STATISTICAL ANALYSIS PLAN

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

Investigational Product: Diacerein 1% Ointment
Protocol Number: CCP-020-302

Sponsor:
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Version Number: 1.0
Date: 17 December 2019

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SIGNATURE PAGE

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We, the undersigned, have reviewed and approve this Statistical Analysis Plan.

Signature	Date
[redacted]	18-Dec-2019
	12/17/2019

Chief Medical Officer and Senior Vice President of Research and Development
Castle Creek Pharmaceuticals, LLC

VERSION HISTORY

Version	Date	Description
1.0	17 Dec 2019	Original signed version

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
AESI	Adverse Event of Special Interest
BSA	Body Surface Area
CSR	Clinical Study Report
DRESS	Drug reaction with eosinophilia and systemic symptoms
EBS	Epidermolysis Bullosa Simplex
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
ICH	International Conference on Harmonization
MedDRA	Medical Dictionary for Regulatory Activities
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operation Procedure
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization

1. INTRODUCTION

The purpose of this document is to provide a description of the statistical methods and procedures to be implemented for the analysis of data from protocol number CCP-020-302. This document is based on the Global Protocol Amendment 3.1 document. If circumstances arise during the study such that more appropriate analytic procedures become available, the statistical analysis plan (SAP) may be revised. Any revisions to the SAP (both alternative and additional methods) will be made prior to database lock. Reasons for such revisions will be described in the final Clinical Study Report (CSR).

2. OVERVIEW

2.1. Objectives

The primary objective of the study is to evaluate the long-term safety and tolerability of diacerein 1% ointment for 2 treatment cycles in subjects with epidermolysis bullosa simplex (EBS) that were previously enrolled in studies CCP-020-301 or CCP-020-101.

2.2. Trial Design

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

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

Subjects/caregivers will apply the assigned study medication to all EBS lesions, including any new EBS lesions that develop (up to 30% BSA), once daily, every evening until the lesions resolve for 8 weeks. After 8 weeks, the subject will return to the site to return the study medication and remain off treatment for 8 weeks. The investigator will re-evaluate the subject after 8 weeks off therapy and if any of the subject's lesions require treatment (up to 30% BSA) the subject will begin another treatment cycle for a maximum of two 8-week treatment cycles allowed in a 52 week period.

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

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

A detailed schedule of procedures is provided in Table 1.

Table 1: Study Flow Chart

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

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

3. STUDY ENDPOINTS

3.1. Safety Endpoints

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

3.1.1. Adverse Events

Adverse events, which include clinical laboratory test variables, will be monitored and documented from the time the subject signs an informed consent AND has any study related procedure conducted, until the subject's study participation is complete OR until 30 days after the subject's last study medication application, whichever is longer.

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

All AEs that occur after the first study medication application in the CCP-020-302 study will be considered treatment-emergent adverse events (TEAEs).

In concert with system-organ classification (SOC) defined by Medical Dictionary for Regulatory Activities (MedDRA) 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

Each AE shall be evaluated for the severity, seriousness, duration, resolution, action taken and its relationship with the study medication.

3.1.2. Safety Laboratory Evaluations

At the timepoints specified in the Study Flow Chart, a qualified staff member will collect blood and urine samples for clinical laboratory analysis.

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

The following tests will be performed:

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

3.1.3. Vital Signs

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

- Body temperature
- Pulse rate
- Respiration rate
- Blood pressure (systolic and diastolic) after the subject sits quietly for at least 5 minutes
- Height
- Weight

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

3.1.4. Electrocardiogram (ECG) Monitoring

Single 12 lead ECGs will be performed as outlined in the Study Flow Chart using sensitive electrodes ensuring the subject's skin is not harmed from the procedure (e.g. SofTouch™ Electrodes). The ECGs will be performed on subjects in supine position.

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

The following ECG data will be collected:

- Heart rate
- PR interval
- QRS duration
- QT interval
- RR interval
- Overall Interpretation

4. ANALYSIS POPULATIONS

4.1. Safety Population

The Safety Population will consist of all subjects who receive at least one application of study drug. All safety summaries and analyses will be conducted using the Safety Population.

5. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

Medpace is responsible for the statistical analyses for this trial. The statistical planning and conduct of analyses of the data from this trial will follow the principles defined in relevant ICH-E9 guidelines and Medpace's Biostatistics SOPs. All tables, figures, and listings will be generated with SAS® (SAS Institute Inc. Cary, North Carolina, USA) Version 9.3 or higher and printed using a Rich Text Format (RTF) file format.

5.1.1. Summary Statistics

Categorical data will generally be summarized with counts and percentages of subjects. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, minimum, and maximum.

5.1.2. Evaluation of Center Effect

Due to the design, objectives, and sample size of the trial, center effects will not be evaluated.

5.1.3. Assessment Windows and Analysis Day

In the descriptive statistics of safety endpoints, only measurements from scheduled visits will be used in the analysis.

For analysis purposes, if the event date is on or after the baseline/initial study visit date, the study day is defined as follows:

Study Day = Event date – Initial study visit date + 1

Therefore, the day of the first study visit will be Day 1. If the event date is prior to the initial study visit date, the addition of 1 will not be included in the calculations; thus, there will be no Day 0.

5.1.4. Assessments Corresponding to Cycle 1 End and Cycle 2 Start

When the End of Cycle visit corresponding to cycle one occurs on the same day as the Cycle Start visit corresponding to cycle two, the assessments will be analyzed in the following manner:

- For adverse events having a start date on the Cycle 1 end date / the Cycle 2 start date, the adverse event will be attributed to Cycle 2.
- For compliance assessments in which a subject reported applying study medication on the Cycle 1 end date / the Cycle 2 start date, the application will be attributed to Cycle 2.

- For clinical assessments (during which the percent BSA of all active lesions that require treatment is determined) occurring on the Cycle 1 end date / the Cycle 2 start date, the assessment will be attributed to both the end of Cycle 1 and the start of Cycle 2 timepoints, for the purposes of the summary analyses.

5.1.5. Baseline Definition

Unless otherwise stated, Baseline is defined as the final study visit of the feeder study, unless the Baseline visit is >7 days from the final visit of the feeder study. Baseline may be considered the Cycle Start Visit if the investigator determines the subject has lesions that require treatment.

5.1.6. Missing Data

5.1.6.1. Date Values

In cases of incomplete dates (e.g. AE, concomitant medication, and medical history start and/or stop dates), the missing component(s) will be assumed as the most conservative value possible. For example, 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 initial treatment month during the study. 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. If day is missing for an end date, the last day of the month will be imputed.

Date imputation will only be used for computational purposes such as treatment-emergent status, etc. Actual date values, as they appear in the original CRFs, will be presented within the data listings.

5.1.6.2. Non-Date Values

Every effort will be made to obtain required data at each scheduled evaluation from all subjects who have been enrolled. No imputation of missing data will be performed for non-date values.

6. SUBJECT DATA AND STUDY CONDUCT

6.1.1. Subject Disposition

Subject disposition information will be summarized. Counts (number and percent) of subjects who are enrolled, who are treated with study medication, who required a second treatment cycle, 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 Safety Population will be used as the denominator for the percentage calculations. Subject disposition, inclusion/exclusion criteria, and comments will be listed.

6.1.2. Protocol Deviations

Protocol deviations will be identified based on the clinical data as defined in the Protocol Deviation Plan. The Protocol Deviation Plan will define all protocol deviations as either CSR reportable or non-CSR reportable deviations. A listing of all CSR reportable protocol deviations will be provided.

6.1.3. Demographic Characteristics

Demographic and baseline characteristics will be summarized. Demographic and baseline characteristics include the following: age at informed consent, sex, and feeder study classification. Unless otherwise stated, all continuous variables will be represented by n, mean, standard deviation, minimum, median, and maximum. All categorical variables will be presented as counts and percentages. Demographic characteristics will also be listed.

6.1.4. Medical History

Medical history information will be listed. A listing of concomitant therapies/procedures will be provided.

6.1.5. Concomitant Medications

All medications administered during the study will be listed including the reported term, start and stop dates, and other relevant data will be provided. Concomitant medications include all medications taken on or after the date of the first study visit (Baseline). Prior medications include all medications taken and discontinued before the date of the first study visit (Baseline). All medications will be coded using the World Health Organization (WHO) Drug Sept 2016E B2 version.

7. ANALYSIS OF SAFETY

Safety will be assessed using the Safety Population. The assessment of safety will include adverse events, clinical laboratory assessments, ECGs, clinical examination findings, and vital signs. Other safety data will be summarized as appropriate.

7.1. Extent of Exposure

Study drug usage is based on data collected from the Drug Accountability eCRF where drug usage is calculated as the number of study drug tubes dispensed minus the number of study drug tubes returned.

Percent compliance with the study medication will be summarized for the Safety Population using descriptive statistics. Compliance will be calculated as 100 x (Number of days study drug application was completed) / (Number of days study drug application was expected). The number of days application was completed is based on data collected from the subject's eDiary. If no information is provided for a given day, it will be assumed that the subject did not complete the application. The number of days application was expected is as follows: (Date of Mid-Cycle Visit – Date of Cycle Start), i.e. the number of days study drug was expected to be applied in the 8-week treatment period. If the subject did not have a Mid-Cycle Visit then 56 expected days (8 weeks) of application will be assigned for the analysis. If a subject had 2 treatment cycles, the number of expected days from each treatment cycle will be calculated as described above and summed for a total number of days study drug application was expected across both treatment cycles.

Compliance will be summarized for each treatment cycle and overall. If no information is provided for any day within a given treatment cycle, then the compliance within that cycle will be set to missing. For subjects that had missing compliance within a given cycle, their overall compliance will be based on only the cycle for which information is provided in the eDiary.

The analysis will include listings for drug exposure and compliance.

7.2. Adverse Events

Adverse events will be coded using the MedDRA version 19.0 and summarized by system organ class and preferred term.

A summary overview of TEAEs will be provided which presents the number and percentage of subjects satisfying each of the following categories:

- All AEs,
- All TEAEs,
- Drug-related TEAEs,
- Maximum severity of TEAEs,
- All AESIs,
- All treatment-emergent SAEs,
- Death due to TEAEs, and
- TEAEs leading to study drug discontinuation.

Similar summary overviews will be provided for TEAEs occurring during Cycle 1 (defined as TEAEs beginning on or after the start of Cycle 1 through the end of Cycle 1) and Cycle 2 (defined as TEAEs beginning on or after the start of Cycle 2 through the end of Cycle 2).

The numbers and percentages of subjects with TEAEs will be summarized by MedDRA preferred term within system organ class. For the summaries, multiple AEs with the same

MedDRA preferred term within system organ class from the same subject will only be counted once.

All TEAEs related to study drug, AESIs, SAEs, and AEs leading to study drug discontinuation will be summarized in the same manner.

All AEs will be included in subject listings containing additional information of interest such as onset and resolution times, maximum severity, causal relationship to study medication, and action taken. Specific subject listings of TEAEs, related to study drug, AESI, SAEs, and TEAEs leading to study discontinuation will be provided.

7.3. Safety Laboratory Parameters

Clinical laboratory results will be summarized with descriptive statistics by visit. Change from baseline will also be summarized. Laboratory values will also be listed by visit, within subject.

7.4. Vital Signs

Vital signs and the change from baseline will be summarized descriptively by visit. The count and percentage of subjects with abnormal values will be summarized by visit. Abnormal blood pressure measurements for subjects age 17 and younger will be defined as either systolic or diastolic measurements above the 95th percentile, according to height, sex, and age. Abnormal blood pressure measurements for subjects age 18 and older will consist of either a systolic blood pressure >140mm Hg or a diastolic blood pressure >90mm Hg. Abnormal weight measurements for subjects age 18 and older will be defined as measurements > 300 pounds (>118 kilograms). Abnormal BMI measurements for subjects age 17 and younger will be defined as measurements above the 95th percentile, according to sex and age. Vital sign data will also be listed by visit, within subject.

7.5. ECG Parameters

Electrocardiogram results will be summarized by visit. Electrocardiogram results will also be listed.

7.6. Clinical Assessment of EBS Lesions

The numbers and percentages of subjects with active EBS lesions requiring treatment will be summarized by visit. The percent BSA of active lesions requiring treatment will be summarized with descriptive statistics by visit. Change from baseline and the percent change from baseline will also be summarized. The clinical assessment findings will also be listed by visit, within subject.

8. INTERIM ANALYSIS

No interim analysis is planned for this extension study.

9. SAMPLE SIZE AND POWER CONSIDERATIONS

No formal sample size calculation was performed for this extension study. The actual number of subjects that are enrolled will depend on the final number of subjects who participate in the CCP-020-301 or participate in the CCP-020-101 study.

10. CHANGES FROM THE PROTOCOL

The Day 0/Baseline visit was reclassified in the SAP compared to the protocol. The SAP refers to the initial visit in the study as the Baseline visit and this will correspond to Study Day 1 in the analysis.