CLINICAL STUDY PROTOCOL

Diacerein 1% Ointment
Protocol Number: CCP-020-301
Protocol Amendment 3a

Version of Protocol	Applicable Countries
Original Protocol	All
Global Protocol Amendment 1	All
Local UK Protocol Amendment 1.1	United Kingdom
Local Protocol Amendment 1.2	Austria, France, Germany
Global Protocol Amendment 2	Australia, Israel, USA
Global Protocol Amendment 3a	All

Protocol Title:
An International, Multicenter, Randomized, Double-Blind, Parallel-Group Phase 2 Study Evaluating the Safety and Efficacy of Diacerein 1% Ointment Topical Formulation in Subjects with Epidermolysis Bullosa Simplex (EBS) [DELIVERS Study]

IND Number:
131,384

EudraCT Number:
2016-004427-24

Indication Studied:
Epidermolysis Bullosa Simplex

Protocol Date:
02-JAN-2018

Sponsor Address:
Castle Creek Pharmaceuticals, LLC
6 Century Drive
Parsippany, NJ 07054
United States of America

Confidentiality Statement

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.

SIGNATURES:

Gregory P. Licholai, MD President and Chief Medical Officer Castle Creek Pharmaceuticals, LLC	Date
Amir Tavakkol, Ph.D., Dip. Bact. Executive VP & Chief Development Officer Castle Creek Pharmaceuticals, LLC	Date

INVESTIGATOR/SPONSOR AGREEMENT

I have received and read the Investigator's Brochure for topical Diacerein 1% Ointment (CCP-020). I have read CCP-020-301 global protocol amendment 3 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

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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, Randomized, Double-Blind, Parallel-Group Phase 2 Study Evaluating the Safety and Efficacy of Diacerein 1% Ointment Topical Formulation in Subjects with Epidermolysis Bullosa Simplex (EBS) DELIVERS Study

Study center(s): Approximately 20

Studied period (years):	**Phase of development:**
Estimated date first subject enrolled: 01-JUN-2017 Estimated date last subject completed: 31-DEC-2018	Phase 2

Objectives:

Primary Objective:

- To compare the efficacy of Diacerein 1% Ointment to Control Ointment based on reduction in body surface area (BSA) of EBS lesions being treated when applied once-daily for 8 weeks in subjects with EBS.

Secondary Objectives:

To compare the effects of Diacerein 1% Ointment to Control Ointment in subjects with EBS in:

- Changes in Investigator Global Assessment (IGA) scores
- Pain
- Pruritus
- Mobility
- Safety and tolerability

Methodology:

This is an international, multicenter, randomized, double-blind, vehicle-controlled, parallel group study to evaluate the safety and efficacy of topical Diacerein 1% Ointment for the treatment of subjects with EBS. Subject randomization will be stratified by genotype (KRT5 and/or KRT14 versus other genotypes) and age group (<8 and ≥8 years old).

Subjects will be screened for inclusion and exclusion criteria at Visit 1 (Week -6). Subjects must have a genotypic confirmation of EBS (based on either existing documentation or results from a sample collected as part of the study) to be randomized to study medication.

At Visit 2 (Week 0) eligible subjects will be randomized in a 1:1 ratio to either receive 8 weeks of once-daily application of Diacerein 1% Ointment or Control Ointment to all EBS lesions in the Assessment Area except plantar areas where >25% of the area has hyperkeratosis that has been present for greater than 12 weeks and the scalp, groin and areas where, in the investigator's opinion, the study medication might become occluded are excluded. At Visit 2 (Week 0) all subjects or their caregivers (subjects/caregivers) will be instructed on the daily study medication application technique. For each application, a thin layer of the assigned study medication, sufficient to cover the lesions and approximately ¾ inch (2 cm) of surrounding uninvolved skin, will be applied and gently rubbed in. Subjects/caregivers will apply the assigned study medication to all EBS lesions, including any new EBS lesions that develop, once daily, every evening during the 8-week treatment period. The subject's first study medication application will be observed by a member of the study staff for approximately 20 minutes. Subsequent study medication applications will be performed by the subject/caregiver. The application technique will be reviewed with subjects/caregivers at all treatment period visits. No study medication applications will be made to any lesion that becomes infected until the infection resolves with appropriate investigational center specific medical care.

Also at Visit 2 (Week 0) subjects/caregivers will be instructed on the use of the electronic diary (eDiary) to record patient reported outcomes of pruritus, pain and mobility and to document bandage use, blister lancing compliance, new lesions that develop in between study visits, routine cleanser use and study medication applications. Proper use of the eDiary will be reinforced at every study visit.

Adverse events, clinical laboratory data, PK sampling, efficacy evaluations and determination of study medication use will be routinely collected. Subjects/caregivers will be instructed on how and when to lance blisters throughout the duration of the study.

The duration of study participation is anticipated to be a maximum of 158 days per subject (~22 weeks). The final study visit (Visit 8/Week 16) has a maximum allowable visit window of 4 days.
Study visits are:

- Visit 1 (Week -6/Day -42 to 0) enrollment, start randomization eligibility assessment period
- Visit 2 (Week 0/Day 1) randomization; first study medication application
- Visit 3 (Week 1/Day 8) treatment period follow-up
- Visit 4 (Week 4/Day 29) treatment period follow-up
- Visit 5 (Week 6/Day 43) treatment period follow-up
- Visit 6 (Week 8/Day 57) end of the treatment period
- Visit 7 (Week 12/Day 85) no treatment follow-up
- Visit 8 (Week 16/Day 113) no treatment follow-up, end of study

An interim analysis will be conducted by an independent data monitoring committee (DMC) once a prespecified number of subjects have completed the study. A formal unblinded analysis will be planned. Details regarding the conduct of the interim analyses will be specified outside of this protocol (e.g. DMC charter). The DMC will advise whether any changes to the sample size or conduct of the study are necessary based on review of safety and efficacy data.

Number of subjects (planned):
Approximately 80 subjects are planned to be randomized in this study at approximately 20 international investigational centers. A planned interim analysis will be performed when approximately 40 subjects have been randomized, and may result in an adjustment of the number of randomized subjects. This will be a formal unblinded analysis that will be detailed in the DMC Charter.

Diagnosis and main criteria for inclusion/exclusion:

Inclusion criteria**:**

1. Subject is male or female at least 4 years of age at Visit 1
2. Subject has a documented genetic mutation consistent with EBS. A blood or saliva sample will be collected for genetic confirmation if no documented gene mutation data is available. Gene mutations acceptable for inclusion are as follows: KRT5, KRT14, PLEC1, TGM5, PKP1, DSP, FERMT1, EXPH5, DST, KLHL24.
3. Subject has an Assessment Area (see Section 9.1.2) of EBS lesions to be treated, that is ≥2% body surface area (BSA) and the EBS lesions are in one or both of the following body areas:

- Localized: plantar and/or palmar areas (plantar areas where >25% of the area has hyperkeratosis that has been present for greater than 12 weeks cannot be included as part of the Assessment Area)
- Generalized: arms, legs, torso, hands and feet (scalp, groin and areas where, in the investigator's opinion, the study medication might become occluded cannot be included as part of the Assessment Area

4. Subject's EBS lesions in the Assessment Area have an Investigator's Global Assessment (IGA) score of ≥3
5. Subject/caregiver agrees to not use any topical therapies other than the study medication that, might influence the status of the EBS lesions during the duration of the study (*e.g.*, medicated cleansers, CBD oil, MediHoney, Silvadine cream 1%, [see Section 7.5.3]); the Investigator should consult the Medical Monitor regarding therapies not specified in the protocol
6. Subject/caregiver agrees to follow topical product application instructions (see Section 7.5.4) 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 (see Section 10.6), 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, might impair evaluation of the EBS lesions or 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
11. Subject/caregiver is able to comprehend and willing to sign an Informed Consent and/or Assent Form.

<u>Exclusion criteria:</u>

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 used any diacerein containing product within 6 months prior to Visit 1

3. Subject has used systemic immunotherapy or cytotoxic chemotherapy within 60 days prior to Visit 1
4. Subject has used systemic steroidal therapy or has used topical steroidal therapy on the EBS lesions to be treated within 30 days prior to Visit 2 (Note: inhaled 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 Visit 1
6. Subject is currently using systemic analgesics and/or anti-histamine therapy for treatment of EBS lesions, unless on a stable regimen (*i.e.*, the same dosing regimen) for at least 4 weeks prior to Visit 1. Note: As needed (PRN) use of acetaminophen/paracetamol or NSAIDs within the 4 weeks prior to Visit 1 are permitted provided the treatment was unrelated to EBS symptom relief.
7. 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 Visit 1
8. Subject has used any topical product containing allantoin on the EBS lesions to be treated within 30 days prior to Visit 1
9. Subject has a current malignancy, or a history of treatment for a malignancy within 2 years prior to Visit 1 (Note: does not include non-melanoma skin cancer)
10. Subject currently has diabetes mellitus (HbA1c ≥6.5%). Note: controlled diabetes (HbA1c < 6.5%) is also considered exclusionary
11. 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) 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
12. Subject has a non-EBS skin disease (*e.g.*, psoriasis, atopic dermatitis, eczema, sun damage, etc.), or condition (*e.g.*, sunburn) 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
13. Subject has a history of sensitivity to any of the ingredients in the study medications. See section 8.8.2

14. Subject has participated in any investigational drug/device trial in which administration of an investigational study medication occurred within 30 days prior to Visit 1.

Investigational product, dosage and mode of administration:

Diacerein 1% Ointment administered topically

Duration of study and treatment:

Twenty-two weeks including an up to 6-week screening period, eight weeks of treatment and eight weeks of no-treatment follow up.

Reference therapy, dosage and mode of administration:

Control ointment lacking active ingredient but containing a colorizing agent to maintain blinding.

Criteria for evaluation:

- To evaluate the efficacy of Diacerein 1% Ointment compared to Control Ointment on the key efficacy measure of success defined as ≥40% reduction in body surface area (BSA) of EBS lesions.
- To evaluate the safety and tolerability of Diacerein 1% Ointment in subjects with EBS.

All efficacy endpoints will be based on the Assessment Area, defined in the protocol Section 9.1.2

The primary efficacy endpoint:

The primary efficacy endpoint is based on the ITT population, and is the proportion of subjects who achieve ≥40% reduction in BSA of EBS lesions from Visit 2 (Week 0) to Visit 8 (Week 16).

The key secondary endpoints:

The secondary endpoints are as follows:

- The proportion of subjects achieving success on the IGA, where success is defined as at least a 2-point reduction, from Visit 2 (Week 0) to Visit 8 (Week 16).
- The proportion of subjects who achieve ≥ 40% reduction in BSA of EBS lesions from Visit 2 (Week 0) to Visit 6 (Week 8).
- The proportion of subjects achieving success on the IGA, where success is defined as at least a 2-point reduction, from Visit 2 (Week 0) to Visit 6 (Week 8).

- The proportion of subjects with a reduction in overall pain intensity from Visit 2 (Week 0) to Visit 6 (Week 8).
- The proportion of subjects with a reduction in overall pruritus intensity from Visit 2 (Week 0) to Visit 6 (Week 8).

If the comparison for the primary endpoint is significant (two-sided p-value < 0.05), then testing will continue for the key secondary endpoints. The key secondary endpoints will be analyzed in a similar manner as the primary endpoint. To control the type I error rate for testing multiple key secondary endpoints, a fixed-sequence approach for the key secondary endpoints will be used.

Exploratory end points

The exploratory endpoints are as follows:

- The proportion of subjects with a reduction in overall pain intensity from Visit 2 (Week 0) to Visit 8 (Week 16).
- The proportion of subjects with a reduction in overall pruritus intensity from Visit 2 (Week 0) to Visit 8 (Week 16).
- The proportion of subjects with an increase in mobility assessment from Visit 2 (Week 0) to Visit 6 (Week 8).
- The proportion of subjects with an increase in mobility assessment from Visit 2 (Week 0) to Visit 8 (Week 16).
- The percent change in BSA of EBS lesions from Visit 2 (Week 0) to Visit 6 (Week 8).
- The percent change in BSA of EBS lesions from Visit 2 (Week 0) to Visit 8 (Week 16).
- The percent change in Reference Lesion Surface Area from Visit 2 (Week 0) to Visit 6 (Week 8).
- The percent change in Reference Lesion Surface Area from Visit 2 (Week 0) to Visit 8 (Week 16).

Population PK endpoint:

Blood draws for population PK analysis will be drawn at protocol specified timepoints.

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
CBD	Cannabidiol
CMH	Cochran-Mantel-Haenszel
CR	Clinically Relevant
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
DRESS	Drug reaction with eosinophilia and systemic symptoms
EBS	Epidermolysis Bullosa Simplex
e.g.	For Example, (Latin; *exempla gratia*)
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EP	European Pharmacopoeia
EU	European Union
DEB	Dystrophic Epidermolysis Bullosa
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
G	Gram
GCP	Good Clinical Practice
eGFR	Estimated Glomerular Filtration Rate
HCG	Human Chorionic Gonadotrophin
HIPAA	Health Insurance Portability and Accountability Act of 1996
Hg	Mercury
IB	Investigator's Brochure
ICF	Informed Consent Form

Abbreviation	Term
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
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
NF	National Formulary
NRS	Numeric Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
OTC	Over-The-Counter
PD	Pharmacodynamic
PK	Pharmacokinetic
PRN	As needed
PP	Per Protocol
PRO	Patient Reported Outcome
SAE	Serious Adverse Event
SI	Subject Identifier
SOP	Standard Operation Procedure
US	United States
USP	United States Pharmacopoeia
WOCBP	Women of childbearing potential

2. SUMMARY OF CHANGES

This section describes the changes made in Global Amendment #3a. Added text is indicated in bold, deleted text is indicated by ~~strikethrough~~. Minor changes to punctuation, administrative changes (i.e. changes in numbering, word order, location, etc.), changes to the table of contents, additions/subtractions from list of abbreviations, changes in the study synopsis, study flow chart, and protocol signatories will not be listed in the summary of changes. Changes repeated throughout the protocol are noted as global changes.

For Austria, France, Germany: Refer to Austria_France_Germany_Summary of Changes Document Protocol Amendment 3.0a

For Netherlands: Refer to Netherlands_Summary of Changes Document Protocol Amendment 3.0a

For United Kingdom: Refer to United Kingdom_Summary of Changes Document Protocol Amendment 3.0a

For Australia, Israel, United States: Refer to Australia_Israel_United States_Summary of Changes Document Protocol Amendment 3.0a

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 IL-6, 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 as part of long-term follow-up 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 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 multiple European countries 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 topical diacerein has potential to down-regulate the activity of IL-1β and reduce the auto-inflammatory effects in the skin of patients with EBS. The favorable product profile of diacerein, an anti-IL-1β small molecule therapeutic, 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.

As part of the clinical development program for Diacerein 1% Ointment there will be an administratively separate, 12-month open-label study subsequent to CCP-020-301 in subjects with EBS. One inclusion criterion for this subsequent study is that the subject has completed study CCP-020-301.

3.1. Dose and Treatment Duration Rationale

In addition to the long history of clinical experience with diacerein after oral administration, recent 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 recent, multi-center, 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. 60% of patients applying Diacerein cream for 4 weeks and followed-up to 3 months achieved a clinically meaningful reduction of at least 40% in blister numbers as compared to 15% in the placebo group, as determined by the investigator. 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 efficacy and safety of a 1% diacerein ointment compared to its placebo in patients with EBS after 8 weeks treatment and 8 weeks off-treatment using reduction in body surface area (BSA) of EBS lesions (assessment area being treated when applied once-daily for 8 weeks). In addition, an Investigator Global Assessment (IGA) scale will be used to determine the proportion of subjects achieving success on the IGA from Visit 2 (Week 0) to Visit 8 (Week 16).

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

Primary Objective:

- To compare the efficacy of Diacerein 1% Ointment to Control Ointment based on reduction in body surface area (BSA) of EBS lesions being treated when applied once-daily for 8 weeks in subjects with EBS.

Secondary Objectives:

To compare the effects of Diacerein 1% Ointment to Control Ointment in subjects with EBS in:

- Changes in Investigator Global Assessment (IGA) scores
- Pain
- Pruritus
- Mobility
- Safety and tolerability

5. STUDY ENDPOINTS

5.1. Primary Endpoint

The primary endpoint is the proportion of subjects who achieve ≥ 40% reduction in BSA of EBS lesions from Visit 2 (Week 0) to Visit 8 (Week 16).

5.2. Key Secondary Endpoints

- The proportion of subjects achieving success on the IGA, where success is defined as at least a 2-point reduction, from Visit 2 (Week 0) to Visit 8 (Week 16).
- The proportion of subjects who achieve ≥ 40% reduction in BSA of EBS lesions from Visit 2 (Week 0) to Visit 6 (Week 8).
- The proportion of subjects achieving success on the IGA, where success is defined as at least a 2-point reduction, from Visit 2 (Week 0) to Visit 6 (Week 8).
- The proportion of subjects with a reduction in overall pain intensity from Visit 2 (Week 0) to Visit 6 (Week 8).
- The proportion of subjects with a reduction in overall pruritus intensity from Visit 2 (Week 0) to Visit 6 (Week 8).

If the comparison for the primary endpoint is significant (two-sided p-value < 0.05), then testing will continue for the key secondary endpoints. The key secondary endpoints will be analyzed in a similar manner as the primary endpoint. To control the type I error rate for testing multiple key secondary endpoints, a fixed-sequence approach for the key secondary endpoints will be used.

5.3. Exploratory End Points

The exploratory endpoints are as follows:

- The proportion of subjects with a reduction in overall pain intensity from Visit 2 (Week 0) to Visit 8 (Week 16).
- The proportion of subjects with a reduction in overall pruritus intensity from Visit 2 (Week 0) to Visit 8 (Week 16).
- The proportion of subjects with an increase in mobility assessment from Visit 2 (Week 0) to Visit 6 (Week 8).
- The proportion of subjects with an increase in mobility assessment from Visit 2 (Week 0) to Visit 8 (Week 16).
- The percent change in BSA of EBS lesions from Visit 2 (Week 0) to Visit 6 (Week 8).
- The percent change in BSA of EBS lesions from Visit 2 (Week 0) to Visit 8 (Week 16).
- The percent change in Reference Lesion Surface Area from Visit 2 (Week 0) to Visit 6 (Week 8).
- The percent change in Reference Lesion Surface Area from Visit 2 (Week 0) to Visit 8 (Week 16).

5.4. Pharmacokinetic Endpoint

Blood draws for PK sampling and modeling will be obtained at the timepoints listed in the Study Flow Chart (see Section 8.1). Quantification of diacerein and its active metabolite, rhein in patient plasma will be performed using a validated bioanalytical assay. Data permitting, population PK and PK/PD analyses will be performed.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is an international, multi-center, randomized, double-blind, parallel group study to evaluate the safety and efficacy of topical Diacerein 1% Ointment for the treatment of subjects with EBS. Subject randomization will be stratified by genotype (KRT5 and/or KRT14 versus other genotype) and age group (<8 and ≥8 years old). Subjects will be screened for inclusion and exclusion criteria at Visit 1 (Week -6). Subjects must have a genotypic confirmation of EBS (or have a blood or saliva sample collected for genetic confirmation). At Visit 2 (Week 0) eligible subjects will be randomized in a 1:1 ratio to either receive 8 weeks of once-daily application of Diacerein 1% Ointment or Control Ointment to all EBS lesions in the Assessment Area except plantar areas where >25% of the area has hyperkeratosis that has been present for greater than 12 weeks and the scalp, groin and areas where, in the investigator's opinion, the study medication might become occluded are excluded. At Visit 2 (Week 0) all subjects or their caregivers (subjects/caregivers) will be instructed on the daily study medication application technique. For each application, a thin layer of the assigned study medication, sufficient to cover the lesion and approximately ¾ inch (2 cm) of surrounding uninvolved skin, will be applied and gently rubbed in. Subjects/caregivers will apply the assigned study medication to all EBS lesions, including any new lesions that develop, provided that the area being treated does not exceed 30% BSA during the 8-week treatment period. At Visit 2 (Week 0, baseline) the subject's first study medication application will be observed by a member of the study staff. Subsequent study medication applications will be performed by the subject/caregiver. The application technique will be reviewed with subjects/caregivers at all treatment period visits. No study medication applications will be made to any lesion that becomes infected until the infection resolves with appropriate investigational center specific medical care.

At Visit 2 (Week 0), subjects/caregivers will be instructed on the use of the electronic diary (eDiary) to record patient reported outcomes of pruritus, pain and mobility and to document bandage use, blister lancing compliance, new lesions that develop in between study visits, routine cleanser use and study medication applications. Application instructions and proper use of the eDiary will be reinforced at every study visit.

Adverse events, clinical laboratory data, efficacy evaluations and determination of study medication use will be routinely collected. Subjects/caregivers will be instructed on how and when to lance blisters, including blisters outside the treatment area, throughout the duration of the study. Blood draws for pharmacokinetic modeling will also be obtained according to the Study Flow Chart.

The duration of study participation is anticipated to be a maximum of 158 days per subject (~22 weeks). The final study visit (Visit 8/Week 16) has a maximum allowable visit window of 4 days.

Study visits are:

- Visit 1 (Week -6/Day -42 to 0) enrollment, start randomization eligibility assessment period
- Visit 2 (Week 0/Day 1) randomization; first study medication application
- Visit 3 (Week 1/Day 8) treatment period follow-up
- Visit 4 (Week 4/Day 29) treatment period follow-up
- Visit 5 (Week 6/Day 43) treatment period follow-up
- Visit 6 (Week 8/Day 57) end of the treatment period
- Visit 7 (Week 12/Day 85) no treatment follow-up
- Visit 8 (Week 16/Day 113) no treatment follow-up, end of study.

7. SELECTION DISPOSITION OF STUDY POPULATION

7.1. Number of Subjects

Approximately 80 subjects are planned to be randomized to one of the 2 treatment groups in this study at approximately 20 international investigational centers. A planned interim analysis will be performed and may result in an adjustment of the total number of randomized subjects.

7.2. Study Population Characteristics

Male or female subjects at least 4 years of age with a genetic confirmation of EBS who meet all the inclusion criteria and none of the exclusion criteria at Visit 1 will be eligible for enrollment in the study.

7.3. Inclusion Criteria

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

1. Subject is male or female at least 4 years of age at Visit 1
2. Subject has a documented genetic mutation consistent with EBS. A blood or saliva sample will be collected for genetic confirmation if no documented gene mutation data is available. Gene mutations acceptable for inclusion are as follows: KRT5, KRT14, PLEC1, TGM5, PKP1, DSP, FERMT1, EXPH5, DST, KLHL24.
3. Subject has an Assessment Area (see Section 9.1.2) of EBS lesions to be treated, that is ≥2% body surface area (BSA) and the EBS lesions are in one or both of the following body areas:

- Localized: plantar and/or palmar areas (plantar areas where >25% of the area has hyperkeratosis that has been present for greater than 12 weeks cannot be included as part of the Assessment Area
- Generalized: arms, legs, torso, hands and feet (scalp, groin and areas where, in the investigator's opinion, the study medication might become occluded cannot be included as part of the Assessment Area)

4. Subject's EBS lesions in the Assessment Area have an Investigator's Global Assessment (IGA) score of ≥3
5. Subject/caregiver agrees to not use any topical therapies other than the study medication that might influence the status of the EBS lesions during the duration of the study (*e.g.*, medicated cleansers, CBD oil, MediHoney, Silvadine cream 1%, [see Section 7.5.3]; the Investigator should consult the Medical Monitor regarding therapies not specified in the protocol
6. Subject/caregiver agrees to follow topical product application instructions (see Section 7.5.4) 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 (see Section 10.6), 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, might impair evaluation of the EBS lesions or 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
11. Subject/caregiver is able to comprehend and willing to sign an Informed Consent and/or Assent Form.

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 therapy to treat an infection)
2. Subject has used any diacerein containing product within 6 months prior to Visit 1

3. Subject has used systemic immunotherapy or cytotoxic chemotherapy within 60 days prior to Visit 1
4. Subject has used systemic steroidal therapy or has used topical steroidal therapy on the EBS lesions to be treated within 30 days prior to Visit 2 (Note: inhaled 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 Visit 1
6. Subject is currently using systemic analgesics and/or anti-histamine therapy, for treatment of EBS lesions unless on a stable regimen (i.e., the same dosing regimen) for at least 4 weeks prior to Visit 1. Note: As needed (PRN) use of acetaminophen/paracetamol or NSAIDs within the 4 weeks prior to Visit 1 are permitted provided the treatment was unrelated to EBS symptom relief.
7. 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 Visit 1
8. Subject has used any topical product containing allantoin on the EBS lesions to be treated within 30 days prior to Visit 1
9. Subject has a current malignancy, or a history of treatment for a malignancy within 2 years prior to Visit 1 (Note: does not include non-melanoma skin cancer)
10. Subject currently has diabetes mellitus (HbA1c ≥6.5%); Note: controlled diabetes (HbA1c < 6.5%) is also considered exclusionary
11. 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) 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
12. Subject has a non-EBS skin disease (e.g., psoriasis, atopic dermatitis, eczema, sun damage, etc.), or condition (e.g., sunburn) 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
13. Subject has a history of sensitivity to any of the ingredients in the study medications (See section 8.8.2)
14. Subject has participated in an investigational drug trial/device in which administration of an investigational study medication occurred within 30 days prior to Visit 1.

7.5. Previous and Concomitant Therapies

7.5.1. Previous therapies

During Visit 1 (Week -6), the investigator or designee will question the subject/caregiver to ensure they have not used any therapies noted in the Exclusion Criteria.

7.5.2. Concomitant therapies

Concomitant therapies are any new or existing/ongoing therapy received from Visit 1 (Week -6) 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).

The use of an investigator approved bland, non-medicated emollient/moisturizer must be reported as a concomitant therapy in the electronic case report forms (eCRFs).

7.5.3. Permitted & Prohibited therapies

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.

A non-exhaustive list of permitted bland, non-medicated emollient/moisturizers are:

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

In addition, routine cleansers and cleaning products, bleach baths, topical antiseptics, and sunscreens are permitted.

A non-exhaustive list of prohibited therapies are:

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

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

7.5.4. EBS lesions treatment instructions:

EBS lesions may be treated as follows during the study:

		Time Period			
		Screening Period (Visit 1 until up to 6 hours prior to Visit 2)	Randomization Day (Visit 2)	Treatment Period (Day after Visit 2 until up to 6 hours prior to Visits 3, 4, 5 & 6)	No Treatment Follow-up Period (Day after Visit 6 until up to 6 hours prior to Visits 7 & 8)
Lesion	Assessment Area	Bland, non-medicated emollient/ moisturizer	Study medication **at the study site** for observation	Study medication daily, in the evening, **regardless of lesion resolution**	Bland, non-medicated emollient/ moisturizer
	Treatment Area (new lesions)	NA (treatment area exists after Visit 2)	NA (treatment area exists after Visit 2)	Study medication daily, in the evening, **until lesion resolution**	Bland, non-medicated emollient/ moisturizer

	All other EBS lesions (lesions >30% BSA, lesions that are occluded (e.g. scalp))	Bland, non-medicated emollient/ moisturizer	Bland, non-medicated emollient/ moisturizer	Bland, non-medicated emollient/ moisturizer	Bland, non-medicated emollient/ moisturizer

7.6. 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. If the subject does not apply the study medication once daily to all EBS lesions for more than seven consecutive days, the subject must be withdrawn from treatment.

7.7. 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. Subjects also have the option to withdraw from treatment at any time. Subjects that withdraw from treatment will continue to follow their visit schedule but will no longer apply the study medication.

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. If the subject does not apply the study medication once daily to all EBS lesions for more than seven consecutive days, the subject must be withdrawn from treatment.

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.

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 eCRFs. 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
- Difficulties in the recruitment of subjects.

7.8. Subject Identifier (SI)

The investigator or designee will register each subject in the Medpace, Inc. Interactive Response Technology (IRT) system at Visit 1 (Week -6) to obtain a SI.

The SI format will be NN-NNN where the first 2 digits are the investigational center site number (using leading zeroes 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.

7.9. Replacement Subjects

Subject enrollment will continue until approximately 80 subjects have been randomized. Subjects who are randomized and do not complete the study will not be replaced.

8. INVESTIGATIONAL PLAN

8.1. Study Flow Chart

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
	Enrollment	**Randomization**	**Treatment period [e]**				**No treatment follow-up [e]**	
Study Day	**-42 to 0**	**1**	**8**	**29**	**43**	**57**	**85**	**113**
Study Week	**-6**	**0**	**1**	**4**	**6**	**8**	**12**	**16**
Informed Consent	X							
Register subject	X							
Inclusion & exclusion	X	X						
Demographics & medical hx	X							
Urine pregnancy test[a]	X	X		X		X	X	X
Physical Examination	X					X		
Vital signs	X	X	X	X	X	X	X	X
Clinical laboratory samples	X	X[b]		X		X		X
ECG		X				X		X
Sample for PK analysis				X		X		X
EBS genotyping blood or saliva sample (if required)	X							
Dispense blister lancing kit[c]	X	X	X	X	X	X	X	
IGA of Assessment Area	X	X	X	X	X	X	X	X
BSA of Assessment Area	X	X	X	X	X	X	X	X
BSA of Treatment Area[d]			X	X	X	X		
Reference Lesion LSA		X				X		X
Total BSA of all EBS Lesions		X				X	X	X
Photography		X				X		X
Pruritus severity		◆———	———	———	———	———	———◆	
Pain severity		◆———	———	———	———	———	———◆	
Mobility Assessment		◆———	———	———	———	———	———◆	
Identify emollient/moisturizer	X							
Dispense/collect/weigh study medication		X	X	X	X	X		
Apply study medication		◆———	———	———	———◆			
Concomitant therapies	X	X	X	X	X	X	X	X
Adverse events[f]		X	X	X	X	X	X	X

a) For WOCBP only
b) V2 clinical labs need not be drawn if within 7 days of the V1 lab draw
c) Subject is not required to use the study issued lancing kits; however, all blisters must be lanced within 24 hours
d) Treatment Area is defined as any NEW lesions that appear after Visit 2. Treatment Area may not exceed 30% BSA.
e) All visit windows during the Treatment and No Treatment Periods are +/- 4 days
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. Visit 1 (Day -42 to 0)

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 and provide a signed and dated copy to the subject/caregiver
2. Register subject in the IRT system to obtain a Subject Identifier
3. Confirm the subject meets all inclusion criteria and no exclusion criterion
4. Collect demographic and medical history information
5. Conduct a physical examination
6. Measure vital signs
7. Collect blood and urine samples for clinical laboratory tests
8. Collect a blood or saliva sample for EBS genotyping if documented EBS genotyping is not already available
9. Perform a urine pregnancy test for women of childbearing potential (WOCBP); results must be negative for the subject to continue in the study
10. Collect concomitant therapies information
11. Define the Assessment Area
12. Perform BSA of the Assessment Area using the palmar method
13. Perform the IGA evaluation, IGA grade must be ≥3 in the Assessment Area
14. Identify an investigator approved bland, non-medicated emollient/moisturizer
15. Dispense a blister lancing kit and instructions to the subject/caregiver
16. Dispense a Subject Instruction Sheet
17. Review the study instructions, including approved emollient/moisturizer use, with the subject/caregiver
18. Schedule Visit 2 to occur within 6 weeks/42 days.

The investigator will mark the general location of all the EBS lesions on the appropriate body chart(s) at each study visit.

8.2.2. Visit 2 (Week 0/Day 1)

This visit must occur within 42 days after Visit 1.

Subsequent study visit dates must be scheduled based on the date of Visit 2.

This visit may not occur until the investigator confirms all items necessary to determine a subject's eligibility for randomization are available.

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

1. Query the subject/caregiver about any changes in the subject's concomitant therapies since the previous visit and report changes on the appropriate form
2. Confirm the subject/caregiver continues to comply with all study restrictions and that the subject is eligible to continue in the study
3. Perform a urine pregnancy test for WOCBP; results must be negative for the subject to be randomized
4. Measure vital signs
5. Perform the IGA evaluation, IGA grade must be ≥3 in the Assessment Area
6. Confirm subject is eligible for randomization
7. Screen fail the study subjects who are not eligible for randomization. Note: subjects may be re-screened if, at a later date, the subject meets eligibility requirements. All protocol required procedures must be repeated (with the exception of genetic testing)
8. Perform Baseline ECG

For subjects who are eligible for randomization the investigator or designee will perform the following procedures:

1. Take standardized color photographs prior to the first study medication application
2. Determine Total BSA of the Assessment Area and of all EBS lesions using the palmar method
3. Identify the Reference Lesion and measure the Lesions Surface Area (LSA)
4. Collect blood & urine samples for clinical laboratory tests prior to the first study medication application
5. Register eligible subjects in the eDiary system in the IRT
6. Randomize eligible subjects
7. Weigh the study medication tube and dispense the tube to the subject
8. Instruct the subject/caregiver on the study medication application technique
9. Observe the first study medication application
10. Weigh the study medication tube after the first study medication application and then return the tube to the subject
11. Monitor the subject for at least 20 minutes after the application to detect any adverse events

12. Dispense a blister lancing kit and instructions to the subject/caregiver if needed
13. Review the study instructions, including eDiary, use of body charts and approved bland, non-medicated, emollient/moisturizer use, with the subject/caregiver
14. Schedule Visit 3 for Week 1/Day 8.

The investigator will mark the general location of all the EBS lesions on the appropriate body chart(s) at each study visit.

8.2.3. Visit 3 (Week 1/Day 8)

This visit must occur 1 week/7 days (±4 days) after Visit 2.

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

1. 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
2. Query the subject/caregiver about any changes in the subject's concomitant therapies since the previous visit and report changes on the appropriate form
3. Confirm the subject continues to comply with all study restrictions, is eligible to continue in the study and has followed all study instructions
4. Measure vital signs
5. Identify any new lesions that require treatment (Treatment Area)
6. Determine BSA of EBS lesions in the Assessment Area and in the Treatment Area (if new lesions exist) using the palmar method; Note: the area being treated may not exceed 30% BSA
7. Perform the IGA evaluation on the Assessment Area
8. Dispense, collect and weigh study medication as appropriate
9. Dispense a blister lancing kit and instructions to the subject/caregiver if needed
10. Review the study instructions, including eDiary, use of body charts and approved bland, non-medicated, emollient/moisturizer use, with the subject/caregiver
11. Schedule Visit 4 for Week 4/Day 29.

The investigator will mark the general location of all the EBS lesions on the appropriate body chart(s) at each study visit.

8.2.4. Visit 4 (Week 4/Day 29)

This visit must occur 4 weeks/28 days (±4 days) after Visit 2.

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

1. 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
2. Query the subject/caregiver about any changes in the subject's concomitant therapies since the previous visit and report changes on the appropriate form

3. Confirm the subject continues to comply with all study restrictions, is eligible to continue in the study and has followed all study instructions
4. Measure vital signs
5. Perform a urine pregnancy test for WOCBP
6. Identify any new lesions that require treatment (Treatment Area)
7. Determine BSA of EBS lesions in the Assessment Area and in the Treatment Area (if new lesions exist) using the palmar method; Note: the area being treated may not exceed 30% BSA
8. Perform the IGA evaluation on the Assessment Area
9. Collect blood & urine samples for clinical laboratory tests
10. Dispense, collect and weigh study medication as appropriate
11. Dispense a blister lancing kit and instructions to the subject/caregiver if needed
12. Review the study instructions, including eDiary, use of body charts and approved bland, non-medicated, emollient/moisturizer use, with the subject/caregiver
13. Schedule Visit 5 for Week 6/Day 43.

The investigator will mark the general location of all the EBS lesions on the appropriate body chart(s) at each study visit.

8.2.5. Visit 5 (Week 6/Days 43)

This visit must occur 6 weeks/42 days (±4 days) after Visit 2.

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

1. 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
2. Query the subject/caregiver about any changes in the subject's concomitant therapies since the previous visit and report changes on the appropriate form
3. Confirm the subject continues to comply with all study restrictions, is eligible to continue in the study and has followed all study instructions
4. Measure vital signs
5. Identify any new lesions that require treatment (Treatment Area)
6. Determine BSA of EBS lesions in the Assessment Area and in the Treatment Area (if new lesions exist) using the palmar method; Note: the area being treated may not exceed 30% BSA
7. Perform the IGA evaluation on the Assessment Area
8. Dispense, collect and weigh study medication as appropriate
9. Dispense a blister lancing kit and instructions to the subject/caregiver if needed
10. Review the study instructions, including eDiary, use of body charts and approved bland, non-medicated, emollient/moisturizer use, with the subject/caregiver
11. Schedule Visit 6 for Week 8/Day 57.

The investigator will mark the general location of all the EBS lesions on the appropriate body chart(s) at each study visit.

8.2.6. Visit 6 (Week 8/Day 57); end of the treatment period

This visit must occur 8 weeks/56 days (±4 days) after Visit 2.

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

1. 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
2. Query the subject/caregiver about any changes in the subject's concomitant therapies since the previous visit and report changes on the appropriate form
3. Confirm the subject continues to comply with all study restrictions, is eligible to continue in the study and has followed all study instructions
4. Conduct a physical examination
5. Measure vital signs
6. Perform a urine pregnancy test for WOCBP
7. Identify any new lesions that appeared since the last visit
8. Determine BSA of EBS lesions in the Assessment Area and new lesions (if new lesions exist), as well as EBS lesions that are not being treated (e.g. >30% BSA or lesions that are occluded) using the palmar method
9. Measure the LSA of the Reference Lesion
10. Perform the IGA evaluation on the Assessment Area
11. Collect blood & urine samples for clinical laboratory tests
12. Take standardized color photographs
13. Collect and weigh all study medication as appropriate
14. Dispense a blister lancing kit and instructions to the subject/caregiver if needed
15. Review the study instructions, including eDiary, use of body charts and approved bland, non-medicated, emollient/moisturizer use, with the subject/caregiver
16. Perform ECG
17. Schedule Visit 7 for Week 12/Day 84.

The investigator will mark the general location of all the EBS lesions on the appropriate body chart(s) at each study visit.

8.2.7. Visit 7 (Week 12/Day 85)

This visit must occur 12 weeks/84 days (±4 days) after Visit 2.

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

1. 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
2. Query the subject/caregiver about any changes in the subject's concomitant therapies since the previous visit and report changes on the appropriate form

3. Confirm the subject continues to comply with all study restrictions, is eligible to continue in the study and has followed all study instructions
4. Measure vital signs
5. Perform a urine pregnancy test for WOCBP
6. Identify any new lesions that appeared since last visit
7. Determine BSA of EBS lesions in the Assessment Area and new lesions (if new lesions exist) using the palmar method
8. Calculate the total BSA of all EBS lesions
9. Perform the IGA evaluation on the Assessment Area
10. Dispense a blister lancing kit and instructions to the subject/caregiver if needed
11. Review the study instructions, including eDiary, use of body charts and approved bland, non-medicated, emollient/moisturizer use, with the subject/caregiver
12. Schedule Visit 8 for Week 16/Day 113.

The investigator will mark the general location of all the EBS lesions on the appropriate body chart(s) at each study visit.

8.2.8. Visit 8 (Week 16/Day 113); end of the study

This visit must occur 16 weeks/112 days (±4 days) after Visit 2.

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

1. 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
2. Query the subject/caregiver about any changes in the subject's concomitant therapies since the previous visit and report changes on the appropriate form
3. Confirm the subject continues to comply with all study restrictions, is eligible to continue in the study and has followed all study instructions
4. Measure vital signs
5. Identify any new lesions that appeared since last visit
6. Determine BSA of EBS lesions in the Assessment Area new lesions (if new lesions exist) using the palmar method
7. Calculate the total BSA of all EBS lesions
8. Measure the LSA of the Reference Lesion
9. Perform the IGA evaluation on the Assessment Area
10. Collect blood & urine samples for clinical laboratory tests
11. Perform a urine pregnancy test for WOCBP
12. Take standardized color photographs
13. Perform ECG
14. Discharge the subject from the study.

The investigator will mark the general location of all the EBS lesions on the appropriate body chart(s) at each study visit.

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. At Visit 1 (Week -6), for each subject the investigator will determine if the subject has EBS lesions that fulfill the inclusion criteria.

The EBS lesions must be on one or both of the following body areas:

- Localized involvement:
  - plantar or palmar areas only
  - plantar areas where >25% of the area has hyperkeratosis that has been present for greater than 12 weeks are excluded.
- Generalized involvement:
  - Arms from the shoulder to the tips of the fingers
  - Legs from the hip to the tips of the toes
  - Front and back of the torso, including the neck from the mandibular line in the front and the hairline in the back, to the beltline

The Assessment Area of EBS lesions to be treated must be ≥2% and ≤30% BSA at Visit 1 (Week -6) for the subject to be enrolled and at Visit 2 (Week 0) for the subject to be eligible for randomization. The area being treated must not exceed 30% BSA at any time.

Between Visit 1 (Week -6) and Visit 2 (Week 0) the status of EBS lesions may change, therefore, at Visit 2 (Week 0), the investigator will evaluate each subject to determine which of the following categories describe the subject's EBS lesions identified at Visit 1 (Week -6):

1. The V1 Assessment Area lesions do not meet the protocol requirements for the subject to be eligible for randomization, and the subject does not have EBS lesions that meet the requirements
2. The V1 Assessment Area lesions meet the protocol requirements for the subject to be eligible for randomization
3. The V1 Assessment Area lesions do not meet the protocol requirements for the subject to be eligible for randomization, but the subject has additional/other EBS lesions that meet the requirements. The Assessment Area is re-defined.

At Visit 2 (Week 0), the investigator will discharge subjects from the study who are in category 1.

At Visit 2 (Week 0), for subjects who are in category 2 or 3 the investigator will follow the procedures below to identify EBS lesions to be treated.

The investigator will mark the general location of all the EBS lesions on the appropriate body chart(s) at each study visit.

8.3.1. Occluded Lesions

The scalp, groin and areas where, in the investigator's opinion, the study medication might become occluded are excluded from treatment with study medication.

8.4. Subject Instructions

An investigational center staff member will dispense the following items to each subject/caregiver to help with compliance to the study requirements as needed at a specified visit schedules

- Subject Instruction Sheet, and blister lancing instructions
- eDiary instructions and body charts.

Updated information and instruction for subjects will be provided as necessary.

Throughout the study, the subjects should:

- Continue their routine cleansing regimen; however, products that, might affect the signs or symptoms of EBS being evaluated (*e.g.*, medicated cleansers, MediHoney, Silvadine cream 1%, CBD oil, etc.) are prohibited. 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.
    - Subjects with evening bathing habits (e.g. pediatric patients), should bathe prior to study medication application and modify evening habits such that sufficient time is left to allow for at least 1 hour before dressing the lesions (if applicable), wearing clothing or retiring to bed to allow for absorption of medication. Loose fitting garments (e.g. robes) that do not rub against the treated areas are acceptable within the hour.
- Continue their routine cosmetics and skin care products
- 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
- Apply study medications to lesions identified by the Investigator that require treatment as described in section 7.5.4:
    - If the lesion is identified as part of the Assessment area, apply study medication to the lesions daily, in the evening, **regardless of lesion resolution**
    - If the lesion is NEW (appears after Visit 2), apply study medication to the lesion **until lesion resolution**
        - Make note using subject body charts any NEW lesions requiring treatment that appear in between study visits (not to exceed 30% BSA)

- Not wear tight clothing or retire to bed for at least 1 hour post application to allow for absorption of medication.
- Use only a bland, non-medicated emollient/moisturizer or routine cleansing products (e.g. Emu oil, Aquaphor, bleach baths, topical antiseptics) to treat EBS lesions as described in sections 7.5.3 & 7.5.4
- For at least 6 hours after a study medication application, DO NOT:
    - Wash/submerge the treated EBS lesions
    - Apply any topical products to the treated EBS 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
- Bring the subject instruction sheet and all study medication tubes with them to each visit.

On study visit days, the subjects should:

- Wear appropriate clothing to ease the photography procedures
- Starting with Visit 3 (Week 1), not apply the study medication or any topical products to the treated EBS lesions within 6 hours prior to a study visit.

8.5. EBS Lesion Care

8.5.1. Blister lancing kit

At Visits 1-7, an investigational center staff member will dispense a 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 on the face), 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

The following section applies to all EBS lesions. Bandaging may be a part of a subject's routine lesion care. Because EB skin may be more fragile in the heat and humidity and due to the fact that there is considerable variation in how and when lesions are dressed and the types of dressings used, subjects should generally be discouraged from bandaging their lesions during their participation in the study. However, bandaging is not prohibited provided the subject maintains their current bandaging routine and remains consistent throughout their participation in the study. Subjects should indicate their bandaging routine which will be recorded in the eCRF as follows:

1) The subject never bandages their EBS lesions
2) The subject occasionally bandages their EBS lesions when:
    a. The lesion requires protection from further trauma or contact and friction from clothes.
    b. The lesion is draining or bleeding.
    c. The lesion is painful, and a dressing may improve comfort.
3) The subjects always bandages their EBS lesions

Note: All bandaging is prohibited 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.

8.6. Subject Diary

At Visit 2 (Week 0), an investigational center staff member will explain the use of the electronic diary (eDiary) to each subject/caregiver. The eDiary will be used to collect daily information regarding:

- Study medication application frequency compliance
- Blister lancing compliance
- New lesions that develop in between study visits
- Bandage use
- Use of routine cleansers
- Pruritus Severity
- Pain Severity
- Mobility

At Visit 2 an investigational center staff member will register each subject who is randomized into the eDiary in the IRT system.

At Visits 3-7 an investigational staff member will reinforce the instructions for proper use of the eDiary with each subject/caregiver. Specifically, staff will ensure each subject/caregiver understands the palmar method for BSA% measurement to estimate new lesions that develop in between study visits and record the information in the eDiary. Staff will also emphasize the importance of not exceeding 30% BSA being treated at any time throughout the treatment period 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.

8.7. STUDY DURATION

The duration of study participation for a subject is anticipated to be a maximum of 158 days. This includes the up to 6-week screening period, an 8-week treatment period and an 8-week no-treatment follow-up period. The final study visit (Visit 8/Week 16) has a maximum allowable visit window of 4 days.

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

8.8. STUDY MEDICATIONS

8.8.1. Study medication identity

The study medications are yellow ointments that are indistinguishable in physical appearance. The study medications must be stored in a secure area with limited access under appropriately controlled and monitored storage conditions.

Study Medication Information		
Study medication name	Diacerein (CCP-020) 1% Ointment	Control Ointment
Manufacturer	TWi Pharmaceuticals, Inc., Taoyuan City, Taiwan	
Diacerein concentration (%)	1	0
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 8 weeks	

8.8.2. Study medication formulation

	Ingredients	Function	Specification	Proposed Clinical Trial Formulation (% w/w)
Diacerein (CCP-020) 1% Ointment	Diacerein	Active	EP monograph 2409	1.0
	Mineral oil, light, NF	Ointment base	NF	12.0
	Petrolatum, white, USP	Ointment base	USP	84.5
	Cetyl alcohol, NF	Thickener	NF	2.0
	Ethylparaben, NF	Preservative	NF	0.5
Control Ointment	FD&C Yellow #5, AL 15% - 17%, Aluminum Lake (5175)	Colorant	EU 231/2012	0.025
	Mineral oil, light	Ointment base/ skin protectant	NF	12.0
	Petrolatum white	Ointment base/ skin protectant	USP	85.475
	Cetyl alcohol	Thickener	NF	2.0
	Ethylparaben	Preservative	NF	0.5

8.8.3. Study medication packaging and labeling

The study medications are yellow colored ointments and will be packaged in identical appearing, aluminum tubes that each contain 30 grams of study medication.

A bulk supply of each 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 carton will be labeled with a two-part label. One part of the label remains attached to the carton, the other part (tear-off) is separated and attached to the subject's drug accountability log when the tube is dispensed.

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

- Tube number
- Protocol number
- Storage conditions
- Instructions for use
- Sponsor information
- Investigational drug warning
- Space to enter site number
- Space to enter subject number.

Each study medication tube will be labeled with a one-part label that remains attached to the tube and shows at least the following:

- Tube number
- Protocol number
- Investigational drug warning
- Space to enter site number
- Space to enter the subject number.

8.8.4. Method of treatment assignment

Prior to the start of the study, Castle Creek Pharmaceuticals, LLC or a designated third party will generate a list of randomization numbers that shall be transmitted to the assigned clinical packaging organization for study medication labeling.

The randomization list will be stored with access limited to designated personnel for study medication labeling. The randomization list will be made available as appropriate to un-blind the database.

8.8.5. 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 Visit 2 (Week 0), after the subject is randomized and the assigned study medication tubes have been identified an investigational center staff member will weigh each tube of study medication (without the carton and with the cap) to the nearest 0.1 gram then give the tube(s) and the carton(s) of study medication to the subject/caregiver.

An investigational staff member will also weigh the study medication tube used for the first study medication to the nearest 0.1 gram after the application.

At Visits 3-5, examine the tube(s) of study medication dispensed to the subject/caregiver, and weigh each opened tube of study medication (without the carton and with the cap) to the nearest 0.1 gram.

Collect tubes and cartons that do not contain a useable amount of study medication. Weigh the returned study medication tubes (without the carton and with the cap).

Dispense an appropriate number of study medication tubes with cartons to the subject/caregiver. Weigh each tube of study medication (without the carton and with the cap) to the nearest 0.1 gram.

At Visit 6 (Week 8), collect all study medication tubes and, if possible, cartons from the subject/caregiver and weigh all the tubes (without the carton and with the cap), whether they were opened or not, to the nearest 0.1 gram.

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 eCRF. 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.

8.8.6. Study medication application

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

At Visit 2 (Week 0), an investigational center staff member will instruct the subject/caregiver on the appropriate application technique. The subject/caregiver will perform the first study medication application and a staff member will observe the application. The staff member must ensure the study medication tube is weighed before AND after the first application.

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.

At Visit 2 a staff member should monitor the subject for at least 20 minutes after the first application to detect any immediate adverse events.

8.8.7. 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.

8.8.8. 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.

If the subject does not apply the study medication once daily to the assessment area for more than seven consecutive days, the subject must be removed 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 eCRF. These subjects should be withdrawn from the study.

8.9. Study medication Management

8.9.1. 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.

8.9.2. 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.

8.10. Other Study Supplies

Castle Creek Pharmaceuticals, LLC (or designee) will provide the following items to each investigational center prior to the initiation of subject enrollment:

- Supplies and instructions for collecting, labeling, shipping and result reporting for the clinical laboratory tests
- Urine pregnancy tests
- Supplies and instructions for blister lancing
- Equipment, supplies and training for taking standardized photographs
- Other supplies as identified by the study site.

8.11. Blinding

8.11.1. Verification of blinding

Blinding of the study medications is important for validity of this study. This study uses a double-blind design. The study medications are indistinguishable in appearance, packaging and labeling.

8.11.2. Un-blinding the study medication

Blinding is important for validity of this clinical study. However, the blind may be broken in the event of a medical emergency, in which knowledge of the study medication identity is critical to the management of the subject's course of treatment. Before breaking the blind the investigator should determine that the information is necessary (*i.e.*, that it will alter the subject's immediate course of treatment). In many cases, particularly when the emergency is clearly not study medication-related, the problem may be effectively managed by assuming that the subject is receiving an active study medication without the need for un-blinding. If deemed necessary to break the blind for a study subject, the investigator has the final decision and unilateral right to break the blind and should notify the Castle Creek Pharmaceuticals, LLC Medical Monitor as soon as possible after breaking the blind for a subject.

To identify a subject's study medication the investigator or designee must electronically contact the Medpace, Inc. IRT system to identify a subject's study medication assignment. Record the date of un-blinding, the reason for un-blinding and the initials of the investigational center staff member who performed the un-blinding on the subject's study file.

Any subject whose blind has been broken must be discharged from 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.

9. STUDY ASSESSMENTS

The investigator, or a designated and appropriately trained staff member, will perform the efficacy assessments according to the schedules noted below.

The same individual should perform the assessments for a given subject throughout the study. If this becomes impossible, an appropriate designee with overlapping experience with the subject and study should perform the assessments.

Similar lighting conditions and subject positioning should be used for all evaluations for a given subject.

9.1. Effectiveness Evaluations

For this study an EBS lesion is defined as a blister, or the crust and/or erosion arising from a previous blister, and the immediately surrounding intense erythema.

9.1.1. Investigator's Global Assessment (IGA)

The IGA is the investigator's (who must be a physician or Physician's Assistant/nurse practitioner in dermatology) clinical assessment of the average overall severity of all the EBS lesions, considered together, at a particular time point. The investigator should NOT refer to any other assessments, study photographs or notes to assist with these assessments.

At Visits 1-8, the investigator will assess the subject's EBS lesions using the scale below and report the one integer that best describes the average overall severity of all the EBS lesions considered together.

Investigator's Global Assessment	
Score	**Definition**
0	Clear: No blisters, no erosions, no crusting, no erythema and/or pigmentary changes may be present
1	Near Clear: Two or few small blisters, faint signs of erosion may be present, barely perceptible evidence of crusting, slight erythema
2	Mild: Predominantly small and some medium blisters, minimal erosions, clear crusting, definite well-defined erythema
3	Moderate: Mix of small and medium blisters, definite erosions, limited areas of crusting, marked erythema
4	Severe: Mix of medium and large blisters, marked erosions, ulceration may be present, marked and extensive crusting, intense erythema

For this evaluation, a blister is defined as a fluid filled thin-walled structure.

Blister size is defined as:

- Small: visible to ≤1cm^2
- Medium: >1cm^2 to ≤2cm^2
- Large: >2cm^2.

At Visit 1 (Week -6) for a subject to be enrolled, and at Visit 2 (Week 0) for the subject to be randomized, the IGA must be ≥3.

At Visit 2 (Week 0) the investigator must complete the IGA prior to the first study medication application.

The IGA must be completed prior to the evaluator reviewing any study photographs.

9.1.2. Assessment Area

At Visit 1, the investigator or designee will identify an "Assessment Area" of EBS lesions to be treated. The Assessment Area is a targeted treatment area from which all IGA assessments and the primary endpoint will be made. The Assessment Area does not need to be contiguous. At Visit 1 (Week -6) for a subject to be enrolled, and at Visit 2 (Week 0) for the subject to be randomized, the Assessment Area must be ≥2% body surface area (BSA), the IGA of the Assessment Area must be ≥3, and the EBS lesions must be in one or both of the following body areas:

- Localized: plantar and/or palmar areas (plantar areas where >25% of the area has hyperkeratosis that has been present for greater than 12 weeks cannot be included as part of the Assessment Area)
- Generalized: arms, legs, torso, hands and feet (scalp, groin and areas where, in the investigator's opinion, the study medication might become occluded cannot be included as part of the Assessment Area)

In this study, the palmer method will be used to determine BSA of EBS lesion. 1% BSA is defined as the area of the subject's hand held flat, including the thumb and fingers held together. Investigational drug will be applied to the Assessment Area for the entire duration of the study 8-week treatment period.

The Assessment Area will remain fixed for the duration of the study with the notable exception at Visit 2 (see also Section 8.3). At Visit 2, the Investigator may re-designate the Assessment Area assigned at Visit 1 for purposes of inclusion provided all criteria noted above are satisfied. All IGAs and the primary endpoint will be graded from the Assessment Area.

9.1.3. Treatment Area

For purposes of this study, the Treatment Area is established after Visit 2 and is defined as all BSA where treatment is applied throughout the treatment period of the study. The treatment area may increase or decrease subsequent to Visit 2 depending on the emergence of blisters and is always inclusive of the Assessment Area. The Treatment Area is NOT the area from which the determination of BSA of EBS lesions or IGA are to be assessed; only the Assessment Area will be assigned an IGA grade and will be assessed for the BSA of EBS lesions. Additional areas of EBS lesions may be added to the Treatment Area during the Treatment Period but Treatment Area cannot be more than 30% BSA at any time. Lesions that are not being treated with study medication (i.e. occluded) are not considered as part of the treatment area. Note: A subject may never have a defined Treatment Area if the subject does not develop lesions outside of the Assessment Area during the Treatment Period.

9.1.4. Reference Lesion Surface Area (LSA)

At Visit 2 the investigator will identify one of each subject's EBS lesions, the Reference Lesion, for measurement of the LSA. The Reference Lesion should have a severity that is approximately equal to the IGA grade, however the investigator is NOT required to perform a separate IGA evaluation for the Reference Lesion.

The investigator must clearly mark the location of the Reference Lesion on the subject's body chart (*e.g.*, using landmarks and distance measurements) so the lesion can be accurately and consistently identified at subsequent visits.

At Visits 2 (Week 0), 6 (Week 8) and 8 (Week 16) the investigator will measure the length and width of the Reference Lesion using the ruler provided (or an equivalent) as follows:

- Length (*i.e.*, the length of the longest axis) to the nearest millimeter (mm)
- Width (*i.e.*, the length of the longest axis perpendicular to the length) to the nearest mm.

At Visit 2 the Lesion Dimensions must be measured prior to the first study medication application.

At Visits 6 and 8 the investigator will measure the Reference Lesion on approximately the same axes for length and width. The investigator should report 0mm for the measurements if the Reference Lesion is clear at Visits 6 or 8.

The length and width will be used to estimate the surface area of the Reference Lesion.

9.1.5. Body surface area (BSA) of the Assessment Area/Treatment Area/All EBS Lesions

All BSA measurements collected at the study site will be obtained by the investigator (who must be a physician, physician's assistant or dermatology nurse practitioner). The investigator should NOT refer to any other assessments, study photographs or notes to assist with these assessments. For this study 1% BSA is defined as the area of the subject's hand held flat, including the thumb and fingers held together.

The BSA of the Assessment Area will be collected for all lesions included within the Assessment Area using the palmar method.

The BSA of the Treatment Area will be collected for all NEW lesions that appear after Visit 2 (if new lesions exist) using the palmar method. The subject/caregiver will use the palmar method for BSA% measurement to estimate new lesions that appear after Visit 2 in between study visits (if new lesions exist) and record the information in the eDiary.

The total BSA of EBS Lesions will be collected for all lesions that are NOT being treated with study medication (e.g. lesions that exceed 30% BSA or lesions that are occluded).

9.1.6. Pruritus Intensity (for Subjects aged 8 years and older)

The Pruritus Intensity Assessment is the subject's assessment of **pruritus at its worst** experienced **over the previous 24 hours** on all EBS lesions. *The subject should NOT refer to any other assessments to assist with these assessments.*

Starting at Visit 2 (Week 0) and **continuing each day** for the duration of the subject's study participation, the subject will report his/her experience of pruritus at its worst in an **electronic diary**.

This assessment should be completed just prior to the daily study medication application using the following scale:

Pruritus Intensity	
Instructions: The following question is about itch related to your epidermolysis bullosa simplex (EBS). Please select the number that best describes your experience with **itch** at its worst over the **past 24 hours**. Please select only one answer. There is no right or wrong answer to this question.	
Rate your **itch** at its worst over the past 24 hours.	0 ☐ **No itch at all** 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ **Worst possible itch**

9.1.7. Pain Intensity (for Subjects aged 8 years and older)

The Pain Intensity Assessment is the subject's assessment of **pain at its worst** experienced **over the previous 24 hours** on all EBS lesions. The subject should NOT refer to any other assessments to assist with these assessments.

Starting at Visit 2 (Week 0) and continuing each day for the duration of the subject's study participation, the subject will report the average overall intensity of pain in an electronic diary.

This assessment should be completed just prior to the daily study medication application.

Pain Intensity	
Instructions: The following question is about pain related to your epidermolysis bullosa simplex (EBS). Please select the number that best describes your experience with **pain** at its worst over the **past 24 hours**. Please select only one answer for each question. There is no right or wrong answer to this question.	
Rate your **pain** at its worst over the past 24 hours.	0 ☐ **No pain at all** 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ **Worst possible pain**

9.1.8. Mobility Assessment

The Mobility Assessment is the subject/caregiver's assessment of the subject's degree of mobility over the previous 24 hours. The subject/caregiver should NOT refer to any other assessments to assist with these assessments. The same individual, subject or caregiver, should perform all Mobility Assessments for a given subject for the duration of the study. Note that the assessment of pain and pruritus must be done by the subject.

Starting at Visit 2 (Week 0) and continuing each day for the duration of the subject's study participation, the subject/caregiver will report the subject's degree of mobility by answering a series of age-appropriate questions in the eDiary. This assessment should be completed at approximately the same time each day, just prior to the study medication application, using the following scale:

Score	Definition
1	Uses wheelchair (May stand for transfers, may do some stepping supported by another person or using a walker/frame)
2	Uses walker or frame: Without help from another person
3	Uses crutches: without help from another person
4	Uses sticks (*e.g.*, canes) (one or two): Without help from another person
5	Independent on level surfaces: Does not use walking aids or need help from another person (if uses furniture, walls, fences, shop fronts for support use 4 description). Requires rails for stairs
6	Independent on all surfaces: Does not use any walking aids or need any help from another person when walking over all surfaces including uneven ground, curbs, etc. and in a crowded environment
7	Crawling: Child crawls for mobility at home
8	Does not apply: For example, child does not complete the distance

This scale is assessed for 3 distances: 5 meters (yards); 50 meters (yards); 500 meters (yards).

9.2. 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.

9.2.1. Demographics/Medical History

At Visit 1 (Week -6), 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 Visit 1 (Week -6):

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

9.2.2. Vital Signs

At Visits 1-8 a qualified staff member will measure each subject's vital signs. At Visit 1 (Week -6) these measurements will be part of the physical examination. 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 (at Visit 1, 6 and 8)
- Weight (at Visit 1, 6 and 8).

Abnormal vital signs must be defined as clinically relevant (CR) or not clinically relevant (NCR) on the eCRFs.

9.2.3. Physical Examination

At Visit 1 (Week -6) and Visit 6 (Week 8) 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 (excluding EBS lesions)
- Cardiovascular system
- Respiratory system
- Head, eyes, ears, nose and throat
- Lymph nodes
- Gastrointestinal/Hepatobiliary (specifically assess for the presence of hepatomegaly and splenomegaly)
- Vital signs.

9.2.4. Clinical laboratory sampling

At Visits 1, 2, 4, 6 and 8 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. Non-fasting blood samples will be collected at all Visits. At Visit 2 (Week 0) the samples must be collected prior to the first study medication application. 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-GT	Eosinophils
Glucose	Lymphocytes

HbA1c
Lactate dehydrogenase (LDH)
Lipase
Potassium
Sodium
Total bilirubin
Total protein
Uric acid
Monocytes
Neutrophils

Complete Urinalysis

The results of the clinical laboratory tests will be reported on the laboratory's standard reports. The investigator 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 must date and initial every laboratory report.

The investigator must review the Visit 1 (Week -6) laboratory results for all the measured analytes for each subject prior to Visit 2 (Week 0). The subject must not be randomized at Visit 2 (Week 0) if any of the Visit 1 (Week -6) results are outside normal range for the laboratory AND, in the opinion of the investigator, CR.

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.

9.2.5. PK Sample Collection

Blood samples for Pharmacokinetic (PK) analyses of diacerein and rhein will be collected at the time points listed in the Study Flow Chart. Population PK modeling and PK/PD analyses will be performed according to a PK/PD analysis plan separate from this protocol and data permitting.

9.2.6. Genetic Confirmation of EBS

At Visit 1 (Week -6), the investigator or designee will obtain a blood or saliva sample to perform EBS genotyping from each subject, unless the subject provides written confirmation of a laboratory diagnosis of EBS.

Documentation (*i.e.*, a written laboratory report) of the presence of KRT5 and/or KRT14 or KRT5, KRT14, PLEC1, TGM5, PKP1, DSP, FERMT1, EXPH5, DST, KLHL24 is acceptable.

Genetic confirmation of EBS is required for a subject to be randomized at Visit 2.

Supplies and detailed instructions for obtaining these samples will be provided to investigational center prior to the initiation of subject enrollment.

9.2.7. Pregnancy tests

The investigator or designee will perform a urine pregnancy test for subjects who are WOCBP at Visits 1, 2, 4, 6, 7 and 8. 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 Visit 1 (Week -6) to be enrolled in the study and at Visit 2 (Week 0) to be randomized.

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

9.3. Other Evaluations

9.3.1. Standardized photography

At Visits 2, 6 and 8 standardized color photographs will be taken as outlined below. These photographs will be used to document the status of the EBS lesions being treated.

Standardized photographs will include:

- Four ½ body images (*i.e.*, anterior and posterior; right-side lateral and left side lateral)
- Body charts including plantar chart.

Photography equipment, supplies and training will be provided to each investigator prior to the initiation of subject enrollment at her/his center.

9.3.2. 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.

9.4. 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 and genotyping measurement. 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.

	Screening Visit 1	**Visit 2**	**Visit 4**	**Visit 6**	**Visit 8**
Adults	**10 ml**	**10 ml**	**10 ml**	**10 ml**	**10 ml**
Children (<18 years)	**3.5 ml**	**3.5 ml**	**3.5 ml**	**3.5 ml**	**3.5 ml**

10. ADVERSE EVENTS

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

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 eCRF.

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 of the first study medication application until the subject's study participation is complete (Visit 8/Week 16) OR until 30 days after the subject's last study medication application, whichever is longer.

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 Visit 1 (Week -6) should not be reported as an adverse event unless the medical condition or signs or symptoms present at Visit 1 (Week -6) 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 or are present at Visit 1 (Week -6) 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.

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. 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.

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 Reporting/Adverse Events of Special Interest – Procedures for Investigators

10.5.1.1 Initial Reports

All SAEs/AESI, regardless of causality, occurring from the time of informed consent until 30 days following study completion OR until 30 days after the subject's last application of study medication, whichever is longer, must be reported to 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.

Safety Contact Information: Medpace Clinical Safety
Medpace SAE/AESI hotline – USA:
Telephone: +1-800-730-5779, ext. 2999 or +1-513-579-9911, ext. 2999
Fax: +1-866-336-5320 or +1-513-579-0444
e-mail: medpace-safetynotification@medpace.com

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 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.

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.

10.6. 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, whichever is longer, 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 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 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.

11. STATISTICAL ANALYSES

11.1. Analysis Populations

The Intent-to-Treat (ITT) Population will consist of all randomized subjects with at least one post-baseline BSA of EBS lesion assessment.

The Per Protocol (PP) Population will consist of all ITT subjects with a BSA of EBS lesions at Week 16 and without a major protocol violation that may interfere with the assessment of drug efficacy. Before data are released for statistical analysis, a blinded review of all data will be performed by the clinical team to identify protocol deviations that may potentially affect the results. At this time, it will be determined if patients and/or data should be excluded from the PP Population. The list of subjects or observations to be excluded from the PP Population, along with the reason for exclusion, will be finalized prior to database unblinding. The Safety Population will consist of all subjects who receive at least one application of study drug.

11.2. Data Analysis

A statistical analysis plan (SAP) will provide additional details on the approach to the analyses and data displays.

11.2.1. Missing Data Handling Methods

Missing data imputation will only be applied to the primary efficacy endpoint, the percentage of subjects with success defined as a ≥40% reduction in BSA of EBS lesions at Week 16, for analysis with the ITT Population. If a BSA value at Week 16 is missing, the value will be imputed using last observation carried forward (LOCF). Other sensitivity imputations will be used to test the robustness of this imputation method corresponding to a best-case and worst-case scenario. The best-case scenario will involve missing values at Week 16 being imputed as a success, while the worst-case scenario will involve missing

values at Week 16 being imputed as a failure. No missing data imputation will be applied to the secondary efficacy endpoints.

Adverse events with missing start dates will be considered as treatment-emergent unless the partial date excludes that possibility, e.g. the adverse event month is prior to the treatment infusion month. Otherwise, the first day of the month will be used to impute missing start days and January will be used to impute missing start months.

11.2.2. Subject Information

A detailed description of subject disposition will be provided. Descriptive summaries of demographic and baseline characteristics will be presented by treatment group based on the ITT Population.

11.2.3. Analysis of Efficacy

Descriptive summaries of efficacy endpoints will be presented by treatment group. The primary efficacy endpoint; the proportion of subjects who achieve success, defined as ≥40% reduction in body surface area (BSA) of EBS lesions from Visit 2 (Week 0) to Visit 8 (Week 16) will be analyzed with a CMH test, with treatment (Diacerein 1% Ointment or Control Ointment) as a factor, and genotype and age group (<8 and ≥8 years old) as strata. Estimated odds ratio and associated 95% confidence interval (CI) and p value will be provided.

Key Secondary efficacy endpoints include the following:

- The proportion of subjects achieving success on the Investigator's Global Assessment (IGA), where success on the IGA is defined as at least a 2-point reduction from Visit 2 (Week 0) to Visit 8 (Week 16).
- The proportion of subjects with ≥ 40% reduction in BSA of EBS lesions from Visit 2 (Week 0) to Visit 6 (Week 8).
- The proportion of subjects achieving success on the IGA, where success on the IGA is defined as at least a 2-point reduction from Visit 2 (Week 0) to Visit 6 (Week 8).
- The proportion of subjects with a reduction in overall pain intensity from Visit 2 (Week 0) to Visit 6 (Week 8).
- The proportion of subjects with a reduction in overall pruritus intensity from Visit 2 (Week 0) to Visit 6 (Week 8).

All key secondary efficacy endpoints will be summarized and listed by treatment group and visit. Count and percentage of subjects in each category will be presented. The percentage of subjects who achieve success in the IGA from baseline to Visit 6 (Week 16) will be analyzed using the same CMH test for primary endpoint. For other endpoints,

Analysis of Covariance (ANCOVA), Chi-square tests or logistic regression will be used for secondary efficacy endpoints, if appropriate. Some secondary efficacy endpoints can be dichotomized before the analysis. For example, for the endpoint 5-Point IGA, all subjects can be dichotomized based on if they have a 2-grade or more improvement in IGA at Visit 8 (Week 16) from baseline Visit 2 (Week 0). Details will be provided in the SAP.

Exploratory end points will be analyzed as described in the SAP.

11.2.4. Analysis of Safety

Safety measures will include the following assessments:

- Demographics\Medical History
- Adverse events and SAEs
- Vital Signs
- Physical Examination
- Clinical laboratory
- 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 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 parameters will be summarized similarly. Occurrence of significant laboratory abnormalities will be summarized by treatment. Physical examination and urine pregnancy tests data will be summarized and listed.

11.3. Interim Analysis

An interim analysis will be conducted by an independent data monitoring committee (DMC) after approximately 40 subjects have completed the study. Details regarding the conduct of the interim analyses will be specified in a separate document outside of this protocol (e.g. DMC charter). After each meeting, the DMC will advise whether any changes to the sample size or conduct of the study are necessary based on review of unblinded safety and efficacy data.

11.4. Sample Size Calculation

Suppose the percentage of subjects with ≥40% reduction in BSA of EBS lesions at Week 16 are 60% and 30%, in Diacerein 1% Ointment or Control Ointment, respectively. Based on a two-

sided, two-sample parallel design for large sample test of proportions with a power of 80% and significance level of 0.05[7], the sample size needed for a fixed sample size design without interim analysis and sample reconsideration is:

$$n_1 = n_2 = \frac{\left(z_{\alpha/2}+z_{\beta}\right)^2\left(p_1(1-p_1)+p_2(1-p_2)\right)}{(p_2-p_1)^2} = \frac{(1.96+0.84)^2\left(0.6\times(1-0.6)+0.3\times(1-0.3)\right)}{(0.6-0.3)^2} \approx 39.$$

One interim analysis is planned and sample size will be reconsidered then. We employ O'Brien and Fleming's method[7], and the sample size is inflated to:

$$n_1' = n_2' = n_1 R_B(2,0.05,0.2) = 39 \times 1.008 \approx 40,$$

in which $R_B(2,0.05,0.2) = 1.008$ is the O'Brien and Fleming's method constant for two-sided test with $\alpha = 0.05$ and $power = 1 - 0.2 = 0.8$.

Thus, at the interim analysis, the sample size per treatment group is $40/2 = 20$. The conditional power will be calculated at the interim analysis, based on which the sample size will be recalculated.

12. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

12.1. 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.

12.2. 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.

12.3. Institutional Review Board (IRB) and Ethic Committee (EC)

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.

12.4. Data Monitoring Committee

An interim analysis will be conducted by an independent data monitoring committee (DMC) after approximately 40 subjects have completed the study. Details regarding the conduct of the interim analyses will be specified in a separate document outside of this protocol (e.g. DMC charter). After each meeting, the DMC will advise whether any changes to the sample size or conduct of the study are necessary based on review of unblinded safety and efficacy data.

13. ETHICS

13.1. 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.

13.2. 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.

13.3. 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. 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.

14. DATA HANDLING AND RECORD KEEPING

14.1. 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 medical history/ physical examination, hematology, clinical chemistry and serology results, inclusion and exclusion criteria, drug administration, and a record of sample collection, hemodynamic measurements, clinical assessments, AEs, and final evaluation as appropriate.

Electronic eCRFs and subject diaries 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.

14.2. 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.

14.3. 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.

15. 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.

16. LIST OF REFERENCES

1. Salavastru, C.M., et al., Recommended strategies for epidermolysis bullosa management in Romania. Maedica (Buchar), 2013. 8(2): p. 200-5.

2. Hon, K.L., et al., Age and etiology of childhood epidermolysis bullosa mortality. J Dermatolog Treat, 2015. 26(2): p. 178-82.

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.

4. Fine, J., Epidemiology of Inherited Epidermolysis Bullosa Based on Incidence and Prevalence Estimates From the National Epidermolysis Bullosa Registry. JAMA Dermatology, 2016: p. 2473.

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.

7. Chow, SC, Shao, J, and Wang, HS. Sample size calculation in clinical research. 2011. John Wiley & Sons, Inc.