Statistical Analysis Plan

Randomized, controlled, double-blind, multi-center trial to evaluate the efficacy and safety of an Esflurbiprofen Hydrogel Patch vs. placebo in the local symptomatic and short-term treatment of pain in acute strains, sprains or bruises of the extremities following blunt trauma, e.g. sports injuries.

(Study No.: TK-254R-0201, EudraCT-No.: 2020-005165-14)

Protocol:

Version	Date	Description
3.0	08 March 2021	Final version

SAP:

Version	Date	Author	Description
Draft 1.0	20 August 2021	[redacted]	Initial Version
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SAP APPROVAL

Reviewed and Agreed by:

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Date

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Abbreviations

Abbreviation	Abbreviation in Full
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical, therapeutical, chemical
AUC	Area under the curve
b. i. d.	bis in die, two times daily
BL	Baseline
BP_d	Blood Pressure diastolic
bpm	Beats per minute
BP_s	Blood Pressure systolic
CMH	Cochran-Mantel-Haenszel
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
IMP	Investigational Medicinal Product
LOCF	Last-observation-carried-forward
LS	Least squares
MedDRA	Medical dictionary for regulatory activities
PID	Pain Intensity Difference
POM	Pain-on-movement
PP	Per Protocol
o. d.	once daily
QC	Quality control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SPID	Sum of Pain Intensity Difference

TFL	Table/Figure/Listing
Vi	Visit i, i=1, 2, …, 7
VAS	Visual Analogue Scale
vs.	versus
WHO	World Health Organization
WOCBP	Women of child-bearing potential

1 INTRODUCTION

General information on methods and procedures for the statistical evaluation are described in the Clinical Study Protocol (CSP), Final Version 3.0 dated 08 March 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 Study Protocol. There were no amendments to the CSP in this clinical trial. 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, double-blind, multi-center, placebo-controlled, parallel group clinical trial of the efficacy and safety of Esflurbiprofen Hydrogel Patch applied once a day versus placebo patch applied once a day in the local symptomatic and short-term treatment of pain in acute strains, sprains or bruises of the extremities following blunt trauma, conducted in Germany.

It is planned to include a total of 200 patients (100 patients per active group and 100 per placebo group) in 3 sites.

The duration of each patient's participation in the study will be 7 (+1) consecutive days (from randomization (V1) to Final Visit (V7)).

3 TIME SCHEDULE

The study consists of 7 visits: randomization visit (Visit 1, 0 h, Day 1), and post-baseline visits Visit 2 (12 h (±1 h) after first treatment, Day 1 or 2), Visit 3 (24 h (±2 h) after first treatment, Day 2), Visit 4 (48 h (±4 h) after first treatment, Day 3), Visit 5 (72 h (±4 h) after first treatment, Day 4), Visit 6 (96 h (±4 h) after first treatment, Day 5) and Visit 7 (168 h (±24 h) after first treatment, Day 8 (± 2 days)). A detailed schedule of Assessments is presented in the CSP, Final Version 3.0 dated 08 March 2021, Table 7-1, p. 30.

4 TRIAL OBJECTIVES

4.1.1 Primary objective

To evaluate the efficacy of a Esflurbiprofen 165 mg Hydrogel Patch applied once a day compared with placebo in patients with acute blunt, soft tissue injuries of the limbs.

4.1.2 Secondary objectives

The secondary objectives are:

- To assess the efficacy of Esflurbiprofen Hydrogel Patch compared with placebo by means of secondary efficacy variables.

- To assess the safety of Esflurbiprofen Hydrogel Patch compared with placebo applied once a day for up to seven days.

5 SUBJECTS ASSESSMENTS

5.1 Efficacy variables

5.1.1 Primary efficacy variable

The primary efficacy outcome is pain-on-movement (POM) change from baseline assessed by Visual Analogue Scale (VAS) to Visit 5 (72 hours after initiating treatment).

5.1.2 Secondary efficacy variables

- POM at injured site in mm measured using a 100 mm VAS at 12, 24, 48, 72, 96 and 168 hours after commencement of study treatment and will additionally presented by subgroups (table and Figure).
- AUC over time during first 12, 24, 48, 72, 96 and 168 hours for POM measured using a VAS; ordinate = POM score in mm, abscissa = time after treatment
- Pain-at-rest (PAR) at injured site in mm measured using a 100 mm VAS at 12, 24, 48 72, 96 and 168 hours.
- Reduction in VAS for POM from baseline:
  - Time to meaningful reduction (30%)
  - Time to optimal reduction (50%)
  - Time to complete resolution of pain
- Responder rate 1 (defined as the proportion of patients achieving ≥50% reduction from baseline in the VAS score for POM at 72 hours)
- Responder rate 2 (defined as the proportion of patients able to resume training / normal physical activity by 168 hours)
- Clinical global assessment of efficacy as judged by investigator and patient at 48, 72 and 168 hours
- Overall dose of rescue medication needed (paracetamol).
- POM on VAS by indication at Visit 5.

Additional outcomes

- Adhesive power of patch (5-point scale)
- Mean adhesion by application site and/or net use.
- If there is significant use of rescue medication, a sensitivity analysis may be performed to assess impact on primary endpoint and responder rate.
- Outcomes will be compared for all use of rescue medication and separately for use to treat blunt trauma. Day 1 and the day of the final visit will count as full days for this purpose. Use of rescue medication on days after study medication has been discontinued will not be counted.
- POM on VAS difference at V4, V5, V6 compared to V1 (BL) (PID V4, PID V5, PID V6) PID V4, PID V5 and PID V6 will be compared between treatment groups using ANCOVA with terms in the model for treatment group, site [as fixed effects], and baseline POM assessment [as a covariate]. Least square mean for each treatment and the

corresponding difference between least square means with the p-value and 95 % confidence interval will be presented from the specified ANCOVA model.

- Sum of Pain Intensity differences (SPID) over 0-24, 0-48, 0-72 and 0-96 hours.
  SPID over 0-24, 0-48, 0-72 and 0-96 hours will be compared between treatment groups using ANCOVA with terms in the model for treatment group, site [as fixed effects], and baseline POM assessment [as a covariate]. Least square mean for each treatment and the corresponding difference between least square means (Active - placebo) with the p-value and 95 % confidence interval will be presented from the specified ANCOVA model.

5.2 Safety variables

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

- Adverse events (AEs).
  AEs will be documented at Visit 2 to Visit 7.

- Vital signs.
  Pulse rate (bpm) and blood pressure (BP_s, BP_d (mmHg) will be documented at the Baseline Visit (Visit 1) and Final Visit (Visit 7)).

- General physical examination.
  Physical examination will be performed at Visit 1 (randomization visit) and at Visit 7 (final visit), as well as when judged necessary by the Investigator. 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 weight.
  Height in centimeters (cm, without shoes) and body weight (kg, in indoor clothing, but without shoes) will be measured at Visit 1. Body weight only will also be measured at Visit 7.

- Pregnancy and assessments of fertility.
  All women of child-bearing potential (WOCBP) and postmenopausal women who are not surgically sterile will have a urine pregnancy test with a dipstick at Visit 1 (Randomization Visit) at Visit 7 (Final Visit).

- Local tolerability
  Local tolerability will be assessed by the Investigator according to the following numerical scale at Visits 3 to 7:
  0: No evidence of irritation
  1: Minimal erythema, barely perceptible
  2: Definite erythema, readily visible; minimal edema or papular response
  3: Erythema and papules
  4: Definite edema
  5: Erythema, edema, and papules
  6: Vesicular eruption
  7: Strong reaction spreading beyond test site

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 (at Visit 1).
- Concomitant medication (every visit).

5.4 Derived variables

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

5.5 Withdrawal/discontinuation

The study can be terminated at any time for any reason by the Sponsor, an IRB or a Health Authority. Such reasons may include, but are not limited to:

- change in the risk/benefit assessment due to unexpected findings related to the potential risk of the treatment,
- Detection of SUSARs that differ in severity, duration or frequency from the known safety profile
- Becoming aware of new evidence through publications or other clinical trials that would negatively impact the risk/benefit assessment

Should this be necessary, all patients should be seen as soon as possible and treated as described in Section 7 of CSP for a prematurely withdrawn patient. The Investigator may be informed of additional procedures to be followed in order to assure that adequate consideration is given to the protection of the patient's best interest.

The Investigator will be responsible for informing the IRB/REB/IEC of the early termination of the study. In the EU CRMB (EU legal representative) and Clinsearch will be responsible for notifying IECs, local authorities and the German Competent Authority, of the early termination

5.5.1 Schedule of assessments

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

Table 5-1: Schedule of Assessments

	Randomization visit (V1)	**V2**	**V3**	**V4**	**V5**	**V6**	**Final visit[3] (V7)**
Day	***1***	***1 or 2***	***2***	***3***	***4***	***5***	***7, 8 or 9***
Time after 1st treatment	0h	12h (±1)	24h (±2)	48h (±4)	72h (±4)	96h(±4)	7d (± 1d)
Written informed consent	x						
Inclusion / exclusion criteria	x						
Demography / Med history	x						
Physical Exam / Vital Signs	x						x
Urine pregnancy test[1]	x						x
Concomitant medication	x	x	x	x	x	x	x
Injury site pain-at-rest (PAR)	x	x	x	x	x	x	x
Exam of soft tissue injury / contusion	x						x
Patch adhesion		x	x	x	x	x	x
Local Tolerability assessment			x	x	x	x	x
Injury site pain-on-movement (POM)	x	x	x	x	x	x	x
Randomization	x						
Dispense IMP (patches)[2]	x					x	
Dispense/Collect diary						x	x
Apply IMP (patch) at clinic	x		x	x	x	x	
Dispense rescue medication	x						
Count used/unused patches		x	x	x	x	x	x
Collect used IMP (patches)		x	x	x	x	x	x
Count rescue medication / Check time of intake		x	x	x	x	x	x
Adverse events		x	x	x	x	x	x
Global efficacy assessments				x	x		x
Collect rescue medication							x
Dispense three patches						x	

[1] Female patients only; [2] Patients will be given pouch containing IMP to take home in case of need to replace a detached patch. Patients bring IMP with them to each subsequent clinic visit. Patient apply patches themselves at 120h and 144h. [3] A final visit will be conducted on all patients, including cases of early termination or withdrawal of consent.

6 SAMPLE SIZE

The calculation of 90 per treatment group is based on the following assumptions and considerations:

- Primary efficacy outcome is the change from baseline for POM at 72 hours after initiating treatment.
- Two-sided t-test situation with $\alpha = 5\%$.
- Assuming SD = 20 mm, the sample size provides approximately 80% power to detect a difference of 10 mm between two treatment groups if 64 patients per group are analysed.
- However, the sample size will be stipulated to n=90 per group in order to power also the two subgroup comparisons.
- Moreover, the sample size will be a total of 200 patients because a dropout-rate of approximately 10 % is taken into account.

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:
  Continous 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 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.

Full Analysis Set (FAS): The Full Analysis Set (FAS) will be all randomized patients who received at least one dose of IMP. The FAS population will be primary for the analysis of efficacy. Any exclusions from the FAS population will be made and documented before unblinding (e.g. never used IMP, ankle is not sprained, randomized twice). The Intention to treat (ITT) population is identical to the Full Analysis Set (FAS).

Per protocol (PP) population: The Per protocol (PP) population will include all patients who are randomized to the clinical trial, satisfy all of the inclusion/exclusion criteria, receive the correct IMP (as randomized), have efficacy data at the 72 hours assessment, with an adhesion score of 0, 1, 2, have taken no pain medication and have no other major protocol violations as defined during a blinded review meeting.

Moreover, the PP population for the adhesion analysis (PP-PA) will include all TDS except those that were intentionally removed early in the study (e.g. because of unacceptable irritation) or those that were on patients who discontinued use of the TDS before the end of the labeled duration of wear for reasons unrelated to adhesion (e.g. because of a protocol violation). The exclusions from the PP-PA population will be described in detail in the CSR. All exclusions will be discussed in the Blind Review Meeting before DBL.

Only the outcomes regarding primary and secondary efficacy variables will be analyzed using this clinical trial 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. This corresponds to the following visit windows: Visit 2 (Hours 12), Visit 3 (Hours 22-24), Visit 4 (Hours 44-52), Visit 5 (Hours 68-76), Visit 6 (Hours 92-100), Visit 7 (Hours 168+). The numbering of the actual visits (from Visit 1 to Visit 7) 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 (Hours 12, 24, 48, 72, 96, 168) 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

Change from baseline in pain-on-movement (POM) at injured site in mm measured using a 100 mm Visual Analogue Scale (VAS) to Visit 5 (72 hours after commencement of study treatment)

The analysis of the primary endpoint will be adjusted for baseline values. The baseline adjusted difference between active treatment and placebo at 72 hours should be > 10 mm. Magnitude of reduction in pain will be used to determine ‘responder rate’.

For the primary variable an analysis-of-covariance (ANCOVA) with baseline as covariate and treatment, center and subgroup as factors will be carried out. A closed testing procedure controlling the multiple α-level of 5 % will be used in the analysis:

1) H_0: $\mu_E=\mu_P$ vs. H_1: $\mu_E\neq\mu_P$. In case of a significant result for this first hypothesis two further hypotheses regarding the subgroups “sprains/strains” and “contusions” will be then be also tested by means of the same baseline adjusted ANCOVA model to the 5 % level. In case of significance, the following subhypotheses are simultaneously tested at the 5 % level of significance.

2a) H_0: $\mu_E(spr/str)=\mu_P(spr/str)$ vs. H_1: $\mu_E(spr/str)\neq\mu_P(spr/str)$ in the subgroup “Sprains/strains”,

2b) H_0: $\mu_E(con)=\mu_P(con)$ vs. H_1: $\mu_E(con)\neq\mu_P(con)$ in the subgroup “contusions”.

The primary analysis population is the Full Analysis Set (FAS).

14.4.2 Secondary efficacy variables

- POM at injured site in mm measured using a 100 mm VAS at 12, 24, 48, 72, 96 and 168 hours after commencement of study treatment and will additionally presented by subgroup (table and Figure).
- AUC over time during first 12, 24, 48, 72, 96 and 168 hours for POM measured using a VAS; ordinate = POM score in mm, abscissa = time after treatment
- Pain-at-rest (PAR) at injured site in mm measured using a 100 mm VAS at 12, 24, 48 72, 96 and 168 hours.
- Reduction in VAS for POM from baseline:
- Time to meaningful reduction (30%)
- Time to optimal reduction (50%)
- Time to complete resolution of pain
- Responder rate 1 (defined as the proportion of patients achieving ≥50% reduction from baseline in the VAS score for POM at 72 hours)
- Responder rate 2 (defined as the proportion of patients able to resume training / normal physical activity by 168 hours)
- Clinical global assessment of efficacy as judged by investigator and patient at 48, 72 and 168 hours
- Overall dose of rescue medication needed (paracetamol).

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

Other important secondary efficacy outcomes are pain-on-movement on VAS at 12, 24, 48, 72, 96 and 168 hours after initiating treatment in the FAS population. These will be analyzed with an analysis-of-covariance (ANCOVA) model and center and subgroup as main effects. All other continuous efficacy outcomes will be analyzed based on the same model (excluding the baseline covariate when there is no appropriate baseline).

Differences between treatments on ordinal outcomes will be tested with Wilcoxon, stratified by center and subgroup.

Figures will show the time course of outcomes by treatment group for key quantitative outcomes. 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 (POM, pain-at-rest) 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 with 95% confidence intervals.

The response outcome (POM reduced by 50% at Visit 5, Yes/No) will be analyzed by the CMH test of general association, stratified by center and also by subgroup.

Differences between treatments in time-to-event outcomes will be tested with the log-rank test stratified by center.

14.4.3 Additional exploratory efficacy variables

-
- Mean adhesion by application site and/or net use.
- If there is significant use of rescue medication, a sensitivity analysis may be performed to assess impact on primary endpoint and responder rate.
- Outcomes will be compared for all use of rescue medication and separately for use to treat blunt trauma. Day 1 and the day of the final visit will count as full days for this purpose. Use of rescue medication on days after study medication has been discontinued will not be counted.
- POM on VAS difference at V4, V5, V6 compared to V1 (BL) (PID V4, PID V5, PID V6) PID V4, PID V5 and PID V6 will be compared between treatment groups using ANCOVA with terms in the model for treatment group, site [as fixed effects], and baseline POM assessment [as a covariate]. Least square mean for each treatment and the corresponding difference between least square means with the p-value and 95 % confidence interval will be presented from the specified ANCOVA model.
- Sum of Pain Intensity differences (SPID) over 0-24, 0-48, 0-72 and 0-96 hours.
  SPID over 0-24, 0-48, 0-72 and 0-96 hours will be compared between treatment groups using ANCOVA with terms in the model for treatment group, site [as fixed effects], and baseline POM assessment [as a covariate]. Least square mean for each treatment and the corresponding difference between least square means (Active - placebo) with the p-value and 95 % confidence interval will be presented from the specified ANCOVA model.

14.5 Safety

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

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. The summary of all AEs by treatment groups will also be presented within subgroups by sex, age and race.

Safety will also be summarized with respect to vital signs and laboratory safety parameters as mean levels by visit and change from baseline. Laboratory values will be further summarized with shift tables. Abnormal observations on physical exams will be listed

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.

Local tolerability assessment will be summarized descriptively by visit.

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

A closed test procedure will be carried out for the primary variable. Therefore, no α-adjustments are necessary. The multiple level of $\alpha = 5\ \%$ is controlled by this procedure.

14.8 Missing data

- If assessments at any visit for Visits 2 (12 h) through Visit 6 (96 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 7 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 7 will be imputed by LOCF from Visit 5 and missing assessments at Visit 5 will not be imputed.
- 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 a patient assesses spontaneous pain intensity and spontaneous pain relief at the time of rescue taken for reason other than blunt trauma pain, any assessment conducted in the following 6 h will be imputed as if the assessment were missed.
- If there are no assessments in the 12-24 h window, or the 24-48 h window,
  - if the patient has not prematurely terminated, a value from the last preceding assessment or assessment window will be carried forward.
  - if the patient has prematurely terminated, imputation will proceed as described for assessments at the site.
- 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 Censoring

- Time to meaningful relief will be censored (if appropriate) at the time of the final assessment of meaningful relief. If the patient discontinues for lack of efficacy before achieving meaningful relief, it will be censored at 24 h.
- Time to perceptible relief will be censored (if appropriate) at 24h or the time of final assessment of spontaneous pain relief (if earlier). If the patient discontinues for lack of efficacy before achieving perceptible relief it will be censored at 24 h.
- Time to resolution of blunt trauma will be censored (if appropriate) at the day of the final visit. If the patient discontinues for lack of efficacy, it will be censored at 7 days.
- Time to first use of rescue medication will be censored (if appropriate) at the last day for which diary records are available.

If a patient takes a disallowed analgesic medication and subsequently provides efficacy assessments, rules will be established on a case-by-case basis, taking into consideration whether the disallowed analgesic medication was taken to treat pain in the injured area and the likely duration of effect of the medication. The rules will be documented before the study is unblinded.

Additional data handling rules will be specified in the minutes of the BRM, if any, to cover issues not anticipated in the above stipulations.

14.10 Interim Analysis

Not applicable.

14.11 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.

14.12 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.

14.13 Treatment compliance, rescue medication, other concomitant therapies

Compliance is defined in terms of the total number of study medication patches used and total number of applications made through Visit 7 as follows:

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

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

The % of patch used through Visit 7 will be computed relative to the actual number of applications made from randomization through Visit 7. Scheduled applications will include all scheduled applications through Visit 7.

Compliance will be summarized descriptively as (1) % of scheduled applications made, (2) % of patches 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 is an efficacy outcome and is discussed further below. Exposure to study drug will be summarized descriptively as (1) number of applications made and (2) total amount of patch used.

14.14 Medical history

Diseases will be coded according to MedDRA Version 24.0.

Details of the Medical History will be listed.

14.15 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 VISIT WINDOWS

All data will be organized and analyzed according to the scheduled visits outlined in the protocol.

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Day	1	1 or 2	2	3	4	5	7, 8 or 9
Time after 1st treatment	0 h	12 h (±1 h)	24 h (±2 h)	48 h (±4 h)	72 h (±4 h)	96 h (±4 h)	7 d (±1 d)

16 LANGUAGE AND HEADINGS

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

17 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).

18 LIST OF STAFF

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

19 REFERENCES

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