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Title Page

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

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Sponsor Signatory - amended PPD

PPD

PPD

Date

Global Medical Category Pain
Medical and Clinical Affairs
Bayer Healthcare LLC.

Medical Monitor name and contact information will be provided separately.

Protocol Amendment Summary of Changes Table

Protocol Amendment (Version 2.0)

The following sections were amended from Version 1.0 to Version 2.0. Also modified were the BAY No., version number, date and Table of Contents.

Section 1.3 Schedule of Activities – amended (changes only reflected here)

Trial Procedure	Screening Phase		Treatment Phase										
	Screening	Baseline											
	Day 1		Day 1	Day 2		Day 3		Day 4		Day 5		Day 6	
	Visit 1		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
	Hours Post First Dose ➡			12 hrs	24 hrs	36 hrs	48 hrs	60 hrs	72 hrs	84 hrs	96 hrs	108 hrs	120 hrs
Prior and Concomitant / Medication History **and Diary Review**[a]	X			X	X	X	X	X	X	X	X	X	X
Vital signs (incl. temperature)[b]	X								X				X
Physical examination (injury assessment)[c]	X			X		X		X		X		X	
Urine pregnancy test	X[f]											X[f]	
Randomization/Kit assignment		X[d]											
IMP administration[e]			X	X	X	X	X	X	X	X	X	X	
Global Assessments					X[g]		X[g]		X[g]				X[g]

[a] **Diary review begins at Visit 2**
[b] Vital signs (blood pressure, respiratory rate, heart rate and body temperature after 5 minutes of rest in a sitting position).
[c] **Full physical exam and injury assessment at Visit 1, limited exam (injury assessment) at all other visits**
[d] Randomization to treatment occurs only for eligible patients.
[e] All topical IMP treatments must be weighed on a digital scale, then applied by the unblinded study staff at the site. Patient will wear a blindfold when being treated.
[f] Urine pregnancy test must be performed (for female patients) and the results must be negative (not pregnant) before dosing **and at Visit 10**
[g] Assessments by the patient will be completed before first rescue medication is taken. If between visits, then the investigator will complete assessments at the next scheduled visit.

Protocol Amendment Summary of Changes Table

Protocol Amendment 2 (Version 3.0)

The following sections were amended from Version 2.0 to Version 3.0.

Type of Amendment: Substantial

Significant Changes:

Changes which are considered significant or substantial have been made to the following sections reflected below:

Page Number	Section Number	Paragraph or Bullet point/number
21	5.2	**Exclusion Criteria 15** 15. ~~Ice and compression are prohibited from the time of injury through the final evaluation~~. **Application of standard care by rest, ice, compression (non-occlusive bandage) or elevation (RICE) may be considered at the discretion of the investigator**
41	9.1	**Statistical Hypotheses** ~~The purpose of the study is to gather preliminary data for the efficacy and safety of the IMP. Therefore, there is no statistical hypotheses to be formulated.~~ **For the comparison of the test gel vs. placebo, the primary efficacy hypothesis to be tested is the equality of Algometry AUC 0-72; the second is the POM VAS AUC 0-72.**
41	9.2	**Sample Size Determination** ~~The study is not statistically powered. From feasibility point of view, sufficient number of participants will be randomized to study intervention in order to achieve an estimated total of 30 evaluable participants for each active treatment (naproxen gel or diclofenac gel) and 15 evaluable participants for placebo gel.~~ **This is a proof of concept study and therefore a specific statistical power calculation cannot be applied, however, assuming a comparable effect of the test gel vs. diclofenac – as suggested by pharmacological studies-, reference is made to similar studies (Predel, Br J Sports Med 2004;38:318–323), in which the standardized effect sizes of Algometry AUC 0-72 and POM VAS AUC 0-72 were over 1; with 30:15**

		patients, a drop out rate of 10%, and a two-sided significance level α = 5%, a power 1 – β of about 80% is reached.
44	9.3	**Analysis Sets – Per Protocol** The primary efficacy analysis population will be PP population and ITT Population will be secondary. The same analysis on ITT Population will be repeated for the primary**,** ~~and~~ secondary **and other** efficacy endpoints to assess the robustness of the results based on PP Population.
44	9.4	**Statistical Analysis** This section is a summary of the planned statistical analyses of the most important endpoints including primary ~~and~~ secondary**,** and other-key endpoints.

Additional Changes:

Not applicable

Protocol Amendment Summary of Changes Table

Protocol Amendment 3 (Version 4.0)

The following sections were amended from Version 3.0 to Version 4.0.

Type of Amendment: Substantial

Significant Changes:

Changes which are considered significant or substantial have been made to the following sections reflected below:

Sponsor Signatory – amended

PPD

PPD ~~, Global Medical Affairs~~

~~Bayer Healthcare LLC.~~

PPD

PPD

Global Medical Category Pain

Medical and Clinical Affairs

Bayer Healthcare LLC.

Table of Contents

Title Page **1**

Sponsor Signatory - amended **2**

Protocol Amendment Summary of Changes Table **3**

1. Protocol Summary **10**
1.1 Synopsis 10
1.2 Scheme 13
1.3 Schedule of Activities (SoA) - amended 14

2. Introduction **15**
2.1 Study Rationale 15
2.2 Background 15
2.3 Benefit/Risk Assessment 16
2.3.1 Risk Assessment 17
2.3.2 Benefit Assessment 19
2.3.3 Overall Benefit: Risk Conclusion 19

3. Objectives and Endpoints **20**

4. Study Design **21**
4.1 Overall Design 21
4.1.1 Study Design Phases 21
4.1.1.1 Screening/Baseline Phase 21
4.1.1.2 Treatment Phase 21
4.1.1.3 Follow-up Phase 22
4.2 Scientific Rationale for Study Design 22
4.3 Justification for Dose 22
4.4 End of Study Definition 22

5. Study Population **23**
5.1 Inclusion Criteria 23
5.2 Exclusion Criteria - Amended 23
5.3 Lifestyle Considerations 25
5.4 Screen Failures 25
5.5 Criteria for Temporarily Delaying Study Intervention Administration 25

6. Study Intervention(s) and Concomitant Therapy **26**
6.1 Study Intervention Administered 26
6.2 Identity of Study Interventions 28
6.3 Preparation/Handling/Storage/Accountability 28
6.4 Measures to Minimize Bias: Randomization and Blinding 29
6.5 Study Intervention Compliance 30
6.6 Dose Modification 30
6.7 Stopping Rules 31
6.8 Continued Access to Study Intervention after the End of the Study 31
6.9 Treatment of Overdose 31
6.10 Concomitant Therapy 31
6.10.1 Rescue Medicine 32

7. Discontinuation of Study Intervention and Participant **33**
7.1 Discontinuation of Study Intervention 33

7.2 Participant Discontinuation/Withdrawal from the Study 33
7.3 Lost during the Treatment Phase 33

8. Study Assessments and Procedures 34
8.1 General Procedures 34
8.1.1 Screening Phase Visit 1 - (Day 1) 34
8.1.2 Baseline Visit 1 - (Day 1) 35
8.1.3 Visit 2 (Day 2 morning) 35
8.1.4 Visit 3 (Day 2 evening) 36
8.1.5 Visit 4 (Day 3 morning) 36
8.1.6 Visit 5 (Day 3 evening) 37
8.1.7 Visit 6 (Day 4 morning) 37
8.1.8 Visit 7 (Day 4 evening) 38
8.1.9 Visit 8 (Day 5 morning) 38
8.1.10 Visit 9 (Day 5 evening) 39
8.1.11 Visit 10 (Day 6 morning) 39
8.1.12 Visit 11 (Day 6 evening, End of Study) 40
8.2 Efficacy Assessments 40
8.2.1 Assessment of Pain on Movement 40
8.2.2 Algometry 40
8.2.3 Global Assessments of Efficacy and Tolerability 41
8.2.4 Sensory Questions 42
8.3 Safety Assessments 42
8.3.1 Physical Examinations 42
8.3.2 Vital Signs 43
8.3.3 Pregnancy Testing 43
8.4 Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting 43
8.4.1 Time Period and Frequency for Collecting AE and SAE Information 43
8.4.2 Method of Detecting AEs and SAEs 44
8.4.3 Follow-up of AEs and SAEs 44
8.4.4 Regulatory Reporting Requirements for SAEs 44
8.4.5 Pregnancy 44
8.5 Pharmacokinetics 45
8.6 Genetics or Pharmacogenomics 45
8.7 Biomarkers 45
8.8 Immunogenicity Assessments 45
8.9 Health Economics 45

9. Statistical Considerations 46
9.1 Statistical Hypotheses - Amended 46
9.2 Sample Size Determination - Amended 46
9.3 Analysis Set - Amended 46
9.4 Statistical Analyses - Amended 46
9.4.1 General Considerations 47
9.4.2 Primary Endpoint 47
9.4.3 Secondary Endpoint 47
9.4.4 Other Endpoints 47
9.4.5 Safety Analysis 48
9.5 Interim Analysis 48

10. Supporting Documentation and Operational Considerations 49

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 49
10.1.1 Regulatory and Ethical Considerations 50
10.1.2 Financial Disclosure 50
10.1.3 Funding 50
10.1.4 Informed Consent Process 51
10.1.5 Data Protection and Confidentiality 52
10.1.6 Compensation for Health Damage of Participants/Insurance 52
10.1.7 Committees Structure 52
10.1.8 Dissemination of Clinical Study Data 52
10.1.9 Data Quality Assurance 53
10.1.10 Source Documents 53
10.1.11 Missing Data 54
10.1.12 Audit and Inspection 54
10.1.13 Archiving 54
10.1.14 Study and Site Start and Closure 55
10.1.15 Publication Policy 55
10.2 Appendix 2: Clinical Laboratory Tests 56
10.3 Appendix 3: AEs and SAEs: Definitions and Procedures 56
10.3.1 Definition of AE 56
10.3.2 Definition of SAE 58
10.3.3 Recording and Follow-Up of AE and/or SAE 59
10.3.4 Reporting of SAEs 61
10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information 61
10.5 Appendix 5: Abbreviations 63

11. References 65

Table of Tables

Table 1 – Dosing Example 27
Table 2 – Study Interventions 28

1. Protocol Summary

1.1 Synopsis

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

Rationale: Proof of concept study to determine the effectiveness of naproxen gel 10% in participants with lower extremity injuries.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To assess the effectivenss of a naproxen gel 10%,diclofenac diethylamine gel 2.32% and placebo for relieving tenderness to pressure in subjects with acute soft tissue injuries of the lower extremities.	• Tenderness (Algometry) over the initial 72 hours (Algometry AUC 0-72).
Secondary	
• To assess the safety of a naproxen gel 10%,diclofenac diethylamine gel 2.32% and placebo during a 5 day treatment period. • To assess adverse events.	• Safety (percentage of subjects with at least one TEAE); • Incidence of adverse events.

Objectives	Endpoints
Other	
• To evaluate pain on movement and tenderness to pressure over various time periods and at individual time points.	• VAS POM over the initial 12-hours (VAS AUC 0-12), 24-hours (VAS AUC 0-24), 36-hours (VAS AUC 0-36), 48-hours (VAS AUC 0-48), 60-hours (VAS AUC 0-60), 72-hours (VAS AUC 0-72), and 120 hours (VAS AUC 0-120); • Change of VAS POM at hours 12, 24, 36, 48, 60, 72 and 120 from baseline; • Change of Algometric Tenderness (N/cm^2) at hours 12, 24, 36, 48, 60, 72 and 120 from baseline; • Algometric Tenderness (N/cm^2) over the initial 12-hours (N/cm^2 AUC 0-12), 24-hours (N/cm^2 AUC 0-24), 36-hours (N/cm^2 AUC 0-36), 48-hours (N/cm^2 AUC 0-48) 60-hours (N/cm^2 AUC 0-60) and 120 hours (N/cm^2AUC 0-120); • Ratio of algometry injured/contralateral sites over 72 hours and 120 hours (N/cm^2 Ratio AUC 0-72 and N/cm^2 Ratio AUC 0-120); • Percent of subjects with no (zero) VAS POM at 120 hours; • Global assessment of treatment efficacy at 24 hours, 48 hours, 72 hours and 120 hours by patients using a 5-point scale (0=none, 1=poor, 2=fair, 3=good, 4=excellent); • Global assessment of treatment efficacy at 24 hours, 48 hours, 72 hours and 120 hours by investigators using a 5-point scale (0=none, 1=poor, 2=fair, 3=good, 4=excellent).

Overall Design: This is a randomized (2:2:1/naproxen:diclofenac:placebo), stratified by injury (contusion or sprain/strain) active- and placebo-controlled (vehicle), double-blind, multi-center (3 sites), parallel study.

Brief Summary:

This is a 6-day clinical trial to test the hypothesis that naproxen gel 10% safely and effectively relieves tenderness to pressure in subjects with acute soft tissue injuries of the lower extremities. Subjects who present to the study within 3 hours of injury will be recruited for the study. In order to assure adequate representation of different types of soft tissue injuries, subjects may enter the study with a lower extremity sprain/strain injury or a lower extremity contusion injury. Eligible subjects will be selected immediately following screening/baseline evaluations. Following selection, subjects will enter the Treatment Phase and will be randomly assigned to one of the three treatment groups- naproxen topical gel 10% (test); diclofenac diethylamine topical gel 2.32% (active comparator); or placebo gel. The randomization assignment is such that there is a

1 in 5 chance of receiving the placebo treatment. Treatment consists of a twice daily application (approximately 12 hours apart) of the assigned topical gel over 5 consecutive days, beginning on the evening of Day 1 and ending (last application) on the morning of Day 6 (total of 10 applications). All treatment applications will be performed by study staff at the site. After the first treatment, two visits each day for five consecutive days are required. Patients who experience a treatment failure can have the option of taking rescue medication for pain relief.

During the screening/baseline and follow-up treatment visits, tenderness will be measured by the pressure required to elicit a response. Pain on movement will also be rated by the subject using a 100 mm visual analogue scale.

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

Study Duration: 6 days

Treatment Duration: 6 days

Visit Frequency: After the first treatment, two visits each day for five consecutive days

Condition/Disease: Soft tissue injury, either a sprain/strain or contusion

Study Hypothesis: Topical naproxen gel, 10% effectively relieves tenderness to pressure in patients with acute soft tissue injuries

Health Measurement/Observation: Algometry measurements for tenderness and Visual Analog Scales for pain will occur pre and post topical treatment.

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

Intervention Groups: Participants will be randomized in 2:2:1 fashion and stratified by injury type with at least 25 participants in the Sprain/Strain cohort and at least 50 participants in the Contusion cohort.

Data Monitoring/Other Committee: No

1.2 Scheme

	Pre-screening	Screening	Baseline	Treatment Phase									
Trial Days	**Day -1**	**Day 1 Injury Assessment**	**Day 1 Visit 1**	**Day 2 Visit 2**	**Day 2 Visit 3**	**Day 3 Visit 4**	**Day 3 Visit 5**	**Day 4 Visit 6**	**Day 4 Visit 7**	**Day 5 Visit 8**	**Day 5 Visit 9**	**Day 6 Visit 10**	**Day 6 Visit 11**
Clinic Visit	**NA**	**Evening (6pm – 10pm)**		**Morning**	**Evening**	**Morning**	**Evening**	**Morning**	**Evening**	**Morning**	**Evening**	**Morning**	**Evening**
		Post first dose ➡		12 Hours	24 Hours	36 Hours	48 Hours	60 Hours	72 Hours	84 Hours	96 Hours	108 Hours	120 Hours
	Sports related lower extremity injury within 3 hours of screening	Contusion Cohort n≥50	🏢 POM VAS Algometry	🏢 POM VAS Algometry	🏢 POM VAS Algometry Global Assessment	🏢 POM VAS Algometry	🏢 POM VAS Algometry Global Assessment	🏢 POM VAS Algometry	🏢 POM VAS Algometry Global Assessment	🏢	🏢	🏢	POM VAS Algometry Global Assessment Patient Discharged
		◈	✱	---------- **Dosing every 12 hours (nominal time ± 1 hour)** ----------									
		Sprain/Strain Cohort n≥25	🏢 POM VAS Algometry	🏢 POM VAS Algometry	🏢 POM VAS Algometry Global Assessment	🏢 POM VAS Algometry	🏢 POM VAS Algometry Global Assessment	🏢 POM VAS Algometry	🏢 POM VAS Algometry Global Assessment	🏢	🏢	🏢	POM VAS Algometry Global Assessment Patient Discharged

◈ = Injury stratification (contusion or sprain/strain cohort) after assessment and prior to randomization

✱ = Randomization at Visit 1 into one of three treatments and first dose:

- **naproxen gel 10%**
- **diclofenac diethylamine gel 2.32%**
- **placebo**

Nominal dosing times (am and pm) established at Visit 1

🏢 = Patient to take IMP at the site (am and pm)

POM = Pain on movement

VAS = Visual analog scale (100 mm)

Patient to keep a daily diary for concomitant/rescue medications and adverse events

1.3 Schedule of Activities (SoA) - amended

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

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

2. Introduction

CCI [redacted] The product is to be used for the temporary relief of minor aches & pains of muscles & joints. This proof-of-concept trial will assess the efficacy and safety of a newly developed 10% naproxen gel formulation compared to a commercially available topical nonsteroidal anti-inflammatory drug (NSAID) gel and placebo in the treatment of common sports related, acute traumatic injuries.

2.1 Study Rationale

This is a proof of concept study to guide decision-making for the naproxen topical gel development program. Bayer needs information on the product's attributes to help determine whether to support further clinical development of this topical gel formulation. Assuming this pilot study is successful, the data will provide supportive data for future clinical studies and a regulatory submission.

2.2 Background

NSAIDs effectively reduce the pain and disability associated with acute ankle sprain and other soft tissue traumas (1,2,3). In some patients however, non-selective NSAIDs, which inhibit both cyclooxygenase (COX)-1 and COX-2, may cause significant adverse events including upper gastrointestinal intolerance and have been associated with serious adverse events such as ulcers and bleeding. Risk of gastrointestinal bleeding is reduced with decreasing dose and treatment duration of non-selective NSAIDs (4).

Topical delivery of an NSAID that is efficacious and limits systemic exposure might offer an improvement over an oral formulation (5) in patients with acute musculoskeletal pain. Minor aches and pains of muscles and joints are amenable to treatment with topical products as the site of injury is closely to the overlying skin where the topical products can be applied. Topical NSAIDs have been shown to be effective in the treatment of aches and pains of muscles and joints (1,6,7,8,9,10). Although skin reactions have been reported with the use of locally delivered NSAIDs, reports of systemic adverse events from the use of these topical products are infrequent. A systematic review found that local and systemic adverse events with topical NSAIDs had a low incidence and are not different from placebo (7). There does not appear to be any significant association of these formulations with gastrointestinal or renal side effects (11,12,13). A recent systematic review and meta-analysis of topical NSAID safety in osteoarthritis found no significant difference in the odds for gastrointestinal disorders between topical NSAIDs and placebo (odds ratio 0.96, 95% CI 0.73–1.27, 14).

Naproxen and naproxen sodium have been commercially available in a variety of dosage forms for decades. Naproxen gel 10% is an OTC topical analgesic gel currently marketed in several countries where it is indicated for a variety of conditions, characterized by pain and inflammation. It has been shown to reduce pain and inflammation in patients with acute soft tissue injuries (15).

Based on this body of evidence supporting topical NSAIDs for acute musculoskeletal pain, CCI [redacted] To date, nonclinical safety

studies conducted include the evaluation of skin sensitization potential utilizing the mouse local lymph node assay, a seven-day dermal dose-range finding pilot study and a 28-day repeated dose study including a four-week recovery period, the latter two studies conducted in minipigs (16). Preclinical studies with the naproxen gel formulation CCI [redacted]

2.3 Benefit/Risk Assessment

Patients with a sports-related injury to the lower extremities who would typically take over-the-counter NSAIDs for pain relief will be enrolled in this study. Patients who experience a treatment failure can have the option of taking rescue medication for pain relief.

During the study, patients will be closely monitored for evidence of adverse events. Weighing between the potential risks of topical analgesics associated with the study and given the ability to mitigate risks through close monitoring, this study is considered clinically and ethically acceptable.

Relevant emerging safety data, e.g., serious adverse events (SAEs), suspected unexpected serious adverse reactions (SUSARs), and serious safety-related protocol deviations, will be communicated as soon as possible between the sponsor, all study sites and investigators and trial subjects according to the requirements of the EMA guideline on strategies to identify risks for early clinical trials.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of naproxen gel 10% and diclofenac diethylamine 2.32% may be found in the Investigator's Brochure (IB) and Voltaren Schmerzgel forte Package Leaflet respectively (16,17).

The potential impact of COVID-19 on study participants will be evaluated before the start of enrollment and monitored during the study in accordance with European Medicines Agency guidance (18).

2.3.1 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention		
The risks associated with naproxen gel 10% are mostly cutaneous and nonserious in nature and include application site reactions such as erythema, pruritus, skin irritation, burning skin sensation, and contact dermatitis. Subjects with hypersensitivity to naproxen, or to any excipient in the test products should avoid exposure and should be excluded from this study.	Naproxen Topical Gel IB section 5.3.3.5 Adverse events	The exclusion criteria for the study and the medical oversight of its conduct for the detection and treatment (if necessary) of adverse events are adequate for subject safety and no special risk mitigation measures are necessary. The following strategies (as numbered below) will be employed to mitigate adverse event risks: 5.2 Exclusion criteria 6.6 Dose modification 6.7 Stopping rules 6.9 Treatment of overdose 7.1 Discontinuation of study intervention 7.2 Participant discontinuation/ Withdrawal from study 8.3 Safety assessments 8.4.3 Follow up of AEs and SAEs
Study Procedures		
Subject may have an underlying medical condition uncovered during screening and baseline procedures.		Investigator will advise subject to seek appropriate medical attention.

Other		
Subject may present to the clinic with an injury that is more serious than described by the inclusion criteria Voltaren gel may cause rare and very rare side effects that may be serious: Rare side effects (may affect up to 1 in 1,000 people) • Skin inflammation with blistering (bullous dermatitis) Very rare side effects (may affect up to 1 in 10,000 people) • wheezing, shortness of breath, or tightness in the Chest (asthma) • Swelling of the face, lips, tongue, or throat (Angioedema) Other side effects with Voltaren gel include skin reactions, gastrointestinal complaints, hypersensitivity reactions, and photosensitivity Voltaren Pain Gel applied extensively to the skin and used over a longer period of time *may cause* systemic side effects (e.g. renal, hepatic or gastrointestinal side effects, systemic hypersensitivity reactions)	Package leaflet: Information for users, Voltaren Schmerzgel forte, 23.2 mg/g Gel, April 2019.	Investigator will advise subject to seek appropriate medical attention if the injury is more serious than allowed by the inclusion criteria. The exclusion criteria for the study and the medical oversight of its conduct for the detection and treatment (if necessary) of adverse events are adequate for subject safety and no special risk mitigation measures are necessary. The following strategies (as numbered below) will be employed to mitigate adverse event risks: 5.2 Exclusion criteria 7.1 Discontinuation of study intervention 7.2 Participant discontinuation/ Withdrawal from study 8.3 Safety assessments 8.4.3 Follow up of AEs and SAEs Subjects participating in this study will have a defined dose and short term exposure to Voltaren gel and will be administered at the study site by a professional

2.3.2 Benefit Assessment

Potential benefits may include:

- Potential benefit of receiving study intervention during the study duration that may result in decreased tenderness and pain of the injured extremity
- Medical evaluations/assessments associated with study procedures (e.g., physical exam, vital signs, etc.).

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified using a topical medication are justified by the anticipated benefits that may be afforded to participants with a soft tissue injury.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the effectivenss of a naproxen topical gel 10%,diclofenac diethylamine 2.32% and placebo for relieving tenderness to pressure in subjects with acute soft tissue injuries of the lower extremities.	• Tenderness (Algometry) over the initial 72 hours (Algometry AUC 0-72).
Secondary	
• To assess the safety of a naproxen gel 10%,diclofenac diethylamine gel 2.32% and placebo during a 5 day treatment period; • To assess adverse events.	• Safety (percentage of subjects with at least one TEAE); • Incidence of adverse events.
Other	
• To evaluate pain on movement and tenderness to pressure over various time periods and at individual time points.	• VAS POM over the initial 12-hours (VAS AUC 0-12), 24-hours (VAS AUC 0-24), 36-hours (VAS AUC 0-36), 48-hours (VAS AUC 0-48), 60-hours (VAS AUC 0-60), 72-hours (VAS AUC 0-72), and 120 hours (VAS AUC 0-120); • Change of VAS POM at hours 12, 24, 36, 48, 60, 72 and 120 from baseline; • Change of Algometric Tenderness (N/cm^2) at hours 12, 24, 36, 48, 60, 72 and 120 from baseline; • Algometric Tenderness (N/cm^2) over the initial 12-hours (N/cm^2 AUC 0-12), 24-hours (N/cm^2 AUC 0-24), 36-hours (N/cm^2 AUC 0-36), 48-hours (N/cm^2 AUC 0-48) 60-hours (N/cm^2 AUC 0-60) and 120 hours (N/cm^2AUC 0-120); • Ratio of algometry injured/contralateral sites over 72 hours and 120 hours (N/cm^2 Ratio AUC 0-72 and N/cm^2 Ratio AUC 0-120); • Percent of subjects with no (zero) VAS POM at 120 hours; • Global assessment of treatment efficacy at 24 hours, 48 hours, 72 hours and 120 hours by patients using a 5-point scale (0=none, 1=poor, 2=fair, 3=good, 4=excellent); • Global assessment of treatment efficacy at 24 hours, 48 hours, 72 hours and 120 hours by investigators using a 5-point scale (0=none, 1=poor, 2=fair, 3=good, 4=excellent).

4. Study Design

4.1 Overall Design

This is a randomized (2:2:1/naproxen:diclofenac:placebo), stratified by injury (contusion or sprain/strain) active- and placebo-controlled (vehicle), double-blind, multi-center (3 sites), parallel study.

The study consists of a Screening/Baseline Phase and a Treatment Phase.

Subjects who present to the site between 6PM – 10PM and within 3 hours of injury will be recruited for the study. Eligible subjects will be selected immediately following screening/baseline evaluations. Following selection, subjects will enter the Treatment Phase. Subjects will be randomized into one of the three treatment groups in a 2:2:1 (active:active:placebo) allocation. Treatment consists of a twice daily application (approximately 12 hours apart) of the assigned topical gel over 5 consecutive days, beginning on the evening of Day 1 and ending (last application) on the morning of Day 6 (total of 10 applications). In order to assure adequate representation of different types of soft tissue injuries, at least 25 randomized subjects must enter the study with a lower extremity *sprain/strain* injury (cohort) and at least 50 randomized subjects with a lower extremity *contusion* injury (cohort).

4.1.1 Study Design Phases

4.1.1.1 Screening/Baseline Phase

Subjects will be screened for eligibility according to the inclusion/exclusion criteria. Basic health information will be collected, and the subject's injury will be examined and assessed by the study investigator/designee. Subjects will be evaluated by the investigator/designee to determine if they qualify based on the injury sustained. Qualified subjects will then be stratified into one of two injury cohorts (sprain/strain or contusion) based on the injury and prior to randomization. Subjects will self-report their level of pain on movement using a 100 mm visual analog scale (VAS). Tenderness of the injured area will be assessed with an algometer and determined as the amount of pressure (N/cm^2) required to produce the first tenderness reaction by the subject. Patients who qualify will be randomized to start the Treatment Phase.

4.1.1.2 Treatment Phase

All treatment applications will be performed by an unblinded staff at the site. The unblinded staff will not be responsible for any pain or tenderness assessments. The correct location for application of the gel will be marked with a water-resistant pen to ensure the gel is applied at the same site for each application during the entire study. The topical investigational medicinal product (IMP) will be gently applied without any massaging.

At site visits on Days 1, 2, 3, 4 and 6, algometric and pain on movement (POM) VAS assessments will be performed. Compliance will be evaluated by the investigator/designee. The investigator and patient will give a global assessment of the treatment efficacy and local tolerability using a 5-point Likert scale.

Patients will use a patient diary to record adverse events, concomitant/rescue medication use on Days 1, 2, 3, 4, 5 and 6.

The algometry/tenderness will be measured such that the greater the algometry value (N/cm^2), the greater the pressure required to produce the first tenderness reaction. Therefore, greater algometry values indicate less pain at the site of interest.

4.1.1.3 Follow-up Phase

Not applicable for this study.

The duration of each patient's participation will be approximately 6 days. For an overview on the trial design and trial procedures see Section 1.2.

4.2 Scientific Rationale for Study Design

The study model for this study is based on published literature (19,20). Both systemic and topical NSAID treatments have been shown to be effective for both contusions and sprains/strains (1). Since pain is subjective, a placebo treatment arm is very important in assessing the effectiveness of the treatment and the sensitivity of the study model. Inclusion of placebo represents no harm to the subject as these studies are of short duration, and because rescue medication is available to any subject who so requests. The primary endpoint, tenderness to pressure, was selected because it has been shown to be both sensitive to treatment effect and a meaningful measure in patients with acute soft tissue injury (19,20).

4.3 Justification for Dose

Preclinical studies have shown that the 10% formulation provides effective penetration to the underlying tissue layers at the site of application and is efficacious in the rat paw carrageenan model (16). The amount of product (CCI) applied at each dosing time is in line with dosing directions of currently approved topical NSAIDS (17). In the case of the naproxen topical gel, 10%, each CCI application delivers CCI of naproxen. This amount falls within currently recommended single doses of naproxen for systemic delivery, with an important caveat. Due to poor systemic absorption of topical NSAIDs, the amount absorbed into systemic circulation is expected to be less than 10% of the amount contained in the product (21).

4.4 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed all phases of the study up to Visit 6 as shown in the Schedule of Activities.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions are not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 18 to 60 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants with a primary diagnosis of acute sports-related acute soft tissue injuries of the lower extremities that do not require hospitalization and that occurred within 3 hours of enrollment.
3. Participants with a baseline algometric measurement values on the injured site of ≤50% of the respective value at the contralateral site.
4. Participants with a baseline (POM) of ≥50 mm on a visual analog scale (VAS) (0–100 mm).
5. Participant's absolute sensitivity to tenderness on the contralateral site is at least 2.5 N/cm^2 as measured by algometry.
6. Participant's size of trauma is between 25 and 150 cm^2.

Informed Consent

7. Capable of giving signed informed consent as described in Section 10.1.4 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 Exclusion Criteria - Amended

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Heart surgery within 2 weeks of enrollment in the study.
2. Suspected bone fracture or torn ligaments related to the injury.
3. Open wounds to the area to be treated.
4. Current skin disorders or localized infection in the area to be treated.
5. Injured area is too hairy for proper assessments.
6. Suspected head injury.
7. History of blood coagulation disorders.

8. Current or past history of gastrointestinal ulceration, gastrointestinal bleeding or other bleeding disorder(s).
9. Relevant concomitant disease such as asthma (exercise induced asthma is permitted).
10. History of significant disease deemed by the investigator to render the patient unsuitable for inclusion, including evidence or history of clinically significant (in the judgment of the investigator) hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular (including hypertension and cardiac arrhythmia), hepatic, psychiatric, neurologic diseases, or malignancies within the last 5 years.
11. Participants with a medical disorder, condition, or history of such that could impair the participant's ability to participate or complete this trial in the opinion of the investigator.
12. Significant ongoing painful condition other than that associated with the sports-related injury/contusion.
13. Any ongoing condition that might interfere with the absorption, distribution, metabolism, or excretion of the study medication.
14. Females who are planning to become pregnant, are pregnant or lactating.

Prior/Concomitant Therapy

15. Application of standard care by rest, ice, compression (non-occlusive bandage) or elevation (RICE) may be considered at the discretion of the investigator.
16. Physical therapy or other comfort measures, or herbal preparations for bruises from the time of injury through the final evaluation.
17. Use of any medications within 5 days of enrollment until discharge from the study site (except oral contraceptives, prophylactic antibiotics, synthetic thyroid hormones, methylphenidate or medications to treat benign conditions such as antibiotics to treat acne).
18. Any other treatment or medication (oral or topical), that could interfere with the trial (e.g. corticosteroids) up to 3 days prior to the trial.
19. Participants with the following medical conditions may be eligible at the discretion of the investigator: ADHD on a stable dose regimen of methylphenidate/(dextro) amphetamine for at least 6 months; participants with hypothyroidism on a stable dose of synthetic thyroid hormone for at least 6 months.
20. Have received any form of treatment in the form of medication for depression in the past 6 months or any form of psychotropic agent (including selective serotonin uptake inhibitors [SSRI] but excluding ADHD medications described above) within the last 6 months.
21. Any previous history of allergy or known intolerance to naproxen, diclofenac, paracetamol or any of the drugs or formulation constituents which, in the investigator's opinion, might preclude use of an NSAID, including aspirin-sensitive asthma or a previous allergic response to a NSAID, including bronchospasm, urticaria, angioedema, and rhinitis; participation in a clinical trial in the previous 30 days.
22. Use of any over the counter (OTC) or prescription medications with which the administration of naproxen, acetaminophen, any other NSAID, is contraindicated.

23. Habituation to analgesic drugs including opioids (i.e., routine use of oral analgesics 5 or more times per week for greater than 3 weeks within the past 2 years).

Other Exclusions

24. More than low-risk alcohol consumption (>24 g (males) or >12 g (females) of alcohol regularly per day). Amount corresponds to 0.6 L of beer/day or 0.24 L of wine/day or 3 glasses (at 2 cL) of liquor/day for males and 0.3 L of beer/day or 0.12 L of wine/day or 1 glass (at 2 cL) of liquor/day for females.
25. Self-reported drug abuse within two years prior to screening.
26. Member or first-degree relative of study staff or the Sponsor directly involved in the study.
27. Unwilling or unable to comply with all requirements outlined in the protocol.

Prior/Concurrent Clinical Study Experience

28. Previous enrollment in this study.

5.3 Lifestyle Considerations

No lifestyle restrictions are required.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

Individuals who do not meet the criteria for participation in this study (screen failure) cannot be rescreened.

5.5 Criteria for Temporarily Delaying Study Intervention Administration

Not applicable

6. Study Intervention(s) and Concomitant Therapy

The study center will dispense a blinded treatment after successfully completing screening and baseline assessments. The tubes of investigational medicinal product (IMP) for each treatment will be dispensed using a computer generated randomization schedule. Participants will get the same randomized treatment for the duration of the study.

6.1 Study Intervention Administered

During screening and injury assessment, after completion of the pre-treatment baseline procedures/assessments, subjects who meet the entry criteria will be sequentially assigned to a unique number in ascending order (randomization number, RNR) according to the randomization schedule prepared prior to the study.

Subjects will be numbered according to the following scheme:

PPD

10 = country code (Germany)

PPD = site number (for site PPD)

PPD = randomization number

Whereas the "PPD s" will be replaced with a four digit sequentially assigned number as each subject enters the study (e.g., first subject number at Site PPD of the study will be PPD).

Once a number has been assigned to a subject, it cannot be reassigned to another subject.

Subjects who do not meet all of the randomization criteria will not be randomized. Upon successful completion of all remaining baseline assessments, subjects enter the Treatment Phase and are randomized into one of three blinded treatments:

- Naproxen Topical Gel, 10%, *bid* for 5 days (final application on morning of Day 6);
- Diclofenac Diethylamine Gel, 2.32% *bid* for 5 days (final application on morning of Day 6);
- Placebo Gel *bid* for 5 days (final application on morning of Day 6).

Approximately CCI of IMP will be dispensed and weighted at the site on a digital scale with an allowance of no more than CCI. The weight of the gel will be recorded on the source documents and case report form and then be applied at each treatment by an unblinded site staff depending upon the location of the injury. **Study staff should make their best attempt to weigh and dispense the topical gel as close as possible to the target of CCI for each application.** The first treatment will start on Day 1 (after being randomized). The topical IMP will be applied in a thin layer over the affected area and lightly rubbed in without using pressure or any massaging. The maximum daily dose is approximately CCI on Days 2, 3, 4 and 5. The maximum dose for Days 1 and 6 are approximately CCI. The total dose for each participant is approximately CCI.

The patient will not see the specific treatment and will be blindfolded during the application of the topical gel. Nominal dosing times will be established after the patient is randomized

(evening of Day 1) with the next application being approximately 12 hours apart from the previous application. A dosing window of ± 1 hour from the established nominal dosing time from Day 1 is allowed (see example).

Table 1 – Dosing Example

	Day 1 PM	**Day 2 AM**	**Day 2 PM**	**Day 3 AM**	**Day 3 PM**	**Day 4 AM**	**Day 4 PM**	**Day 5 AM**	**Day 5 PM**	**Day 6 AM**	**Day 6 PM**
Dose	1	2	3	4	5	6	7	8	9	10	No dose applied
Dosing Time	19:40	7:40	19:40	7:40	19:40	7:40	19:40	7:40	19:40	7:40	
Dosing Window	18:40 to 20:40	6:40 to 8:40	18:40 to 20:40	6:40 to 8:40	18:40 to 20:40	6:40 to 8:40	18:40 to 20:40	6:40 to 8:40	18:40 to 20:40	6:40 to 8:40	

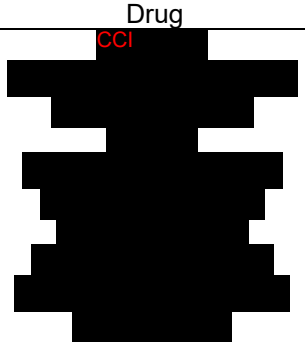
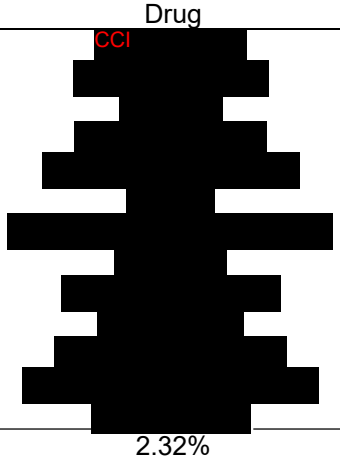
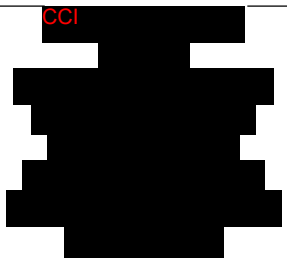
Note: All dosing times are in military time.

Any dosing-related deviations outside of the allowable window (± 1 hour) will be documented in the subject's medical record, source documents and/or diary.

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to a study participant according to the study protocol.

6.2 Identity of Study Interventions

Table 2 – Study Interventions

Intervention	Naproxen gel	Diclofenac gel	Placebo gel
UI Number	1614000-268	NA	1614000-272
Type	Drug	Drug	Vehicle
Dose Formulation			
Dose Strength	10%	2.32%	NA
Dosage	CCI	CCI	CCI
Route of Administration	Topical	Topical	Topical
Use	Test	Comparator	Placebo
Packaging and Labeling	Study Intervention will be provided in tubes. Each tube will be labeled as required per country requirements	Study Intervention will be provided in tubes. Each tube will be labeled as required per country requirements	Study Intervention will be provided in tubes. Each tube will be labeled as required per country requirements
Batch Number	available in the study file	available in the study file	available in the study file
Manufacturer	Formulated Solutions Largo, Florida USA	GlaxoSmithKline Consumer Healthcare GmbH & Co. KG Munich, Germany	Formulated Solutions Largo, Florida USA

All study drugs will be manufactured and labeled according to Good Manufacturing Practice (GMP) and applicable local laws. Label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

For all study drugs, a system of numbering in accordance with all requirements of GMP will be used, ensuring that each dose of study drug can be traced back to the respective bulk batch of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies Quality Assurance (QA) group.

A complete record of batch numbers and expiry dates of all investigational products as well as the labels will be maintained in the clinical supply file.

The source of test and reference products will be documented in the clinical supply file.

6.3 Preparation/Handling/Storage/Accountability

Only participants randomized in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator or the head of the institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in a separate document.

6.4 Measures to Minimize Bias: Randomization and Blinding

Study using Pre-Coded Randomization provided to the site	On Day 1 participants will be assigned a unique number (randomization number) in ascending numerical order at each study site. The randomization number encodes the participant's assignment to one of the 3 arms of the study, according to the randomization schedule generated prior to the study by the Statistics Department at Bayer. Each participant will be dispensed blinded study intervention, labeled with his/her unique randomization number, throughout the study.
Blind Break (Envelopes)	A sealed envelope that contains the study intervention assignment for each participant will be provided to the investigator. The sealed envelope will be retained by the investigator (or representative) in a secured area. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. Once the study is complete, all envelopes (sealed and opened) must be inventoried and returned to the sponsor.

Blinded study with unblinded site staff who is dispensing study intervention	Participants will be randomly assigned in a 2:2:1 ratio to receive study intervention. Investigators and designated staff will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain the blind, the participant will wear a blindfold so they cannot see the topical treatment applied to the injured area. Additionally, the unblinded staff at the site will be responsible for the dispensing, weighing and topical application to the injured area of all study interventions and will endeavor to ensure that there are no differences in time taken to dispense following randomization. **The unblinded staff at the site is not responsible for adverse events, global assessments, pain and tenderness measurements.** This unblinded study staff will instruct the participant to avoid discussing the smell, color, texture or packaging of the study intervention with the investigator and other blinded staff at the site. Prior to presenting to the investigator for assessment, the treated area will be cleaned with water at room temperature to eliminate residual gel quantity and the smell related to the gel. In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

If necessary, Bayer Pharmacovigilance may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy.

6.5 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date, time and weight (in grams) of each dose administered at the site will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.6 Dose Modification

Dose modification (increase or decrease) from the standard CCI [redacted] is not permitted. Randomized participants will receive ten (10) consecutive topical treatments over 6 days.

6.7 Stopping Rules

Dosing will be stopped for all subjects under the following conditions:

- A serious adverse reaction considered related to IMP administration in one subject.
- Severe non-serious adverse reactions related to IMP administration in two subjects, within the skin and subcutaneous tissue system, or gastrointestinal system organ classes.

Restart of the study is possible if the review/investigation leads to a conclusion that the adverse reaction was not related to the IMP administration. The subject(s) in whom the adverse reaction occurred may not restart.

6.8 Continued Access to Study Intervention after the End of the Study

No study intervention will be available after Visit 6 (Day 11).

6.9 Treatment of Overdose

For this study, any dose of study intervention greater than [redacted] within a 24-hour time period will be considered an overdose (17).

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE until study intervention can no longer be detected systemically (at least 7 days).
- Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.10 Concomitant Therapy

Any medication (including OTC or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.10.1 Rescue Medicine

The study site will supply paracetamol (Paracetamol HEXAL® 500 mg tablets) with a maximum daily dose of 1000 mg as rescue medication during the study, except 6 hours prior to the next site visit. Rescue medication will be provided by the investigator and documented on the source documents.

If the participant decides to take rescue medication during the study, the patient will be instructed to complete the Global Assessments (both efficacy and tolerability) prior to taking the rescue medication.

7. Discontinuation of Study Intervention and Participant

7.1 Discontinuation of Study Intervention

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

7.2 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued both from the study intervention and from the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

7.3 Lost during the Treatment Phase

A participant will be considered lost if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 2 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. Study Assessments and Procedures

8.1 General Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1.1 Screening Phase Visit 1 - (Day 1)

At the Screening visit, the Principal Investigator or appropriate designee will discuss with each patient the nature of the trial, its requirements and its restrictions. Written informed consent will be obtained prior to performance of any protocol-specific procedures. Patients will present with a lower extremity injury within 3 hours of screening between 6 pm and 10 pm.

The following will be conducted during the Screening Visit to determine eligibility:

- Signed Informed Consent;
- Review Inclusion and Exclusion Criteria;
- Patient demographics;
- Medical History (lower extremity injury is a self-reported history)
- Medication history of all prescription and OTC drugs (including topicals, herbal products, vitamins and nutritional supplements), use of topical heat or cold, and other products of topical application and investigational drugs, taken within 30 days prior to screening;
- History of drug, alcohol and tobacco use;
- Height, weight, and Body Mass Index (BMI);
- Physical examination (general routine and injury-related assessment);
- Urine pregnancy test (female patients only);
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature after 5 minutes in a sitting position);
- Discuss the procedure to report adverse events;
- Diary distribution and training;

The Principal Investigator or his/her designee must review all screening results before proceeding to the Treatment phase of the study. Patients must have a lower extremity injury within 3 hours of Screening for participation into the study. Patients with the appropriate sports-related lower extremity injury will be designated into one of two cohorts for baseline testing.

8.1.2 Baseline Visit 1 - (Day 1)

Patients will undergo baseline pain and tenderness testing to determine eligibility for randomization. All patients must score at least 50 on the 0 – 100 mm visual analog scale (VAS) for POM and have algometric measurement values on the injured site of ≤50% of the respective value at the contralateral site in order to qualify for treatment. Additionally, the absolute tenderness sensitivity of the contralateral site must be at least 2.5 N/cm^2. The investigator will stratify patients into 2 injury cohorts. One cohort is contusion cohort and the other is the sprain/strain cohort. The contusion cohort will enroll at least 50 patients and the sprain/strain cohort will enroll at least 25 patients.

The site will randomize Investigational Medicinal Product (IMP or treatment kit) based on computer generated randomization schedule stratified by injury type (either contusion or sprain/strain cohorts).

Patients entering the Treatment Phase are randomized in a 2:2:1 fashion into one of three blinded treatments:

- Naproxen Topical Gel, 10%, every 12 hours for 5 days
- Diclofenac Diethylamine Topical Gel, 2.32% every 12 hours for 5 days
- Placebo Topical Gel every 12 hours for 5 days

Patients will be reminded to discontinue use of all pain medications including supplements, use of topical heat or cold, and other products of topical application once the patient is deemed eligible to participate.

The investigator or designee will mark the injured lower extremity with a water-resistant pen so that the treatment area is consistently targeted through the Treatment Phase. After randomization, the ***first*** topical treatment will be applied the evening of Day 1. The topical treatment will be weighed on a digital scale, then applied by an unblinded study staff at the site who is not responsible for adverse events, global assessments, pain and tenderness measurements. Patients will wear a blindfold during treatment so that the identity of the IMP is blinded. Patients will be instructed to return approximately 12 hours to the site for their ***second*** treatment. The nominal repeat dosing times will be established for the rest of the study that conform to the dosing time established on Day 1.

Rescue medication will be dispensed. If the patient decides to take rescue medication prior to the next treatment, the patient will be instructed to complete the Global Assessments prior to taking the rescue medication.

8.1.3 Visit 2 (Day 2 morning)

Patients will return to the site approximately 12 hours after Day 1 dosing. The following activities will be performed:

- Cleaning of the treated area by the unblinded staff
- Limited physical exam (injured extremity);
- Review diary for rescue/concomitant medications;
- Rescue medicine drug accountability;
- Adverse Event assessment;
- POM VAS;
- Algometry measurements.

Patients will undergo the ***second*** topical treatment at the site weighed on a digital scale, then applied by an unblinded study staff at the site who is not responsible for adverse events, global assessments, pain and tenderness measurements. Patients will wear a blindfold during treatment so that the identity of the IMP is blinded. Patients will be instructed to return approximately 12 hours to the site for the ***third*** treatment based on their established nominal time.

If the patient decides to take rescue medication prior to the next treatment, the patient will be instructed to complete the Global Assessments prior to taking the rescue medication.

8.1.4 Visit 3 (Day 2 evening)

Patients will return to the site approximately 12 hours after Day 2 morning dosing. The following activities will be performed:

- Cleaning of the treated area by the unblinded staff
- Review diary for rescue/concomitant medications;
- Rescue medicine drug accountability;
- Adverse Event assessment;
- POM VAS;
- Algometry measurements.
- Global assessments for efficacy and tolerability;

Patients will undergo the ***third*** topical treatment at the site weighed on a digital scale, then applied by an unblinded study staff at the site who is not responsible for adverse events, global assessments, pain and tenderness measurements. Patients will wear a blindfold during treatment so that the identity of the IMP is blinded. Patients will be instructed to return approximately 12 hours to the site for the ***fourth*** treatment based on their established nominal time.

If the patient decides to take rescue medication prior to the next treatment, the patient will be instructed to complete the Global Assessments prior to taking the rescue medication.

8.1.5 Visit 4 (Day 3 morning)

Patients will return to the site approximately 12 hours after Day 2 evening dosing. The following activities will be performed:

- Cleaning of the treated area by the unblinded staff
- Limited physical exam (injured extremity);
- Review diary for rescue/concomitant medications;
- Rescue medicine drug accountability;

- Adverse Event assessment;
- POM VAS;
- Algometry measurements.

Patients will undergo the ***fourth*** topical treatment at the site weighed on a digital scale, then applied by an unblinded study staff at the site who is not responsible for adverse events, global assessments, pain and tenderness measurements. Patients will wear a blindfold during treatment so that the identity of the IMP is blinded. Patients will be instructed to return approximately 12 hours to the site for the ***fifth*** treatment based on their established nominal time.

If the patient decides to take rescue medication prior to the next treatment, the patient will be instructed to complete the Global Assessments prior to taking the rescue medication.

8.1.6 Visit 5 (Day 3 evening)

Patients will return to the site approximately 12 hours after Day 3 morning dosing. The following activities will be performed:

- Cleaning of the treated area by the unblinded staff
- Review diary for rescue/concomitant medications;
- Rescue medicine drug accountability;
- Adverse Event assessment;
- POM VAS;
- Algometry measurements;
- Global assessments for efficacy and tolerability.

Patients will undergo the ***fifth*** topical treatment at the site weighed on a digital scale, then applied by an unblinded study staff at the site who is not responsible for adverse events, global assessments, pain and tenderness measurements. Patients will wear a blindfold during treatment so that the identity of the IMP is blinded. Patients will be instructed to return approximately 12 hours to the site for their ***sixth*** treatment based on their established nominal time.

If the patient decides to take rescue medication prior to the next treatment, the patient will be instructed to complete the Global Assessments prior to taking the rescue medication.

8.1.7 Visit 6 (Day 4 morning)

Patients will return to the site approximately 12 hours after Day 3 evening dosing. The following activities will be performed:

- Cleaning of the treated area by the unblinded staff
- Limited physical exam (injured extremity);
- Review diary for rescue/concomitant medications;
- Rescue medicine drug accountability;
- Adverse Event assessment;
- POM VAS;
- Algometry measurements.

Patients will undergo the ***sixth*** topical treatment at the site weighed on a digital scale, then applied by an unblinded study staff at the site who is not responsible for adverse events, global assessments, pain and tenderness measurements. Patients will wear a blindfold during treatment so that the identity of the IMP is blinded. Patients will be instructed to return approximately 12 hours to the site for the ***seventh*** treatment based on their established nominal time.

If the patient decides to take rescue medication prior to the next treatment, the patient will be instructed to complete the Global Assessments prior to taking the rescue medication.

8.1.8 Visit 7 (Day 4 evening)

Patients will return to the site approximately 12 hours after Day 4 morning dosing. The following activities will be performed:

- Cleaning of the treated area by the unblinded staff
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature after 5 minutes in a sitting position);
- Review diary for rescue/concomitant medications;
- Rescue medicine drug accountability;
- POM VAS;
- Algometry measurements;
- Adverse Event assessment;
- Global assessments for efficacy and tolerability.

Patients will undergo the ***seventh*** topical treatment at the site weighed on a digital scale, then applied by an unblinded study staff at the site who is not responsible for adverse events, global assessments, pain and tenderness measurements. Patients will wear a blindfold during treatment so that the identity of the IMP is blinded. Patients will be instructed to return approximately 12 hours to the site for the ***eighth*** treatment based on their established nominal time.

If the patient decides to take rescue medication prior to the next treatment, the patient will be instructed to complete the Global Assessments prior to taking the rescue medication.

8.1.9 Visit 8 (Day 5 morning)

Patients will return to the site approximately 12 hours after Day 4 evening dosing. The following activities will be performed:

- Cleaning of the treated area by the unblinded staff
- Limited physical exam (injured extremity);
- Review diary for rescue/concomitant medications;
- Rescue medicine drug accountability;
- Adverse Event assessment.

Patients will undergo the ***eighth*** topical treatment at the site weighed on a digital scale, then applied by an unblinded study staff at the site who is not responsible for adverse events, global assessments, pain and tenderness measurements. Patients will wear a blindfold during treatment so that the identity of the IMP is blinded. Patients will be instructed to return

approximately 12 hours to the site for their ***ninth*** treatment based on their established nominal time.

If the patient decides to take rescue medication prior to the next treatment, the patient will be instructed to complete the Global Assessments prior to taking the rescue medication.

8.1.10 Visit 9 (Day 5 evening)

Patients will return to the site approximately 12 hours after Day 5 morning dosing. The following activities will be performed:

- Cleaning of the treated area by the unblinded staff
- Review diary for rescue/concomitant medications;
- Rescue medicine drug accountability;
- Adverse Event assessment.

Patients will undergo the ***ninth*** topical treatment at the site weighed on a digital scale, then applied by an unblinded study staff at the site who is not responsible for adverse events, global assessments, pain and tenderness measurements. Patients will wear a blindfold during treatment so that the identity of the IMP is blinded. Patients will be instructed to return approximately 12 hours to the site for the ***tenth and final*** treatment based on their established nominal time.

If the patient decides to take rescue medication prior to the next treatment, the patient will be instructed to complete the Global Assessments prior to taking the rescue medication.

8.1.11 Visit 10 (Day 6 morning)

Patients will return to the site approximately 12 hours after Day 5 evening dosing. The following activities will be performed:

- Cleaning of the treated area by the unblinded staff
- Limited physical exam (injured extremity);
- Urine pregnancy test (female patients only);
- Review diary for rescue/concomitant medications;
- Rescue medicine drug accountability;
- Adverse Event assessment.

Patients will undergo the ***tenth*** topical treatment at the site weighed on a digital scale, then applied by an unblinded study staff at the site who is not responsible for adverse events, global assessments, pain and tenderness measurements. Patients will wear a blindfold during treatment so that the identity of the IMP is blinded. Patients will be instructed to return approximately 12 hours to the site based on their established nominal time for final assessments.

If the patient decides to take rescue medication prior to the next treatment, the patient will be instructed to complete the Global Assessments prior to taking the rescue medication.

8.1.12 Visit 11 (Day 6 evening, End of Study)

Patients will return to the site approximately 12 hours after Day 6 morning dosing. The following activities will be performed:

- Cleaning of the treated area by the unblinded staff
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature after 5 minutes in a sitting position);
- Review diary for rescue/concomitant medications;
- Rescue medicine drug accountability;
- Adverse Event assessment;
- POM VAS;
- Algometry measurements;
- Global assessments for efficacy and tolerability;
- Sensory questions related to smell and touch;
- Return of diary and rescue medication.

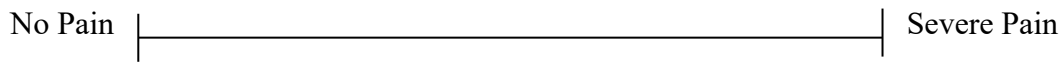
No topical treatment is performed for this visit. Upon return of all study materials and completion of all study procedures, the patient will be discharged from the study.

8.2 Efficacy Assessments

8.2.1 Assessment of Pain on Movement

Pain on Movement will be assessed using a 100 mm visual analogue scale at baseline and at each subsequent study visit.

Place a line on the 'Scale' that best characterizes how your injured extremity feels when it's moved *now*.



8.2.2 Algometry

Algometry will be performed at baseline and at each study visit. Algometric measurements will be performed using a calibrated caliper with digital pressure recording). Increases in pressure during measurement will be kept constant at 10 $N/cm^2/s$. The site of measurement will be marked with a water resistant marker, and measurements will be repeated at the same site. The measurements will be performed in such a way that the patient and the investigator cannot read the actual pressure exerted (covered display). The device stores the last exerted pressure,

which is then recorded on the case report form. A tenderness reaction is defined as the pressure that, under the above conditions, produced a painful sensation.

Additional information related to the algometry procedures will be detailed in a separate document.

8.2.3 Global Assessments of Efficacy and Tolerability

At 24 hours, 48 hours, 72 hours and 120 hours post dose, the patient and the investigator will rate global assessment of the treatment efficacy using a 5-point Likert scale.

Global Efficacy

How would you rate the study medication you received as a pain-reliever?

- 0 = poor
- 1 = fair
- 2 = good
- 3 = very good
- 4 = excellent

At 24 hours, 48 hours, 72 hours and 120 hours post dose, the patient and the investigator will rate global assessment of tolerability (quality of life) using a 5-point Likert scale.

Global Tolerability

Considering all the ways this treatment has affected you since you started in the clinical trial, how well are you doing?

- 0 = poor
- 1 = fair
- 2 = good
- 3 = very good
- 4 = excellent

If the patient completes the Global Assessment not at the time of the scheduled clinic visit (or between visits), then the investigator will complete the Global Assessment at the next scheduled visit.

Planned time points for all efficacy assessments are provided in the SoA and Section 8.1.

8.2.4 Sensory Questions

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

What is your opinion of the scent of the product?

- Strongly liked
- Liked
- Neutral
- Didn't like
- Strongly disliked
- Did not notice a scent

How do you feel about the appearance of the product on your skin post application?

- There is no difference in the appearance of my skin
- Strongly like
- Like
- Neutral
- Dislike
- Strongly dislike

8.3 Safety Assessments

All safety assessments are detailed in Sections 8.3.1, 8.3.2 and 8.3.3. Planned visits for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A general physical examination will include the injured extremity and assessments of the Dermatological, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems at Screening (Visit 1). Height and weight will also be measured and recorded.

A limited physical examination of the injured extremity will be performed at Visits 2, 4, 6, 8 and 10. Changes related to the physical exam will be documented on the source documents and case report form.

8.3.2 Vital Signs

Blood pressure, heart rate, respiratory rate and body temperature (oral) will be assessed. Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest in a sitting position for the participant in a quiet setting without distractions (e.g., television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded.

8.3.3 Pregnancy Testing

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

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Section 10.3. The definition of unsolicited and solicited AEs can be found in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the informed consent form (ICF)] at the time points specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours of learning of the event, as indicated in Section 10.3. The investigator will submit any updated SAE data to Bayer Pharmacovigilance within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.4.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

For all studies except those using medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.4.5 Pregnancy

A subject's participation is to be terminated immediately if a pregnancy is supposed (i.e. in case her pregnancy test becomes positive). The investigator must report to the sponsor any pregnancy occurring in a female subject during her participation in this study. The outcome of the pregnancy should be followed up carefully, and any outcome of the mother and the child at delivery should be reported.

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant pregnancy.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs, and will be reported as such.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

For all reports, the forms provided are to be used. The investigator should submit them within the same timelines as an SAE (see Section 10.3.4.). Send the completed pregnancy forms to:

bv-med-ams@bayer.com or phone +49 21 43 05 1699 (Germany)

8.5 Pharmacokinetics

PK and pharmacodynamic parameters are not evaluated in this study.

8.6 Genetics or Pharmacogenomics

Genetics are not evaluated in this study.

8.7 Biomarkers

Biomarkers are not evaluated in this study.

8.8 Immunogenicity Assessments

Not Applicable

8.9 Health Economics

Health Economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1 Statistical Hypotheses - Amended

For the comparison of the test gel vs. placebo, the primary efficacy hypothesis to be tested is the equality of Algometry AUC 0-72; the second is the POM VAS AUC 0-72.

9.2 Sample Size Determination - Amended

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

9.3 Analysis Set - Amended

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Intent To Treat (ITT)	All subjects who are randomized and provide at least one measure of primary efficacy parameters after the first application of IMP.
Per Protocol (PP)	The Per Protocol population will include all subjects in ITT who complete the study and do not have any major protocol violations. Any exclusion from PP Population will be determined and documented prior to the database lock. The primary efficacy analysis population will be PP population and ITT Population will be secondary. The same analysis on ITT Population will be repeated for the primary and secondary and other efficacy endpoints to assess the robustness of the results based on PP Population.
Safety	All randomized subjects who take at least one application of IMP. Safety analyses will be conducted on the safety population.

9.4 Statistical Analyses - Amended

The statistical analysis plan (SAP) will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary, secondary, and other key endpoints.

9.4.1 General Considerations

Statistical analysis will be performed using statistical analysis system and the version used will be specified in the Statistical Analysis Plan (SAP) and placed on file. The SAP will contain a more comprehensive explanation than described below of the methodology used in the statistical analyses. The SAP will also contain the rules and data handling conventions used to perform the analyses, and the procedure used for accounting for missing data.

All endpoints will be summarized descriptively by treatment. Statistical testings may be conducted at significance level of 0.05 if deemed necessary and no multiplicity adjustment will be made.

9.4.2 Primary Endpoint

The primary efficacy variable is:

- Tenderness (Algometry) over the initial 72 hours (Algometry AUC 0-72).

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

9.4.3 Secondary Endpoint

- Safety (percentage of subjects with at least one TEAE).

- The secondary endpoint will be summarized descriptively by body system and preferred term.

9.4.4 Other Endpoints

- VAS POM over the initial 12-hours (VAS AUC 0-12), 24-hours (VAS AUC 0-24), 36-hours (VAS AUC 0-36), 48-hours (VAS AUC 0-48), 60-hours (VAS AUC 0-60), 72-hours (VAS AUC 0-72), and 120 hours (VAS AUC 0-120);
- Change of VAS POM at hours 12, 24, 36, 48, 60, 72 and 120 from baseline;
- Change of Algometric Tenderness (N/cm^2) at hours 12, 24, 36, 48, 60, 72 and 120 from baseline;
- Algometric Tenderness (N/cm^2) over the initial 12-hours (N/cm^2 AUC 0-12), 24-hours (N/cm^2 AUC 0-24), 36-hours (N/cm^2 AUC 0-36), 48-hours (N/cm^2 AUC 0-48) 60-hours (N/cm^2 AUC 0-60) and 120 hours (N/cm^2AUC 0-120);
- Ratio of algometry injured/contralateral sites over 72 hours and 120 hours (N/cm^2 Ratio AUC 0-72 and N/cm^2 Ratio AUC 0-120);
- Percent of subjects with no (zero) VAS POM at 120 hours;
- Global assessment of treatment efficacy at 24 hours, 48 hours, 72 hours and 120 hours by patients using a 5-point scale (0=none, 1=poor, 2=fair, 3=good, 4=excellent);

- Global assessment of treatment efficacy at 24 hours, 48 hours, 72 hours and 120 hours by investigators using a 5-point scale (0=none, 1=poor, 2=fair, 3=good, 4=excellent).

9.4.5 Safety Analysis

Safety will be measured by adverse events (AEs) and vital signs. Only descriptive analyses will be conducted on the Safety Population. No imputation will be made for missing safety data. Quantitative data for safety variables will be described by summary statistics for the original data as well as for the differences to baseline when it is appropriate. Frequency tables will be provided for qualitative data. No statistical test will be planned regarding the safety analyses.

Only treatment-emergent AEs will be included in the summary analysis, i.e., AEs that begin or worsen after the first application of Investigational Medicinal Product (IMP). The number and percent of subjects who experience any event and the number of events overall, by System Organ Class, and by Preferred Term will be displayed by treatment group. Tables will also be produced by severity and relationship to IMP. Seriousness, severity, relationship to IMP duration, and outcome will also be listed.

Listings of individual data will be presented.

9.5 Interim Analysis

No interim analysis is planned for this study.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

Investigator(s) and other study personnel

Sponsor's medical expert for the study

Name: PPD

Title: PPD Global Medical Affairs

Address: Bayer Healthcare
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Phone: PPD

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Coordinating investigator for the study (LKP)

Name: Prof. Dr. Hans Georg Predel

Title: Physician

Address: Deutsche Sporthochschule Köln
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Fax: PPD

Email: PPD

CRO and PPD for the study

Name PPD

CRO: Clinsearch GmbH

Address: Zugerstrasse 80 a
Walchwil, Zug, Switzerland

Phone: PPD

Email: PPD

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Any substantial modification of the protocol will be submitted to the competent authorities as substantial amendments for approval, in accordance with ICH Good Clinical Practice and national and international regulations.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Funding

This study will be funded by the sponsor.

10.1.4 Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center. Each participant will be informed about the following aspects of premature withdrawal:

- Each participant has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The participant's consent covers examinations as specified in the visit description described in Section 8.1.12 to be conducted after withdrawal of consent.
- The participant's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the statistical analysis plan.
- Participant-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g., image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analyzed in accordance with the statistical analysis plan. The participant has the right to object to the generation and processing of this post-withdrawal data. For this, he/she needs to sign a corresponding declaration of objection; alternatively, the participant's oral objection may be documented in the participant's source data.

Each participant will have ample time and opportunity to ask questions.

Only if the participant agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator will personally sign and date the form. The participant will receive a second original of the informed consent form.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be consented to the most current version of the ICF(s) during their participation in the study.

The informed consent form and any other written information provided to participants will be revised whenever important new information becomes available that may be relevant to the participant's consent, or there is an amendment to the protocol that necessitates a change to the content of the participant information and / or the written informed consent form. The investigator will inform the participant of changes in a timely manner and will ask the participant to confirm his/her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IRB`s approval / favorable opinion in advance of use.

A copy of the ICF(s) must be provided to the participant. Participants who are rescreened are required to sign a new ICF.

10.1.5 Data Protection and Confidentiality

Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or biological samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

All records identifying the participant will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Participant names will not be supplied to the sponsor. Only the participant numbers (SNR and RNR) will be recorded in the CRF/eCRF data collection system, and if the participant name appears on any other document (e.g., pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the participants will be informed in writing that representatives of the sponsor, IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the participant's identity will remain confidential.

The investigator will maintain a list to enable participants to be identified.

10.1.6 Compensation for Health Damage of Participants/Insurance

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

10.1.7 Committees Structure

Not applicable

10.1.8 Dissemination of Clinical Study Data

The sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov as applicable to local regulations.

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Regarding public disclosure of study results, the sponsor will fulfill its obligations according to all applicable laws and regulations. The sponsor is interested in the publication of the results of every study it performs.

10.1.9 Data Quality Assurance

Participant data necessary for analysis and reporting will be provided to the Sponsor in CDISC (Clinical Data Interchange Standards Consortium) standards.

Clinical data management will be performed in accordance with applicable sponsor's/CRO's standards and data cleaning procedures. This is applicable for data recorded on the CRF/eCRF data collection system as well as for data from other sources (e.g., laboratory). Guidance on completion of CRFs will be provided with the paper case report forms.

For data coding (e.g., AEs, medication), internationally recognized and accepted dictionaries will be used.

Reasons for missing data, especially inability to perform a test, must be documented.

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF. The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents. Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan or applicable monitoring SOP.

The sponsor or designee is responsible for the data management of this study including quality checking of the data. The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.10 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.11 Missing Data

Reasons for missing data, especially inability to perform a test, must be documented.

10.1.12 Audit and Inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator/institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s)/IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

10.1.13 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Participant files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator / institution notifies the sponsor if the archival arrangements change (eg relocation or transfer of ownership). The investigator site file is not to be destroyed without the sponsor's approval. The contract with the investigator/institution will contain all regulations relevant for the study center.

10.1.14 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first subject screened and is considered the first act of recruitment and will be the study start date.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.15 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

Not applicable

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures

10.3.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) associated with the use of study intervention.

Definition of Unsolicited and Solicited AE

- An unsolicited adverse event is an adverse event that was not solicited using a Participant Diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.
- Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalisation, or emergency room visit, or visit to/by a health care provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by participant will be collected during interview with the participants and by review of available medical records at the next visit.
- Solicited AEs are predefined local at the application site and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any AE that, at any dose:	
a.	**Results in death**
b.	**Is life-threatening** • The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c.	**Requires inpatient hospitalization or prolongation of existing hospitalization** • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d.	**Results in persistent or significant disability/incapacity** • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e.	**Is a congenital anomaly/birth defect**
f.	**Other situations:** • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is not acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:
- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission** of the SAE data.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to Bayer Pharmacovigilance via Paper Data Collection Tool
• Email transmission of the SAE paper data collection tool is the preferred method to transmit this information to Bayer Pharmacovigilance. • In rare circumstances and if email transmission is not feasible, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames. • Contacts for SAE reporting: bv-med-ams@bayer.com or phone +49 21 43 05 1699 (Germany)

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
  - While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
  - A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

10.5 Appendix 5: Abbreviations

ADHD	attention deficit hyperactivity disorder
AE	adverse event
AUC	area under the curve
BAY no.	BAY number is the main identifier for compounds within the Bayer HealthCare Organization
bid	twice a day
BMI	body mass index: weight [kg] / (height [m])²
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
cm	centimeter
COX	cyclooxygenase
CRO	contract research organization
CV	coefficient of variation
(e)CRF	(electronic) case report form
e.g.	exempli gratia (for example)
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
g	grams
GCP	good clinical practice
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
HRT	hormonal replacement therapy
i.e.	id est (that is)
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
kg	kilogram
(c)L	(centi)liter
MedDRA	medical dictionary for regulatory activities
mm	millimeter
NSAID	nonsteroidal anti-inflammatory drug
OTC	over the counter
POM	pain on movement
QA	quality assurance
RNR	randomization number

SoA	schedule of events
SAE	serious adverse event
SAP	statistical analysis plan
SNR	screening number
SoA	Schedule of Activities
SOP	standard operating procedure
SSRI	selective serotonin uptake inhibitors
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
UI	unique identifier (drug formula)
USA	United States of America
VAS	visual analog scale
WOCBP	woman of childbearing potential

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