CLINICAL STUDY PROTOCOL

DIACEREIN 1% OINTMENT
GLOBAL PROTOCOL NUMBER: CCP-020-302
PROTOCOL AMENDMENT 3.1

Protocol Title:

An International, Multicenter, Open-label, Long Term Extension Study Evaluating the Safety of Diacerein 1% Ointment Topical Formulation in Subjects with Epidermolysis Bullosa Simplex (EBS)

IND Number:

131,384

EudraCT Number:

2017-003757-41

Indication Studied:

Epidermolysis Bullosa Simplex

Protocol Date:

29-MAY-2019

Sponsor Address:

Castle Creek Pharmaceuticals, LLC
6 Century Drive, Suite 200
Parsippany, NJ 07054
United States of America

REPRESENTATIVES FROM CASTLE CREEK PHARMACEUTICALS/CONTRACT RESEARCH ORGANIZATION

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.

SIGNATURES:

[redacted]

5/29/2019
Date

Senior Director of Clinical Operations
Castle Creek Pharmaceuticals, LLC

INVESTIGATOR/SPONSOR AGREEMENT

I have received and read the Investigator's Brochure for topical Diacerein 1% Ointment (CCP-020). I have read the CCP-020-302 protocol amendment 1 and agree to conduct the study as outlined in this protocol and relevant revisions. 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

SPONSOR'S CONTACT INFORMATION

Role in Study	Name	Address and Telephone Number
Clinical Operations Leader (Sponsor)	[redacted]	[redacted]
Clinical Operations Leader (Sponsor)	[redacted]	[redacted]
Responsible Physician (Sponsor)	[redacted]	[redacted]
Global Clinical Project Manager	[redacted]	[redacted]
Medical Monitor	[redacted]	[redacted]

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1. SYNOPSIS

Name of Sponsor/Company: Castle Creek Pharmaceuticals, LLC	
Name of Investigational Product: Diacerein 1% Ointment	
Name of Active Ingredient: Diacerein	
Title of Study: An International, Multicenter, Open-label, Long-Term Extension Study Evaluating the Safety of Diacerein 1% Ointment Topical Formulation in Subjects with Epidermolysis Bullosa Simplex (EBS)	
Study center(s): Approximately 20-24	
Studied period (years): Estimated date first subject enrolled: 15-NOV-2017 Estimated date last subject completed: 15-NOV-2019	**Phase of development:** **2**
Objective: The primary objective of this study is to evaluate the long-term safety and tolerability of Diacerein 1% Ointment for 2 treatment cycles in subjects with EBS that were previously enrolled in studies CCP-020-301 or CCP-020-101.	
Methodology: This is an international, multicenter, open-label, long term extension study evaluating the safety of topical Diacerein 1% Ointment for the treatment of subjects with EBS. At Visit 1, EBS subjects who participate in the CCP-020-301 double-blind safety and efficacy study or participate in the CCP-020-101 PK study (feeder studies) who meet all the inclusion/exclusion criteria will be eligible to complete two treatment cycles of CCP-020. Each treatment cycle will consist of 8 weeks on treatment (once-daily, at home study medication applications) followed by 8 weeks off treatment (only investigator approved bland, non-medicated emollient/moisturizer, routine cleansing products and sunscreens) with a maximum of two treatment cycles allowed for up to 52 weeks. At Baseline (corresponding to the final study visit of the feeder study), the investigator will perform a clinical assessment and determine if any of the subject's lesions require treatment (up to 30% BSA). If the subject has active lesions as determined by the Investigator's clinical assessment, the subject will initiate a cycle of once-daily, at home study medication application to their EBS lesions for 8 weeks (treatment period) followed by an 8-week period where no treatment will be administered. Subjects presenting with no active lesions (as determined by the Investigator's clinical assessment) will not begin treatment and instead, will be instructed to return to the clinic for re-evaluation in 8 weeks or upon worsening of EBS lesions, whichever happens first.	

During the treatment period of each cycle, subjects/caregivers will apply a thin layer of the assigned study medication, sufficient to cover the subject's EBS lesions and approximately ¾ inch (2 cm) of surrounding uninvolved skin, and gently rub in the study medication. Subjects/caregivers will apply the assigned study medication to all EBS lesions, including any new EBS lesions that develop (up to 30% BSA), once daily, every evening until the lesions resolve, for 8 weeks. After 8 weeks, the subject will return to the site to return the study medication and remain off study medication for 8 weeks. The investigator will re-evaluate the subject after the 8 weeks off therapy and if any of the subject's lesions require treatment (up to 30% BSA) the subject will begin another treatment cycle for a maximum of two treatment cycles allowed for up to 52 weeks.

Safety will be monitored throughout the study by repeated clinical and laboratory evaluations, vital signs, ECG monitoring and adverse event monitoring.

The duration of a subject's participation in the extension study may be as short as 32 weeks or as long as 52 weeks depending on the cycle initiation schedule. Subjects may not start a new treatment cycle past Week 36 from Baseline Visit without prior sponsor approval.

Number of subjects (planned):
Approximately 80 subjects are expected to be enrolled in this study at approximately 20-24 international investigational centers. The actual number of subjects that are enrolled will depend on the final number of EBS subjects who participate in the CCP-020-301 or participate in the CCP-020-101 study.

Diagnosis and main criteria for inclusion/exclusion:

Inclusion criteria**:**

1. Subject has a documented genetic mutation consistent with EBS.
2. Subjects who participated in the CCP-020-301 or the CCP-020-101 study are eligible to be rolled into the CCP-020-302 open label extension study, regardless of their completion status on the feeder study.
3. Subject/caregiver agrees to report use of any topical therapies applied to EBS lesions (e.g. medicated cleansers, bleach baths, topical antiseptics, topical disinfectants, topical steroids, etc.)
4. 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 (see Section 10), for the duration of the study.
5. Subject is non-lactating and is not planning for pregnancy during the study period
6. Subject is willing and able to follow all study instructions and to attend all study visits
7. Subject/caregiver is able to comprehend and willing to sign an Informed Consent and/or Assent Form.

Exclusion criteria:

1. Subject has EBS lesions to be treated that are infected (*i.e.*, EBS lesions that require therapy to treat an infection)

2. Subject has evidence of a systemic infection or has used systemic antibiotics within 7 days prior to Baseline 3. The subject was discontinued from the feeder study due to an adverse event 4. Subject has experienced a change in clinical status from the feeder study that, in the investigator's opinion, puts the subject at undue risk to participate
Investigational product, dosage and mode of administration: Diacerein 1% Ointment administered topically once daily
Duration of study and treatment: Approximately 32-52 weeks.
Reference therapy, dosage and mode of administration: Not applicable. Every subject on this study will be assigned to Diacerein 1% Ointment.
Safety evaluations: Assessment of adverse events, ECGs, vital signs, clinical assessment and laboratory tests will be performed throughout the study.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
BSA	Body Surface Area
°C	Degrees Centigrade
CMH	Cochran-Mantel-Haenszel
CR	Clinically Relevant
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
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
ICH	International Conference on Harmonization
i.e.	That Is (Latin; id est)
IGA	Investigator's Global Assessment
IRB	Institutional Review Board

Abbreviation	Term
IRT	Interactive Response Technology
ITT	Intent-To-Treat
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
NRS	Numeric Rating Scale
OTC	Over-The-Counter
PRN	As needed
PP	Per Protocol
SAE	Serious Adverse Event
SI	Subject Identifier
SOP	Standard Operation Procedure
US	United States
WOCBP	Women of childbearing potential

2. SUMMARY OF CHANGE

Section	Description of Change	Rationale
Signature page	Content modified	New title and representative
Sponsor's contact information	Content Added	Sponsor's contact information page added to include new Sponsor Physician and team members. Updated to include new CRO Medical Monitor.
Synopsis	Content modified	Updating participation to allow all subjects into the study.
Synopsis	Content modified	Inclusion Criteria #2: Clarification regarding allowing not only feeder study completers into the study but allowing all subjects who participated to enroll.
3.0	Content modified	Updating participation to allow all subjects into the study.
6.1	Content modified	Updating participation to allow all subjects into the study.
7.1	Content modified	Clarification regarding allowing all EBS subjects on 301 and 101 to enter the extension study
7.3	Content modified	Inclusion Criteria #4: Clarification regarding allowing not only feeder study completers into the study but allowing all subjects who participated to enroll.
7.7	Content modified	Clarification regarding participation on the study.
12.4	Content modified	Updating participation to allow all subjects into the study.

3. 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.[5] 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% Topical Ointment Investigator's Brochure.

This study is an open-label, long term extension of studies CCP-020-301, a randomized double- blind, phase II study evaluating the efficacy and safety of Diacerein 1% Ointment in subjects with EBS and CCP-020-101, a phase I study evaluating the pharmacokinetics of Diacerein 1% Ointment in subjects with EBS and healthy volunteers. Subjects who participate in the CCP-020-301 or the CCP-020-101 study are eligible to be rolled into the CCP-020-302 open label extension study, regardless of their completion status on the feeder study.

3.1. Dose and Treatment Duration Rationale

In addition to the long history of clinical experience with diacerein after oral administration, studies with topical diacerein have been conducted. Results from a 12-week, phase 1 pilot

study in 5 EBS-DM patients demonstrated a substantial reduction in blisters after 2 weeks of daily application of 1% diacerein cream. In this study, treatment continued open-label for an additional 4 weeks. In period 2 of the study, the effects lasted an additional 6 weeks in patients administered diacerein or placebo indicating a durable response from the initial open-label 6-week treatment period. There were no adverse events reported during the study.

A multicenter, European, phase 2 placebo-controlled, randomized, double-blind crossover study of 17 EBS patients (aged 4 to 19) was completed. The study was run over 2 years with a 4-week treatment period and 3-month follow-up period in each year of the study (1% diacerein cream or placebo). In this study, the dose (1%), dose duration (4 weeks), and application area (3% BSA) established a highly significant reduction in blister counts in both years of treatment at the end of the 4-week treatment period as well as continued response at 3 months post-treatment compared to placebo. Secondary endpoints also demonstrated an effect of the treatment arm compared to placebo as measured by time to reach initial blister counts and patient reported outcomes of improvements in pain and itching. There were no drug-related AEs in the study and no discontinuations related to treatment.

These preliminary clinical studies demonstrated proof-of-concept efficacy of a 1% diacerein cream in EBS-DM patients. This current trial will seek to establish long term safety and tolerability of a 1% diacerein ointment in patients with EBS.

Subjects entering the open-label long term extension study after completing the CCP-020-301 or CCP-020-101 studies will have been exposed to treatment with 1% diacerein ointment or placebo.

3.2. Risks and/or Benefits to Subjects

The dose of study medication administered in this study is anticipated to induce therapeutic benefit with prolonged treatment. 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. Additionally, subjects will receive study medication at no cost for the duration of the study.

The safety monitoring practices employed by this protocol (i.e. vital signs, clinical and laboratory evaluations, ECGs, 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 EBS 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.

4. TRIAL OBJECTIVES

4.1. Objective

The primary objective of this study is to evaluate the long-term safety and tolerability of Diacerein 1% Ointment in subjects with EBS that were previously enrolled in studies CCP-020-301 or CCP-020-101.

5. ENDPOINTS

5.1. Safety Endpoints

Safety will be evaluated in terms of the occurrence of AEs and changes in clinical laboratory parameters, clinical examination findings, vital signs, weight, and urine measurements.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is an international, multicenter, open-label, long term extension study evaluating the safety of topical Diacerein 1% Ointment for the treatment of subjects with EBS. At Baseline, EBS subjects who participated the CCP-020-301, double-blind safety and efficacy study or participated in the CCP-020-101, PK study (feeder studies) and who meet all the inclusion/exclusion criteria will be eligible to enroll in this study.

Each treatment cycle will consist of 8 weeks on treatment (once-daily, at home study medication applications) followed by 8 weeks off treatment with a maximum of two treatment cycles allowed for up to 52 weeks.

At Baseline (corresponding to the final study visit of the feeder study), the investigator will perform a clinical assessment and determine if any of the subject's lesions require treatment (up to 30% BSA). If the subject has active lesions as determined by the Investigator's clinical assessment, the subject will initiate a cycle of once-daily, at home study medication application to their EBS lesions for 8 weeks (treatment period) followed by an 8-week period where no treatment will be administered. Subjects presenting with no active lesions as determined by the Investigator's clinical assessment will not begin treatment and instead will be instructed to return to the clinic for re-evaluation in 8 weeks or upon worsening of EBS lesions, whichever happens first.

During the treatment period of each cycle, subjects/caregivers will apply a thin layer of the assigned study medication, sufficient to cover the subject's EBS lesions and approximately ¾ inch (2 cm) of surrounding uninvolved skin, and gently rub in the study medication. Subjects/caregivers will apply the assigned study medication to all EBS lesions, including any new EBS lesions that develop (up to 30% BSA), once daily, every evening until the lesions resolve for 8 weeks. After 8 weeks, the subject will return to the site to return the study medication and remain off treatment for 8 weeks. The investigator will re-evaluate the subject after 8 weeks off therapy and if any of the subject's lesions require treatment (up to 30% BSA) the subject will begin another treatment cycle for a maximum of two treatment cycles allowed for up to 52 weeks.

Safety will be monitored throughout the study by repeated clinical and laboratory evaluations, vital signs, ECG monitoring and adverse event monitoring.

Each treatment cycle will consist of 8 weeks on treatment, followed by 8 weeks off treatment with a maximum of two treatment cycles allowed for up to 52 weeks. Subjects should be assessed at minimum every 8 weeks for disease activity. Once a subject completes two cycles of treatment or reaches Week 52, the subject will be discharged from the study. Subjects may not start a new treatment cycle past Week 36 without prior sponsor approval. The duration of a subject's participation in the extension study may be as short as 32 weeks or as long as 52 weeks depending on the cycle initiation schedule for each individual subject.

7. SELECTION DISPOSITION OF STUDY POPULATION

7.1. Number of Subjects

Approximately 80 subjects are anticipated to be enrolled in this study at approximately 20-24 international investigational centers. The actual number of subjects that are enrolled into the CCP-020-302 study will depend on the final number of EBS subjects who participated in the CCP-020-301 or CCP-020-101 study.

7.2. Study Population Characteristics

Subjects enrolled in the extension study will have genetic confirmation of EBS verified in the feeder study.

7.3. Inclusion Criteria

In order to be eligible for the study, subjects must fulfill all of the following criteria**:**

1. In the opinion of the Investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent/assent form and any required privacy authorization prior to the initiation of any study procedures.
3. Subject has a documented genetic mutation consistent with EBS.
4. Subjects who participated in the CCP-020-301 or the CCP-020-101 study are eligible to be rolled into the CCP-020-302 open label extension study, regardless of their completion status on the feeder study.
5. Subject/caregiver agrees to report use of any topical therapies applied to EBS lesions (e.g. medicated cleansers, bleach cleansers, bleach baths, topical antiseptics, topical disinfectants, etc.).
6. 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 (see Section 10), for the duration of the study.
7. Subject is non-lactating and is not planning for pregnancy during the study period.
8. Subject is willing and able to follow all study instructions and to attend all study visits.

7.4. Exclusion Criteria

Any subject who meets one or more of the following criteria will not be included in this study:

1. Subject has EBS lesions to be treated that are infected (*i.e.*, EBS lesions that require topical antibiotic therapy to treat an infection).
2. Subject has evidence of a systemic infection or has used systemic antibiotics within 7 days prior to Baseline.
3. The subject was discontinued from the feeder study due to an adverse event judged to be related or possibly related to the study medication.

4. Subject has experienced a change in clinical status from the feeder study that, in the investigator's opinion, puts the subject at undue risk to participate.

7.4.1. Concomitant therapies

Concomitant therapies are any new or existing/ongoing therapy received from Baseline 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. The use of an investigator approved bland, non-medicated emollient/moisturizer, medicated cleansers, bleach baths, topical antiseptics, topical disinfectants, etc. must be reported as a concomitant therapy in the case report forms (CRFs).

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).

7.4.2. Prohibited therapies

Subjects will be prohibited from taking any investigational product (with the exception of Diacerein 1% Ointment) throughout their participation in the study.

7.4.3. Infected Lesions

EBS lesions that become infected (i.e., EBS lesions that require therapy to treat an infection) during the course of the study should be managed following the investigator's routine practice and all concomitant therapies reported in the eCRFs.

No study medication applications should be made to infected lesions. If any EBS lesions are not treated with study medication because they are infected, this situation must be noted as an adverse event.

7.5. Subject Discontinuation from the Study

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.

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

7.6. Subject Identifier (SI)

The investigator or designee will register each subject in the CRO, Inc. Interactive Response Technology (IRT) system at Baseline to obtain a SI.

The SI format will be NN-NNN where the first 2 digits are the investigational center site number (using leading zeros as appropriate). The final 3 digits are the subject number

The subject will be identified using the SI in all study documentation for the duration of the study.

Instructions for use of the IRT system will be provided to each investigator prior to the initiation of subject enrollment at her/his center.

7.7. Replacement Subjects

Subject enrollment will continue until all subjects who participate in the CCP-020-301 study and participate in the CCP-020-101 study are considered for enrollment. Subjects who are enrolled in this study and do not complete the study will not be replaced.

8. INVESTIGATIONAL PLAN

Each treatment cycle will consist of 8 weeks on treatment, followed by 8 weeks off treatment with a maximum of two treatment cycles allowed for up to one year. Subjects should be assessed at minimum every 8 weeks for disease activity. Once a subject completes two cycles of treatment or reaches Week 52, the subject will be discharged from the study. Subjects may not start a new treatment cycle past Week 36 from Baseline Visit without prior sponsor approval. The duration of a subject's participation in the extension study may be as short as 32 weeks or as long as 52 weeks depending on the cycle initiation schedule for each individual subject.

8.1. Study Flow Chart

Visit[c]	**Baseline[a]**	**Cycle Start[a,c]**	**Mid-Cycle [c]**	**End of Cycle [c]**
Study Day/Week (approximate)	**Day 0**	**Day X**	**Day X +8 weeks**	**Day X +16 weeks**
Informed Consent/Assent	X			
Subject identifier	X			
Inclusion & exclusion	X			
Demographics & medical history	X			
Vital signs	X[a]			X
Clinical laboratory samples	X[a]			X
ECG	X[a]			X
Pregnancy test[b]	X[a]	X	X	X
Clinical Assessment	X[a]	X	X	X
Dispense/collect study medication[d]		X	X	X
Study medication application[e]		X ------ →	X---------- →	
Dispense blister lancing kit		X	X	
Concomitant therapies		X	X	X
Adverse events[f]		X	X	X

a). Results from feeder study will be used as data point for this extension study and need not be repeated unless the Day 0/Baseline visit is >7 Days from the Final visit of the feeder study. Day 0/Baseline may be considered the Cycle Start Visit if the investigator determines the subject has lesions that require treatment.
b). WOCBP only
c). All visits windows are +/- 4 days from target day
d). Initial study medication dispensation will be dependent on lesion activity of individual subject's EBS and should only be dispensed if the subject meets treatment criteria (e.g. if the Investigator determines no lesions require treatment, no study medication will be dispensed). Collection of used study medication will begin at the visit following the first dose of study medication dispensation
e). Study medication application will be dependent on lesion activity of individual subject's EBS. Each treatment cycle will consist of 8 weeks on treatment (once-daily, at home study medication applications) followed by 8 weeks off treatment. Subjects will be required to record treatment application and lesion activity via the eDiary.
f) At each visit the Investigator should examine the lesions being treated for any adverse events specific to treatment

8.2. Study Visits Description and Procedures

A written, signed informed consent form (ICF) and assent form as appropriate must be obtained from each subject/caregiver prior to performing any study related procedure.

8.2.1. Day 0/Baseline Visit

Results from feeder study will be used as data point for this extension study and need not be repeated unless the Day 0/Baseline visit is >7 Days from the Final visit of the feeder study. At this visit, the investigator or designee will:

1. Review and explain the nature of the study to the subject/caregiver, obtain the subject's/caregiver's signature on the appropriate approved ICF, assent form as appropriate and Health Insurance Portability and Accountability Act (HIPAA) authorization (US subjects only) and provide a signed and dated copy to the subject/caregiver
2. Confirm the subject meets all inclusion criteria and no exclusion criterion
3. Register subject in the IRT system to obtain a Subject Identification number
4. Collect demographic and medical history information
5. Measure vital signs
6. Collect blood and urine samples for clinical laboratory tests
7. Perform an ECG
8. Collect urine pregnancy test for all subjects who are women of childbearing potential (WOCBP); the results must be negative for the subject to be enrolled in this study
9. Review the eDiary instructions
10. Perform a Clinical Assessment:
    a. For subjects with lesions that require treatment as determined by the Investigator proceed to Cycle Start Visit activities.
    b. For subjects with lesions that do not require treatment as determined by the Investigator who are not initiating study medication applications:
        i. Instruct the subject/caregiver to contact the investigator if she/he feels their EBS has worsened
        ii. Schedule the next study visit in 8 weeks or upon worsening of disease. **Note: if subject returns for the next visit and does not meet criteria for initiating cycle (lesions require treatment), the site should repeat step 10b. Cycles may only start if subject has lesions that require treatment as determined by the Investigator.**

8.2.2. Cycle Start Visit

Note: Day 0/Baseline may be considered the Cycle Start Visit if subjects have lesions that require treatment as determined by the Investigator.

For subjects with lesions that require treatment who are initiating the treatment period:

1. Dispense study medication as appropriate
2. Review the study medication application technique with the subject/caregiver
3. Provide a Subject Instruction Sheet
4. Dispense a blister lancing kit and instructions to the subject/caregiver if needed
5. Report the subject's ongoing concomitant therapies
6. Document the subject's ongoing adverse events, all events continuing from feeder studies and any new adverse events must be reported
7. Review the study instructions, including eDiary, with the subject/caregiver
8. Schedule the Mid-Cycle Visit in 8 weeks.

8.2.3. Mid-Cycle Visit

The Mid-Cycle visit should be scheduled 8 weeks after the Cycle Start Visit. After this visit is performed, the subject will remain off treatment for 8 weeks.

At this visit, the investigator or designee will perform the following procedures:

1. Perform a urine pregnancy test for all subjects who are WOCBP
2. Perform the Clinical Assessment
3. Collect all study medication
4. Dispense a blister lancing kit and instructions to the subject/caregiver if needed
5. Query the subject/caregiver about any changes in the subject's concomitant therapies since the previous visit and report changes on the appropriate form
6. Query the subject/caregiver in a non-directive manner about any changes in the subject's health since the previous visit and report all AEs on the appropriate form
7. Confirm the subject continues to comply with all study restrictions, is eligible to continue in the study and has followed all study instructions
8. Review the study instructions, including eDiary, with the subject/caregiver
9. Schedule the End of Cycle Visit in 8 weeks

8.2.4. End of Cycle Visit

After the subject has gone 8 weeks without study medication, the investigator will re-evaluate the subject and to determine if the subject is eligible to initiate another treatment cycle. Note: subjects may not start new treatment cycle past week 36 without prior sponsor approval.

At this visit, the investigator or designee will:

1. Measure vital signs
2. Collect blood and urine samples for clinical laboratory tests
3. Perform an ECG

4. Perform a urine pregnancy test for all subjects who are WOCBP
5. Perform a Clinical Assessment:
    a. For subjects with lesions that require treatment as determined by the Investigator proceed to Cycle Start Visit activities. Note: Once a subject completes two cycles of treatment or reaches Week 52, the subject will be discharged from the study. Subjects may not start a new treatment cycle past Week 36 without prior sponsor approval.
    b. For subjects with lesions that do not require treatment as determined by the Investigator who are not initiating study medication applications:
        i. Instruct the subject/caregiver to contact the investigator if she/he feels their EBS has worsened
        ii. Query the subject/caregiver about any changes in the subject's concomitant therapies since the previous visit and report changes on the appropriate form
        iii. Query the subject/caregiver in a non-directive manner about any changes in the subject's health since the previous visit and report all AEs on the appropriate form
        iv. Confirm the subject continues to comply with all study restrictions, is eligible to continue in the study and has followed all study instructions including eDiary
        v. Schedule the next study visit in 8 weeks or upon worsening of disease. **Note: if subject returns for the next visit and does not meet criteria for initiating cycle (lesions require treatment), the site should repeat step 5b. Cycles may only start if subject has lesions that requirement treatment as determined by the Investigator.**

8.3. EBS Lesion Identification

For this study, an EBS lesion is defined as a blister (*i.e.*, a fluid filled thin-walled structure), or the crust and/or erosion arising from a previous blister, and the immediately surrounding intense erythema. Investigators will use clinical judgment to determine if the EBS lesion requires treatment. Investigators are encouraged to assess the overall severity of lesions (e.g. blisters, erosions, crusting, erythema and/or pigmentary changes) to determine which lesions require treatment.

8.4. Subject Instructions

An investigational center staff member will provide a subject instruction sheet to each subject/caregiver to help with compliance to the study requirements. Updated information and instruction for subjects will be provided as necessary.

Throughout the study, the subjects should:

- Continue their routine cosmetics and skin care products
- Bleach medicated cleansers, bleach baths, topical antiseptics, topical disinfectants, etc. are allowed and details of use must be reported to the site.

- Avoid exposing the treated EBS lesions to excessive natural or artificial ultraviolet radiation (*e.g.*, sunlight, tanning beds) and use sunscreen on the lesions, if excessive exposure cannot be avoided
- Only use a tube of study medication for a maximum of 28 days (after 28 days has elapsed from date of opening, a new tube of medication should be opened)
- Apply study medications to lesions identified by the Investigator that require treatment
- Apply study medication daily, in the evening, until lesions resolve for up to 8 weeks
- Apply study medication daily, in the evening, to any new lesions that appear in between study visits (up to 30% BSA) until lesions resolve for up to 8 weeks
- Follow the instructions for blister lancing management and care
- Bring the subject instruction sheet and all study medication tubes with them to each mid-cycle visit.

8.5. EBS Lesion Care

8.5.1. Blister lancing kit

An investigational center staff member will dispense an optional blister lancing kit(s) and instructions to every subject/caregiver as appropriate. The subject will be instructed to lance all EBS lesions, including study medication treated lesions and those not treated with study medication (*e.g.*, lesions exceeding 30% BSA), within 24-hours of appearance.

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.

8.5.2. Bandaging/Dressing Use

Bandaging of EBS lesions is not prohibited during this study. Subjects should be encouraged to remain consistent with their bandaging routine; however, this is not required. Bandaging should be recorded in the eCRF as a concomitant therapy.

Note: All bandaging is prohibited for the first hour after study medication application.

8.6. Study Duration

The duration of study participation for a subject is anticipated to be a maximum of 52 weeks and 4 days or 2 treatment cycles, whichever is shorter. Subjects may not initiate a new treatment cycle beyond Week 36 without prior sponsor approval.

The study end date is the date of the last subject's last study visit.

8.7. Study Medications

8.7.1. Study medication identity

The study medication is a yellow sterile ointment. The study medication must be stored in a secured area with limited access under appropriately controlled and monitored storage conditions.

Study Medication Information	
Study medication name	Diacerein (CCP-020) 1% Ointment, Sterile
Manufacturer	TWi Pharmaceuticals, Inc., Taoyuan City, Taiwan
Diacerein concentration (%)	1
Pharmaceutical Form	Ointment
Storage Conditions	59°F to 86°F (15°C to 30°C)
Dose regimen	
Route	Topical
Frequency	Once-daily application to all EBS lesions
Duration of administration	Once-daily applications for a maximum of 8 weeks in a single treatment cycle

8.7.2. Study medication formulation

Diacerein (CCP-020) 1% Ointment	[redacted]

8.7.3. Study medication packaging and labeling

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

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.

8.7.4. Method of treatment assignment

All subjects will be assigned to receive Diacerein 1% Ointment.

8.7.5. Subject treatment assignment

At the study visit when a subject initiates a treatment cycle, the investigator or designee will electronically contact the IRT system to identify the tube number(s) to be dispensed to the subject.

Instructions for use of the IRT system will be provided to each investigator prior to the initiation of subject enrollment at her/his center.

8.7.6. Dispensing study medication

The study medication must be dispensed only to study subjects, only at investigational centers specified on the Form FDA 1572 (or its equivalent) and only by authorized personnel as required by applicable regulations and guidelines.

The subject/caregiver must bring dispensed study medication tubes and, if possible, cartons with them to all visits.

At a study visit when a subject is eligible to be dispensed study medication and the assigned study medication tubes have been identified, an investigational center staff member will complete the labels and dispense the tube to the subject/caregiver.

At all applicable visits, examine the tube(s) of study medication dispensed to the subject/caregiver. Unopened tubes previously dispensed can be re-dispensed to a subject/caregiver.

At the end of a treatment period, all study medication tubes will be collected from the subject/caregiver.

The investigational center staff should make every effort to obtain all dispensed and unused study medication. Two documented telephone contacts followed by a registered letter to the subject/caregiver are adequate follow-up efforts. If these efforts fail, the reason for the failure must be noted in the CRF. All unused and un-dispensed study medication should be held for inspection by the monitor. Upon completion of the study, all study medication will be returned to Castle Creek Pharmaceuticals, LLC or a designated third party by the monitor using a traceable method.

8.7.7. Study medication application

The study medication is for external, topical use on the subject's EBS lesions only.

At the study visit where a subject initiates treatment for the first time on the study, 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 EBS lesions and to about ¾ inch (2cm) of uninvolved skin surrounding each lesion with a thin layer and gently rub it in
- A general rule to follow is 1 fingertip unit of study medication is sufficient to cover approximately 1 % BSA (palmar method measurement) for that particular subject

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

Each opened tube of study medication can only be used for 28 days. A new tube of study medication should not be opened until the first tube is either empty or has been open for >28 days.

The subject/caregiver will continue once-daily applications to every active (e.g. not healed) EBS lesion, in the evening, until the lesions resolve for the 8-week treatment period.

At all treatment period visits, a staff member will review the application technique with the subjects/caregivers to confirm it is being properly performed.

New EBS lesions (up to 30% BSA) that develop during a treatment period (after cycle start but prior to cycle end) should be treated once-daily with study medication until resolved.

EBS lesions that are excluded from treatment with the study medication (*e.g.* those exceeding 30% BSA) may be treated following standard of care.

8.7.8. Dose compliance record

Each subject/caregiver will record the subject's compliance with the study medication application frequency on a daily basis in an eDiary. Subjects/caregivers will also be required to report any new EBS lesions that require treatment that develop in between study visits using the eDiary. Subjects/caregivers will be required to report adherence to blister lancing recommendations using the eDiary.

8.7.9. Dose modification

Subjects/caregivers should not modify the study medication application procedure or frequency without approval from the investigator or designee.

If any significant study medication intolerance or safety issue occurs the investigator or designee may direct the subject/caregiver to reduce the study medication application frequency as determined by the investigator.

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.

8.8. Study medication Management

8.8.1. 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.

8.8.2. Return and disposition of study supplies

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.

8.9. Blinding

8.9.1. Verification of blinding

This is an open-label study, the study medication identity is known to both the subject and the investigator.

9. STUDY ASSESSMENTS

9.1. Safety Evaluations

In addition to reporting adverse events throughout the study the investigator, a designated and appropriately trained staff member or the subject/caregiver, will perform the following safety assessments according to the schedules noted below.

9.1.1. Demographics/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 Baseline:

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

9.1.2. 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 sits quietly for at least 5 minutes
- Height
- Weight

The vital signs collected from the feeder studies (final visit) will be used as the Baseline data for this study and need not be repeated unless the visit occurs outside the window allowed in the Study Flow Chart.

9.1.3. Clinical laboratory sampling

At the timepoints specified in the Study Flow Chart, a qualified staff member will collect blood and urine samples for clinical laboratory analysis. Topical anesthetics may be used during the blood sample collection. If used, the topical anesthetics should be reported as a concomitant therapy.

The results of the feeder studies (final visit) clinical laboratory samples will be used as the Baseline data for this study and need not be repeated unless the visit occurs outside the window allowed in the Study Flow Chart.

The following tests will be performed:

Chemistry Panel	**Complete Blood Count**
Albumin	Hematocrit
Alkaline phosphatase (ALP)	Hemoglobin
Alanine aminotransferase (ALT)	Platelet count
Amylase	Red blood cell morphology
Aspartate aminotransferase (AST)	Red blood cell count
Blood urea nitrogen (BUN)	White blood cell count
Bicarbonate	White blood cell differential
Chloride	% and absolute:
Creatinine	Basophils
Gamma-Glutamyl Transferase (G-GT)	
Glucose	Eosinophils
HbA1c	Lymphocytes
Lactate dehydrogenase (LDH)	Monocytes
Lipase	Neutrophils
Potassium	
Sodium	**Complete Urinalysis**
Total bilirubin	
Total protein	
Uric acid	

The results of the clinical laboratory tests will be reported on the laboratory's standard reports. The investigator or designee must review all laboratory reports in a timely manner and note NCR or CR to define the clinical relevance of any result that is outside the normal range for the laboratory. The investigator or designee must date and initial every laboratory report.

The investigator must report all laboratory results that are BOTH outside the normal range for the laboratory AND, in the opinion of the investigator, CR as medical history if found prior to the first study medication treatment or as an AE if found after the first study medication treatment begins.

9.1.4. Electrocardiogram (ECG) Monitoring

Single 12 lead ECGs will be performed as outlined in the Study Flow Chart using sensitive electrodes (or other precautionary measure) ensuring the subject's skin is not harmed from the procedure (e.g. SofTouch™ Electrodes). ECGs will be performed on subjects in supine position. All ECG tracings will be reviewed by the Study Physician or his/her designee. A subject will be withdrawn from the study by the Study Physician or his/her designee if, in their medical judgment, ECG findings are present which make continued study participation not in the subject's best interest.

The ECG corresponding to the final visit of the feeder studies will be used as the Baseline data for this study and need not be repeated.

9.1.5. Pregnancy tests

At the timepoints specified in the Study Flow Chart, a qualified staff member will perform a urine pregnancy test for subjects who are WOCBP. The urine pregnancy test kits used must have a minimum sensitivity of 25-mIU ß-HCG/mL of urine.

Subjects who are WOCBP must have a negative pregnancy test result at Baseline 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.

The pregnancy test result from the feeder studies (final visit, as applicable) will be used as the Baseline data for this study and need not be repeated unless the visit occurs outside the window allowed in the Study Flow Chart.

9.2. Other Evaluations

9.2.1. Clinical Assessment

The investigator will determine if the subject has active EBS lesions (e.g. EBS lesions that require treatment with the study medication) at the time points specified in the Study Flow Chart. The investigator will be responsible for recording presence or absence of active lesions and associated % BSA of all active lesions that require treatment. The investigator will not be required to assess lesion severity.

9.2.2. Total Volume of Blood Collected

The total number of venipunctures and the total volume of blood collected during the study will be limited to that needed for safety monitoring. The total blood volume collected for each subject for the entire study will be compliant with WHO guidelines. Due to WHO compliance, safety laboratory tests will be prioritized if not all laboratory samples can be collected due to volume.

	Baseline*	**End of Cycle**
Adults	**NA; sample used from feeder study**	**7.0 ml**
Children (<18 years)	**NA; sample used from feeder study**	**7.0 ml**

*if samples need to be re-collected because visit occurs outside allowable window, 7 ml of blood will be drawn for Baseline.

10. ADVERSE EVENTS

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

10.1. 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 CRF.

Worsening of any EBS lesion assessment should be reported as an AE ONLY if the use of the study medication is interrupted or discontinued, or if therapy is required to manage the event. 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 the subject signs an informed consent AND has any study related procedure conducted, until the subject's study participation is complete OR until 30 days after the subject's last study medication application, whichever is longer.

Adverse events that were reported in the CCP-020-301 or CCP-020-101 studies and are ongoing at Baseline for this study must be reported for this study.

Subject/caregivers should be instructed to report any adverse event that they experience to the Investigator. Investigators should make an assessment for adverse events at each visit and record the event on the appropriate adverse event CRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the CRF. 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 CRF. 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 Baseline, that is not reported as an ongoing AE from the CCP-020-301 or CCP-020-101 studies, should not be reported as an adverse event unless the medical condition or signs or symptoms 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.*, electrocardiogram) findings that are detected during the study, are reported as ongoing AEs from the CCP-020-301 or CCP-020-101 studies at Baseline 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 CR. CR abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer CR.

Any abnormal test that is determined to be an error does not require reporting as an adverse event.

10.2. 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).

10.3. 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.

10.4. 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.

10.4.1. 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.

10.4.2. 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 Rechallenge).

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.

10.4.3. 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. Certain AEs will be categorized as AEs of special interest (AESIs) in this study will include the following:

- 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.

10.5. 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.

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

10.5.1.1. Initial Reports

All SAEs/AESI, regardless of causality, occurring from the time of informed consent until completion of the subject's last study visit OR until 30 days after the subject's last application of

study medication, whichever is longer, must be reported to CRO 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.

SAEs/AESI that were reported from the feeder studies and are ongoing at Baseline for this study must be reported for this study.

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/AESI 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.

Safety Contact Information: Medpace Clinical Safety
Medpace SAE hotline – USA:
Telephone: [redacted]
Fax: [redacted]
e-mail: [redacted]

10.5.1.2. 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 CRO 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.

10.5.1.3. 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.

11. 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.

All WOCBP must use an effective, active 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).

All pregnancies occurring from the time of informed consent until completion of the subject's last study visit OR until 30 days after the subject's last application of study medication, whichever is longer, must be reported to CRO Clinical Safety within 24 hours of knowledge of the pregnancy. CRO 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 terminated 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 and early termination study procedures will be performed unless contraindicated by pregnancy. 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 CRO 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.

12. STATISTICAL ANALYSES

12.1. Analysis Populations

The Safety Population will consist of all subjects who receive at least one application of study medication.

12.2. Data Analysis

12.2.1. Missing Data Handling Methods

Only the observed data will be summarized for efficacy and safety of the study. No missing data will be imputed.

12.2.2. Subject Information

A detailed description of subject disposition will be provided. Descriptive summaries of demographic and baseline characteristics will be presented for the Safety Population.

12.2.3. Analysis of Safety

Safety measures will include the following assessments:

- Demographics/Medical History
- Adverse events and SAEs
- Vital Signs
- Clinical examination
- Laboratory testing
- ECGs
- Urine pregnancy tests.

Adverse events and medical histories will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). New or worsening adverse events after dosing of study drug will be summarized by system organ class, preferred term, and treatment. Lists of subjects who have an SAE/AESI or who discontinue from the study due to an adverse event will be provided.

Summary statistics for laboratory values will be provided at baseline, post-baseline visits, and for changes from baseline to post-baseline by treatment. Vital signs and ECG parameters will be summarized similarly. Occurrence of significant laboratory abnormalities will be summarized by treatment. Clinical examination and other safety measurements will be summarized and listed.

12.3. Interim Analysis

No interim analysis is planned.

12.4. Sample Size Calculation

No formal sample size calculation was performed for this extension study.

Approximately 80 subjects are anticipated to be enrolled in this study at approximately 20-24 international investigational centers. The actual number of subjects that are enrolled will depend on the final number of subjects who participate in the CCP-020-301 or participate in the CCP-020-101 study.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. 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/AESI have been properly documented on CRFs and confirm any SAEs/AESI have been forwarded to Castle Creek Pharmaceuticals, LLC, and their representatives and confirm those SAEs/AESI that met criteria for reporting have been forwarded to the IRB/EC, as applicable.

14. ETHICS

14.1. 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.

14.2. 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 and the Castle Creek Pharmaceutical's policy on Bioethics.

14.3. Written Informed Consent/Assent

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. Parents/guardians (caregivers) must be given an IRB/EC approved ICF to review, sign and date. Local IRB/EC requirements surrounding assent should be followed.

15. DATA HANDLING AND RECORD KEEPING

15.1. 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.

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

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

15.2. 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.

15.3. 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.

16. 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.

17. REFERENCES

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3. Fine, J.D., et al., Inherited epidermolysis bullosa: updated recommendations on diagnosis and classification. J Am Acad Dermatol, 2014. 70(6): p. 1103-26.
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5. Nicolas, P., Clinical Pharmacokinetics of Diacerein, Clin Pharmacokinet, 1998 Nov; 35 (5), p. 347-59.
6. Wally, V., et. al., Diacerein for the treatment of epidermolysis bullosa – a phase II randomized, placebo controlled, double-blind multi-center clinical trial. Presented at the 25th European Academy of Dermatology and Venerology Congress, 2016 October 2, Vienna, Austria.