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STATISTICAL ANALYSIS PLAN

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]

Investigational Product: Diacerein 1% Ointment
Protocol Number: CCP-020-301

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

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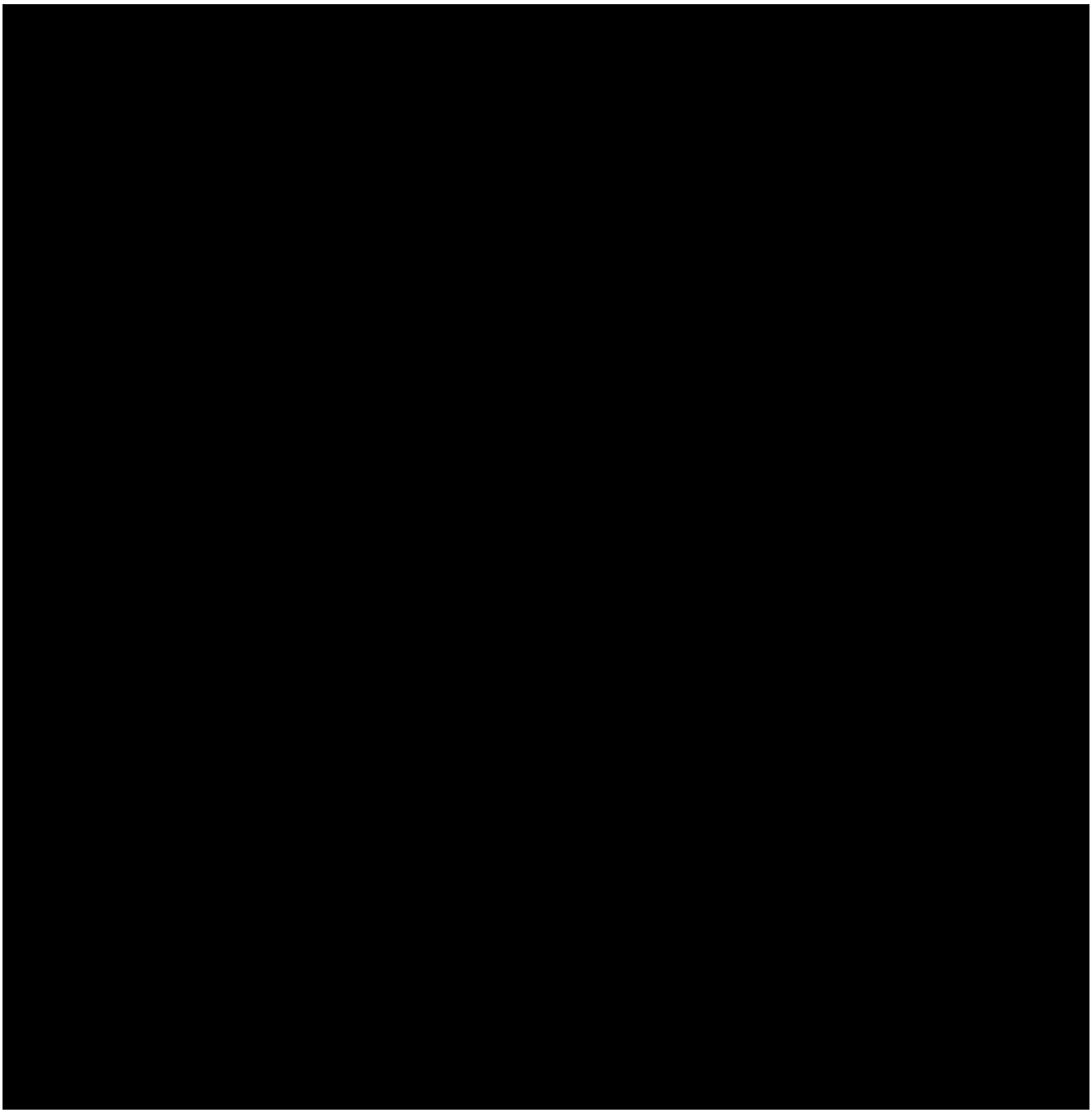

VERSION HISTORY

Version	Date	Description
1.0	2 January 2018	Original signed version
2.0	31 August 2018	Revised for primary endpoint and FDA Advice Letter

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
BSA	Body Surface Area
CMH	Cochran-Mantel-Haenszel
CR	Clinically Relevant
CSR	Clinical Study Report
EBS	Epidermolysis Bullosa Simplex
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
ICH	International Conference on Harmonization
IGA	Investigator's Global Assessment
ITT	Intent-To-Treat
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MAR	Missing at random
NCR	Not Clinically Relevant
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol
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-020-301 (DELIVERS trial). During the conduct of the DELIVERS trial, the Sponsor, Investigators, and all currently blinded teams at Medpace will be remain blinded until completion of the trial. This document is based on the Global Protocol Amendment 3a 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 compare the efficacy of Diacerein 1% Ointment to Control Ointment when applied once-daily for 8 weeks in subjects with epidermolysis bullosa simplex (EBS).

The secondary objectives are to compare the effects of Diacerein 1% Ointment to Control Ointment in subjects with EBS in:

- Pain
- Pruritus
- Safety and tolerability

2.2. Trial Design

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. Subjects at least 4 years of age with a genetic confirmation of EBS (based on either existing documentation or results from a sample collected as part of the study) who meet all the inclusion criteria and none of the exclusion criteria at Visit 1 will be eligible for enrollment in the study.

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. Approximately 80 subjects will be randomized at approximately 22 international investigational centers. The randomization will be stratified by genotype (KRT5 and/or KRT14 versus other genotypes) and age group (<8 and ≥8 years old). 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. No study medication applications will be made to any lesion that becomes infected until the infection resolves with appropriate investigational center specific medical care.

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. Adverse events, clinical laboratory data, pharmacokinetic (PK) sampling, efficacy evaluations and determination of study medication use will be routinely collected.

The duration of study participation is anticipated to be a maximum of 158 days per subject (~22 weeks). This includes the up to 6-week screening period, an 8-week treatment period and an 8-week no-treatment follow-up period.

Study visits are summarized as follows:

- 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

A detailed schedule of procedures is provided in Table 1.

Table 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

3. STUDY ENDPOINTS

3.1. Efficacy Variables

3.1.1. Primary Endpoint

The proportion of subjects who achieve ≥ 60% reduction in BSA of EBS lesions within the Assessment Area from Baseline to Visit 6 (Week 8).

3.1.2. Key Secondary Endpoint

The proportion of subjects achieving success on the IGA of the Assessment Area, where success is defined as at least a 2-point reduction, from Baseline to Visit 6 (Week 8).

3.1.3. Other Secondary Endpoints

The other secondary endpoints are as follows:

- The percent change in Reference Lesion Surface Area from Baseline to Visit 6 (Week 8).
- The proportion of subjects who achieve ≥ 60% reduction in BSA of EBS lesions within the Assessment Area from Baseline to Visit 8 (Week 16)
- The proportion of subjects achieving success on the IGA of the Assessment Area, where success is defined as at least a 2-point reduction, from Baseline to Visit 8 (Week 16).

3.1.4. Exploratory Endpoints

The exploratory endpoints are as follows:

- The percent change in Reference Lesion Surface Area from Baseline to Visit 8 (Week 16).
- The proportion of subjects with a reduction in overall pain intensity from Baseline to Visit 6 (Week 8).
- The proportion of subjects with a reduction in overall pruritus intensity from Baseline to Visit 6 (Week 8).
- The proportion of subjects with a reduction in overall pain intensity from Baseline to Visit 8 (Week 16).
- The proportion of subjects with a reduction in overall pruritus intensity from Baseline to Visit 8 (Week 16).

3.2. Safety Variables

3.2.1. Adverse Events

Adverse events (AEs), 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 (Week 16). 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 AE electronic Case Report Form (eCRF). All AEs that occur after the first study medication application and up to 30 days after the subject's last study medication application will be considered treatment-emergent adverse events (TEAEs).

In concert with system-organ classification (SOC) defined by MedDRA the following AEs will be categorized as AEs of special interest (AESIs) in this study:

- All gastrointestinal (GI) disorders defined by MedDRA SOC
- 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.

3.2.2. Safety Laboratory Evaluations

At Visits 1, 2, 4, 6 and 8 a qualified staff member will collect blood and urine samples for clinical laboratory analysis. 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
Albumin
Alkaline phosphatase (ALP)
Alanine aminotransferase (ALT)
Amylase
Aspartate aminotransferase (AST)
Blood urea nitrogen (BUN)
Bicarbonate
Chloride
Creatinine
Gamma-GT
Glucose
HbA1c
Lactate dehydrogenase (LDH)
Lipase
Potassium
Sodium
Total bilirubin
Total protein
Uric acid

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

Complete Urinalysis

3.2.3. 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)

3.2.4. 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

3.2.5. 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 following ECG data will be collected:

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

3.2.6. Pharmacokinetic Variables

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

4. ANALYSIS POPULATIONS

4.1. Intent-to-Treat Population

The Intent-to-Treat (ITT) Population will consist of all randomized subjects who are dispensed study medication. All efficacy analyses will be conducted using the ITT population. Subjects will be included in the treatment group to which they were randomized.

4.2. 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. Subjects will be included in the treatment group based on the treatment that was received (if different from the subject's randomized treatment assignment).

4.3. Per Protocol Population

The Per Protocol (PP) Population will consist of all ITT subjects with a BSA and IGA of EBS lesions at Week 8 and without a major protocol deviation as defined by International Conference of Harmonisation (ICH) E3 (*Structure and Content of Clinical Study Reports*) that may interfere with the assessment of drug safety, efficacy and overall integrity of the data. Before data are released for statistical analysis, a blinded review of all data will be performed by the Sponsor's 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 can be finalized prior to database unblinding.

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. Evaluation of Center Effect

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

5.2. Assessment Windows

In the descriptive statistics of safety and efficacy endpoints, only measurements from scheduled visits will be used if values are available. If no values from a scheduled visit are available but values from unscheduled visits are available, the values from the unscheduled visit closest to the target date for that visit will be used for the summary statistics. The date of an unscheduled visit will be used to assign the unscheduled visit to the nearest scheduled visit date.

For analysis purposes, if the event date is on or after the first treatment date, the study day is defined as follows:

Study Day = Event date – First treatment date + 1

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

5.3. Handling of Dropouts and Missing Data

5.4. 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 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. 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.

5.5. Non-Date Values

Every effort will be made to obtain required data at each scheduled evaluation from all subjects who have been enrolled.

For the primary analysis of the primary efficacy endpoint (proportion of subjects who achieve ≥ 60% reduction in BSA of EBS lesions with the Assessment Area from Baseline to Visit 6/Week 8), subjects whose status at Week 8 is unknown will be defined to be a non-success/non-responder.

For sensitivity analysis of this endpoint, the following analyses will be performed:

1. Subjects with missing values at Week 8 in the Diacerein treatment group will be imputed as a success, while all subjects in the Placebo treatment group will imputed as a non-success.
2. Subjects with missing values at Week 8 in the Diacerein treatment group will be imputed as a non-success, while all subjects in the Placebo treatment group will imputed as a success.
3. Subjects with missing values at Week 8 will be imputed using multiple imputation (MI) under the assumption of missing at random (MAR). Based on the imputed value at Week 8, the subjects will be assigned accordingly as either a success or non-success.
   Missing values for the BSA of EBS lesions within the Assessment Area will be imputed using multiple imputation methodology in two steps. Initially, ten datasets will be generated containing imputed values for non-monotone missing values in the original dataset. The variables used to guide this imputation will include the following: treatment group, age group (<8 and >=8 years old), genotype (KRT5/KRT14 and Other), and BSA

of EBS lesions in the Assessment Area at Baseline, Week 1, Week 4, Week 8, and Week 16. In this step it will be assumed that any intermediate missing data points are MAR. In the second step, the remaining monotone missing values will be imputed. The same variables will be used to guide the imputation as in the first step.

For each imputation dataset, the proportion of subjects who achieve success will be analyzed using the Cochran-Mantel-Haenszel test described in Section 7.1 below. A log transformation will be performed to normalize the relative risk estimates and the standard error of the transformed estimate will be obtained from the log-transformed confidence limits for the relative risk estimate. The results from these ten analyses will be combined and then back-transformed to the original log scale. The corresponding relative risk estimate and confidence interval will be presented.

For the key secondary endpoint, the same imputation methods will be employed as with the primary endpoint. No imputation will be performed on the other secondary or exploratory endpoints.

6. ANALYSIS OF DISPOSITION AND SUBJECT CHARACTERISTICS

6.1. Disposition and Analysis Populations

Subject disposition information will be summarized. Counts (number and percent) of subjects who are randomized, who are treated with study medication, 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. The number and percent of patients in each analysis population will also be tabulated.

6.2. Protocol Deviations

A listing of all major protocol deviations will be provided.

6.3. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment for each of the analysis populations. Demographic and baseline characteristics include the following: age at informed consent, sex, race, ethnicity, genotype, IGA score at baseline, BSA of assessment area at baseline BSA of treatment area at baseline, total BSA of all EBS lesions at baseline, pruritus severity at baseline, pain severity at baseline, and mobility score at baseline. 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.

Baseline for all analysis variables will be the last measurement prior to the first application study medication, unless otherwise stated. For data collected from the eDiary, Baseline will be the value recorded from the first day that the subject received study medication.

Medical history will be summarized for the number and percentage of patients for each medical term. Medical history information will be listed. A listing of concomitant therapies/procedures will be provided.

6.4. 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 treatment of study medication. Prior medications include all medications taken before the date of the first treatment of study medication and discontinued before the first treatment of study medication. All medications will be coded using the World Health Organization (WHO) Drug Sept 2016E B2 version.

7. ANALYSIS OF EFFICACY

Descriptive summaries of efficacy endpoints will be presented by treatment group and visit. All efficacy endpoints will be based on the Assessment Area, defined in the protocol, unless otherwise stated. The ITT population and PP population will be used for this analysis. A by-subject listing of efficacy endpoints will be provided.

7.1. Primary Efficacy Analysis

Descriptive summaries of the proportion of subjects who achieve ≥ 60% reduction in BSA of EBS lesions will be presented by treatment group at each visit.

The primary endpoint is the proportion of subjects who achieve ≥ 60% reduction in BSA of EBS lesions from Baseline to Visit 6 (Week 8). Subjects whose status at Visit 6 is unknown will be defined to be nonresponders. The primary analysis will be conducted using the Cochran-Mantel-Haenszel (CMH) test, stratified by genotype (KRT5/KRT15 and Other) and age group (<8 and ≥8 years old). Estimated relative risk, associated 95% confidence interval (CI), and p-values will be provided.

At the final analysis, the treatment groups will be compared using a two-sided test at the alpha=0.049 level of significance in order to account for the alpha spent in the Interim Analysis as described in Section 10 below.

7.2. Key Secondary Efficacy Analysis

The key secondary endpoint is the proportion of subjects achieving success on the IGA of the Assessment Area, where success on the IGA is defined as at least a 2-point reduction from Baseline to Visit 6 (Week 8). Subjects whose status at Visit 6 is unknown will be defined as non-responders. The key secondary endpoint will be analyzed using the CMH test, as described for the primary analysis. However, if the primary analysis is not statistically significant, then the results for the key secondary endpoint will be exploratory rather than confirmatory. This fixed sequence testing procedure maintains the overall level of significance for the primary and key secondary endpoints.

7.3. Other Secondary Efficacy Analyses

All other secondary endpoints will be analyzed using two-sided tests at the alpha=0.05 level of significance, with no adjustment for multiplicity.

7.3.1. Percent Change in Reference Lesion Surface Area (LSA)

Descriptive statistics of the percent change in Reference Lesion surface area from Baseline to Visit 6 (Week 8) will be presented by treatment. An Analysis of Covariance (ANCOVA) model with treatment, genotype, and age group as fixed effects and baseline surface area of the Reference Lesion as a covariate will be used to analyze the data. Treatment differences in the percent change from baseline between Diacerein 1% Ointment and Control Ointment will be evaluated by the least-squares mean, standard error, 2-tailed 95% confidence interval, and a 2-sided p-value.

7.3.2. BSA success at Visit 8 (Week 16)

The proportion of subjects who achieve ≥ 60% reduction in BSA of EBS lesions from Baseline to Visit 8 (Week 16) will be analyzed using the CMH test, as described for the primary efficacy endpoint.

7.3.3. IGA Success at Visit 8 (Week 16)

The proportion of subjects achieving success on the IGA of the Assessment Area, where success on the IGA is defined as at least a 2-point reduction from Baseline to Visit 8 (Week 16), will be analyzed using the CMH test, as described for the primary efficacy endpoint.

7.4. Exploratory Efficacy Analyses

Descriptive statistics for the exploratory endpoints will be presented by treatment group at each visit. All exploratory efficacy analyses will be conducted using two-sided tests at the alpha=0.05 level of significance, with no adjustment for multiplicity.

7.4.1. Reduction in Pain Intensity at Visit 6 (Week 8) and Visit 8 (Week 16)

The proportion of subjects with a reduction in overall pain intensity from Baseline to Visit 6 (Week 8) and Baseline to Visit 8 (Week 16) will be analyzed in the same manner as described previously for the IGA success at Visit 6 (Week 8). The overall pain intensity at a given visit will be based on the average of the subject's reported pain intensity from the 7 days prior to the visit assessment, based on the data collected from the subject's eDiary.

7.4.2. Reduction in Pruritus Intensity at Visit 6 (Week 8) and Visit 8 (Week 16)

The proportion of subjects with a reduction in overall pruritus intensity from Baseline to Visit 6 (Week 8) and Baseline to Visit 8 (Week 16) will be analyzed in the same manner as described previously for the IGA success at Visit 6 (Week 8). The overall pruritus intensity at a given visit will be based on the average of the subject's reported pruritus intensity from the 7 days prior to the visit assessment, based on the data collected from the subject's eDiary.

8. ANALYSIS OF SAFETY

Safety will be assessed using the Safety Population. The assessment of safety will include adverse events, clinical laboratory assessments, ECGs, physical examinations, and vital signs. The safety analysis will be based primarily on the frequency of new or worsening adverse events, laboratory abnormalities, and serious adverse events (SAEs). Other safety data will be summarized as appropriate.

8.1. Extent of Exposure

Amount of study drug used will be summarized by treatment group for the Safety Population using descriptive statistics. Study drug usage is based on data collected from the Drug Accountability eCRF where drug usage is calculated as the amount of study drug dispensed minus the amount of study drug returned, in grams.

Percent compliance with the study medication will be summarized by treatment group for the Safety Population using descriptive statistics. Compliance with study medication application is based on data collected from the subject's eDiary. The analysis will include listings for drug exposure and compliance.

8.2. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 and summarized by treatment group, system organ class, and preferred term.

A summary overview of TEAEs will be provided which presents the number and percentage of patients in each treatment group satisfying each of the following categories:

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

The numbers and percentages of patients with TEAEs will be summarized by MedDRA preferred term within system organ class, by treatment group and overall. For the summaries by treatment group, multiple AEs with the same MedDRA preferred term within system organ class from the same patient within a given treatment will only be counted once. For overall summaries, multiple AEs with the same MedDRA preferred term within system organ class from the same patient 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. Summaries will also be provided for the numbers and

percentages of patients by system organ class, preferred term, and maximum severity, for TEAEs, AESIs, and drug-related TEAEs.

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

8.3. Safety Laboratory Parameters

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

8.4. Vital Signs

Vital signs and the change from baseline will be summarized descriptively by treatment and visit. The count and percentage of subjects with abnormal values will be summarized by treatment and 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. Abnormal values will be defined as clinically relevant (CR) or not clinically relevant (NCR) on the eCRFs. Vital sign data will also be listed by visit, within patient.

8.5. ECG Parameters

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

8.6. Physical Examinations

Physical examinations and the change from baseline will be summarized by treatment and visit. Physical examination results will also be listed by visit, within patient.

8.7. Pharmacokinetic Analysis

Blood draws for PK sampling and modeling will be obtained at the timepoints listed in the Study Flow Chart (see Table 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 pharmacokinetic/pharmacodynamic (PK/PD) analyses will be performed. A separate Pharmacokinetic Analysis Plan will be prepared describing the details regarding the PK analysis, including the data handling and methods for the analysis.

9. DATA MONITORING COMMITTEE

An independent data monitoring committee (DMC) will monitor the safety of subjects over the course of the study. An interim analysis will also be conducted by the DMC. Details related to the DMC responsibilities, authorities, and procedures will be documented in the DMC charter. After each meeting, the DMC will advise whether any changes to the conduct of the study are necessary.

10. INTERIM ANALYSIS

An interim analysis of the two confirmatory endpoints (primary endpoint, key secondary endpoint) for efficacy, futility, and sample size re-estimation will be conducted by an independent data monitoring committee (DMC) when 40 subjects (50% of the planned total sample size) have completed Visit 6 (Week 8). The Sponsor and the study investigators will remain blinded. Following the interim analysis, the DMC will make one of the following four recommendations to the Sponsor:

- Terminate the study for futility.
- Continue the study as planned.
- Increase the sample size to n=XXX subjects, where the maximum value of XXX is equal to 200.
- Terminate the study on the basis of having demonstrated overwhelming evidence of efficacy.

Based on the Lan-DeMets method for group sequential trials using O'Brien-Fleming boundaries (Reboussin, 2000), the levels of significance for the interim and final analyses corresponding to a single interim analysis at the 50% information fraction are alpha=0.00305 and alpha=0.049, respectively.

If the two-sided p-values at the interim analysis for both the primary efficacy endpoint and the key secondary endpoint are less than 0.00305, then the DMC may recommend to the sponsor that the trial be terminated early for efficacy.

If the DMC does not recommend early termination for efficacy, then the conditional power (Jennison, 2000) for the final analysis of the primary endpoint will be computed under the assumption that the treatment difference and variability observed at the interim analysis represent the true values of the unknown parameters. If the estimated conditional power for the final analysis of the primary endpoint is less than 10%, then the DMC may recommend to the sponsor that the trial be terminated early for futility.

If the DMC does not recommend early termination (for efficacy or futility), then for each of the two endpoints (primary endpoint, key secondary endpoint), the sample size required to achieve 80% power at the final analysis will be re-estimated based on the treatment difference and variability observed at the interim analysis. The DMC may then recommend that the sample size be increased to the larger of the two sample size estimates in order to maintain 80% power.

Due to the sample size re-estimation component of the interim analysis, the final analysis will be conducted using the approach of Cui, Hung, and Wang. (Cui, 1999)

11. SAMPLE SIZE AND POWER CONSIDERATIONS

The original sample size calculation was based on the endpoint of the proportion of subjects with ≥ 40% reduction in BSA of EBS lesions at Week 16. The assumed true rates were 60% and 30% in the Diacerein 1% Ointment and Control Ointment groups, respectively. Based on a two-sided, two-sample comparison of proportions at the alpha=0.049 level of significance, a total sample size of 80 subjects provides 77% power. No data are available on which to base a sample size calculation for the primary endpoint, now defined at Week 8 and now based on the proportion of subjects with ≥ 60% reduction in BSA.

12. CHANGES FROM THE PROTOCOL

Reference is made to FDA Advice Letter dated 26 March 2018, whereby the Agency noted its position on IGA as the primary endpoint. The update to this SAP incorporates FDA guidance as it relates to consideration of IGA as a key secondary endpoint in addition to BSA as the primary endpoint. Additionally, CCP has implemented the FDA recommendation regarding the number of secondary endpoints; thus, this SAP has been updated to address multiplicity. Table 2 summarizes the changes made to the SAP and the corresponding impacted section to the current CCP-020-301 (3a) protocol. The protocol will be amended at the time of the next major amendment or at the time of the IND annual reporting, whichever to occur first.

Table 2: Summary of Changes and Impact to Protocol (CCP-020-301; 3a)

SAP Section	SAP Section	Description of Change	Impacted Protocol (3a) Section
2.1	Objectives	Change primary endpoint analysis to ≥ 60% reduction from Visit 8 (week 16) to Visit 6 (Week 8)	N/A
		Reduced number of secondary outcomes by removing "mobility"	
3.1.1	Primary endpoints	Primary endpoint to ≥ 60% reduction at Visit 6 (Week 8) versus Visit 8 (Week 16) Note: in addition to increasing % reduction from 40 to 60, this change in assessment range merely moves a pre-specified secondary endpoint to the primary outcome	5.1 Primary Endpoints
3.1.2 (NEW)	Key secondary endpoint	Promoted secondary endpoint to "Key secondary" assessing Baseline to Visit 6 (Week 8).	5.2 Key Secondary Endpoints
3.1.3 (Amended from version 1.0)	Other secondary endpoints	Defined other secondary endpoints are as follows: • The percent change in Reference Lesion Surface Area from Baseline to Visit 6 (Week 8). • The proportion of subjects who achieve ≥ 60% reduction in BSA of EBS lesions from Baseline to Visit 8 (Week 16) • The proportion of subjects achieving success on the IGA of the Assessment Area, where success is defined as at least a 2-point reduction, from Baseline to Visit 8 (Week 16). Note: Reference lesion surface area (Baseline to Visit 6 (Week 8) has been reclassified from exploratory. Secondary outcomes for pain intensity and intensity of itch from Baseline to Visit 6 (Week 8) has been moved to Section 3.1.4 Exploratory endpoints. "Mobility" endpoint has been eliminated.	

Table 2: Summary of Changes and Impact to Protocol (CCP-020-301; 3a) (Continued)

SAP Section	SAP Section	Description of Change	Impacted Protocol (3a) Section
3.1.4. (Amended from version 1.0)	Exploratory endpoints	Redefined "exploratory endpoints" as follows: • The percent change in Reference Lesion Surface Area from Baseline to Visit 8 (Week 16). • The proportion of subjects with a reduction in overall pain intensity from Baseline to Visit 6 (Week 8). • The proportion of subjects with a reduction in overall pruritus intensity from Baseline to Visit 6 (Week 8). • The proportion of subjects with a reduction in overall pain intensity from Baseline to Visit 8 (Week 16). • The proportion of subjects with a reduction in overall pruritus intensity from Baseline to Visit 8 (Week 16)." Note: "Mobility" outcomes has been removed; expanded exploratory analysis to include pain intensity and intensity of itch from Baseline to Visit 6 (Week 8)	5.3 Exploratory Endpoints
3.2	Adverse Events	AEs of special interest (AESIs) have been updated to include all gastrointestinal (GI) disorders defined by MedDRA SOC	10.4.3. Adverse Events of Special Interest
4.1.1	Intent-to-Treat Population	Intent-to-Treat Population (ITT) was clarified to include all randomized subjects who are dispensed study medication (per FDA Advice Letter 26-March 2018	11.1 Analysis Populations
4.1.3	Per Protocol Population	Editorial update to clarify a major protocol deviation as defined by ICH E3 (Structure and Content of Clinical Study Reports) that may interfere with the assessment of drug safety, efficacy and overall integrity of the data.	

Table 2: Summary of Changes and Impact to Protocol (CCP-020-301; 3a) (Continued)

SAP Section	SAP Section	Description of Change	Impacted Protocol (3a) Section
5.3.3	Data imputation	Incorporated guidance from FDA Advice Letter dated 26 March 2018: *"Missing data for the placebo arm will be considered as success while missing data for the diacerein arm will be imputed as failure."*	11.2.1 Missing Data Handling Methods
7.1	Primary Efficacy Analysis	Updated: changed to ≥ 60% reduction in BSA and assessment period from Baseline to Visit 6 (Week 8)	11.2.3 Analysis of Efficacy
7.2 (Amended from version 1.0)	Key Secondary Efficacy Analysis	Defined hierarchical statistical approach to key secondary endpoint: *"The key secondary endpoint is the proportion of subjects achieving success on the IGA of the Assessment Area, where success on the IGA is defined as at least a 2-point reduction from Baseline to Visit 6 (Week 8). Subjects whose status at Visit 6 is unknown will be defined as non-responders. The key secondary endpoint will be analyzed using the CMH test, as described for the primary analysis. However, if the primary analysis is not statistically significant, then the results for the key secondary endpoint will be exploratory rather than confirmatory. This fixed sequence testing procedure maintains the overall level of significance for the primary and key secondary endpoints."*	
10 (NEW)	Interim Analysis	Greater specificity provided per DMC possible recommendations; e.g. maximum re-estimation of sample size has been set at 200	11.3 Interim Analysis

13. REFERENCES

Cui L, Hunt HM, Wang SJ. (1999) Modification of sample size in group sequential clinical trials. Biometrics, 55:853-857.

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