STATISTICAL REPORTING AND ANALYSIS PLAN

A randomized, double blind, multi center, active-controlled, 2 treatment arm, parallel group non inferiority study to evaluate the efficacy and safety of diclofenac diethylamine 2.32% gel applied twice daily versus diclofenac diethylamine 1.16% gel applied four times daily for one week in subjects with acute ankle sprain

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Phase: Phase III

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Document History

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
0.1	*02FEB2020*	*Not Applicable*
0.2	*03SEP2020*	*Updated client comments received on Draft 1 and added COVID-19 analysis.*
1.0	11JAN2021	Updated Per Protocol definition. Made changes to PP exclusion reason w.r.t compliance category. Added sensitivity analysis for primary endpoint.
2.0	20JAN2021	Made changes to PP exclusion reason w.r.t compliance category.

Amendments incorporate all revisions to date.

Table of contents

The purpose of this Statistical Reporting and Analysis Plan (RAP) is to describe the planned analyses and outputs to be included in the Clinical Study Report (CSR) for Protocol 211206.

This RAP is intended to describe the Final analyses required for the study.

1 Summary of Key Protocol Information

Topical diclofenac products are well established globally for the treatment of pain and inflammation due to acute trauma as well as the relief of pain associated with non-serious osteoarthritis (OA) of the peripheral joints e.g. knee and fingers. The originator product diclofenac diethylamine (DDEA) 1.16% gel (Volatran Emulgel in the UK) was first registered in 1985 in Switzerland and Romania for use at a doce of 2-4gram applied three to four times daily and is currently registered in over 130 countries of which over 80 countries market this product as over-the-counter (OTC).

As part of global expansion for the product, China has been identified as a desirable market for registration of DDEA 2.32% gel. The identified registration pathway in China for the DDEA 2.32% gel is variation specifying addition of a new strength to the already registered DDEA 1.16% gel (License Number H20160648/H20160649 issued on 12 March 2013), with the same indications as currently registered for DDEA 1.16% gel, i.e. for relief of mild to moderate pain in muscles, soft tissues, joints, e.g., muscles and soft tissue pains caused by sprain, pilling injury, contusions, strain, waist-back injury and various arthralgia etc, and symptomatic treatment of OA.

In support of the proposed registration, the National Medical Products Administration (NMPA) approved a clinical trial application (CTA) on November 06, 2016 (CTA No. 2016L09875). The approved CTA stipulated that a non-inferiority study assessing the efficacy and safety of the DDEA 2.32% versus that of the registered DDEA 1.16% should be conducted in a local population.

To this effect, Glaxo SmithKline Consumer Health (GSKCH) intends to conduct a randomized, double-blind, multiple-dose, multi-center parallel group, non-inferiority study to evaluate the efficacy and safety of DDEA 2.32% gel applied twice daily versus DDEA 1.16% gel applied four times daily in subjects with ankle sprain in China.

1.1 Study Design

This is a Phase III, randomized, double blind, multi-center, active controlled, 2 treatment arm, parallel group, non-inferiority study to evaluate the efficacy and safety of diclofenac diethylamine 2.32% gel applied twice daily versus diclofenac diethylamine 1.16% gel applied four times daily for 1 week in subjects with acute ankle sprain.

To qualify, subjects must experience an acute Grade I -II sprain of the ankle within the past 24 hours. Subjects should be randomized as soon as possible after the injury.

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio to one of the following two treatment arms:

Table 1-1 Treatment Schedule Details

Treatment Arms	Morning(Upon Rising)	Noon	LateAfternoon (Evening)	Late Evening (Bed Time)
DDEA 2.32% four times daily	DDEA 2.32% Gel	Placebo Gel	DDEA 2.32% Gel	Placebo Gel
DDEA 1.16% four times daily	DDEA 1.16% Gel	DDEA 1.16% Gel	DDEA 1.16% Gel	DDEA 1.16% Gel

1.2 Study Objectives

Table 1-2 Objectives

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
• To demonstrate non-inferiority between DDEA 2.32% and DDEA 1.16% with regard to pain relief after acute ankle sprain	Change from baseline in pain on movement (POM) on Day 5 of treatment as assessed by a 100 mm VAS scale
Secondary Objective	**Secondary Endpoint**
Efficacy	
• To assess efficacy of treatments for pain relief as measured by POM on Days 3 and 8	Change from baseline of POM on VAS on Day 3 and Day 8 of treatment assessed by 100 mm VAS scale
• To assess efficacy of treatments for inflammation of the affected ankle as measured by pressure algometry on Days 3, 5, and 8	Change from baseline in tenderness as measured by pressure algometry on Days 3,5 and 8
• To assess efficacy of treatments for inflammation of the affected ankle as measured by pressure algometry on Days 3, 5, and 8	Difference between measurement in affected ankle and contralateral ankle on Days 3,5 and 8
• To assess efficacy of treatments for ankle joint function as measured on the Karlsson Scoring Scale	Change from baseline in Ankle Joint Function (Karlsson Scoring Scale) on Days 3,5 and 8
• To assess efficacy of treatments for swelling of affected ankle as measured Figure of Eight Method	Change from baseline in circumference of affected ankle as measured by Figure of Eight method on Days 3,5 and 8

Objectives	Endpoints
• To assess efficacy of treatments for swelling of affected ankle as measured by Figure of Eight method	Difference between circumference of affected ankle to unaffected ankle by Figure of Eight method on Days 3, 5 and 8
• To assess efficacy of treatments for effect on pain intensity as measured by Sum of Pain Intensity Difference (SPID)	SPID from 0 – 24 hours post first dose (Day 1) and from 0 – 24 hours post first dose (Day 5)
• To assess effect of treatments for effect on pain relief as measured by Total Pain Relief (TOTPAR)	TOTPAR from 0 – 24 hours post first dose (Day 1) and from 0 – 24 hours post first dose (Day 5)
• To assess the use of rescue medication among subjects	Number of tablets usedto treat ankle pain and overall
• To assess the use of rescue medication among subjects	Number of days on which rescue medication was used to treat ankle pain and overall
Safety	
• To assess safety of DDEA 1.16% and DDEA 2.32% gels after 1 week of use	Number, incidence, and severity of adverse events following dosing with study medication

1.3 Treatments

The following treatments will be administered in the study

Table 1-3 Study Product Details

	Active Treatment[a]	Active Comparator[b]	Placebo Product for Blinding of Active Treatment[a]
Product Name	DDEA 2.32% gel	DDEA 1.16% gel	Placebo gel -0% diclofenac gel
Pack Design	2 x 50 g tubes	4 x 50 g tubes	2 x 50 g tubes
Dispensing Details	1 kit per subject at visit 1[a]	1 kit per subject at visit 1[b]	1 kit per subject at visit 1[a]
Product Master Formulation Code (MFC)	CCI	Commercial Product	CCI
Dose/Application	Gel – 5 cm (2 g) on 200 cm^2	Gel – 5 cm (2 g) on 200 cm^2	Gel – 5 cm (2 g) on 200 cm^2
Route of Administration	Topical	Topical	Topical
Usage Instruction	Two times daily (BID) morning and late afternoon	Four times daily (QID)	Two times daily (BID) morning and late afternoon

a The study treatments for the Active Treatment and Placebo for blinding of Active Treatment will be provided in a single kit containing 4 tubes (2 tubes each of study treatment)

b The study treatments for the Active Treatment will be provided in a single kit containing 4 tubes

1.4 Sample Size Calculation

Approximately 300 subjects will be randomized to ensure at least 240 evaluable subjects complete the study for the Per Protocol (PP) analysis population. A maximum of 40 randomized subjects per center will be considered.

Approximately 120 subjects per treatment arm has been determined to provide 80% power to demonstrate non-inferiority of DDEA 2.32% gel b.i.d with DDEA 1.16% gel q.i.d. by comparing the two-sided 95% CI of the difference in mean change from baseline of VAS POM score between the two products with the non-inferiority margin of 13 mm. This assumes a treatment standard deviation of 22mm and allows for a possible small true treatment difference of 5mm in favor of DDEA 1.16%.

The margin of 13 mm (on a 100 mm VAS scale) was chosen as the literature reported minimally important clinical difference for an acute musculoskeletal injury (Todd et al 1995), with treatment differences smaller than 13mm considered as not clinically important. The standard deviation was obtained from a previous placebo-controlled ankle sprain study VOPO-P-307 with DDEA 2.32% gel.

2 Planned Analyses

2.1 Interim Analysis

No interim analysis is planned.

2.2 Final Analyses

The final planned analyses will be performed after the completion of the following sequential steps:

1. All subjects have completed the study as defined in the protocol
2. Finalization and signature the RAP.
3. All required database cleaning activities have been completed and database has been locked.
4. All criteria for unblinding the randomization codes have been met and the randomization codes have been distributed.

3 Considerations for data analyses and Data Handling Conventions

3.1 Baseline Definition

For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value. Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.

3.2 Centers Pools

In this study, maximum subject per centre will be approximately 40. Since, it is a small sample size, the pooling of centres is not required and we will be summarizing the analysis by centre.

All centers will be analyzed together.

3.3 Timepoints and Visit Windows

Before the study is unblinded, each actual post-baseline visit will be mapped to the target visit date to which it is chronologically closest. This corresponds to the following visit windows: Visit 2 (Days 2–4), Visit 3 (Days 4–6), Visit 4 (Days 7+). The numbering of the actual visits (from Visit 1 to Visit 4) will then be changed as needed to improve the correspondence of the actual visit dates to the protocol-specified schedule of visits, particularly in relation to Visit 3 (primary). Final determinations will also be made and documented before the study is unblinded to address visits that occur on Day 4 (which maps to two visit windows) or visits occurring well beyond the target date for the final visit or any other irregularities.

4 Data Analysis

Data analysis will be performed by Biostatistics and Programming Team at IQVIA Biotech Pvt. Ltd. The statistical analysis software used will be SAS version 9.4 or higher in a WINDOWS environment.

Prior to database closure a Blind Data Review Meeting (BDRM) will be conducted in which various aspects of the trial will be discussed and agreed.

Except as described below, all listings will be produced for Enrolled and/ or Intent To Treat (ITT) subjects.

4.1 Subgroups/Stratifications

Center/Site will be used as stratification factor where ever it is required. Based on study requirement sub group analyis will be conducted.

4.2 Populations for Analysis

Tables described in this section will be produced for all ITT subjects, unless otherwise specified in the sub section.

4.2.1 Subject Disposition

Subject disposition summary will include the number of screened subjects and screen failures, number of subjects randomized, number of subjects treated, number of subjects completed the study and number of subjects permanently discontinued by overall using enrolled population.

The number and percentage of subjects, in the Safety, ITT , mITT and PP populations will be presented by treatment and overall. The percentages will be based upon the total number of subjects in the enrolled population.

The number and percentage of subjects completing the study and those who discontinuing the study, including a breakdown of the reasons (reason for discontinuation will be due to adverse event, subject did not meet study criteria, protocol deviation, lost to follow-up, withdrawal of consent and other) for not completing the study, will be presented per treatment group and overall. The percentages are based upon the total number of subjects in ITT population (PPD).

Subject disposition including the subject status (completer, Yes/No), demographic data (age, gender, race), the duration of treatment before discontinuation and the specific reason for discontinuation (related to COVID also, etc.), will be listed in PPD . by treatment group and center.

4.2.2 Protocol Deviations

Protocol deviations will be tracked by the study team throughout the conduct of the study. Data will be reviewed during Blinded Data Review Meeting (BDRM) prior to database lock to ensure all important deviations are captured and categorised.

Protocol deviations that would exclude subjects from PP population may include (but are not limited to) the following:

- Subjects failing to meet inclusion and exclusion criteria but are included in the study
- Subjects without a Day 5 POM VAS assessment
- Subjects with get application compliance <=80% or weight compliance <=65% or weight compliance >=143% or application compliance >=143% with study treatment.
- Subjects taking prohibited medication (Refer Appendix 4)
- Subjects identified with other major protocol deviations

Full details of the major and minor protocol deviations are provided in Appendix 3.

The number and percentage of subjects with any major protocol deviations and with each type of major protocol deviations will be presented by treatment group (PPD) using ITT population and listed in PPD . Any minor protocol deviations will also be listed similarly PPD .

4.2.3 Analysis Populations

There are five analysis populations defined as below:

Table 4-1 Analysis Population

Population	Definition / Criteria	Analyses Evaluated	Treatments to used for Analyses
Enrolled	Comprise of all the subjects who have signed ICF, though may or may not be randomized later into the study.	Disposition	
Intent-To-Treat (Randomised)	Comprise of all randomized subjects. This population will be based on the treatment to which the subject was randomized. Any subject who receives a treatment randomization number will be considered to have been randomized.	Efficacy Demographics/Disposition/Medical History/Concomitant Mediaction/Compliance	Planned treatment received
Safety	Comprise of all subjects who receive at least one dose of study treatment. This population will be based on the treatment the subject actually received.	Study Population Safety	Actual treatment received
Intent-To-Treat (Modified)	Comprise of all randomized subjects who have at least one post baseline POM VAS assessment.	Efficacy Demographics	Planned treatment received
Per-Protocol (PP)	All subjects from the mITT population who do not have any major protocol deviations (which are not affecting primary efficacy endpoint) and also weight compliance > 65% and application compliance > 80%that could confound the interpretation of the efficacy analyses. Protocol deviations that would exclude subjects from the PP population will be discussed in the BDRM.	Primary Efficacy Demographics.	Actual treatment received

The numbers of subjects included in each of the analysis populations, and the number excluded from each population broken down by the reason for exclusion will be presented (PPD) using enrolled population. Subjects excluded from any of the analysis populations will be listed in PPD , with the reason for exclusion.

4.3 Subject Demographics and Other Baseline Characteristics

Demographic and baseline characteristics summaries will be produced for the ITT, mITT, PP and SAF.

4.3.1 Demographic Characteristics

Categorical demographic variables include gender (Male, Female), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White). These variables will be summarized by the number and percentage of subjects with each relevant characteristic in each treatment group.

Body Mass Index (BMI) will be calculated as weight (kg)/[height (m)]^2. Age in years, weight in kg, height in cm and BMI in kg/m^2 will be summarized by the mean, standard deviation, median, minimum and maximum values in each treatment group.

All the demographic related information will be taken from Demographic CRF page. Other baseline characteristics information will be taken from the corresponding CRF page for the baseline visits.

Examination on Ankle sprain will be taken from the Examination of Ankle Sprain/Diagnostic Testing for Ankle CRF page.

All demographic information will also be tabulated for ITT, mITT and SAF populations in PPD .

Demographic variables will be listed in PPD using ITT population.

4.3.2 General Medical History

Medical diagnoses/surgeries will be listed by subject using ITT population, with date of diagnosis/surgery, and whether or not the diagnosis/surgery was an active problem at the start of study drug administration (PPD) (CRF page: Medical History).

The presence/absence of any relevant medical history or current medical conditions will be tabulated.

Medical conditions will also be summarized using ITT population by numbers and percentages of subjects having a condition (PPD).

4.3.3 Characteristics of Disease

Baseline disease characteristics will be tabulated from the screening CRF page of Pain on Movement, Tenderness, Ankle Joint Function, Ankle Swelling.

The tables will be provided using ITT population (PPD). All information will be listed in the listing (PPD).

4.4 Treatments (Study Drug, Rescue Medication, other Concomitant Therapies, Compliance)

Compliance data will be summarized for the safety population and ITT population. Exposure and other medications will be summarized on the safety population.

4.4.1 Study Drug Compliance and Exposure

Compliance:

Compliance will be summarized descriptively based on the following points in PPD using ITT and Safety population respetively, PPD by ITT population on the following three :

1. % of scheduled applications made
2. % of gel used relative to number of actual applications * 2g, and
3. compliance category (Good/Moderate/Poor).

1. % of scheduled applications made will be calculated in following way -
    a. **% of scheduled applications compliance per tube:**
    - Total number of applications made: Compliance will be summerized based on the percent of scheduled application made. Percent of scheduled application made for each dosing time morning, noon, late afternoon and late evening respectively will be calculated in the following manner.
    - If replacement kit number and replacement date (CRF: Study Medication Replacement) are missing -
        - Expected number of application from tube k=(number of applications per day from tube k) * duration of days in the study ; where, k=1,2,3,4
        - Actual number of application from tube k= (Expected number of application) –[sum of (number of missed applications per day from tube k)* duration of days gel is applied i.e. (Day i – Day 1)]; where, i=1,2,3,4,5,6,7,8; k=1,2,3,4
        - Percent of scheduled application made from tube k= (Actual number of application from tube k (where k= 1 to 4) / Expected number of application from tube k) *100.

- If replacement kit number and replacement date (CRF: Study Medication Replacement) are non-missing then
    - Expected number of application from tube k=Sum of [(number of applications per day from tube k from kit no. x) +(number of applications per day from tube k from kit no. y)* duration of days in the study] ; where x= Old kit # and y= New kit #, k=1,2,3,4
    - Actual number of application from tube k= (Expected number of application from tube k from kit no. x) –[sum of (number of missed applications per day from tube k from kit x)+ sum of (number of missed applications per day from tube k from kit y)]* duration of days gel is applied i.e. (Day i – Day 1)]; where, i=1,2,3,4,5,6,7,8; k=1,2,3,4; x= Old kit # and y= New kit #

- Percent of scheduled application made from tube k= (Actual number of application from tube k (where k= 1 to 4) / Expected number of application from tube k) *100**% of scheduled applications compliance overall:**

    - Over all Compliance % = [sum of (actual # of application from each tube)/sum of (expected # of application from each tube)*100]

Scheduled applications will include all scheduled applications through the day before the final visit. On day 1, the percentage of gel used will be calculated based on the possible number of administrations on that day. If only 3 were possible, then 100 % compliance on that day will be considered 3 applications.

- % of gel used relative to number of actual applications * 2g will be derived as following -
    - Total weight of study medication used:The percent (%) of gel used will be computed relative to the actual number of application made from randomization through the final visit multiplied by 2 g.in two ways –
    - If replacement kit number and replacement date (CRF: Study Medication Replacement) are missing then
    - Expected weight of study medication used from tube k= (number of applications per day from tube k)*2g * Expected number of days gel to be applied from tube k
    - Actual weight of study medication used from tube k= [(Baseline weight of tube k – (weight of tube k after last day of application ; k=1, 2, 3, 4

Percent of total medication used = (Actual weight of medication used/Expected weight of medication used)*100

In case there is repeated usage of single tube in a day then the over usage of the medication will be reflected in weight compliance.

- Compliance category: Compliance category will be defined in the following way -
    - Good: > 80% of the gel has been applied and > 80% of scheduled applications made,
    - Moderate: not Good and not Poor
    - Poor: < 50% of the gel has been applied or < 50% of scheduled applications made.

For subjects applying active gel only twice per day (DDEA 2.32%), an additional compliance computation will be performed relative to the tubes and applications of active gel. If a subject is falls into good compliance category in both (separately for the active gel and also combined with placebo) then that subject will be included in the PP protocol population.

For each subjects time of the first application, application of the study drug each time point each day and the weight of the four tubes on Day 1, 3, 5 and 8 will be listed in PPD :

Exposure:

Exposure to study drug will be summarized descriptively using safety population in PPD as :

- number of applications made
- total amount of gel used.

Study drug exposure will also be listed using safety population along with the drug compliance in the PPD .

4.4.2 Prior and Concomitant Medication/Non-Drug Therapies or Procedures

Prior medications (stopped prior to day 1) will be listed by subject, with preferred term, indication, dose, dose form, frequency, route, start date and start and end day (PPD).

Prior medications will be summerized using ITT population in PPD .

Concomitant medications (ongoing at Day 1 or started on or after Day 1) will be listed similarly, with the addition of a flag for forbidden concomitant therapies (PPD).

Tables and listings described in this section will be presented for the ITT population. The medication listing will include the preferred term, indication, single dose, frequency, route, start

date, and end date or ongoing at final visit (when appropriate) and a flag whether the medication was Prior or Concomitant (PPD).

Concomitant medications (ongoing at randomization or started after randomization) will be summarized by treatment, anatomical area and therapeutic use or preferred term, and the number and percentage of subjects who took any concomitant medication will be presented (PPD) using ITT population.

The number and percent of subjects taking disallowed concomitant medications will be summarized similarly (PPD).

All the information related to concomitant medication will be obtained from Current/Prior/Concomitant Medication CRF page.

Non-drug therapies/procedures will be listed using ITT population (PPD). Information related to non-drug procedures/therapies will be taken from Non-Drug Treatments/Procedures CRF Page.

4.4.3 Rescue Medication

The investigator will provide rescue medication (paracetamol 500mg tablets) to the subjects at the baseline visit. Rescue medication will be re-dispensed on Day 5 i.e.at Visit 3. Subjects are not allowed to take rescue medication within 6 hours of study visits and within 12hours of Day 5. Following information will be documented in the Rescue Medication CRF page –

- Rescue medication taken (yes/no) (RMYN)
- Pain intensity (RMPI) and pain relief (RMPR) before taking rescue medication
- Reason for use of rescue medication (RMREAS)
- Time (RMSTTM) and date (RMSTDTC) of rescue medication
- Number of tablets taken (RMNUM)

Summuary of all the above mentioned points will be displayed in PPD . and will be listed in PPD .

Time to first use of rescue medication will be analyzed using the survival estimate of median time to event for each treatment group along with the CI for median. P-value from Log Rank test will be used to compare the median times between the treatment groups (PPD).

Kaplan Meier plot will be presented for the survival probabilities against the time points for both the treatment groups (In case number of events are considerable).

Subjects with no use of rescue medication will be censored at their last available date in the study.

Censoring Rule:

Event : If event occurred then value of censor is 0, time will be derived as follows:
Date of First Occurrence of Event- Date of Randomization + 1

Censor: If event not occurred then value of censor is 1, time will be derived as follows:
Last Available Date in the study - Date of Randomization + 1

Where, Last Available Date in the study = Maximum of (Date of Discontinuation, Date of Death, Date of Follow-up, Study Completion Date)

4.5 Analysis of Efficacy

4.5.1 Primary Efficacy Endpoint

4.5.1.1 Primary Efficacy Endpoint Definition

The primary efficacy endpoint is change from baseline in Pain On Movement (POM) on Day 5 of treatment as assessed by a 100 mm VAS scale.

4.5.1.2 Statistical Hypothesis, Model, and Method of Analysis

The hypothesis of the study is stated below:

H_0: The Diclofenac 2.32% DDEA Gel administered BID is inferior to Diclofenac1.16% DDEA gel administered QID.

$\mu_T - \mu_S \geq \delta$

Where, μ_S is the mean for a standard therapy (Diclofenac 1.16% DDEA Gel administered QID) and μT is the mean for test therapy (Diclofenac 2.32% DDEA Gel administered BID). δ is the non-inferiority margin of 13 mm.

H_1: Diclofenac 2.32% DDEA Gel administered BID is non-inferior to Diclofenac 1.16% DDEA gel administered QID.

$\mu_T - \mu_s < \delta$

δ=13mm

The primary efficacy analysis will be performed on PP population without imputation of missing data.The primary endpoint (Change from baseline in POM)will be analysed using

Analysis of Covariance (ANCOVA) model with treatment and center as factors and baseline POM as covariate.
Diclofenac 2.32% DDEA Gel administered BID will be declared non-inferior to Diclofenac 1.16% DDEA gel administered QID if the upper limit of the two-sided 95% confidence interval of the difference between their mean changes from baseline VAS POM responses is less than the established margin of 13 mm.
Refer sample SAS code in APPENDIX 4.

Assumptions of normality and homogeneity of variances in the ANCOVA model will be evaluated after study un-blinding. If violations are observed then the following will be performed as a post-hoc sensitivity analysis and results will be compared with primary analysis results:

1. Suitable data transformations will be tried to achieve the assumptions.
2. If suitable transformations cannot be found, then the non-parametric Van Elteren tests will be performed using center as strata.Two sided 95% CI and p value will be presented.

POM by 100 mm VAS analogue scale (CRF page: Pain on Movement ; variable VASSCRL)will be summarized over time (PPD) using mITT population. Also POM by 100 mmVAS analogue scale will be summerarized over time by center using mITT population (PPD). Above tables (PPD) will be repeated for the PP population. POM by 100 mm VAS analogue scale for COVID 19 patients if any will be summarized in PPD using mITT population.

Statistical analysis for the primary endpoint will be dispayed in the tables (PPD) with mITT and PP population respectively.

4.5.1.3 Supportive Analyses

1. To assess the treatment-by-center interaction an additional analysis will be performed for the primary endpoint on mITT population as following , where change from baseline on POM will be analysed using ANCOVA model with treatment, center as fixed factor, baseline POM as covariate and treatment-by-center as interaction (PPD)
   If there is evidence of an significant interaction ($p<0.05$) effect, then the primary endpoint outcome will also be summarized by center for further investigation and assessment.

Reference SAS code is given in APPENDIX 4:

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2. Sensitivity analysis will be perfomed on POM for compliance category -good. For good category greater than or equal to 80% compliance will be considered for both in application and amount of gel used for this sensitivity analysis. The sensitivity analysis for the primary endpoint will be dispayed in the tables (PPD) .
3. The primary efficacy endpoint will be analyzed using ANCOVA model on ITT population using imputed data.
4. The Change from baseline on POM will be analyzed using Mixed Model Repeated Measure (MMRM) with multiple imputation (day 3,5,8) model with treatment, center as fixed factor, baseline POM as covariate and visit as repeated measure; using ITT population.
5. Same as above mentioned point 3 without imputed data, ie, observed data.
6. Same as above point 3 using PP population.
7. Same as above point 4 using PP population.

Early discontinued subjects data due to any reason- will be analyzed in this section using imputation.

4.5.2 Secondary Efficacy Variables

The secondary efficacy analyses will be performed and also be listed on mITT and PP population.

- Change from baseline of POM (CRF page: Pain on Movement; VAS score will be obtained from VASSCRL) on VAS on days 3 and 8 respectively (PPD).
- Tenderness measured by pressure algometry on days 3, 5 and 8 which will be analysed using change from baseline and difference between the measurement in injured area (CRF page: Tenderness; measurement for study ankle : QS_INJA) and contralateral area (CRF page: Tenderness; measurement for study ankle : QS_CLTA) (PPD)..
- Change from baseline Ankle Joint Function (Karlsson Scoring Scale; CRF page: Ankle Joint Function: Variable : Total Score KSSTS) on days 3, 5 and 8 (PPD)..
- Circumference measurement of swelling on days 3, 5 and 8 which will be analysed using change from baseline in circumference of affected ankle and comparison to non-affected ankle by Figure of Eight method (CRF Page:Ankle swelling; Variables: FOEMINSC and FOEMCASC respectively.) (PPD)..

- Pain Intensity and Pain Relief (CRF Page: Subject Diary(Day 1/5) ; variables will used to calculate the Pain Intensity and Pain Relief are DPI and DPR respectively for each timepoint (DSTMPT))
- Pain Intensity (PPD).
    - Pain intensity will be analysed based on the Sum of Pain Intensity Difference (SPID). SPID is defined as from 0 -24 hours post first dose corresponding to day 1 and from 0-24 hours post first dose corresponding to day 5.
    - $SPID_t=\sum PID_t(time_t-time_{t-1})(h)$, where, PID_t=pain intensity score (DPI from CRF page corresponding to day); $time_t$=time in hours post first dose
- Pain Relief (PPD).:
    - Pain relief will be analysed based on the Total Pain Relief (TOTPAR). TOTPAR is defined as from 0-24 hours post first dose corresponding to day 1 and from 0-24 hours post first dose corresponding to day 5.
    - $TOTPAR=\sum R_t(time_t-time_{t-1})$, whert e R_t =pain relief score (DPR from CRF page corresponding to day)

4.5.3 Handling of Missing Values/Censoring/Discontinuations

As a part of missing data analysis a Multiple Imputation (MI) simulation method for imputing missing data will be conducted on ANCOVA analysis for the primary efficacy endpoints on the ITT population. This will help to assess the impact of missing data on the primary analysis.

Subjects who withdraw from the study prematurely will also be included in the statistical analyses up to the point of discontinuation.

The SAS procedure MI will be used and the details of MI procedure will be stated in the dataset specification document. If the data is monotone missing, an imputation model with regression baseline parameters will be applied, otherwise Markov Chain Monte Carlo(MCMC) will be applied. All variables included in the analysis model which are used in the primary model will be used for imputation andvalues at day 3 for the primary endpoint (For Day 5) will be included in the imputation model. To reduce the sampling variability from the imputation process, 50 datasets will be generated.
In the estimation step, separate analysis will be performed using the model mentioned for the primary endpoint statistical analysis Section 4.5.1.2.
After the completion of the estimation step SAS procedure MIANALYZE will be used to pool the estimates.
Refer APPENDIX 4 for sample SAS codes.

No imputation is planned for missing diary card pain intensity and relief assessments.

4.6 Analysis of Secondary Objectives

4.6.1 Efficacy (Secondary)

All the secondary endpoints POM at day 3 and 8, Karlsson score, tenderness, swelling and diary assessments (SPID and TOTPAR) will be analyzed using an ANCOVA model with treatment and center as fixed effect, baseline assessment for the corresponding endpoints as covariate. Treatment differences and two-sided 95% CI will be presented.

The secondary efficacy analyses will be performed and also be listed on mITT and PP population.

- Change from baseline of POM (CRF page: Pain on Movement; VAS score will be obtained from VASSCRL)on VAS on days 3 and 8 respectively (PPD).
- Tenderness measured by pressure algometry on days 3, 5 and 8 which will be analysed using change from baseline and difference between the measurement in injured area (CRF page: Tenderness; measurement for study ankle : QS_INJA) and contralateral area (CRF page: Tenderness; measurement for study ankle : QS_CLTA) (PPD)..
- Change from baseline Ankle Joint Function (Karlsson Scoring Scale; CRF page: Ankle Joint Function: Variable : Total Score KSSTS) on days 3, 5 and 8 (PPD)..
- Circumference measurement of swelling on days 3, 5 8 which will be analysed using change from baseline in circumference of affected ankle and comparison to non-affected ankle by Figure of Eight method (CRF Page:Ankle swelling; Variables: FOEMINSC and FOEMCASC respectively.) (PPD ;)..
- Pain Intensity and Pain Relief (CRF Page: Subject Diary(Day 1/5) ; variables will used to calculate the Pain Intensity and Pain Relief are DPI and DPR respectively for each timepoint (DSTMPT))
- Pain Intensity (PPD)
    - Pain intensity will be analysed based on the Sum of Pain Intensity Difference (SPID). SPID is defined as from 0 -24 hours post first dose corresponding to day 1 and from 0-24 hours post first dose corresponding to day 5.
    - $SPID_t=\sum PID_t(time_t-time_{t-1})(h)$, where, PID_t=pain intensity score (DPI from CRF page corresponding to day); $time_t$=time in hours post first dose

- Pain Relief (PPD)
  - Pain relief will be analysed based on the Total Pain Relief (TOTPAR). TOTPAR is defined as from 0-24 hours post first dose corresponding to day 1 and from 0-24 hours post first dose corresponding to day 5.
  - TOTPAR=$\sum R_t(time_t\text{-}time_{t-1})$, where R_t =pain relief score (DPR from CRF page corresponding to day)

4.6.2 Pharmacokinetic (Secondary)

Not Applicable

4.7 Analysis of Safety

4.7.1 Adverse Events and Serious Adverse Events

Adverse events (AE) recorded during the study will be mapped to a system organ class (SOC) and preferred term (PT) using the current medical dictionary for regulatory activities (MedDRA).

Treatment emergent adverse events (TEAEs) are defined as new AEs that occur on or after the date/time of the first administration of study product or worsens if AE started prior to start of first administration. .

Summary of all TEAE (PPD)will be presented with the following information –

- Number and % of subjects with at least one TEAE
- Time at risk in weeks (Patient-weeks [PW=YY.Y] = sum of the time on study in weeks=[(sum of the time on study in days) /7]
- Number of adverse events (cases)
- Exposure-Adj-TEAE in 100 weeks= 100*(number of patients with AE/sum of days at risk for AE) x 7days/weeks. It represents the number of events occurring in 100 Patient-Weeks
- P-value (P-value will be obtained from Poisson regression model with number of subjects with AE as dependent variable, treatment and treatment as independent fixed effect. logarithm of time at risk will be considered as offset. Risk ratio and 95% confidence interval will also be presented along with the p-value.)

Refer Appendix 4 for sample SAS code.

All other TEAE will be presented with the following information –

- Number of cases

- Number of subjects with AE
- % of subjects with AE

All the AE information will be taken from the Adverse Event CRF page.

The following summary tables and listings will be presented by treatment group and overall for safety population:

- Table of TEAEs by System Organ Class and Preferred Term (PPD)
- Table of Serious TEAEs by System Organ Class and Preferred Term (PPD)
- Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Intensity (PPD)
- Treatment Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term by Relationship status (PPD)
- Treatment Emergent Adverse Events by Preferred Term leading to Drug Withdrawal (PPD)
- Treatment Related Treatment Emergent Serious Adverse Events by Preferred Term (PPD)
- Treatment Emergent Adverse Events Leading to Study Discontinuation by Preferred Term (PPD)
- PPD All Treatment Emergent Adverse Events by Preferred Term
- Listing of all AEs (including all subjects: PPD) for all safety subjects.
- Listing of all Serious Adverse Events (PPD)

Additionally, all treatment-emergent adverse events will be listed (PPD).

Deaths occurring during treatment (if any) will be listed by treatment, including the date and study day of death, and the principal cause of death (PPD).

4.7.2 Laboratory Tests

Laboratory results will be summerised using safety population. Chemistry and hematology samples will be collected at Visit 1 (Screening/Baseline) and Visit 4 (Early D/C). The results will be summarized by visit and treatment. Descriptive statistics the mean, standard deviation, median, minimum and maximum values in each treatment group will be presented (PPD). Shifts in laboratory results for both chemistry and hematology will be presented in tables (PPD). Laboratory hematology, chemistry and Urine Pregnancy test parameters will be listed in PPD respectively.

As per the protocol following tests will be conducted for chemistry and hematology. Hematology related information should be mapped with Hematology CRF page and blood chemistry related information will be mapped with Chemistry CRF page. For other test Urine Pregnancy CRF page will be used.

Table 4-2 Laboratory Tests

Chemistry	Hematology	Other
BUN/Urea/Creatinine	Hemoglobin	Urine Pregnancy test
Glucose (fasting)	Hematocrit RBC count	
Calcium	Platelet count	
Sodium	WBC cont	
Magnesium	Total Neutrophil (Abs)	
Potassium	Eosinophil (Abs)	
Total CO2 (Bicarbonate)	Monocytes (Abs)	
AST, ALT	Basophils (Abs)	
Direct Bilirubin	Lymphocytes (Abs)	
Indirect Bilirubin		
Total Bilirubin		
Alkaline Phophatase		
Uric acid		
Albumin		
Total Protein		
PT/INR		

Definitions: RBC= Red blood cell; WBC= White blood cells; BUN=Blood urea nitrogen; HIV= Humanimmunodeficiency virus; AST= transaminase; ALT= alanine transaminase; PT/INR= prothrombin time/international normalized ratio;

Urine pregnancy test will be conducted at Visit 1 (Screening/Baseline) and Visit 4(Early D/C). Urine pregnancy test will be listed in PPD . Unire pregnancy related information will be taken from urine pregnancy test pafe from CRF.

All laboratory results will be listed including data from unscheduled visits. For lab summary and shift tables, the last available record/value for a particular lab test for a subject at a particular visit; will be considered for analysis. In case there are some unscheduled tests (irrespective of schedule visit or not) are conduted in any center due to some safety concerns then those tests will be listed. This information will be gathered from hematology and chemistry CRF page.

4.7.3 Vital Signs

Vital sign parameters will be summarized using safety population. Vital signs parameters sitting systolic and diastolic blood pressure (mmHg), sitting pulserate (beats/minute), height (cm) and

weight (kg) will be recorded at Visit 1(Baseline) and at Visit 4(Early D/C) and will be summarized by the mean, standard deviation, median, minimum and maximum values by visit and treatment group (PPD). Change from baseline in vital signs parameters will also be summarized in the above table. Vital signs at each assessment will also be listed (PPD). All Vital sign related information will be taken from Vital Signs CRF page.

4.7.4 Findings on Physical Examination

Physical examination (PE) performed at Visit 1 (Baseline) and Visit 4(Early D/C) will be listed (PPD) and the physical examination conditions (normal/abnormal/not examined) will be summerrized in PPD . Physical examination will include general condition, dermatologic, eyes, ears, nose, throat, neck, thyroid, heart, respiratory system, abdomen, kidneys, skeletal system, extremities, lymphatic system, CNS and neurological condition. All the PE information will be taken from Physical Examination CRF page.

4.7.5 COVID-19 Assessment

Covid-19 related assessment will be listed from COVID-19 Diagnosis CRF page using ITT population. If in case of any subject diagnosed with COVID-19 positive then the details of the diagnosis and treatment will be provided. (PPD)

4.8 Analysis of Other Variables

Not Applicable.

4.8.1 Quality of Life

Not Applicable

4.8.2 Patch Adhesion Performance

Not Applicable.

5 Changes to the Protocol Defined Statistical Analysis Plan

1. Rescue medication analysis has been performed considering time to event data. Whereas, protocol planned “Hodge Lehmann” analysis has not been performed.
2. For Pain Intensity and Pain Relief, as per protocol for Day 1 it is “Sum of 0-24 hrs” and “Sum of 96-120 hrs”. Based on discussion and time consideration Day 5 will also be displayed as “Sum 0-24 hours”.

3. Compliance-Sensitivity analysis: Subjects with good compliance has been added in analysis to check if there is any change in variability in POM.
4. There will be additional sensitivity analysis conducted for COVID 19 affected subjects for which protocol will not be updated.
5. The definition of Per Protocol Population has been modified in the RAP.
6. The protocol deviation criterion of compliance has been modified.

Any changes from the originally planned statistical analysis specified in the protocol are outlined in Table 3.

Table 3 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis section	**Statistical Analysis Plan**	**Rationale for Changes**
• Section 12, Subsection 12.2.6	• Section 4.4.3	• Rescue medication can be clearly analysed defining time to event data.
• Section 12, Subsection 12.2.6	• Section 4.5.2	• Sine the "Day 5", 96 hour is not actual 96th hour with respect to first treatment start time, so as per clinical consideration it's start of Day 5 and consider as 0 hour of Day 5.
• New addition	• Section 4.5.1	• Compliance Sensitivity Analysis: This analysis has been done to check if there is any change in variability in POM based on good compliance..
• New addition	• Section 4.7.5	• COVID analysis: As the pandemic started at the time of recruitment, as per regulatory requirement sensitivity analysis is planned for COVID patients, if any.
• Section 12.2. Subsection 12.2.1	• Section 4.2.3	• It was observed that most of the subjects has 50% ≤ weight compliance ≤ 80%. However these subjects has full and proper Pain on Movement measurements available. Based on these observations it has been decided to re look on the definition of PP Population.
• New addition	• Section 4.2.2	• For overdosed subjects the PP exclusion reason was updated as "Other deviation-weight compliance >=143% or application

Protocol	Reporting & Analysis Plan	
Statistical Analysis section	**Statistical Analysis Plan**	**Rationale for Changes**
		compliance >=143%" and for less dosed subjects, the PP exclusion reason was “Subjects with gel application compliance <= 80% or weight compliance <= 65% with study treatment”.

6 References

1. Refer Protocol Section 14 of “Reference”
2. Subject Case Report Forms 211206_Version 4.0_22JUN2020 – Unique

Appendix 1: Subgroups.

Not Applicable

Appendix 2: Center pools in multicenter studies.

Not Applicable

Appendix 3: Major Protocol Deviations Definitions.

Protocol deviations are the deviations from the procedure outlined in the protocol. All the protocol deviations (PDs) will be summarized by ITT population and will be listed using ITT population as obtained from Clinical Trial Management System (CTMS) logs. PDs will be identified and discussed with the Investigator/Sponsor in PD review discussion to categorize them, and to finalize analysis set assignment. PDs may include COVID 19 related deviations as. COVID 19 related deviations will be listed separately.

PDs will be grouped into the standardized terms, e.g., IP compliance deviation; Informed consent deviation; Study procedure deviation; or equivalent terms in the PD log will be used for reporting purpose in tables and listings.

Any PD will be categorized into one of the following severity categories:

Critical: A deviation from protocol-related procedure that threatens integrity of data, adversely affects subjects, and/or could invalidate acceptability of a project (or part of it). Such deviations require immediate action.

Major: A deviation from protocol-related procedures that could affect integrity of the data or adversely affect subjects. Such deviations require timely action.

Minor: A deviation from accepted procedures that will not adversely affect subjects or data integrity but should be dealt with appropriately.

Appendix 4: Sample SAS Code

SAS code for primary End point Analysis

Consider below mentioned SAS Code for primary model :

1a) Subset for PP population and

1b) Subset for mITT population

*the variance-covariance matrix structure will be selected based data.

SAS code for Supportive Analysis

*The variance-covariance matrix structure will be selected based on data

SAS code Repeated Measure Mixed Effect Model

*The variance-covariance matrix structure will be selected based on data

SAS code for Multiple Imputation

Step1: Check on the missing patten of the data

Step2: Based on the missing pattern decide on the method

Step3: SAS code for MI

Step4:to get combined estimate use following code:

SAS code for Rescue Medication Analysis:

SAS code for Poisson Regression for Adverse Event :

where,
1. nAE is number of patients with TEAE.

2. Logt=Logarithim (time to first AE or time at risk)(where time at risk = sum of (if a subject experienced an event it is time to first AE, if the subject did not experience event, it is time on study))

Appendix 5: Prohibited Medication

The following concomitant medications and/or therapies are prohibited:

- Systemic or topical NSAIDs;
- Steroids (injected or oral, except inhaled topical asthma and hayfever treatments and topical dermal treatments not applied to the sprained ankle);
- Physiotherapy (including, but not exclusive to, transdermal electro neural stimulation (TENS), ultrasound, massage, and spinal manipulation) or any other kind of pain therapy throughout the course of the study;
- Tranquilizers, anxiolytics, hypnotics, or sedatives, unless the subject's prescribed daily dose has been unchanged for a month before the randomization visit; this regimen must continue unchanged for the entire study;
- Amphetamines, barbiturates, benzodiazepines, cocaine, methamphetamines, opiates,phencyclidine, and tetrahydrocannabinol;
- Traditional, herbal or homeopathy treatments (oral and topical);
- Adhesive and/or immobilizing casts, bandages, Aircast splints, treatment by rest, ice,compression, or elevation (RICE) are not allowed.

Attachment 1: List of Data Displays

1. Work Sheet 1 is for CSR.

Study_211206 PPD