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Statistical Analysis Plan

Randomized, Controlled, Double-blind, Placebo-controlled, Multi-center Hypothesis-finding Trial to Compare the Efficacy and Safety of a 10% Naproxen Gel vs. a 2.32% Diclofenac Diethylamine Gel and Placebo in the Treatment of Acute Soft Tissue Injuries of the Lower Extremities.

(Study No.: 21559)

Protocol:

Version	Date	Description
4.0	09 Nov 2021	Final version/Amendment 3

SAP:

Version	Date	Author	Description
Final 1.0	09 February 2022	PPD	Final Version

SAP APPROVAL

Reviewed and Agreed by:

SAP Author:

PPD

PPD

Date

CRM Biometrics GmbH

SAP Reviewer:

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Abbreviations

Abbreviation	Abbreviation in Full
AE	Adverse Event
AMD	Advanced Micro Devices
ANCOVA	Analysis of Covariance
AUC	Area-under-the-curve
BL	Baseline
BMI	Body Mass Index
BP_d	Blood Pressure diastolic
BP_s	Blood Pressure systolic
CD	Compact disc
CMH	Cochran-Mantel-Haenszel test
CNS	Central nervous system
CRMB	Clinical Research Management Biometrics
CRF	Case Report/Record Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DD	Drug Dictionary
DMP	Data Management Plan
DBRM	Data Blind Review Meeting
FAS	Full Analysis Set
ICH	International Conference on Harmonization
ICTR	Integrated Clinical Trial Report
IEC	Institutional Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention-to-treat
LOCF	Last-observation-carried-forward
LS	Least squares
MD	Doctor of Medicine
MedDRA	Medical dictionary for regulatory activities
PAR	Pain-at-rest
POM	Pain-on-movement
PP	Per Protocol
REB	Research Ethics Board
QC	Quality control
SAE	Serious Adverse Event

Abbreviation	Abbreviation in Full
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard deviation
SoA	Schedule of Assessments
TFL	Tables/Figures/Listings
Vi	Visit i, i=1, 2, …, 7
VAS	Visual Analogue Scale
vs.	versus
WHO	World Health Organization

1 INTRODUCTION

General information on methods and procedures for the statistical evaluation are described in the Clinical Study Protocol (CSP), Final Version/Amendment 3, dated 09 November 2021. The Statistical Analysis Plan (SAP) presented here outlines the evaluations to be performed in the final statistical analysis, including details with respect to endpoint derivation, applied statistical methods, and presentation of the results.

This SAP refers to the latest version of the amended Study Protocol (Version 4.0). The SAP will be finalized after the Data Blind Review Meeting (DBRM) and contains a comprehensive and detailed elaboration of the statistical methodology section of the protocol.

2 DESIGN OF THE CLINICAL TRIAL

The study is a Phase II (proof-of-concept), randomized (2:2:1), double-blind, multi-center, active- and placebo-controlled, parallel group clinical trial to compare the efficacy and safety of 10 % Naproxen Gel versus a 2.32 % diclofenac diethylamine gel and placebo in the treatment of acute soft tissue injuries of the lower extremities, conducted in Germany.

Approximately 100 participants will be screened to achieve 75 randomized to study intervention for an estimated total of 30 evaluable participants per each active cohort and 15 participants in the placebo cohort.

The duration of each patient's participation in the study will be 6 consecutive days (from randomization (V1) to Final Visit (V11)).

3 TIME SCHEDULE

The study consists of 11 visits: randomization visit (Visit 1, 0 h, Day 1), and post-baseline visits Visit 2 (12 h after first treatment, Day 2), Visit 3 (24 h after first treatment, Day 2), Visit 4 (36 h after first treatment, Day 3), Visit 5 (48 h after first treatment, Day 3), Visit 6 (60 h after first treatment, Day 4) and Visit 7 (72 h after first treatment, Day 4), Visit 8 (84 h after first treatment, Day 5), Visit 9 (96 h after first treatment, Day 5) Visit 10 (108 h after first treatment, Day 6), and final Visit 11 (120 h after first treatment, Day 6). A detailed schedule of Assessments is presented in the CSP, Final Amended Version 4.0 approved 09 November 2021, Chapter 1.3, p. 13.

4 TRIAL OBJECTIVES

4.1 Primary objective

To assess the effectiveness of a naproxen topical gel 10% diclofenac diethylamine 2.32%, and placebo for relieving tenderness to pressure in subjects with acute soft tissue injuries of the lower extremities.

4.2 Secondary objectives

The secondary objectives are:

- To assess the safety of a naproxen gel 10% diclofenac diethylamine gel 2.32% and placebo during a 5-day treatment period;
- To assess adverse events.

4.3 Other objectives

To evaluate pain on movement and tenderness to pressure over various time periods and at individual time points.

5 SUBJECTS ASSESSMENTS

5.1 Efficacy variables

5.1.1 Primary efficacy variable

The primary efficacy outcome is Tenderness (Algometry) over the initial 72 hours (Algometry AUC_{0-72}).

5.1.2 Other efficacy variables

Other efficacy variables are:

- VAS POM over the initial 12-hours (VAS AUC_{0-12}), 24-hours (VAS AUC_{0-24}), 36-hours (VAS AUC_{0-36}), 48-hours (VAS AUC_{0-48}), 60-hours (VAS AUC_{0-60}), 72-hours (VAS AUC_{0-72}), and 120 hours (VAS AUC_{0-120});
- Change of VAS POM at hours 12, 24, 36, 48, 60, 72 and 120 from baseline (BL);
- VAS POM over the initial 72-hours (VAS AUC_{0-72}) in the subgroups “sprain/strain” and “contusion”.
- Change of Algometric Tenderness (N/cm²) at hours 12, 24, 36, 48, 60, 72, and 120 from baseline;
- Algometric Tenderness (N/cm^2) over the initial 12-hours (N/cm^2 AUC_{0-12}), 24- hours (N/cm^2 AUC_{0-24}), 36-hours (N/cm^2 AUC_{0-36}), 48-hours (N/cm^2 AUC_{0-48}) 60-hours (N/cm^2 AUC_{0-60}) and 120 hours (N/cm^2 AUC_{0-120});
- Ratio of algometry injured/contralateral sites over 72 hours and 120 hours (N/cm^2 Ratio AUC_{0-72} and N/cm^2 Ratio AUC_{0-120});
- Algometry over the initial 72-hours (N/cm^2 AUC_{0-72}) in the subgroups “sprain/strain” and “contusion”.
- Percent of subjects with no (zero) VAS POM at 120 hours;
- Global assessment of treatment efficacy at 24 hours, 48 hours, 72 hours, and 120 hours by patients using a 5-point scale (0=none, 1=poor, 2=fair, 3=good, 4=excellent);
- Global assessment of treatment efficacy at 72 hours in the subgroups “sprain/strain” and “contusion”.
- Change of VAS PAR at hours 12, 24, 36, 48, 60, 72 and 120 from baseline (BL).

5.2 Safety variables

Secondary efficacy variables are:

- Safety (percentage of subjects with at least one TEAE);
- Incidence of adverse events.

The following parameters are recorded to assess the safety of the study drug:

- Adverse events (AEs).
  AEs will be documented at Visit 1 to Visit 11.

- Vital signs and body temperature.

Pulse rate (bpm) and blood pressure (BP_s, BP_d (mmHg) as well as body temperature will be documented at the Baseline Visit (Visit 1), Visit 7, and Final Visit (Visit 11)).

- General physical examination.
  Physical examination will be performed at Visit 1 (randomization visit), Visit 2, Visit 4, Visit 6, Visit 8, and Visit 10, as well as when judged necessary by the Investigator.
  A general physical examination will be performed at Visit 1 and include the injured extremity and assessments of the Dermatological, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems.

  A limited physical examination of the injured extremity will be performed at Visits 2, 4, 6, 8 and 10. Any issues will be described as adverse event.

  Examination will include general condition, dermatologic, eyes, ears, nose, throat, neck, thyroid, heart, respiratory system, abdomen, kidneys, skeletal system, extremities, lymphatic system, CNS, neurological conditions and other (to be specified).

- Height and body weight.
  Height in centimeters (cm, without shoes) and body weight (kg, in indoor clothing, but without shoes) will be measured at Visit 1. The corresponding Body Mass Index (BMI) will be calculated.

- Pregnancy and assessments of fertility.
  Female participants of child-bearing potential will undergo urine pregnancy testing at Visit 1 (prior to first dose) and Visit 10 (prior to last dose).

- Global tolerability
  Global tolerability will be assessed by the investigators and the patients according to the following numerical scale at Visits 3, 5, 7, and 11, respectively:
  0: poor
  1: fair
  2: good
  3: very good
  4: excellent.

- Sensory questions
  During the final visit of the study (Visit 11), patients will be asked two sensory questions related to the IMP they received.

5.3 Other variables

The following other variables are documented in this clinical trial:

- Demographics and other baseline characteristics (documented at Visit 1; age, sex, height, weight, race, ethnicity, localization of injury).
- Check of contraception (at Visit 1).
- Medical history and concomitant diseases (at Visit 1).
- Prior and concomitant medication (every visit)
- Diary review.

5.4 Derived variables

Area under the curves, calculated using the trapezoidal rule [1], will be determined for POM VAS pain scores and algometric tenderness. For quantitative variables the absolute changes from baseline (Visit 1) will also be determined.

5.5 Withdrawal/discontinuation

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for efficacy and safety. See the SoA for data to be collected at the time of discontinuation of study intervention for any further evaluations that need to be completed.

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon. At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention and from the study at that time. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

A participant will be considered lost if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 2 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

The investigator will be responsible for informing the IRB/REB/IEC of the early termination of the study. Clinsearch will be responsible for notifying IECs, local authorities and the German Competent Authority, of the early termination.

5.6 Schedule of assessments

The following table shows the amended Assessment Schedule of the clinical trial.

Table 5-1: Schedule of Assessments – amended

Trial Procedure	Screening Phase		Treatment Phase										
	Screening	Baseline	Day 1	Day 2		Day 3		Day 4		Day 5		Day 6	
	Day 1		Day 1	Day 2	Day 3	Day 3	Day 3	Day 4	Day 4	Day 5	Day 5	Day 6	Day 6
	Visit 1		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
	Hours Post First Dose ➡			12 hrs	24 hrs	36 hrs	48 hrs	60 hrs	72 hrs	84 hrs	96 hrs	108 hrs	120 hrs
Signed Informed Consent	X												
Inclusion/Exclusion Criteria Review	X												
Patient Demographics	X												
Medical History	X												
Prior and Concomitant / Medication History and Diary Review[a]	X			X	X	X	X	X	X	X	X	X	X
History of drug, alcohol and tobacco use	X												
Body weight, height, and BMI	X												
Vital signs (incl. temperature)[b]	X								X				X
Physical examination (injury assessment)[c]	X			X		X		X		X		X	
Injury Stratification (cohort)	X												
Urine pregnancy test	X[f]											X[f]	
Diary distribution/training	X												
Randomization/Kit assignment		X[d]											
IMP administration[e]			X	X	X	X	X	X	X	X	X	X	
Dispense rescue medication		X											
Rescue medicine accountability				X	X	X	X	X	X	X	X	X	X
Algometry		X	X	X	X	X	X	X	X				X
POM VAS		X	X	X	X	X	X	X	X				X
Global Assessments					X[g]		X[g]		X[g]				X[g]
Sensory Questions													X
Diary and rescue medicine return													X
End of Study (pt. discharged)													X
Adverse events			X	X	X	X	X	X	X	X	X	X	X

[a] Diary review begins at Visit 2
[b] Vital signs (blood pressure, respiratory rate, heart rate and body temperature after 5 minutes of rest in a sitting position).
[c] Full physical exam and injury assessment at Visit 1, limited exam (injury assessment) at all other visits
[d] Randomization to treatment occurs only for eligible patients.
[e] All topical IMP treatments must be weighed on a digital scale, then applied by the unblinded study staff at the site. Patient will wear a blindfold when being treated.
[f] Urine pregnancy test must be performed (for female patients) and the results must be negative (not pregnant) before dosing.
[g] Assessments by the patient will be completed before first rescue medication is taken. If between visits, then the investigator will complete assessments at the next scheduled visit.

6 SAMPLE SIZE

This is a proof-of-concept study and therefore a specific statistical power calculation cannot be applied, however, assuming a comparable effect of the test gel vs. diclofenac – as suggested by pharmacological studies, reference is made to similar studies (Predel, Br J Sports Med 2004;38:318–323), in which the standardized effect sizes of Algometry AUC 0-72 and POM VAS AUC 0-72 were over 1; with 30:15 patients, a drop-out rate of 10 %, and a two-sided significance level $\alpha = 5$ %, a power $1 - \beta$ of about 80 % is reached.

7 DATA ENTRY AND VALIDATION

The data entry of all records documented in the CRFs is carried out by two independent data entry persons and result in two different data sets, which will be compared. Trial Master File will be corrected until conformity is proved. Furthermore, the data will be analyzed for completeness and several plausibility checks will be carried out (see Chapter 10).

8 COMPUTER SYSTEMS, SOFTWARE, AND VALIDATION OF PROGRAMS

8.1 Hardware

Used Hardware at CRMB is:

- Network servers:
- TERRA SERVER 6530 G3, 946 GB SSD, 16 GB RAM.
- Desktops (workstations):
  6 Desktops based on AMD and Intel
- Scanners:
  F-Secure Antivirus 7.0 for Windows Server
  ESET NOD 32 Antivirus Version 9 is used on the desktops
- Backup method:
  Continuous backup using VEEM.
  On every Friday a full backup with Acronis True Image echo for Windows server is performed (system and data). For the rest of the week a differential backup is created. The backups are stored on internal (RAID 5) and external hard discs.

8.2 Software

Used Software at CRMB is:

- DMSys from Sigmasoft, Version 5.1,
- SAS Version 9.4,
- Windows Server 2019 Network servers,
- Windows 10 on Workstations,
- Microsoft Office 2019 and Adobe Professional for reports, tracking of CRFs.

The data management is performed using the validated Data Management System DMSys, Version 5.1, and the statistical analysis is performed using the validated statistical analysis program SAS, Version 9.4 under Windows 10.

8.3 Validation of programs

All SAS programs start with a header in which the following information is contained:

- Name of the program,
- author,
- date of creation,
- used analysis DATA sets.

All tables, graphics and listings contain in footer the name of the program with which they were created, and the date of creation.

All formats will be filed in a permanent format catalogue.

All SAS programs will be checked by a second SAS programmer responsible for the quality control (QC). He/she will also check all LOG files for ERROR messages and WARNINGS. ERRORs must not occur. WARNINGs must be checked as to whether they lead to wrong results. Furthermore, the SAS programmer responsible for the QC will check the tables, figures, and listing for completeness and consistency. The review will be documented on the Program Validation Form.

The biometrician responsible for evaluation will make sure that the specifications of planned analysis have been correctly converted in SAS programs.

8.4 Restitution of programs

All SAS programs used in the analysis as well as the OUTPUT (listings, tables) will be stored, and archived together with the source code of the programs at CRM Biometrics GmbH.

9 CODING

Concomitant medications will be coded by means of the Drug Dictionary (WHO-DD, June 2021). Adverse events and diseases will be coded using MedDRA (Version 24.0), respectively.

10 DATA CHECKS

Before starting the statistical analysis, plausibility checks will be performed. A detailed list of edit checks can be found in the Data Management Plan (DMP, Appendix 5).

11 QUERIES

After performing the plausibility checks and the comparisons of the two data entry databases, the errors of the data entry will be corrected. Queries/Data Clarification Forms will be generated in the case of inconsistencies or missing data in the CRF. According to the resolved queries, changes of the data will be performed in the Master file, if necessary. In the case of remaining unsolved queries, the Principal Investigator, the responsible statistician, the medical advisor and the project manager will decide how to handle these data and all decisions taken will be documented in detail.

12 BLIND REVIEW

A data blind review meeting will take place before unblinding the randomization code. Any potential factors that could lead to unblinding of the study will be considered before this review. A listing of all protocol deviations with the proposed classification into minor and major protocol deviations and a list of all data irregularities or unresolved queries and a proposal for how the data are to be handled in the analysis, if necessary, will be provided in the Blind Review Meeting. At least the responsible biometrician and the Clinical Project Manager will sign the Blind Review protocol.

13 DATABASE CLOSURE

After all queries have been replied, the master file will be corrected, if necessary, and the decisions regarding the handling of the unresolved queries will be made, and the database will be closed.

14 STATISTICAL EVALUATION

14.1 General

All statistical analyses will be performed in accordance with the ICH E9 guideline.

14.2 Analysis populations

The following analysis populations will be used for analysis of study data:

Safety population: The safety population will include all randomized patients who received at least one dose of the IMP. Safety (e.g., AEs) will be analyzed in this population.

Intent to treat (ITT)/ Full Analysis Set (FAS): All subjects who are randomized and provide at least one measure of primary efficacy parameters after the first application of IMP.

Per protocol (PP) population: The Per Protocol population will include all subjects in ITT who complete the study and do not have any major protocol violations. Any exclusion from PP Population will be determined and documented prior to the database lock. The primary efficacy analysis population will be PP population and ITT/FAS Population will be secondary. The same analysis on ITT/FAS Population will be repeated for the primary and secondary and other efficacy endpoints to assess the robustness of the results based on PP Population.

Before the study is unblinded, each actual post-baseline visit will be mapped to the target visit time to which it is chronologically closest. The numbering of the actual visits (from Visit 1 to Visit 11) will then be changed as needed to improve the correspondence of the actual visit times to the protocol-specified schedule. Final determinations will also be made and documented before the study is unblinded to address visits that are equidistant to two nominal visit times or any other irregularities.

Before the study is unblinded, the timing of the diary assessments will be reviewed, and assessments will be reclassified into time slots as appropriate to ensure that all assessments in a given comparison were made a comparable amount of time after start of treatment.

14.3 Patient disposition and characteristics

Demography and other baseline characteristics will be summarized descriptively for both the FAS and Safety population (if different), overall and by treatment group. Demography and other baseline characteristics will be summarized descriptively overall and by treatment group as well as by subgroup (sprains/strains, contusions). For quantitative data, means, medians, standard deviations and extremes will be determined. For qualitative data, absolute and relative frequencies will be calculated. Important baseline characteristics will be further summarized by sex, race and age.

14.4 Efficacy

14.4.1 Primary efficacy variable

The primary efficacy variable is:

- Tenderness (Algometry) over the initial 72 hours (Algometry AUC_{0-72}).

For the comparison of the test gel vs. placebo, the primary efficacy hypothesis to be tested is the equality of Algometry $AUC_{0-72.}$, i. e.

$$H_0: \mu_T = \mu_P \text{ vs. } H_1: \mu_T \neq \mu_P.$$

The primary efficacy endpoint will be analyzed using analysis-of-covariance (ANCOVA) with treatment as the factor and baseline tenderness (algometry) as the covariate. Pair-wise comparisons may be made from above model.

The primary analysis population is the Per protocol population (PP).

14.4.2 Secondary efficacy variables

Secondary efficacy variables are:

- Safety (percentage of subjects with at least one TEAE);
- Incidence of adverse events.

14.4.3 Other efficacy variables

Other efficacy variables are:

- VAS POM over the initial 12-hours (VAS AUC_{0-12}), 24-hours (VAS AUC_{0-24}), 36-hours (VAS AUC_{0-36}), 48-hours (VAS AUC_{0-48}), 60-hours (VAS AUC_{0-60}), 72-hours (VAS AUC_{0-72}), and 120 hours (VAS AUC_{0-120});
- Change of VAS POM at hours 12, 24, 36, 48, 60, 72 and 120 from baseline (BL);
- VAS POM over the initial 72-hours (VAS AUC_{0-72}) in the subgroups “sprain/strain” and “contusion”.
- Change of Algometric Tenderness (N/cm^2) at hours 12, 24, 36, 48, 60, 72, and 120 from baseline;
- Algometric Tenderness (N/cm^2) over the initial 12-hours (N/cm^2 AUC_{0-12}), 24- hours (N/cm^2 AUC_{0-24}), 36-hours (N/cm^2 AUC_{0-36}), 48-hours (N/cm^2 AUC_{0-48}) 60-hours (N/cm^2 AUC_{0-60}) and 120 hours (N/cm^2 AUC_{0-120});
- Ratio of algometry injured/contralateral sites over 72 hours and 120 hours (N/cm^2 Ratio AUC_{0-72} and N/cm^2 Ratio AUC_{0-120});

- Algometry over the initial 72-hours (N/cm^2 AUC_{0-72}) in the subgroups "sprain/strain" and "contusion".
- Percent of subjects with no (zero) VAS POM at 120 hours;
- Global assessment of treatment efficacy at 24 hours, 48 hours, 72 hours, and 120 hours by patients using a 5-point scale (0=none, 1=poor, 2=fair, 3=good, 4=excellent);
- Global assessment of treatment efficacy at 72 hours in the subgroups "sprain/strain" and "contusion".
- Change of VAS PAR at hours 12, 24, 36, 48, 60, 72 and 120 from baseline (BL).

Figures will show the time course of outcomes by treatment group for the key quantitative outcomes VAS POM, Change of VAS POM, Algometric Tenderness and Change of Algometric Tenderness. A Kaplan-Meier plot of zero VAS POM scores will also be performed, with the first time point with zero VAS POM and all subsequent VAS POM scores are zero. The primary outcome will also be summarized by center (if there is evidence of a treatment-by-center interaction), sex, age and race but without formal statistical comparisons of treatments.

For quantitative outcomes assessed each null hypothesis will be tested with an analysis-on-covariance (ANCOVA) model including treatment group and center as main effects, and the baseline value as covariate (those outcomes for which there is a baseline). The model will be fit both with and without the treatment-by-center interaction. The primary model will be the model without the interaction. If the treatment/center interaction is statistically significant ($p<0.05$), additional ANCOVAs will be run to identify the center(s) driving the interaction and to lay out the evidence for efficacy among the centers whose results are concordant and centers driving the interaction. ANCOVA outputs will be presented in the Statistical Appendix for the primary and various secondary outcomes to allow an outside reviewer to assess the acceptability of the primary statistical model.

The treatment effects will be estimated as mean differences between the active and placebo groups and between the two active groups with 95% confidence intervals.

The percentage of subjects with no VAS POM at 120 hours will be analyzed by means of Fisher's exact test.

The ordinal outcome (global assessment of treatment efficacy)) will be analyzed by the Cochran-Mantel-Haenszel test of general association, stratified by center and also by subgroup (strain/sprain, contusion).

Statistical test results for secondary variables will only be interpreted exploratorily.

14.5 Safety

The assessment of safety will be based mainly on the frequency of AEs that are treatment-emergent in the Safety Population. Formal statistical tests will not be conducted for differences in safety parameters between treatment groups. Only descriptive analyses will be conducted.

The incidence of all treatment-emergent AEs will be after grouping by body system and preferred term. For each preferred term and summarized over each body system overall, the table will present the number of patients in each treatment group in whom the event occurred and the rate (%) of occurrence. The incidence of all suspected-drug-related AEs will be tabulated similarly. The incidence of all treatment-emergent AEs will also be tabulated by severity

categories and relationship to the IMP. Seriousness, severity, relationship to IMP duration and outcome will also be listed.

Safety will also be summarized with respect to vital signs as mean levels by visit and change from baseline. Abnormal observations on physical exams will be listed.

The ordinal outcome (global assessment of tolerability) will be analyzed by the Cochran-Mantel-Haenszel test of general association, stratified by center and also by subgroup (strain/sprain, contusion).

Furthermore, the ordinal outcome (sensory questions) will also be analyzed by the Cochran-Mantel-Haenszel test of general association, stratified by center and also by subgroup (strain/sprain, contusion).

Listings of individual data will be presented.

14.5.1 Adverse events

Adverse events will be coded according to MedDRA, Version 24.0.

The incidence of all treatment-emergent AEs will be tabulated after grouping by body system and preferred term. For each preferred term and summarized over each body system overall, the table will present the number of patients in each treatment group in whom the event occurred and the rate (%) of occurrence. The incidence of all suspected-drug-related AEs will be tabulated similarly. The incidence of all treatment-emergent AEs will also be tabulated by severity categories.

14.5.2 Other variables related to safety

Summary statistics for the absolute vital sign value and the changes from baseline will be presented using n, mean, standard deviation, median, minimum, and maximum.

Abnormal observations on physical examinations will be listed.

Furthermore, weight, pregnancy and assessments of fertility data will only be listed.

14.6 Multi-site study

Individual site results will be presented by means of descriptive statistical methods for the demographical and primary efficacy data. Moreover, the treatment-by-site interaction will be assessed by means of an ANCOVA model for the primary variable and other selected secondary variables.

14.7 Multiplicity

In this Phase II and proof-of-concept study all endpoints will be summarized descriptively by treatment. Statistical tests will be conducted at the significance level of 5 % and no multiplicity adjustments will be made.

14.8 Missing data

- If assessments at any visit for Visits 2 (12 h) through Visit 10 (108 h) are missing, they will be imputed as the average of the preceding and the following assessments. Fractional values will be rounded down (including ordered categorical assessments). If assessment at Visit 11 is missing, the last observation will be carried forward.
- If a patient terminates prematurely,
  - all subsequent visits will be imputed by carrying the last non-missing observation forward,
  - for an adverse event suspected to be study-drug-related, then all subsequent visits will be imputed by carrying the baseline observation forward,
  - for lack of efficacy, all subsequent assessments will be imputed as the worst of all documented assessments,
  - for lack of efficacy or for an adverse event suspected to be study-drug-related and does not complete the global assessment of treatment satisfaction, it will be assigned the worst possible score,
  - If a patient discontinues for any other reason, missing global assessments at Visit 11 will be imputed by the worst possible outcome.
- If a patient assesses efficacy at the site < 6 hours after using rescue medication, imputation will be discussed in the Blind Review Meeting, with consideration given to the frequency of this issue in the database and the elapsed time between rescue and assessment of efficacy.
- If a patient assesses spontaneous pain intensity and spontaneous pain relief at the time of rescue taken because of blunt trauma pain, any assessment conducted in the following 6 h will be replaced by the corresponding assessment done at the time of rescue.
- If the patient provides no post-baseline efficacy data, imputation will be considered in the Blind Review Meeting.

A Blind Review Meeting will take place before unblinding the randomization code. Handling of missing values/censoring/discontinuation, if necessary, will be provided and discussed in the Blind Review Meeting. Additional data handling rules will be specified in the BRM minutes to cover issues not anticipated in the above stipulations.

14.9 Interim Analysis

Not applicable.

14.10 Subject disposition

Subject disposition data (number of subjects screened, assigned to treatment, completing each assessment and the primary reason for withdrawal, number of each analysis population, subjects excluded from each analysis population) will be summarized overall for all subjects.

A by-subject listing will be provided showing all screened subjects who were not eligible to be assigned to treatment together with the reason for non-eligibility.

Number and percentage of subjects assigned to treatment who discontinued the study prematurely will be summarized for the overall population and stratified by reason for study discontinuation. Multiple reasons are possible.

A by-subject listing will be provided showing for all subjects assigned to treatment whether they completed study (yes/no), the reason(s) for study discontinuation (where applicable), and the dates of:

- the informed consent,
- the first application of study medication,
- the last application of study medication,
- discontinuation / withdrawal, where applicable.

14.11 Extent of exposure

For each subject, the individual study duration will be calculated in days as "$d_{lastVisit} - d_{Visit\ 1} + 1$", where $d_{lastVisit}$ is the date of last visit documented and $d_{Visit\ 1}$ is the date of Visit 1, respectively.

Exposure to IMP will be summarized descriptively as (1) number of applications made and (2) Study duration (in days).

Summary statistics will be tabulated for the safety population.

14.12 Treatment compliance, rescue medication, other concomitant therapies

Compliance is defined in terms of the total number of study medication used and total number of applications made through Visit 11 as follows:

- Good: > 80% of the application has been applied and > 80% of scheduled applications made,
- Moderate: not Good and not Poor
- Poor: < 50% of the application has been applied or < 50% of scheduled applications made.

Compliance in patients with missing data will be documented in the Blind review meeting before unblinding.

The % of applications used through Visit 11 will be computed relative to the actual number of applications made from randomization through Visit 11. Scheduled applications will include all scheduled applications through Visit 11.

Compliance will be summarized descriptively as (1) % of scheduled applications made, (2) % of applications used relative to number of actual applications and (3) compliance category (Good/Moderate/Poor).

Use of concomitant therapies will be listed. Use of rescue medication will also be listed. Exposure to study drug will be summarized descriptively as (1) number of applications made and (2) total amount of gel used.

14.13 Medical history

Diseases will be coded according to MedDRA Version 24.0.

Details of the Medical History will be listed.

14.14 Previous and concomitant medications

Medications will be coded by means of DRL (WHO-DD).

A previous medication is a medication used only before the date of first dose of study medication (medication end date < date of first dose of study medication). All other medications are concomitant.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study medication. Medications will be assumed to be concomitant, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started and stopped prior to the first dose of study medication. If there is clear evidence to suggest that the medication stopped prior to the first dose of study medication, the medication will be assumed to be previous.

Medications starting after the completion/withdrawal date will be listed but will not be classified or summarized.

Information on previous and/or concomitant medication will be listed with flags to differentiate previous and/or concomitant medications.

15 LANGUAGE AND HEADINGS

All tables, figures and listings as well as the Integrated Clinical Trial Report (ICTR)/Clinical Study Report (CSR) will be produced in English language.

16 ARCHIVING

After the finalization of the analysis and the reporting, the following documents will be provided to the sponsor for archiving purposes:

- the CRFs,
- the resolved queries,
- the Statistical Analysis Plan (pdf format),
- the Blind Review protocol (pdf format),
- database on CD (SAS files),
- the Clinical Study Report (CSR) (WORD 2010 format and pdf format).

17 LIST OF STAFF

A list of key study personnel can be found in the Data Management Plan (DMP, Appendix 1).

18 REFERENCES

[1] Gibaldi M, Perrier D. Estimation of Areas. Pharmakokinetics. Marcel Dekker Inc, New York, 1982, 445-449.