STATISTICAL ANALYSIS PLAN

A MULTI-CENTER STUDY TO EVALUATE THE PHARMACOKINETICS OF DIACEREIN AND RHEIN AND THE SAFETY OF DIACEREIN AFTER MAXIMUM USE, TOPICAL ADMINISTRATION OF CCP-020 (DIACEREIN 1% OINTMENT) TO PATIENTS WITH EPIDERMOLYSIS BULLOSA (EB)

Protocol Number:	CCP-020-101
EudraCT No:	2018-000439-29
IND Number:	131,384
Study Medication:	CCP-020 (Diacerein 1% Ointment)
Sponsor:	Castle Creek Pharmaceuticals, LLC 6 Century Drive, 2nd Floor Parsippany, NJ 07054
Current Protocol:	V1.0 / February 07, 2018
SAP:	V1.0 / January 7, 2019

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

Protocol Number:	CCP-020-101
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This Statistical Analysis Plan has been reviewed and approved by:

[redacted]

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1 SUMMARY OF CHANGES

SAP Version History		
Version	**Date**	**Description of Changes**
0.1	March 21, 2018	Original Document
0.2	October 26, 2018	Update Section 5.1 by adding Nuventra which was contracted to perform the statistical analysis of PK data
0.3	December 28, 2018	Accepted revision
1.0	January 7, 2019	Deleted language about PK analysis in Section 5.1

2 INTRODUCTION

This Statistical Analysis Plan (SAP) provides a description of the statistical methods and procedures to be implemented for the analyses of data from Castle Creek Pharmaceuticals, LLC Protocol CCP-020-101. Any deviations from this analysis plan will be substantiated by sound statistical rationale and will be documented in the final clinical study report.

3 STUDY OBJECTIVES

3.1 Primary Objective

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

3.2 Secondary Objectives

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

4 STUDY OVERVIEW

4.1 Study Design

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

1. 8-10 adolescent and adult patients with EB (aged 12 and older)

   a. EBS subjects: lesions encompassing $\geqslant$ 2% BSA for study entry. Diacerein application area to be $\geqslant$ 5% BSA and include lesioned and non-lesioned skin (if lesions account for less than 5% BSA); however, topical administration must be $\leqslant$ 30% BSA.

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

2. 8-10 infants/children with EB (aged 6 months to 11 years, inclusive)

   a. EBS subjects: lesions encompassing ⩾ 2% BSA for study entry. Diacerein application area to be ⩾ 5% BSA and include lesioned and non-lesioned skin (if lesions account for less than 5% BSA); however, topical administration must be ⩽ 30% BSA.

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

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

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

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

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

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

Eligible, assented (consented via guardian) infant/child patients aged 6 months to 11 years, inclusive with EB lesions encompassing ⩾ 2% BSA will be enrolled in the study. On Day 1,

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

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

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

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

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

Figure 1: Study Design

Cohort 1 (adolescents and adults)

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

Cohort 2 (infants and children*)

	CCP-020 (Diacerein 1% Ointment) Application		
Screening	**Day 1**	**Day 3 - Day 9**	**Day 10**
	PK Blood Sampling Times		
	Pre-dose, 1, 2, 4, 6, and 8 hours post-dose	None	Pre-dose, 1, 2, 4, 6, and 8 hours post-dose

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

4.2 Randomization and Blinding

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

4.3 Investigational Medicinal Products

Diacerein 1% Ointment will be administered topically. The study medication must be stored in a secure area with limited access under appropriately controlled and monitored storage conditions.

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

4.4 Duration of Treatment

The duration of treatment is 10 Days; EB (excluding DEB/JEB) patients that complete this study or receive at least one dose of study drug will be eligible for rollover into an open-label extension study conducted under a separate protocol (Study CCP-020-301).

5 CRITERIA FOR EVALUATION

5.1 Pharmacokinetics

The PK statistical analysis will be performed by Nuventra using their Bioanalystical methods and standards.

5.2 Safety

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

6 STATISTICAL METHODOLOGY

6.1 General Statistical Considerations

Descriptive statistics (n, mean, standard deviation [SD], coefficient of variation [CV%], minimum, median, and maximum) will be used to summarize the continuous data.

Individual subject data will be listed by subject identification, cohort and EB type, and, if applicable, by assessment time.

Unless specified otherwise, data will be used as it is reported.

6.2 Analysis Populations

6.2.1 Safety Population

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

6.2.2 Pharmacokinetic Concentration Analysis Set

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

6.2.3 Pharmacokinetic Evaluable Population

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

6.3 Subject Disposition

Subject disposition will be presented overall and by cohort and EB type using randomized subjects.

Number and percentage of subjects who received any amount of drug, who are in each analysis population, who complete the study, and who withdraw early from the study will be presented. The primary reasons for early withdrawals will also be tabulated. The number of randomized subjects within each group will be used as the denominator for the percentage calculations.

6.4 Eligibility Criteria

Eligibility criteria (inclusion/exclusion) will be listed based on the screened subjects.

6.5 Protocol Deviation

Subjects with protocol deviations will be listing for Safety Population.

6.6 Demographic and Baseline Characteristics

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

Demographics and baseline characteristics will be summarized descriptively overall and by cohort and EB type for Safety Population.

Demographic and baseline characteristics include, but are not limited to, age at informed consent, gender, race, ethnicity, and body weight. The baseline is defined as the values at Screening. If the value is missing, the last reading prior to dosing will be used as baseline.

6.7 Medical History and Genotyping Sample

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

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

Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology and data will be summarized by cohort and EB type. At each level of summation (overall, system organ class, preferred term), subjects reporting more than one event are counted only once. A subject may contribute to more than one preferred term.

All data for medical history and genotyping sample will be listed for Safety Population.

6.8 Concomitant Medications/Procedures

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

All concomitant medication verbatim terms will be coded using the World Health Organization Drug Dictionary. The numbers and percentages of subjects taking concomitant medications will be summarized by anatomic and therapeutic chemical term and preferred term for each cohort and EB type and overall using Safety Population.

All concomitant medications will also be listed.

6.9 Treatment Compliance/Drug Accountability

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

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.

Data will be listed for Safety Population.

6.10 Diary

Diary data will be listed by subject based on Safety Population.

6.11 Safety Analyses

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

All safety analyses will be conducted on Safety Population.

6.11.1 Adverse Events

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.

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.

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

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

6.11.2 Serious Events

Any untoward medicinal occurrence or effect that at any dose:

- Results in death,
- Is life-threatening,
- Requires hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity, or
- Is a congenital anomaly or birth defect.

6.11.3 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, and
- Jaundice.

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

6.11.4 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as those AEs that start on or after the first dose of study medication, or occur prior to the first dose and worsen in severity or relationship to study medication after the first dose.

Adverse events will be coded and classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). Subjects with more than one AE for a given SOC or PT will be counted only once for that term using the most severe incident.

An overview of AEs will be provided by cohort and EB type and overall for the following information:

- All AEs,
- All TEAEs,
- Study drug-related TEAEs,
- Maximum severity of TEAEs,
- Maximum severity of drug-related TEAEs,
- All AESI, if applicable,
- Drug-related AESIs, if applicable,
- Maximum severity of AESIs, if applicable,
- All treatment-emergent SAEs,
- Drug-related treatment-emergent SAEs,
- Death due to TEAEs,
- Withdrawals due to TEAEs, and
- Withdrawals due to study drug-related TEAEs.

TEAEs, if applicable, and AESI, will be summarized by treatment at onset and EB type and overall. The following summaries will be presented:

- TEAEs by SOC and PT;
- TEAEs by SOC, PT, and relationship to the study drug;
- TEAEs by SOC, PT, and maximum severity;
- TEAEs by SOC, PT, maximum severity, and the relationship to the study drug.

All AEs will be listed. If any serious adverse events (SAEs), AEs leading to death, AEs leading to the discontinuation of study drug occur, they will be listed in separate data listings.

6.11.5 Vital Signs and Weight

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

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

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

The observed values will be summarized by cohort and EB type and scheduled time point. Change and percentage change from baseline to each scheduled post-dose time point will also be summarized similarly. Baseline is defined as the last measurement prior to the first dosing.

All data will also be listed for Safety Population.

6.11.6 Laboratory Assessments

Subjects will not be required to fast prior to laboratory sample collection.

6.11.6.1 Hematology

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

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

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

The observed values will be summarized by cohort and EB type and scheduled time point. Change and percentage change from baseline to each scheduled post-dose time point will also be summarized similarly. Baseline is defined as the last measurement prior to the first dosing.

All data will also be listed for Safety Population.

6.11.6.2 Blood Chemistry

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

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

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

The observed values will be summarized by cohort and EB type and scheduled time point. Change and percentage change from baseline to each scheduled post-dose time point will also be summarized similarly. Baseline is defined as the last measurement prior to the first dosing.

All data will also be listed for Safety Population.

6.11.6.3 Urinalysis

A complete urinalysis will be performed at the timepoints listed in the Study Flow Chart.

The observed values will be summarized by cohort and EB type and scheduled time point. Change and percentage change from baseline to each scheduled post-dose time point will also be summarized similarly. Baseline is defined as the last measurement prior to the first dosing.

All data will also be listed for Safety Population.

6.11.6.4 Pregnancy Screen

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

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

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

All data will also be listed for Safety Population.

6.11.7 Physical Examination

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

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

Data will be listed for Safety Population.

6.11.8 Follow-Up Phone contact

Data will be listed for Safety Population.

7 GENERAL INFORMATION

The mock-ups for SAS-generated tables/figures/listings will be prepared in a separate document and finalized before database lock for the study.

7.1 Statistical Software

The creation of analysis datasets and all statistical analyses will be done using SAS® version 9.4 or higher. The Medpace standard operating procedures will be followed for the validation of all SAS programs and outputs.

7.2 Format

The format of tables, listings, and figures will be described in a stand-alone programming specifications document

8 APPENDIX

8.1 Study Flow Chart

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

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