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.

Authors:
Coordinating Investigator (& Principal Investigator): [redacted]

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Release date:	08 March 2021

Signature page Sponsor

I agree to conduct the clinical trial in accordance with the clinical trial protocol described in this document and in compliance with the Declaration of Helsinki (Version 2013), ICH-GCP, AMG, GCP-V and other affected regulatory requirements.

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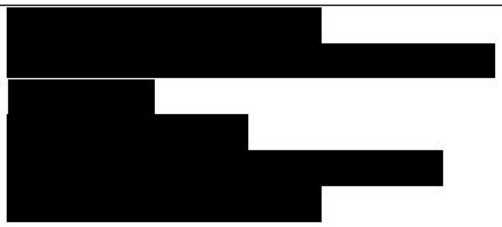

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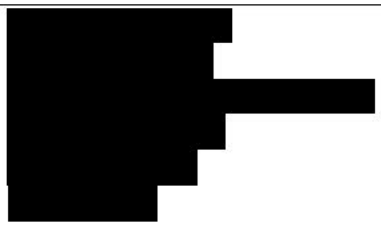

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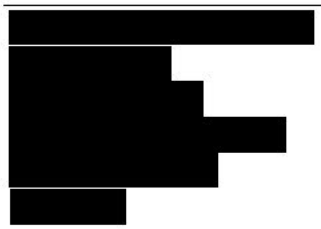

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List of abbreviations AE

Adverse event ANCOVA

Analysis-of-covariance AUC

Area under the curve

BOCF	Baseline-observation-carried-forward
cGCP	Current Good Clinical Practice
CMH	Cochran-Mantel-Haenszel
CRF	Case Report/Record Form
CRO	Contract Research Organization
CSR	Clinical Study Report
DSP	Drug Safety and Pharmacovigilance
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEA	Global Efficacy Assessment
GP	General practitioner
IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICF	Informed consent form
i.e.	Id est, that is
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Non-steroidal anti-inflammatory drug
PAR	Pain at Rest
POM	Pain-on-movement
QA	Quality assurance
REB	Research Ethics Board

RICE	Rest - ice - compression - elevation
SAE	Serious adverse event
SAF	Safety set
SAP	Statistical Analysis Plan
SD	Standard deviation
S.E.	Standard error
SOP	Standard Operating Procedure
VAS	Visual Analogue Scale WHO

World Health Organization WOCBP

Women of child-bearing potential

Glossary of terms

Assessment	A measurement
Control (or reference) drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Early termination	Termination prior to the planned completion of all study drug administration and assessments
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational Medicinal Product (IMP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Medication number	A unique identifier on the label of each medication package in studies that dispense medication using an IVR system
Patient number	A number assigned to each patient who is randomized into the study (or who is officially entered in some other fashion if there is no randomization). When combined with the center number, a unique identifier is created for each patient in the study.
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Period	A minor subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Termination	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of early termination
Outcome	Information used in the data analysis

Protocol Synopsis

Protocol Number	TK-254R-0201
Date of Final Protocol	08 March 2021
Sponsor	Teikoku Seiyaku Co Ltd., 567 Sanbonmatsu, Higashikagawa, Kagawa 769-2695, Japan
Study Title	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 Phase	II (proof-of-concept)
Indication	Local symptomatic and short-term treatment of pain in acute strains, sprains or bruises of the extremities following blunt trauma.
Key Dates	Estimated start (first patient in): Estimated end (last patient out):
Principal & Coordinating Investigator	[redacted]
Study Sites	[redacted]
Ethics Committee Regulatory Oversight	Physician's Chamber of North Rhine Westphalia Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM).
Study Objectives	To determine efficacy and safety of a Esflurbiprofen Hydrogel Patch compared to placebo in patients with acute strains, sprains or bruises of the extremities following blunt trauma, e.g. sports injuries.

	To demonstrate that the Esflurbiprofen Hydrogel Patch is superior to placebo, and that the patch has acceptable local tolerability.
Study Design	Randomized (1:1) (stratified by center and 2 subgroups), controlled, double-blind, multi-centric study in parallel groups.
Patient Population/Sample size/Study Sites	The clinical trial population will consist of male or female patients, 18 – 60 years suffering from acute; strains, sprains or bruises of the extremities following blunt trauma, and meeting all clinical trial entry criteria. In order to ensure at least 90 evaluable patients per group, up to 200 patients will be enrolled (assumes a drop-out-rate of ≤10%). The study will be performed in Germany in 3 sites. Each site should enroll a minimum of 30 and a maximum of 90 patients.
Statistical Considerations	<u>Samplesize</u> 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 <u>Analysis</u> Analysis-of-covariance for primary variable with baseline as covariate and treatment, center and subgroup as factors. An a priori ordered testing procedure controlling the multiple α-level of 5 % will be carried out: 1) H_o: $\mu_E = \mu_P$ 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” and “contusions” will be

then be also tested by means of the same baseline adjusted ANCOVA model to the 5 % level.

2a) H_o: $\mu_{E(str)}=\mu_{P(str)}$ vs. H_1: $\mu_{E(spr/str)}\neq\mu_{P(spr/str)}$ in the subgroup "sprains/strains",
2b) H_o: $\mu_{E(con)}=\mu_{P(con)}$ vs. H_1: $\mu_{E(con)}\neq\mu_{P(con)}$ in the subgroup "contusions".

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

Other important secondary efficacy outcomes are pain-on-movement on VAS at 12, 24, 48, 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 which will be more detailed described in the Statistical Analysis Plan (SAP). 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 categorical outcomes will be tested with Cochran-Mantel-Haenszel tests of treatment mean ridits or of general association, stratified by center.

Inclusion Criteria

The following must apply:

- acute sports-related soft-tissue injury/contusion (strains, sprains, bruises) of the upper or lower limb
- location of injury such that pain-on-movement (POM) is elicited on passive manipulation of nearest joint by investigator
- enrollment within 6 hours of the injury
- baseline VAS score for POM of injured extremity $\geq$ 50 mm on a 100 mm VAS
- size of injury, as assessed by investigator, ≥ 25 cm^2 and ≤ 120 cm^2
- adult male or female patients
- age 18 to 60 years
- having given written informed consent
- satisfactory health as determined by the Investigator based on medical history and physical examination

Exclusion Criteria

The following must <u>not</u> apply:

- significant concomitant injury in association with the index acute sports-related soft-tissue injury/contusion; e.g. fracture, nerve injury, ligament disruption, tear of muscle or cartilage, or open wound
- excessively hairy skin at application site, cutting the hair in the injured site prior to patch application will qualify for inclusion

- current skin disorder or shaving hair at application site
- history of excessive sweating/hyperhidrosis inclusive of application site
- intake of NSAIDs or analgesics within 36 hours, opioids within 7 days, or corticosteroids within 60 days of inclusion in the study
- intake of long-acting NSAIDs or application of topical medication since the injury (RICE allowed)
- participation in a clinical study within 30 days before inclusion in the study or concomitantly
- drug or alcohol abuse in the opinion of the investigator
- pregnant and lactating women
- women of child-bearing potential without medically accepted contraception
- known hypersensitivity to Esflurbiprofen or one of the excipients of the patch
- patients with any ongoing condition that may interfere with the absorption, distribution, metabolism, or excretion of Esflurbiprofen
- history of previous significant injury to the same extremity within 6 months
- patients with a disease affecting the same limb, such as synovitis, rheumatoid arthritis, arthrosis, etc.
- patients having an ongoing painful condition associated with sports-related injury/contusion
- patients suffering from symptoms of an infectious disease including swelling of any joint of the affected upper or lower limbs
- patients who had surgery of the affected upper or lower limb within one year of study entry
- patients with significant diseases (defined as a disease which, in the opinion of the investigator, may either put the patient at risk because of participation in the study or a disease which may influence the results of the study or the patient's ability to participate in the study; includes patients with a history of gastrointestinal bleeding, significant cardiovascular, liver or renal disease).
- patients with a blood coagulation disorder
- patients who use any impermissible medication (see below)

Concomitant Treatment

1. Rescue medication
   In case of unbearable pain, patients are allowed to take paracetamol tablets (2 x 500 mg). Patients needing more than 6

tablets (3 g) per day or another drug from the list of impermissible medication will be withdrawn from the study as non-responders.

Application of standard care by rest, ice, compression (non-occlusive bandage), or elevation (RICE) can be considered at the discretion of the Investigator.

Also allowed are:

the use of crutches,

elastic, temporary bandages, that could be easily removed to assess the primary variable.

Physiotherapeutic measures (i.e. isomeric exercises to train the muscles) if they don't interact with the injured area

2. Impermissible medication
   Use of systemic or topical NSAIDs, analgesics (other than paracetamol), opioids, corticosteroids (except for topical treatment of bronchial asthma), heparin, or psychotropic agents, as well as the use of adhesive and fixing tapes and casts that would jeopardize the assessment of the primary variable (pain on movement).

3. Other treatments
   . Ultrasound, physical therapy and acupuncture will not be allowed

Dosage

Patients will be randomly assigned to one of the following treatment arms in a ratio of 1:1.

A: Esflurbiprofen Hydrogel Patch applied once per day to the affected injury site

B: Placebo patch applied once per day to the affected injury site

The dose regimen is a single hydrogel patch (investigational drug) applied topically to the injured site once a day for 7 days. The hydrogel patch should be positioned directly over the injury site and marked with a water-resistant pen to ensure the patch is applied at the same site throughout the study. The placebo patch (placebo) is identical in composition to the Esflurbiprofen 165 mg Hydrogel Patch, without the active ingredient. Placebo is applied as described for the investigational drug. Both patients and investigators will be blinded to study treatment. If the hydrogel patch begins to peel-off (>10% of the total surface), the edges of the topical system may be pressed down. If problems with adhesion persist, patients may overlay the topical system with a mesh netting sleeve, where appropriate (e.g., to secure topical systems applied to ankles, knees, or elbows). The mesh netting sleeve must allow air to pass through and not be occlusive (non-breathable)

No. of Visits	A total of 7 visits
Visit Schedule	Visit 1 on Day 1 (enrollment) Visit 2 on Day 1/2, depending on am/pm enrollment (12 hours) Visit 3 on Day 2 (24 hours) Visit 4 on Day 3 (48 hours) Visit 5 on Day 4 (72 hours) Visit 6 on Day 5 (96 hours) Visit 7 on Day 8 (168 hours).
Assessments	Efficacy will be assessed based on the following: Primary assessment: Pain-on-movement (POM) measured by 100 mm VAS [performing standardized movements as described in Section 7.5.1] at baseline, 12, 24, 48, 72, 96 and 168 hours Secondary assessments: AUC over time between baseline and the first 12, 24, 48, 72, 96 and 168 hours for POM measured by VAS Pain at rest measured by VAS (at baseline, 12, 24, 48, 72, 96 and 168 hours) Time to meaningful/optimal reduction of pain defined as 30% (meaningful) and 50% (optimal) reduction of baseline VAS for POM. Both time points will be calculated Responder rate 1 (defined as the number of patients achieving 50% reduction from baseline in the VAS score for POM at 72 hours) Global efficacy assessments by physician (GEA, 5 point scale: 0=no response; 1=poor response; 2=fair response; 3=good response; 4=excellent response) at 48, 72 and 168 hours Global efficacy assessments by patient (GEA, 5 point scale: 0=no response; 1=poor response; 2=fair response; 3=good response; 4=excellent response) at 48, 72 and 168 hours Use of rescue medication at every visit except Visit 1 Responder rate 2 (defined as the number of patients able to resume training / normal physical activity by 168 hours) Other assessments include patch adhesion and patch safety as follows: Patch adhesion: Adhesive power of the patch measured by a 5 point numerical scale (0=≥ 90% adhered / 1= ≥75% to <90% adhered / 2=≥50% to <75% adhered / 3=>0% to <50% adhered / 4=completely detached) at every visit except V1 Safety assessments: Physical examination at V1 and V7 Pregnancy test (female patients only) at V1 and V7 Local tolerability (skin damage/reaction seen at patch removal according to an 8-point scale) at every visit except V1 and V2

- Vital signs (including blood pressure and pulse rate) at V1 and V7
- Adverse events (AEs) at every visit

Efficacy Variables

Primary efficacy outcome:

- 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 $\geq$ 10 mm. Magnitude of reduction in pain will be used to determine 'responder rate'.

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
- AUC over time during first 24, 48, 72 and 96 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: o
  - Time to meaningful reduction (30%)
  - o Time to optimal reduction (50%)
  - o 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)

Other:

- Adhesive power of patch (5-point scale)
- If there is significant use of rescue medication, a sensitivity analysis may be performed to assess impact on primary endpoint and responder rate.

Variables of Tolerability and Safety	Adverse events, vital signs, physical examinations including local examination for assessment of tolerability, sensitization & damage to skin associated with patch removal (8-point scale).

1 Background

Blunt injuries consists of contusions, strains, sprains and combinations of thereof. Contusions are among the most common sports-related injuries [Best 1997, Nozaki 2008], second only to strains. Documented muscle contusions account for one third of all sports injuries. Most blunt injuries are unreported and untreated. They are caused by blunt trauma to skin, muscles, tendons and connective tissue structures resulting in tissue and cellular damage [Best 1997].

A blunt injury is aggravated by blood that has escaped from damaged capillaries into the interstitial tissues. Within a few hours after the injury, the presence of necrotic tissue and hematoma initiates an inflammatory reaction [Farges 2002]. Because inflammation initiates macrophage action with subsequent phagocytosis of necrotic debris and stimulation of capillary production, it is vital to the process of tissue regeneration. However, inflammation invariably causes edema that leads to anoxia and further cell death.

Fresh impact injuries usually resolve spontaneously, but may nevertheless cause considerable discomfort, marked functional limitation, absence from work and withdrawal from activities [Inklaar 1994]. The goal of therapy is to minimize hemorrhage and inflammation and control pain. NSAIDs are commonly used to reduce pain and inflammation in order to facilitate rehabilitation and achieve earlier recovery [Dreiser 1993, Ekman 2002].

The efficacy and safety of topical NSAIDs in the treatment of acute, painful musculoskeletal conditions is widely recognized [Mason 2004, Rainsford 2008, Zacher 2008]. Over the past 20 years, an increasing number of topical NSAID formulations (diclofenac, ibuprofen, indomethacin, ketoprofen, and naproxen) have been approved. Topical NSAIDs, regardless of the status of the clinical condition (acute or chronic), must be applied at regular intervals in order to obtain maximum therapeutic benefit. A topical NSAID formulation is therefore not intended to be applied as needed and so is distinct in its mode of use when compared to that of oral NSAIDs.

Bioavailability studies suggest systemic absorption from topically applied NSAIDs is only 3-5% of the total systemic absorption achieved with oral administration [Heyneman 2000]. Pharmacokinetic data have shown that diclofenac, when applied topically, penetrates the skin barrier to reach joints, muscles and synovial fluid, in sufficiently high concentration to exert local therapeutic activity [Zacher 2008]. Further advantages of topical delivery include circumventing the gastrointestinal tract and avoiding first-pass metabolism in the liver.

Esflurbiprofen was approved by Pharmaceuticals and Medical Devices Agency of Japan (PMDA) on Sep 28, 2015. Esflurbiprofen is a cyclooxygenase (COX) inhibitor indicated for the treatment of osteoarthritis pain and inflammation.

Esflurbiprofen is available on the Japanese market as a patch formulation, containing 40 mg of the active principle.

2 Purpose and rationale

Oral non-steroidal anti-inflammatory drugs (NSAIDs) are well known to reduce pain and inflammation and improve physical function [Ogilvie-Harris 1995]. However, due to their systemic availability they can cause intolerable and potentially life-threatening side effects, such as gastrointestinal symptoms (upset stomach, ulceration, hemorrhagic ulceration), alteration of platelet function, impairment of renal function, and interaction with other agents.

With an increasing number of people undertaking sports activities and with a parallel increase in the number of acute contusions, there is a need for an effective alternative treatment available with better tolerability. Topically applied Esflurbiprofen has been shown to have low systemic bioavailability. Based on those existing data the novel Esflurbiprofen 165 mg Hydrogel Patch which is the target treatment of this study is not expected to significantly exceed 10% of the systemic exposure achieved following standard oral dosing with Flurbiprofen 100 mg tablets (3 times a day). Accordingly, it is appropriate to test the efficacy and safety of the Esflurbiprofen Hydrogel Patch in the treatment of blunt injuries.

A parallel-group design is utilized as a within patient comparison based on repeated or simultaneous contusions is clearly inappropriate. Measurement of pain and disability over approx. 72 hours should be sufficient to prove efficacy based on previous experience [Predel 2004, Bonnekoh 1992, Hess 1996, Pabst 2001]. Dosing continues through resolution of the injury in order to adequately assess safety over the entire dosing interval.

POM measured by VAS at 12, 24, 48 and 72 hours after initiating treatment (clinic visit) are important secondary endpoints to demonstrate an early and continued of treatment effect.

The overall reduction of pain on movement after 72 hours is considered a good indicator to assess the postulated efficacy in the frame of this proof-of-concept study.

Patients should be treated as soon as possible after the injury because early treatment may reduce swelling, thereby increasing the likelihood of treatment success. Treatment will therefore be initiated no more than 6 hours after the blunt injuries event.

To minimize unnecessary risk to patients during study participation they will be screened at baseline to ensure absence of the various clinical disorders described in the exclusion criteria. This comprehensive process will include a baseline physical examination, vital signs, medical and drug history.

To avoid bias, double blinding and randomization are important features of this study.

3 Objectives

3.1 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.

- 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).
- Important secondary efficacy outcomes are POM on VAS at Visit 2, 3, 4, 6 and 7 (12, 24, 48, 96 and 168 hours after initiating treatment).

3.2 Secondary objective

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

4 Study design

This is a Phase II randomized, double-blind, 2-arm (1:1) (stratified by center and subgroup), multi-center, placebo-controlled, parallel group study of the efficacy and safety of Esflurbiprofen Hydrogel Patch applied once a day for up to 8 days (maximum of 7 patches) to treat acute blunt, soft tissue injuries of the limbs.

To qualify, patients must experience acute blunt, soft tissue injuries of the limbs. Patients should be randomized as soon as possible after the injury. Anticipated time from injury until initial treatment should not exceed 6 hours.

In order to ensure at least 90 evaluable patients per group, up to 200 patients (100 in each group)

Approximately 200 patients suffering from acute blunt, soft tissue injuries of the limbs are to be randomized to be treated with Esflurbiprofen Hydrogel Patch or placebo (assumes a drop-out-rate of ≤10%).

The study will be performed in Germany in 3 sites. Each site should enroll a minimum of 30 and a maximum of 90 patients.

The first five doses of study drug will be applied at the study site. The patients will be instructed on how to apply the patch once daily at home for the last two treatment days.

After the randomization visit (V1), patients will return to the study center for post-baseline visits V2-V7 to complete efficacy and safety assessments. In addition, patients will assess pain on movement and spontaneous pain intensity at rest at visits 2, 3, 4, 5, 6 and 7.

The schedule of visits is described below.

Table 4–1: Study site visits

	Time after initiating treatment	Visit Day
Randomization/Baseline visit V1	0 h	Day 1
1st interim visit V2	12 h (□ 1 h) after V1	Day 1
2nd interim visit V3	24 h (□ 2 h) after V1	Day 2
3rd interim visit V4	48 h (□ 4 h) after V1	Day 3

4th interim visit V5	72h (□ 4 h) after V1	Day 4
5th interim visit V6	96 h (□ 4 h) after V1	Day 5
Final visit V7	168 h (□ 24 h) after V1	Day 8 □ 2day

Rescue medication (paracetamol, 500 mg tablets, up to 3000 mg daily) is allowed during the study, except for the 6 hours prior to V5 (72h).

5 Population

The study population will consist of male or female patients aged 18-60 years with blunt, soft tissue injuries of the limbs.

5.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria:
The following must apply:

1. acute sports-related soft-tissue injury/contusion (strains, sprains, bruises) of the upper or lower limb
2. location of injury such that pain-on-movement (POM) is elicited on by the exercises described in Section 7.5
3. enrollment within 6 hours of the injury
4. baseline VAS score for POM of injured extremity ≥ 50 mm on a 100 mm VAS
5. size of injury, as assessed by investigator, ≥ 25 cm^2 and ≤ 120 cm^2
6. adult male or female patients
7. age 18 to 60 years
8. having given written informed consent
9. satisfactory health as determined by the Investigator based on medical history and physical examination.

5.2 Exclusion criteria

Patients eligible for inclusion in this study must not fulfill any of the following criteria:

1. significant concomitant injury in association with the index acute sports-related soft-tissue injury/contusion; e.g. fracture, nerve injury, ligament disruption, tear of muscle or cartilage, or open wound
2. excessively hairy skin at application site, cutting the hair in the injured site prior to patch application will qualify for inclusion
3. current skin disorder or shaving hair at application site
4. history of excessive sweating/hyperhidrosis inclusive of application site
5. intake of NSAIDs or analgesics within 36 hours, opioids within 7 days, or corticosteroids within 60 days of inclusion in the study
6. intake of long-acting NSAIDs or application of topical medication since the injury (RICE allowed)

7. participation in a clinical study within 30 days before inclusion in the study or concomitantly
8. drug or alcohol abuse in the opinion of the investigator
9. Pregnant and lactating women
10. Women of child-bearing potential (defined as all women physiologically capable of becoming pregnant) who are not using an acceptable method of contraception defined as:

- Surgical sterilization
- Hormonal contraception
- IUD
- Double barrier method
- Total abstinence throughout the study at the discretion of the Investigator.

Periodic abstinence is NOT an acceptable method of contraception. An acceptable method of contraception must be maintained throughout the study.

A woman who is post-menopausal must have a negative urine pregnancy test at screening but will not need to comply with an acceptable method of contraception. Women are considered post-menopausal and not of child bearing potential if they had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

11. known hypersensitivity to Esflurbiprofen or one of the excipients of the patch
12. patients with any ongoing condition that may interfere with the absorption, distribution, metabolism, or excretion of Esflurbiprofen
13. history of previous significant injury to the same extremity within 6 months
14. patients with a disease affecting the same limb, such as synovitis, rheumatoid arthritis, arthrosis, etc.
15. patients having an ongoing painful condition associated with sports-related injury/contusion
16. patients suffering from symptoms of an infectious disease including swelling of any joint of the affected upper or lower limbs
17. patients who had surgery of the affected upper or lower limb within one year of study entry
18. patients with significant diseases (defined as a disease which, in the opinion of the investigator, may either put the patient at risk because of participation in the study or a disease which may influence the results of the study or the patient’s ability to participate

in the study; includes patients with a history of gastrointestinal bleeding, significant cardiovascular, liver or renal disease).

19. patients with a blood coagulation disorder
20. patients who use any impermissible medication (section 6.5.6)

6 Treatment

6.1 Investigational drug and reference drugs

CLINSEARCH will supply the study drugs and rescue medication (section 6.5.5).

Study drugs will be packed and labelled by CSM, Clinical Supplies Management Europe GmbH.

Esflurbiprofen Hydrogel Patch and the placebo patches are packaged in [redacted]. One sachet contains 1 plaster.

The number of IMP units to be packaged will be specified prior to the start of the packaging operations, including units necessary for carrying out quality control and any retention samples to be kept.

The clinical trial supplies will be packed into secondary containers (boxes). Supplies for replacements will be packed separately into further secondary containers.

The IMPs will be labelled in accordance with the GMP Annex 13 and with the GCP regulation ("GCP-Verordnung") § 5.

Investigational drug:

- Active ingredient: Esflurbiprofen Hydrogel Patch containing 165 mg Esflurbiprofen
- Excipients: [redacted]

One unit dose of the drug is one patch applied to the painful area.

Control drug:

Placebo patch that does not contain the active ingredient but is otherwise indistinguishable from the investigational drug Esflurbiprofen Hydrogel Patch.

Rescue medication:

Paracetamol (500 mg tablets, up to 3000 mg daily) is allowed during the study, except for the 6 hours prior to Visit 5 (72h).

6.2 Treatment arms.

Eligible patients will be randomized to one of two treatment arms in a ratio of 1:1

- Esflurbiprofen Hydrogel Patch once a day
- Placebo patch once a day

6.3 Treatment assignment

At Visit 1, all patients who fulfill all the inclusion/exclusion criteria will be given the lowest available number on the randomization list. This number assigns them to one of the treatment arms. The Investigator or designee will enter the randomization number on the CRF.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A randomization list – stratified by center and subgroup - will be produced by the independent statistician [redacted] and a copy provided to CSM in order to package the clinical supplies accordingly. Balanced stratification by indication subgroups (sprains/strains and contusions) will be achieved by assigning full randomization blocks to a respective group only. The packaging company (CSM) will verify the code assignments and block size against the randomization request and will distribute to investigator, as warranted.

Randomization data are kept strictly confidential by CRMB and the packaging company, accessible only to authorized persons, until the time of unblinding. At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to the packaging company. Only when the study has been completed, the database locked, and the Statistical Analysis Plan finalized will the drug codes be broken and made available for data analysis.

6.4 Treatment blinding

The study will be double-blind. Patients, investigator staff, persons performing the assessments, monitors and data analysts will remain blinded to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) Randomization data are kept strictly confidential, accessible only to authorized persons, until the time of unblinding. (2) the identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance and odor.

Unblinding will only occur in the case of patient emergencies (see section 6.5.10) and at the conclusion of the study.

6.5 Treating the patient

6.5.1 Patient numbering

Each patient is uniquely identified in the study by a randomization number, i.e. a combination of the center number and patient number. A center number is assigned by the packaging company to each investigative site. At Visit 1, each patient who qualifies for randomization will be given the lowest patient number available at the center. The Investigator or designee will enter the randomization number on the CRF. Once assigned to a patient, a randomization number will not be re-used.

6.5.2 Dispensing the study drug

Each of the investigator sites (study centers) will be supplied by the packaging company with study drug in packaging of identical appearance.

The study medication packaging has a 2-part label. A unique randomization number is printed on each part of this label which corresponds to a treatment arm (active or placebo patch), according to the confidential randomization list. Immediately before dispensing study drug to the patient, investigator staff will detach the outer part of the label from the packaging, and affix it to the patient's CRF.

6.5.3 Study drug supply, storage and tracking

Study drug must be received by a designated person at each study center, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated assistants have access. All study drugs should be stored according to the instructions specified on the drug label. The patches must be stored at room temperature (15-30C). Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in the local language (German) and comply with the legal requirements of the Germany. They will include storage conditions for the drug, but no information about the patient except for the randomization number.

The Investigator or designee must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Drug accountability will be monitored by the study monitor during monitoring visits and at the completion of the study. Patients will be asked to return all used and unused study drug and packaging at the end of the study or at the time of discontinuation.

At the conclusion of the study, and as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to the Clinsearch monitor or to the Clinsearch address provided in the investigator folder at each site.

6.5.4 Instructions for prescribing and taking the study drug

All patients will be treated with 1 patch of study drug at every visit during the first 6 visits (except for visit 2). The first five patches will be applied at the study center. The site of the first application will be marked with a water-resistant pen to ensure the same application site at every treatment. Additional 3 patches will be dispensed at Visit 6. The patients will be instructed to apply one patch every day at approx. the same time. Dosing times should be distributed as evenly as possible, preferably once every 24 hours after the last application.

Patients can take a shower or bathe prior to the application.

The Investigator or study staff will instruct the patients to apply the study drug exactly as prescribed and state that compliance is necessary for the patients' safety and the validity of the study. The patients will be told to contact the Investigator or study staff if they are unable for any reason to apply the patch as prescribed. All dosages prescribed and dispensed to the patient

and all dose changes during the study must be recorded on the Dosage Administration Record CRF page.

If the hydrogel patch begins to peel-off (>10% of the total surface), the edges of the topical system may be pressed down. If problems with adhesion persist, patients may overlay the topical system with a mesh netting sleeve, where appropriate (e.g., to secure topical systems applied to ankles, knees, or elbows). The mesh netting sleeve must allow air to pass through and not be occlusive (non-breathable)

6.5.5 Rescue medication

The Investigator will provide rescue medication (paracetamol, 20 x 500 mg tablets) to the patients at the baseline visit (visit 1).

Patients will be instructed to only take the rescue medication provided for pain in the injured area or any other pain (e.g., headache) or fever (e.g., due to common cold) they might experience during the study. One or two tablets may be taken, repeated after at least 4 hours, if needed, up to a maximum of 3000 mg per day. No rescue medication is allowed within 6 hours immediately preceding Visit 5 (72h).

The patient will receive a diary at Visit 1 to record the time and date that each dose of rescue medication is taken, the number of tablets taken and the reasons for the intake (for contusion-related pain or another reason). The patient will also assess spontaneous pain intensity immediately prior to each dose of rescue medication. At each visit, the Investigator or designee will review the diary. Empty packages and rescue medication not used will be shown to the Investigator or designee. The Investigator or designee will then compare the packages vs. the patient's record of rescue medication use and any discrepancies will be noted in the CRF. Further instruction, how to use the diary are highlighted in Chapter 6.5.8

The Investigator will further investigate any instances in which rescue medication was taken for reasons other than contusion and complete the Adverse Event Form, if appropriate.

6.5.6 Other concomitant treatment

Concomitant therapies prohibited during the study:

The following treatments may NOT be used after the start of study drug:

Use of systemic or topical NSAIDs, analgesics (other than paracetamol), opioids, corticosteroids (except for topical treatment of bronchial asthma), heparin, or psychotropic agents.

Concomitant therapies allowed during the study:

- Rescue medication (section 6.5.5) except for the 6 hours prior to visit 5 (72h).
- Application of standard care by rest, ice, compression (non-occlusive bandage), or elevation (RICE) can be considered at the discretion of the Investigator.

The Investigator will instruct the patient to notify the study center about any new medications and significant non-drug therapies (i.e. RICE) he/she takes after the start of the study drug. All medications and significant non-drug therapies taken during the 30 days prior to Visit 1 (0h,

Day 1) (including physical therapy and blood transfusions) or administered after the patient starts treatment with study drug must be listed on the Concomitant medications/Significant non- drug therapies CRF page. An AE CRF page should also be completed, if appropriate.

6.5.7 Patient card

To avoid the intake of non-permitted concomitant medication, it is important to inform other physicians who might treat the patient while participating in the study. Therefore, a card will be given to the patient at Visit 1 containing relevant information about his/her study participation, i.e., study medication, name and address of the Investigator with telephone numbers.

6.5.8 Diary

A diary will be handed out to the patient at Visit 1.

The patient has to fill in the diary in handwriting and provide the following information:

- Every time patch is applied the patient has to document the time and date of application.
- Every time rescue medication is taken (not allowed within 6 hours before Visit 5 (72h)), the patient has to document:
  - The time and date of rescue.
  - The number of tablets taken.
  - The reason for rescue (blunt trauma pain/other).
  - If the pain is related to the blunt trauma, the spontaneous pain intensity prior to the intake on a VAS scale

The Investigator or designee will ensure that all diary entries completed by the patient are legible.

The Investigator or designee will review the diary at every visit and collect it at Visit 7 (Day 8±2).

6.5.9 Study drug discontinuation and premature patient withdrawal

The study drug must be discontinued and the patient withdrawn from the study if the Investigator determines that continuing it would result in a significant safety risk for that patient. The following circumstances require study drug discontinuation:

- Withdrawal of informed consent
- Pregnancy
- Emergence of any clinically relevant serious adverse events
- Any other protocol deviation that results in a significant risk to the patient’s safety

In addition to these requirements for study drug discontinuation, the Investigator should discontinue study drug for a given patient if, on balance, he/she thinks that continuation would be detrimental to the patient’s well-being.

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, or fail to return for visits, or become lost to follow up for any other reason. If premature withdrawal occurs for any reason, the Investigator must determine the primary reason for a patient's premature withdrawal from the study and this information must be recorded on the Study Completion CRF.

Patients who are prematurely withdrawn from the study will not be replaced.

If a patient is discontinued or decides to withdraw from the study, all evaluations scheduled for the final visit will be performed within one week of study drug discontinuation. Every effort must be made to collect all the required data at the time of patient discontinuation. The Investigator or designee must complete the Study Drug Discontinuation, giving the date and primary reason for stopping the study drug.

For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the Investigator or designee should show "due diligence" by documenting in the source documents the steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc., in order to establish the reason for discontinuation and to check presence of any AEs.

6.5.10 Emergency unblinding of treatment assignment

An individual decoding unit containing emergency identification of the package will be provided with each treatment unit. These decoding units are not to be opened unless an actual medical emergency occurs. If the Investigator feels breaking the code is required, a Clinsearch representative should be consulted first, unless the delay would endanger the patient's health. The date, time the code was broken and reason for breaking the blind must be recorded. In the event that a decoding unit is opened, the Project Manager at Clinsearch and the monitor must be informed within 24 hours. The unblinded treatment code should not be recorded on the CRF.

It is the Investigator's responsibility to ensure that there is a procedure in place to allow access to the code break cards in case of emergency. The Investigator or designee will inform the patient who to contact in case of emergency when the investigator is unavailable. The protocol number, study drug name if available, patient number, and instructions for contacting the local Clinsearch affiliate (or any entity to which it has delegated responsibility for emergency code breaks) will be provided to the patient in case emergency unblinding is required at a time when the Investigator and backup are unavailable.

Study drug must be discontinued after emergency unblinding. Study drug also must be discontinued for any patient whose treatment code has been broken inadvertently or for any non-emergency reason.

6.5.11 Study completion and post-study treatment

No continuation supplies will be made available for the patients as no further treatment is expected to be necessary at the end of the study. However, if necessary, the Investigator will continue to treat the patient until the injury is resolved. Alternatively, the Investigator will inform the patient's general practitioner (GP) at the end of the study period and the patient will then be advised to visit his GP directly.

6.5.12 Early study termination

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 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 of the study.

7 Visit schedule and assessments

Visit 1 (0 hour, Day 1) - Randomization visit

- Written informed consent (section 10.2).
- Check inclusion/exclusion criteria (section 5.1).
- Demographic data (section 7.2).
- Brief, general physical examination is performed including vital signs, weight and height. Urine dipstick pregnancy test (WOCBP and postmenopausal women who are not surgically sterile only) (section 7.6).
- Medical history (previous and concomitant diseases) (section 7.2).
- Concomitant medication (section 6.5.6).
- Assessment of injury (size of traumatization and localization).
- Spontaneous pain intensity, pain at rest (PAR) (section 7.5.1)
- Injury site pain-on-movement (POM) (section 7.5.1).
- Eligible patients receive a randomization number (section 6.5.1).
- The Investigator or a study nurse/doctor's assistant applies the first dose of study drug at the study center. Record information on AEs that occur after treatment (section 8.1).
- Dispense rescue medication and instruct the patient about appropriate use (section 6.5.5).

Visits 2 (12h ± 1h), 3 (24h ± 2h), 4 (48h ± 4h)

These visits will entail the following procedures, except as noted:

- Apply next dose of study medication.
- Count used/unused patches & collect used patches

- Documentation of use of rescue medication, if needed (diary check).
- Record changes in the use of concomitant medication (section 6.5.6).
- Record information on AEs (section 8.1).
- Spontaneous pain intensity, pain at rest (PAR) (section 7.5.1)
- Injury site pain-on-movement (POM) (section 7.5.1).
- Visit 4: Global efficacy assessments (GEA) by patient and investigator (section 7.5.1).
- Adhesive power of patch (section 7.5.1).
- Local tolerability assessment (except V2).

Visit 5 (72h± 4 h)

- Apply next dose of study medication.
- Count used/unused patches & collect used patches.
- Check for last intake of rescue medication no later than 6 hours prior to Visit.
- Documentation of use of rescue medication
- Record changes in the use of concomitant medication (section 6.5.6).
- Record information on AEs (section 8.1).
- Spontaneous pain intensity, pain at rest (PAR) (section 7.5.1)
- Injury site pain-on-movement (POM) (section 7.5.1).
- Global efficacy assessments (GEA) by patient and investigator (section 7.5.1).
- Responder rate 1 (number of patients achieving 50% reduction from baseline in the VAS score for POM)
- Adhesive power of patch (section 7.5.1).
- Local tolerability assessment.

Visit 6 (96h±4h)

- Apply next dose of study medication.
- Count used/unused patches and collect used patches.
- Use of rescue medication.
- Record changes in the use of concomitant medication (section 6.5.6).
- Record information on AEs (section 8.1).
- Spontaneous pain intensity, pain at rest (PAR) (section 7.5.1).
- Injury site pain-on-movement (POM) (section 7.5.1).

- Adhesive power of patch (section 7.5.1).
- Local tolerability assessment.
- Dispense patient card (section 6.5.7) and diary (section 6.5.8) and instruct patient about appropriate use.
- Dispense three patches to the patient.
- The patient is instructed on the method and time of application of study drug (section 6.5.4).

Visit 7 (Day 8 ± 2 days) - Final visit

Procedures for this visit are also to be completed if the patient terminates the study prematurely.

- Count used/unused patches and collect used patches.
- Record changes in the use of concomitant medication (section 6.5.6).
- Record information on AEs (section 8.1).
- Spontaneous pain intensity, pain at rest (PAR) (section 7.5.1)
- Injury site pain-on-movement (POM) (section 7.5.1).
- Global efficacy assessments (GEA) by patient and investigator (section 7.5.1).
- Responder rate 2 (number of patients able to resume training/ normal physical activity)
- Adhesive power of patch (section 7.5.1)
- Local tolerability assessment.
- Collect remaining unused study drug and rescue medication.
- Collect diary.
- Review diary
    - Review the time and date of each patch application.
    - Review rescue medication use. Count and document remaining rescue medication; (section 6.5.5).
- Perform a brief, general physical examination including vital signs and weight (section 7.6.1, 7.6.2). Urine dipstick pregnancy test (WOCBP and postmenopausal women who are not surgically sterile only) (section 7.6.4).
- Record changes in the use of concomitant medication (section 6.5.6).
- Record information on AEs (section 8.1).
- Investigator evaluates whether the soft tissue injury/contusion has resolved and, if resolved, records the day and time it resolved.

Table 7–1: Assessment schedule

	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 (± 2d)
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

7.1 Information to be collected on screening failures

If a patient is screened but not randomized, only demographic information and the Screening Log entry with the primary reason for non-randomization will be completed.

7.2 Patient demographics/other baseline characteristics/medical history

Demographics and baseline characteristics are to be collected on all patients including age, sex, race, height and weight.

Relevant specific medical history will be captured especially the information highlighted below:

- Concurrent injuries concerning the lower and upper limbs.

- History of allergy.

7.3 Assessment of injury

The size of injury is measured by the Investigator. The size must be at least 25 cm^2 and at most 120 cm^2 on the basis of the largest perpendicular diameters. The localization should also be documented in detail in the patient CRF.

7.4 Treatment exposure and compliance

The patient will record in the diary the date and time of every application of study drug.

The patient will return the study drug (used or unused) at the last visit. The number of patches used and unused will be recorded in the accountability form in the CRF.

The Investigator or designee will store the study drugs until the monitor arranges for their return. The Investigator must not destroy any drug. The monitor will check the number of patches at every monitoring visit to verify the drug accountability details entered in the CRF.

7.5 Efficacy

7.5.1 Clinic visit efficacy assessments

The following chronological sequence will be observed for the efficacy assessments below:

1. Pain at rest/spontaneous pain (PAR)
2. Pain-on-movement (POM)

The global assessments may be completed at any time during the assessment process.

Pain-at-rest (PAR)

PAR will be measured at injured site in mm using a 100 mm VAS at Visits 1-7

The patient will then answer the question:

“How would you describe the pain in the injured area at rest?”

The patient will draw a perpendicular line on a 100 mm Visual Analogue Scale (VAS) with a pen between 0 = “no pain” and 100 = “Extreme pain” to reflect the pain intensity at rest.

|----------|

No pain Extreme Pain

Pain-on-movement (POM)

POM will be assessed at the study center at Visits 1–7 using a 100 mm VAS. The result will be written in the CRF.

To standardize the procedure for the assessment of pain-on-movement a special movement should be performed by the patient, either for the upper limb or the lower limb depending on which limb is injured.

- To assess pain-on-movement of the upper limb, the patient will be instructed to grab a 3 kg bar with the hand of the injured arm, slowly lift the bar by bowing the elbow from the 0 position to a 160 degree position and then slowly move the arm back to the starting position.

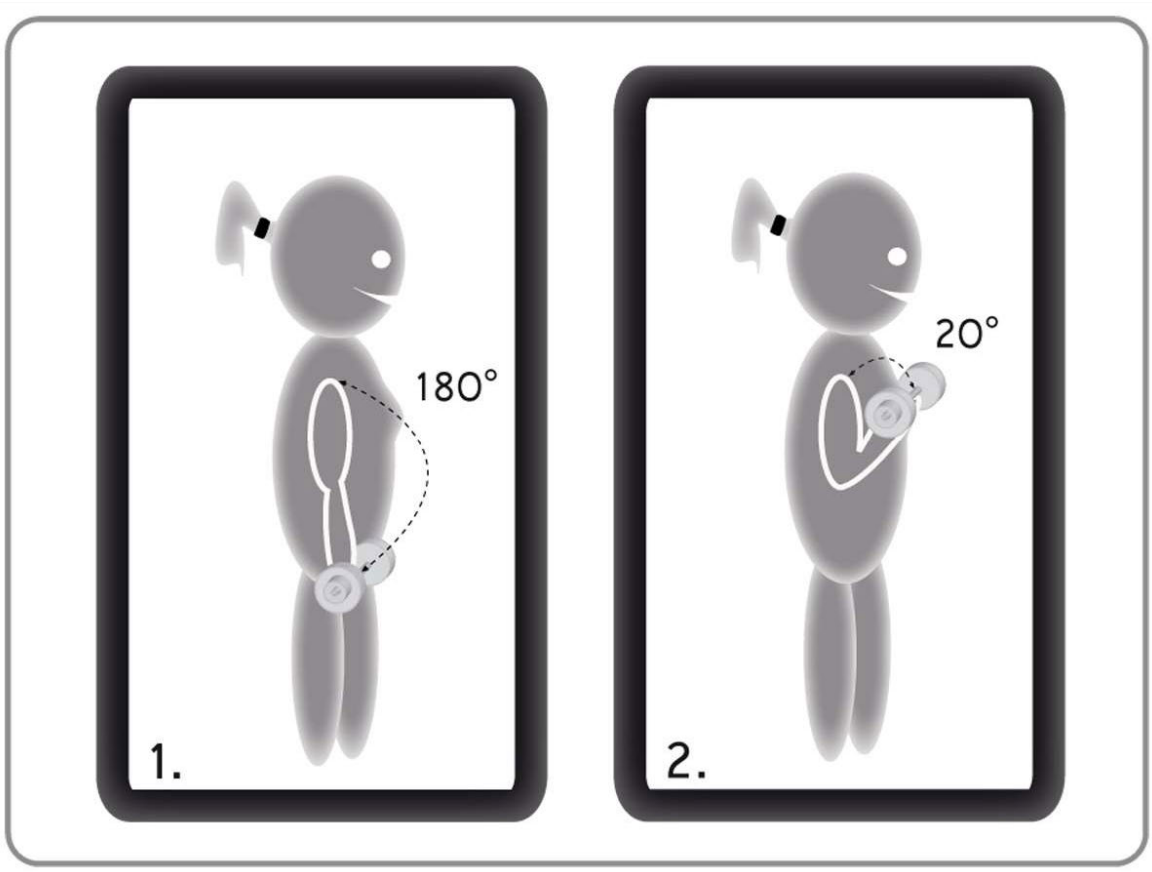

Figure 7.5.1: Exercise to assess pain-on-movement of the upper limbs

The patient will then answer the question:

"How would you describe the pain in the injured area while you were moving your arm?"

- To assess the pain-on-movement of the lower limb, the patient will be instructed to slowly walk 5 steps on an even surface. The patient must initiate the walk with the injured limb (i.e. take 3 of the 5 steps with the injured limb).

The patient will then answer the question:

"How would you describe the pain in the injured area while you were walking?"

The patient will draw a perpendicular line on a 100 mm Visual Analogue Scale (VAS) with a pen between 0 = “no pain” and 100 = “Extreme pain” to reflect the pain intensity during movement.

|----------|

No pain Extreme Pain

Global efficacy assessments

The global efficacy assessments are evaluated by the patient at Visits 4, 5 and 7 as the response to following questions:

- “Considering all the ways this treatment has affected you since you started in the study, how well are you doing?” It is assessed on the following 5-point Likert scale:

0 = very good

1 = good

2 = fair

3 = poor

4 = very poor.

- “How do you rate this medication as a treatment for your soft tissue injury/contusion?” It is assessed on the following 5-point Likert scale:

0=excellent

1=very good

2=good

3=fair

4=poor

The global efficacy assessments are evaluated by the Investigator at Visits 4, 5 and 7 as the response to following questions:

- “Considering all the ways this treatment has affected the patient since he/she started in the study, how well is he/she doing?” It is assessed on the following 5-point Likert scale:

0 = very good

1 = good

2 = fair

3 = poor

4 = very poor.

Adhesive power of the patch

The adhesive power of the patch will be measured by a 5 point numerical scale (0=≥ 90% adhered / 1= ≥75% to <90% adhered / 2=≥50% to <75% adhered / 3=>0% to <50% adhered / 4=completely detached) at every visit except V1.

Assessment of local tolerability of the patch

Local tolerability will be assessed by the Investigator according to the following numerical scale:

Score	Definition
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible, minimal edema or minimal papular response
3	Erythema and papules
4	Definite edema
5	Erythema, edema and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site

Use of rescue medication

Each use of rescue medication will be recorded in the CRF or in the diary. The Investigator/ the patient will record the date and time, the number of tablets taken and the reason for rescue (blunt trauma pain or other).

Resolution of soft tissue injury/contusion

Resolution of soft tissue injury/contusion is assessed by the Investigator at the final study visit. Time to resolution is the time of last application of study medication because the soft tissue injury/contusion has resolved. This is based on the record of applications of study medication and the assessments of efficacy.

7.5.2 Appropriateness of efficacy measurements

The efficacy outcomes selected are standard for this indication.

7.6 Safety

7.6.1 Physical examination

A brief, general physical examination will be performed at Visit 1 (randomization visit) and at Visit 7 (study termination - 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 according to the state of the art.

7.6.2 Vital signs

Vital signs (including systolic blood pressure, diastolic blood pressure and pulse rate) will be measured at Visit 1 and at final visit:

- Blood pressure: Measurement after at least 5 minutes at rest in sitting position.
- Pulse rate: Measured after at least 5 minutes at rest in sitting position.

7.6.3 Height and Weight

Height in centimeters (cm) and body weight (kg, in indoor clothing, but without shoes) will be measured at Visit 1. Body weight only will be measured at Visit 7.

7.6.4 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). Patients with a positive urine pregnancy test result must not be randomized. A urine dipstick pregnancy test will also be performed at Visit 7 (final visit).

7.6.5 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

8 Safety monitoring

8.1 Adverse events

An adverse event (AE) is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Study drug includes the investigational drug under evaluation and the comparator drug or placebo that is given during any phase of the study. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered

by the patient during or between visits or through physical examination, , or other assessments. All adverse events must be recorded on the Adverse Events CRF with the following information:

1. the severity grade (mild, moderate, severe)
2. its relationship to the study drug(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

An SAE is defined as an event which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons or respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

  Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements.

All AEs and SAEs will be recorded, including their severity, their duration and relationship to study drug.

All adverse events should be treated appropriately. Treatment may include one or more of the following:

- no action taken (i.e., further observation only);
- study drug dosage temporarily interrupted;
- study drug permanently discontinued due to this adverse event;
- concomitant medication given;
- non-drug therapy given;
- patient hospitalized/patient's hospitalization prolonged.

The action taken to treat the adverse event should be recorded on the Adverse Event CRF page.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is later) must be reported to CRMB (EU Legal Representative) and Clinsearch immediately without undue delay, but latest within 24 hours of learning of its occurrence.

The CRMB (EU Legal Representative) Drug Safety & Pharmacovigilance fax number is:

[redacted]

The CRMB (EU Legal Representative) Drug Safety & Pharmacovigilance email is:

[redacted]

Any SAE experienced after this 30 day period should only be reported to CRMB and Clinsearch if the Investigator suspects a causal relationship to the study drug.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the Investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The Investigator must assess the relationship to study drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to CRMB and Clinsearch DSP. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study center.

Follow-up information will be sent to the same person to whom the original SAE Report Form will be sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study drug, a DSP associate may urgently require

further information from the Investigator for Health Authority reporting. Clinsearch may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be reported to the competent authorities and relevant ethics committees in accordance with the applicable regulatory requirements.

8.3 Pregnancies

To ensure patient safety, each pregnancy in a patient on study drug must be reported to CRMB and Clinsearch within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the Investigator to the Clinsearch Safety department (as above in section 8.2) Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

9 Data review and database management

9.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Clinsearch representative will review the protocol and CRFs with the investigators and their staff. During the study, the study monitors will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications, according to the ICH-GCP-Guidelines and the related SOPs. Site personnel must be available to assist the study monitors during these visits. Source data verification is done by direct inspection of the patient's original files by authorized persons.

The Investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. Data not requiring a separate written record will be defined before study start (i.e. efficacy assessments described in section 7.5.1) and will be recorded directly on the CRFs. The Investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

Study documents, including the Essential Documents collected in the Investigator File, must be kept at the site until at least two (2) years after the last approval of a marketing application in an ICH region or after the formal discontinuation of the clinical development of the investigational product or for at least 15 years after the study end, whichever is the longest. It is the responsibility of Clinsearch to inform the Investigator as to when these documents no longer need to be retained.

The Investigator must give the study monitors access to all relevant source documents to confirm their consistency with the CRF entries. Clinsearch monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety outcomes. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed in the monitoring reports.

9.2 Data collection

Designated investigator staff must enter the information required by the protocol onto the CRFs that are printed on 3-part, non-carbon-required paper. Study monitors will review the CRFs for completeness and accuracy and instruct site personnel to make any required corrections or additions. The CRFs are then forwarded to the Data Management CRO (CRMB) working on behalf of Clinsearch by study monitors or by the investigational site, with one readable copy being retained at the investigational site. Once the CRFs are received at Data Management, their receipt is recorded, the original copy is placed in Central Files, and the non-carbon-required copy is forwarded to the responsible Data Management staff for processing.

9.3 Database management and quality control

The study database is constructed, validated and maintained by the designated Data Management CRO. Data items from the CRFs are entered, using double entry, into the study database by the CRO Data Management staff following their own internal standard operating procedures that have been reviewed and approved by Clinsearch.

Subsequently, the entered data are systematically checked by Data Management staff, using error messages printed from validation programs and database listings. Obvious errors are corrected by authorized Data Management personnel. Other errors or omissions are entered on Data Query Forms, which are returned to the investigational site for resolution. The signed original and resolved Data Query Forms are kept with the CRFs at the investigator site, and a copy is sent to the Data Management CRO so the resolutions can be entered into the database. Quality control audits on all key safety and efficacy data in the database are to be performed by the Data Management CRO prior to locking the database.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List (current version), which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA, current version) terminology.

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Clinical Project Leader, the Project Statistician and the

Project Data Manager with authorization from Teikoku Seiyaku Co Ltd. Director & Executive Officer, Clinical Development & Regulatory Strategy center .

Data Analysis

A review of the database will be conducted shortly before the study is unblinded in the Blind Data Review Meeting, and any decisions made at that meeting concerning the statistical analysis, e.g., additional outcomes and populations, pooling of centers for efficacy analysis, will be documented in the Statistical Analysis Plan. Any changes that must be made after the study is unblinded will be documented separately, as well as any changes that must be made to the study database after the study is unblinded.

9.4 Populations for analysis

Full Analysis Set	The Full Analysis Set will be all randomized patients who received at least one dose of study drug. The FAS population will be primary population for the analysis of efficacy. Any exclusions from the FAS population will be made and documented before unblinding (e.g. never used study medication, randomized twice). Additional secondary populations may be defined before unblinding and will be described in detail in the SAP.
Safety Set	The safety set (SAF) will include all randomized patients who received at least one dose of the study drug. Safety will be analyzed in this 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.

9.5 Demography/other baseline characteristics

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.

9.6 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

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 SAP 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.

9.7 Efficacy

9.7.1 Outcomes

Primary Outcome

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’.

Secondary Outcomes

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
- 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)

Other:

Adhesive power of patch (5-point scale)

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.

9.7.2 Statistical hypothesis, model, and method of analysis

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

1) H_o: $\mu_E=\mu_P$ 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.

2a) H_o: $\mu_{E(spr/str)}=\mu_{P(spr/str)}$ vs. H_1: $\mu_{E(spr/str)}\neq\mu_{P(spr/str)}$ in the subgroup “Sprains/strains”,
2b) H_o: $\mu_{E(con)}=\mu_{P(con)}$ vs. H_1: $\mu_{E(con)}\neq\mu_{P(con)}$ in the subgroup

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

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 which will be more detailed described in the Statistical Analysis Plan (SAP). 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 categorical outcomes will be tested with Cochran-Mantel-Haenszel tests of treatment mean ridits or of general association, stratified by center.

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.

For ordered categorical outcomes, (the global assessments), differences between treatments will be tested with the CMH test of treatment mean ridits, stratified by center.

Differences between treatments on each quantitative rescue medication outcome will be tested with the CMH test of treatment means, stratified by center.

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

9.7.3 Handling of missing values/censoring/discontinuations

Assessments at the site

- If assessments at any visit for Visits 2 (12h) through Visit 7 (168h) 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 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 the final assessment and the baseline assessment.
- 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 considered in the Statistical Analysis Plan, 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 6h 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 6h will be imputed as if the assessment were missed.
- If there are no assessments in the 12-24h window, or the 24-48h 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 Statistical Analysis Plan.

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 24h.
- 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 24h.
- 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 Statistical Analysis Plan to cover issues not anticipated in the above stipulations.

9.8 Safety

The assessment of safety will be based mainly on the frequency of AEs that are treatment-emergent. Formal 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.

9.9 Sample size calculation

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

9.10 Interim analysis

No interim analysis will be conducted.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study is designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice [European Medicines Agency 2006], with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent, The patient must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Clinsearch will provide to investigators in a separate document a proposed informed consent form that complies with the ICH-GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the Investigator must be agreed to by Clinsearch/Teikoku before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy occurs during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

10.3 Insurance

CRMB will procure insurance for every patient enrolled in the clinical study in line with applicable regulatory requirements. Every patient will receive an information sheet on insurance coverage together with the patient information.

10.4 Responsibilities of the Investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Clinsearch before study initiation. Prior to study start, the Investigator is required to sign a protocol

signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Clinsearch monitors, auditors, Quality Assurance representatives, designated agents of Clinsearch, IRBs/IECs/REBs, and regulatory authorities, as required.. Patient privacy and data confidentiality will be observed according to the applicable regulatory requirements and/or local laws.

If an inspection of the clinical site is requested by a regulatory authority, the Investigator must inform Clinsearch immediately that this request has been made. SAEs will be reported by the Investigator to the IRB/IEC/REB, as required.

10.5 Quality Assurance Audits and Health Authority Inspections

The clinical investigator study site may be patient to quality assurance audits performed by Clinsearch or its agents on behalf of Clinsearch, and/or regulatory inspections by the appropriate health authorities. The Investigator and the institution will allow Clinsearch, its agents, and/or appropriate regulatory authorities direct access to study records including source records, CRFs and other study relevant documentation for review. Patient privacy and data confidentiality will be observed accordingly to the applicable regulatory requirements and/or local laws.

The Investigator must immediately notify Clinsearch if they have been contacted by a regulatory agency concerning an upcoming inspection. It is important that investigators and their relevant personnel are available during audits and/or inspections and that sufficient time is devoted to the process.

10.6 Publication of study protocol and results

Clinsearch confirms that a synopsis of the study results will be submitted to the authorities and the Ethics Committees in ICH E3 format within one year after the end of the clinical trial. Furthermore, protocol information and clinical results will also be submitted in EudraCT within one year after the end of the clinical trial. . In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in other publicly accessible database of clinical study results.

11 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the Investigator contact Clinsearch or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Clinsearch and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR, as defined in the note for Guidance ICH E3.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Clinsearch, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Clinsearch should be notified of this action and the IRB/IEC/REB at the study site should be informed within 10 working days.

12.1 End of Trial

The End of this clinical trial is defined as “the last visit of the last patient” included in the trial.

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