time during the study. In this case, it should be reported as an adverse event.

Clinically significant abnormal laboratory or other examination (*e.g.*, physical examination) findings that are detected during the study or are present at screening and worsen during the study to the point where the investigator defines it as clinically significant should be reported as adverse events. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an adverse event.

13.2. Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. "Responses" to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (*i.e.*, the relationship cannot be ruled out).

13.3. Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

13.4. Assessments of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each adverse event as mild, moderate, or severe, and will also categorize each adverse event as to its potential relationship to study drug using the categories of yes or no.

13.4.1. Assessment of Severity:

Mild – An event that is easily tolerated and generally not interfering with normal daily activities.

Moderate – An event that is sufficiently discomforting to interfere with normal daily activities.

Severe – An event that is incapacitating with inability to work or perform normal daily activities.

13.4.2. Causality Assessment:

The relationship of an adverse event to the administration of the study drug is to be assessed according to the following definitions:

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 re-challenge).

The following factors should also be considered:

- The temporal sequence from study drug administration-
  - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases-
  - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant drug-
  - The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug-
  - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses-
  - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study drug-
  - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

13.5. Adverse Events of Special Interest

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Suspicion of such an event might warrant further investigation in order to characterize and understand it. The following AEs will be categorized as AEs of special interest (AESIs) in this study:

- Moderate to severe diarrhea
- Hepatic injury
- Pancreatitis
- Urticaria/angioedema
- Epidermal necrolysis
- Drug reaction with eosinophilia and systemic symptoms (DRESS)
- Purpura/cutaneous vasculitis
- Jaundice

All AESIs will be summarized as narratives in the Clinical Study Report.

13.6. Serious Adverse events (SAE)

An adverse event or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
  - NOTE: An adverse event or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the subject *at immediate risk of death*. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or prolongation of existing hospitalizations,
  - NOTE: Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (*i.e.*, no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly/birth defect, or
- An important medical event.
  - NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may 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 hospitalizations, or the development of drug dependency.

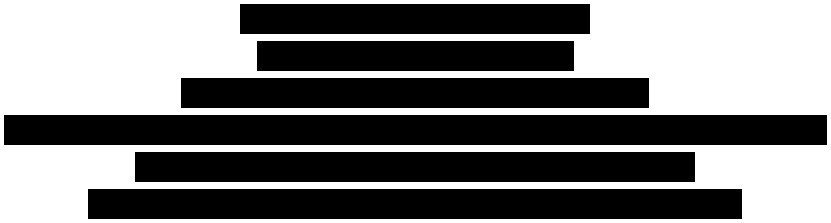
13.6.1. Serious Adverse Event Reporting/Adverse Events of Special Interest – Procedures for Investigators

13.6.1.1. Initial Reports

All SAEs/AESI, regardless of causality, occurring from the time of informed consent until 30 days after the subject's last application of study medication, must be reported to Medpace 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/AESI occurring after the 30-

day follow-up period AND considered related to study drug must also be reported to the Sponsor.

To report an SAE/AESI, complete the SAE/AESI form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at medpace-safetynotification@medpace.com or call the Medpace SAE/AESI hotline (phone number listed below), and fax the completed paper SAE form to Medpace (fax number listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE/AESI information must be entered within 24 hours of the system becoming available.



13.6.1.2. Follow-up Reports

The Investigator must continue to follow the subject until the SAE/AESI has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE/AESI form electronically in the EDC system for the study and submit any supporting documentation (*e.g.*, subject discharge summary, autopsy reports, etc.) to Medpace Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs/AESI.

13.6.1.3. Expedited Reports

The Sponsor will report all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening as soon as possible to the FDA, applicable competent authorities in all the Member States concerned, and to the Central Ethics Committee, and in any case, no later than 7 days after knowledge by the Sponsor of such a case, and that relevant follow-up information will subsequently be communicated within an additional 8 days.

All other suspected unexpected serious adverse reactions/AESI will be reported to the FDA, applicable competent authorities concerned and to the Central Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor.

The Sponsor will also inform all investigators as required.

13.6.1.4. Pregnancy Reporting

WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (e.g., hysterectomy, bilateral tubal ligation, bilateral oophorectomy) or is not postmenopausal. Postmenopausal is defined as ≥12 months with no

menses without an alternative medical cause. Women who are WOCBP and are using an active method of birth control, are practicing abstinence or where the partner is sterile (e.g., vasectomy), should be considered to be WOCBP.

Sexually active WOCBP must use an effective method of birth control for the duration of study participation in a manner such that risk of failure is minimized. Periodic and/or temporary abstinence such as declaration of abstinence during study participation or fertility awareness-based methods to prevent pregnancy (including but not limited to symptothermal and ovulation estimation by either calendar day or salivary/cervical secretions) are not considered effective methods of birth control; however, true [absolute] sexual abstinence (i.e., in line with the preferred and usual lifestyle of the patient) may be permitted. Effective methods of birth control approved for use in this study are:

- Implants (*e.g.*, Norplant ® system)
- Injectable (*e.g.*, Depo-Provera®)
- Transdermal patch
- Combined oral contraceptives
- Barrier methods (condoms and diaphragm with spermicide) – note: double barrier method is required if no other methods of birth control are in use
- Intrauterine devices (e.g. ParaGard® and Mirena®)

Prior to trial enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for a pregnancy. The subject/caregiver must sign an informed consent/assent form documenting this discussion. During the trial, all WOCBP will be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period).

If a subject becomes pregnant during the study, or within 30 days of discontinuing study medication, the Investigator should report the pregnancy to Medpace Clinical Safety within 24 hours of being notified. Medpace Clinical Safety will then forward the Exposure *in utero* form to the Investigator for completion.

If a subject/caregiver or investigator suspects that the subject may be pregnant prior to study medication administration, the study medication must be withheld until the results of a pregnancy test are available. If pregnancy is confirmed, the subject must not receive study medication and must be discharged from the study.

If, following study medication administration, it is determined that the subject may have been or was pregnant at the time of study medication exposure (including at least 2 days after study medication administration), the subject will immediately be withdrawn from the study. The investigator must immediately (within 24 hours) notify the Castle Creek Pharmaceuticals, LLC Medical Monitor.

Protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy. Other appropriate pregnancy follow-up procedures should be considered if indicated.

The subject's pregnancy should be followed by the Investigator until completion and for at least 6 weeks after birth. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify Medpace Clinical Safety. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (*i.e.*, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

14. STATISTICS

14.1. Analysis Populations

Pharmacokinetic Evaluable Population: The PK Evaluable Population will comprise all subjects receiving at least one dose of CCP-020 who have sufficient (> 4 quantifiable concentrations) plasma concentration data to calculate PK parameters for rhein and if possible, diacerein.

Pharmacokinetic Concentration Population: The PK Concentration Population will comprise all subjects receiving at least one dose of CCP-020 who have at least one quantifiable plasma concentration for rhein and if possible, diacerein.

Safety Population: The safety population will consist of all subjects who receive any amount of study drug.

14.2. Pharmacokinetic Analysis

Summaries of plasma concentration will be based on PK Concentration Population.

Individual and mean graphs of plasma diacerein (if measurable) and rhein concentrations versus time after single dose and multiple dose of CCP-020 will be constructed and displayed for relevant comparisons, as data permit.

Plasma concentrations of diacerein and rhein will be summarized by Cohort and EB type using descriptive statistics (sample size, mean, median, coefficient of variation [CV%], standard deviation [SD], minimum, and maximum). Corresponding by-subject data listings will be tabulated. The summary statistics for each scheduled time will only be reported when at least 50% of subjects have quantifiable concentrations.

Summaries of plasmas PK parameters will be based on PK Evaluable Population.

Derived plasma PK parameters (Cmax, tmax and AUC), if available, for diacerein and rhein will be summarized by Cohort and EB type using descriptive statistics (sample size, arithmetic mean, CV%, SD of the arithmetic mean, median, minimum, and maximum). Geometric mean and geometric CV will also be provided for Cmax and AUC. Corresponding by-subject data listings will be tabulated.

14.3. Safety Analysis

The number and percentage of subjects reporting any treatment-emergent AE will be tabulated by system organ class and preferred term for each Cohort and EB type (coded using Medical Dictionary for Regulatory Activities). Treatment-emergent AEs will be further classified by maximum severity and relationship to treatment.

Physical examinations, electrocardiogram, vital signs, application site assessment, and clinical laboratory test data (observed and change from baseline) will be summarized using appropriate descriptive statistics.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of Castle Creek Pharmaceuticals, LLC will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Castle Creek Pharmaceuticals, LLC or its representatives. This will be documented in a Clinical Study Agreement between Castle Creek Pharmaceuticals, LLC and the investigator.

During the study, a monitor from Castle Creek Pharmaceuticals, LLC or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data is being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require access to all records for each patient (*e.g.*, clinic charts).
- Record and report any protocol deviations not previously sent to Castle Creek Pharmaceuticals, LLC.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Castle Creek Pharmaceuticals, LLC, and their representatives and confirm those SAEs that met criteria for reporting have been forwarded to the IRB/EC, as applicable.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

15.2. Audits and Inspections

Authorized representatives of Castle Creek Pharmaceuticals, LLC, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Castle Creek Pharmaceuticals, LLC audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact Castle Creek Pharmaceuticals immediately if contacted by a regulatory agency about an inspection.

15.3. Institutional Review Board (IRB)

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The investigator must submit written approval to Castle Creek Pharmaceuticals, LLC before he or she can enroll any patient/subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Castle Creek Pharmaceuticals, LLC will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements.

16.3. Written Informed Consent

The investigator at each investigational center will ensure that written informed consent forms that provide information about the study will be given to adult subjects. For child/adolescent subjects, written informed consent and assent forms will be given to the caregiver and to the applicable subject, respectively. Informed consent forms will contain all the elements required by the ICH E6 Guideline for GCP and any additional elements required by local regulations. The information provided in the informed consent will be in a language understandable to the adult subjects or caregiver of child/adolescent subjects.

The investigator will provide the subject and/or caregiver sufficient time to consider whether to participate in the trial. The investigator will explain to the subject/caregiver that trial participation is voluntary and withdrawal from the study is allowed at any time and withdrawal will not adversely affect the subject's medical care.

At the first study visit, prior to the initiation of any study related procedures, subjects/caregivers will be asked to give written informed consent, and child/adolescent subjects will be asked to give assent, after having been informed of the nature of the study, study procedures and restrictions and risks and benefits. The informed consent and assent documents, as applicable, must be signed and dated by the subject/caregiver prior to study participation. Copies of the signed informed consent and assent documents must be given to the subject/caregiver.

The US FDA does not define the required elements of an assent; however, they must be accurate, not be coercive and must incorporate age appropriate wording. The assent must have a date and signature line for the child. Use of an assent is not a substitute for parental permission. Parents/guardians (caregivers) must be given an IRB/EC approved ICF to review, sign and date.

17. DATA HANDLING AND RECORDKEEPING

17.1. Electronic Case Report Forms

Adequate and accurate case records will be maintained, and all relevant observations and data related to the study will be recorded. This will include at minimum, medical history/physical examination, hematology, clinical chemistry, inclusion and exclusion criteria, drug administration, and a record of sample collection, clinical assessments, AEs, and final evaluation, as appropriate.

Electronic eCRFs will be used in this study. The eCRF will be electronically signed and dated by the Principal Investigator or his designee after his/her review. After the completion of the study, completed eCRFs will be retained in the archives.

Completed eCRFs will be reviewed by the study monitor in the electronic data capture system against the source documentation for accuracy and completeness.

17.2. Inspection of Records

Castle Creek Pharmaceuticals, LLC will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

17.3. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Castle Creek Pharmaceuticals, LLC or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

18. PUBLICATION POLICY

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During the study, only the Sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

The Sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

If the study is being conducted as part of a multicenter clinical study, data from all sites participating in the study will be pooled and analyzed by the Sponsor or the Sponsor's designee. The first publication of the study results shall be made in conjunction with the results from other study sites as a multicenter publication. If a multicenter publication is not forthcoming within 24 months of completion of the study at all sites, the investigator may publish or present the results generated at his or her site.

The investigator will provide the Sponsor with a copy of any proposed publication or presentation for review and comment at least 60 days prior to such presentation or submission for publication. The Sponsor shall inform the investigator in writing of any changes or deletions in such presentation or publication required to protect the Sponsor's confidential and proprietary technical information and to address inaccurate data or inappropriate interpretations in the context of any pooled multicenter results. At the expiration of such 60-day period, the investigator may proceed with the presentation or submission for publication unless the Sponsor has notified the institution or the investigator in writing that such proposed publication or presentation discloses the Sponsor's confidential and proprietary technical information. Further, upon the request of the Sponsor, the investigator will delay the publication or presentation for an additional 90 days to permit the Sponsor to take necessary actions to protect its intellectual property interests.

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