CLINICAL STUDY PROTOCOL

EFFICACY & SAFETY OF PIROXICAM PLUS COUNTERIRRITANT GEL VS DICLOFENAC GEL IN MUSKULOSCLETAL PAIN : A RANDOMIZED CLINICAL STUDY

NO. PROTOCOL : CT_CTPPXM_PRT_V001/II/2025

Clinical Research Team

dr. Erica kholinne, Sp.OT (K), Ph.D

dr. Astuti Pitarini, Sp.OT (K)

dr. A. Andi Kurniawan, Sp.KO Subsp. ALK (K)

dr. Wawan Budi Susilo, Sp.KO

dr. Marion Cinta Kuntjoro, Sp.KFR

Supported by:

PT Taisho Pharmaceutical Indonesia TBK

2025

History of CT_CTPPXM protocol changes as follows:

Protocol Version	Description
CT_CTPPXM_PRT_V001/II/2025	This is the first protocol that reviewed by Clinical Research Team, TPI and TPI's consultant

Changes to this protocol have been reviewed and acknowledged by:		
Sponsor **PT Taisho Pharmaceutical Indonesia**		**Clinical Research Team**
Digitally signed by Dr. Ni Putu Ardini Kartasasmita DN: cn=Dr. Ni Putu Ardini Kartasasmita, o=PT Taisho Pharmaceutical Indonesia Tbk, ou=Ramad, email=Ardini.Kartasasmita@ma.taisho.co.id, c=ID Date: 2025.02.03 08:57:59 +07'00' **dr. Ardini Kartasasmita** **Medical Manager**	Digitally signed by Aryani Pratami Dewi DN: cn=Aryani Pratami Dewi, o=PT Taisho Pharmaceutical Indonesia, Tbk, ou=Regulatory Affairs and Medical , email=aryani.dewi@ma.taisho.co.id , c=ID Date: 2025.02.03 15:25:05 +07'00' **Aryani Pratami Dewi** **Head of Regulatory Affairs and Medical**	**dr. Erica Kholinne, Sp. OT (K), Ph.d** **Principal Investigator**

PROTOCOL SIGNATURE PAGE

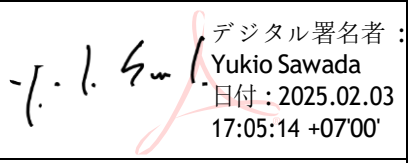
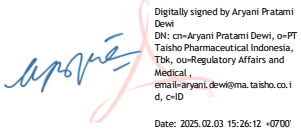
Clinical Research Team

I agree to conduct the study in accordance with this Protocol and in compliance with all applicable Health Authority requirements, Good Clinical Practice and National Laws.

Name & Position		Signature & Date of Signature
dr. Erica Kholinne, Sp.OT (K), Ph.d Principal Investigator		Signature:  Date:
dr. Astuti Pitarini, Sp.OT (K) Sub- Principal Investigator		Signature:  Date:
dr. A. Andi Kurniawan, Sp.KO SubSp. ALK (K) Sub- Principal Investigator		Signature:  Date:
dr. Wawan Budisusilo, Sp.KO Sub- Principal Investigator		Signature:  Date:
dr. Marion Cinta Kuntjoro, Sp.KFR Sub- Prinicpal Investigator		Signature:  Date:

Sponsor Acknowledgement for the Study:

We approve the design of the clinical study protocol and are willing to provide the necessary funds to carry out this clinical study.

Name & Position		Signature & Date of Signature
Yukio Sawada Director		Signature :  デジタル署名者： Yukio Sawada 日付：2025.02.03 17:05:14 +07'00' Date :
Aryani Pratami Dewi Head of Regulatory Affairs and Medical		Signature :  Digitally signed by Aryani Pratami Dewi DN: cn=Aryani Pratami Dewi, o=PT Taisho Pharmaceutical Indonesia, Tbk, ou=Regulatory Affairs and Medical , email=aryani.dewi@ma.taisho.co.id, c=ID Date: 2025.02.03 15:26:12 +07'00' Date :

1. GENERAL INFORMATION

Clinical Study Tittle	: Efficacy and safety of Piroxicam Plus Counterirritant gel versus Diclofenac gel in Musculosceletal Pain: a randomized clinical study.
Clinical Study Phase	: Phase III
Protocol Number	: CT_CTPPXM_V001/II/2025
Protocol Date Version	: V001- Feb 3rd , 2025
Principal Investigator	: dr. Erica Kholinne, Sp.OT (K), Ph.D
Sub- Principal Investigator	: 1) dr. Astuti Pitarini, Sp.OT (K) 2) dr. A. Andi Kurniawan, Sp.KO Subsp. ALK (K) 3) dr. Wawan Budi Susilo, Sp.KO 4) dr. Marion Cinta Kuntjoro, Sp.KFR
Study Coordinator 1	: dr. Theresia Indriani Prima Chesar
Study Coordinator 2	: dr. Pretika Prameswari
Sites	: Sports Medicine Clinic 1) Klinik Utama Eminence 2) St. Carolus Sports Clinic by Eminence
Sponsor	: PT Taisho Pharmaceutical Indonesia TBK Millenium Centennial Center 8th Floor,Jalan Jend.Sudirman Kav. 25 Jakarta

2. INTRODUCTION

2.1 Musculosceletal Pain

Musculosceletal health refers to the performance of the locomotor system, comprising intact muscles, bones, joints, and adjacent connective tissues. Musculosceletal impairments comprise more than 150 different diseases/conditions that affect the system and are characterized by impairments in the muscles, bones, joints, and adjacent connective tissues, leading to temporary or lifelong limitations in functioning and participation. Musculosceletal conditions are typically characterized by pain (often persistent) and limitations in mobility and dexterity, reducing people's ability to work and participate in society. Pain experienced in musculosceletal structures is the most common form of non-cancer pain.[1]

Musculosceletal conditions are relevant across the life course – from childhood to older age. They range from those conditions that arise suddenly and are short-lived (such as fractures, sprains, and strains associated with pain and limitations in functioning) to long-term conditions such as chronic primary low back pain and osteoarthritis.[1]

Musculosceletal conditions include conditions that affect[1]:

- joints, such as osteoarthritis, rheumatoid arthritis, psoriatic arthritis, gout, spondyloarthritis;
- bones, such as osteoporosis, osteopenia and associated fragility fractures, traumatic fractures;
- muscles, such as sarcopenia;
- Multiple body areas or systems, such as regional (e.g., back and neck pain) and widespread (e.g., fibromyalgia) pain conditions, inflammatory diseases such as connective tissue diseases and vasculitis that have musculosceletal manifestations, for example, systemic lupus erythematosus, or amputation as a result of disease or trauma.

Musculosceletal diseases are one of the leading causes of disability globally. According to data in 2019, about 1.71 billion people worldwide have musculosceletal disorders, and pain is the most common complaint. The prevalence of musculosceletal pain in adults can range from 18% to 80%. Musculosceletal pain is also one of the leading causes of musculosceletal disease burden. According to the UK Health and Safety Executive (HSE), 5.7 million workdays were lost in 2001–2002 due to low back pain, and 4.1 million workdays were lost due to musculosceletal disorders of the upper extremities and neck. [2]

Pain is recognized as an undesirable sensory input, an experience that has affective and cognitive repercussions. This perception is determined by age, gender, personality, and previous pain experiences. This perception is determined by nociceptive, neuropathic, or mixed. Nociceptive pain is due to stimulation of pain receptors, which are either visceral or somatic. Acute pain can be from an inflammation or musculosceletal injury or is of neurovascular origin, e.g., ischemia. Neuropathic pain, on the other hand, results from a pathophysiologic disturbance of either the peripheral or the central nervous system; typical examples include postherpetic neuralgia and diabetic neuropathy. Alternatively, pain may be mixed, that is, having origins that are both nociceptive and neuropathic.[3]

Musculosceletal pain encompasses a broad spectrum of disorders, from simple ligamentous injuries (e.g., ankle sprains) to intraarticular disorders (e.g., osteoarthritis and rheumatoid arthritis), muscle pain syndromes (e.g., myofascial pain and fibromyalgia), and various spine-related neck and low back conditions (e.g., disc degeneration, disc herniation, facet arthropathies, and spondylosis). These disorders are highly prevalent and exact an enormous toll in terms of individual quality of life and cost to society. Topical analgesics may provide a safe and effective therapeutic approach for some musculosceletal pains.[4]

2.2 Topical Non-Steroid Anti Inflammation Agents

Musculosceletal pain encompasses a broad spectrum of disorders, from simple ligamentous injuries (e.g., ankle sprains) to intraarticular disorders (e.g., osteoarthritis and rheumatoid arthritis), muscle pain syndromes (e.g., myofascial pain and fibromyalgia), and various spine-related neck and low back conditions (e.g., disc degeneration, disc herniation, facet arthropathies, and spondylosis). These disorders are highly prevalent and exact an enormous toll in terms of individual quality of life and cost to society.[4]

Topical analgesics may provide a safe and effective therapeutic approach for some musculosceletal pains. Pharmacokinetic data suggest that topically applied NSAIDs can result in enhanced local concentrations without significant toxic systemic levels.[4]

Topical NSAIDs are formulated for direct application to the painful site and to produce a local pain-relieving effect while avoiding the body-wide distribution of the drug at physiologically active levels. This application method (dosing) limits their use to more superficial painful conditions such as sprains, strains, and muscle or tendon soreness. They would not, for example, be indicated for deep visceral pain or headaches. They are also not appropriate for use on broken skin, so would not be used on open wounds (accidental or surgical).[5]

NSAIDs act by inhibiting cyclo-oxygenase, the enzyme that catalyzes the production of prostaglandins and thromboxane. Prostaglandins mediate various physiological functions such as maintenance of the gastric mucosal barrier, regulation of renal blood flow and endothelial tone, and play an important role in inflammatory and nociceptive processes. Cyclo-oxygenase inhibition leads to a reduction in pain, fever, platelet aggregation and the inflammatory response. Topical NSAIDs operate under the same mechanism of action as oral NSAIDs but with localized absorption and effect. Topical NSAIDs provide analgesic concentrations at the site of pain/inflammation, while avoiding systemic distribution of drug at physiologically active levels.[6]

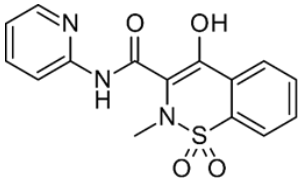
In the treatment of acute musculosceletal pain (e.g., sprains, strains, and overuse injuries) in adults, topical NSAIDs were found to provide significantly higher rates of clinical success (more patients with ≥50% pain reduction) than topical placebo during short-term use (∼7 days), with an efficacy comparable to that of oral NSAIDs. Topical NSAIDs were well tolerated during short-term use. Local skin reactions were generally mild and transient and did not differ from those with topical placebo. Systemic adverse events or patient withdrawals due to adverse events were few.[6]

Asia-Pacific expert group consensus statements on use of topical NSAIDs in musculosceletal pain[6]:
Statement 1: There are different topical analgesic preparations indicated for musculosceletal pain – topical NSAIDs relieve pain by a distinct mode of action.
Statement 2: Topical NSAIDs are effective and should be recommended as a first-line intervention for mild to moderate pain associated with musculosceletal disorders.
Statement 3: Topical NSAIDs have comparable efficacy with oral NSAIDs in terms of providing relief in musculosceletal conditions and are preferred over systemic treatment of acute and acute-on-chronic, mild to moderate pain when local areas are affected.
Statement 4: The use of therapeutic ultrasound enhances local penetration and absorption of topical NSAID gels, thus increasing drug effectiveness.
Statement 5: Topical NSAID gel formulations have better absorption and acceptability compared with other formulations.
Statement 6: Topical ketoprofen gel has the property of achieving higher local tissue concentration than plasma concentration.
Statement 7: Topical NSAIDs are generally safe and have fewer of the systemic adverse effects associated with oral NSAIDs.
Statement 8: While most topical NSAIDs are effective in the treatment of acute and acute-on-chronic musculosceletal pain, there are limited head-to-head randomized controlled trials comparing the different topical NSAIDs.

Piroxicam

Piroxicam as the main ingredient, is an analgesic nonselective nonsteroidal anti- inflamatory drug. Chemically, piroxicam has the following formula[7]:

C15H13N3O4S



Piroxicam is a non-steroidal anti-inflammatory agent (NSAID) in the oxicam group. In the form of a gel, it has anti-inflammatory, analgesic qualities. Piroxicam works by preventing the production of endogenous prostaglandins which are involved in the mediation of pain, stiffness, tenderness and swelling[7].

Pharmacokinetic data of Piroxicam gel[8]

Absorption	: Applied locally in the form of a gel, piroxicam is absorbed slowly through the skin. Its level of accumulation in the body is low. Compared to the oral forms of piroxicam, the passage into the system of the gel is along the lines of 5%.
Distribution	: The elimination half-life is around 50 hours. Binding to plasma proteins is significant: in the order of 99%.
Biotransformation/Elimination	: Piroxicam is eliminated slowly. It is almost completely metabolised. A significant amount is eliminated in the urine in the form of hydroxy-5-metabolite.

The combination of Methol and Eugenol has an unexpected and very significant enhancement effect. This study confirmed the University of Shanghai study to the extent that it confirms that a product with the composition of Piroxicam Plus Counterirritant (Methyl Salicylate, Menthol and Eugenol) penetrates faster than a comparable product without counterirritant.[8]

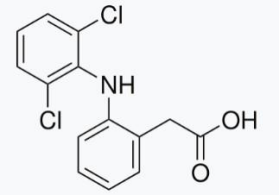
This medicinal product is contraindicated in the following situations[8]:

- hypersensitivity to the active substance or to any of the excipients
- pregnancy, from the start of the 6th month (beyond 24 weeks of amenorrhoea)
- history of allergy or asthma triggered by taking piroxicam or substances with similar activity, such as other NSAIDs, aspirin,
- broken skin, regardless of the type of wound: weeping dermatitis, eczema, infected wound, burn or cut.

Diclofenac

Diclofenac a nonsteroidal anti-inflammatory drug. Chemically, diclofenac has the following formula[9]:

C14H11Cl2NO2



Diclofenac inhibits the enzyme, cyclooxygenase (COX), an early component of the arachidonic acid cascade, resulting in the reduced formation of prostaglandins, thromboxanes and prostacylin. It is not completely understood how reduced synthesis of these compounds results in therapeutic efficacy. Diclofenac, has anti-inflammatory, anti-nociception, and antipyretic effects.[9]

Pharmacokinetic data of Diclofenac[9]

Protein binding	: More than 99%
Metabolism	: Liver, oxidative, primarily by CYP2C9, also by CYP2C8, CYP3A4, as well as conjugative by glucuronidation (UGT2B7) and sulfation; no active metabolites exist
Onset of action	: Within 4 hours (gel), 30 min (non-gel)
Elimination half-life	: 1.2–2 h (35% of the drug enters enterohepatic recirculation)
Excretion	: 35% bile, 65% urine

The use of Diclofenac gel is contraindicated in patients with a known hypersensitivity to diclofenac. It should not be administered in patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients. It is contraindicated in the setting of coronary artery bypass graft (CABG) surgery. [9]

3. CLINICAL STUDY

3.1 Clinical Study Design

Randomized Control Trial, Open-label, Parallel group at 1 week duration of data collection after topical application to compare the efficacy and safety of standard treatment of musculosceletal pain in adult populations.

3.2 . Study Objective

To establish the relative clinical effectiveness and safety profile of both medicines, topical piroxicam plus counterirritant and diclofenac in musculosceletal pain in adult populations in primary care.

3.2.1 Primary End-Point:

The primary end-point is the pain reduction of the response to treatment at day 7 or 8 that can be seen through Brief Pain Inventory (BPI).

3.2.2 Secondary End-Point:

a) In data related to safety assessment, the number of subjects who experienced adverse events (including serious adverse events) with each symptom present will be recorded and causality of adverse events and serious adverse events assesses with the help of Naranjo's algorithm
b) Average Score of Investigator's Checklist Nonverbal Pain Indicators (CNPI)
c) Average on Investigator's assessment on Range of Motion (ROM), Muscle test
d) Average scale of Thermal sensation, Thermal comfort and Thermal Acceptance
e) Average time (in minutes) starting to feel the thermal sensation.

3.3 Subjects

In selecting outpatient subjects, the Investigator shall carefully examine whether it is appropriate to ask for participation in the study, paying attention to matters including dependence on the Principal Investigator or other personnel from the perspective of protection of human rights.
Among patients who have "3.3.1 Target Disease," those who meet "3.3.2 Inclusion Criteria" and do not meet any of "3.3.3 Exclusion Criteria" will be examined.

3.3.1 Target Populations

Subjects who were diagnosed with musculosceletal pain caused by osteoarthritis (OA) with Grade I until III Kellgren-Lawrence (KL) grading or musculosceletal disorders such as ankle sprain, patella tendinitis, tennis elbow, and back pain. Diagnosis criteria were made by history taking, physical examination and radiologic evaluation if necessary.

3.3.2 Inclusion criteria

- Outpatient in a primary care setting.
- Between the ages of over 30 and under 60 years of either sex.
- Patients diagnosed with musculosceletal pain as described in the target population.
- Patient has mild to moderate pain based on the Investigator's assessment, confirmed with a pain numeric scale below 7.
- Patient can read and understand how to fill out the assessment form and diary.
- Patients gave written consent to participate in the study independently.

3.3.3 Exclusion criteria

- Patient who has osteoarthritis with Grade IV Kellgren-Lawrence (KL) grading.
- Patients who underwent any of the following treatments:
    - Paracentesis and drainage of joint
    - Intraarticular injection (joint protection agents, local anesthetic, etc.)
    - Nerve block (including trigger points)
- Patients are being treated with an analgesic opioids for their musculosceletal pain.
- Patients being treated with anti coagulant therapy such as warfarin, clopidogrel.
- Patients being treated with oral corticosteroids 7 days before and until signed the informed consent.
- Patients being treated using rigid orthoses those requiring such treatment
- Patients with a history of autoimmune arthritis (e.g., rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, etc).
- Patients with neuropsychiatric disorders including depression, dementia, schizophrenia, and anxiety neurosis
- Patients with Grade 3 hypertension (systolic blood pressure ≥ 180 mmHg and diastolic blood pressure ≥ 110 mmHg regardless of the use of an antihypertensive drugs)
- Patients with acute peptic ulcer
- Patients with bronchial asthma or those with current or previous aspirin-induced asthma (asthmatic attacks induced by NSAIDs and other relevant drugs)
- Patients with a history of hypersensitivity or allergy to NSAIDs
- Patients with serious hepatic disease, renal disease, cardiac disease, hematologic disease, or malignancy
- Patients with a history of dermatitis requiring treatment with topical agents

- Patients with dermatitis or wounds at the application site of the study drug
- Pregnant women, women who may be pregnant, women who wish to become pregnant during the study, or nursing women
- Patients considered by the Investigator to be inappropriate as subjects of this study

3.3.4 Withdrawal Criteria

- Any clinical adverse event, serious illness, or other medical condition identified by the investigator or treating doctor that suggests continued participation is not in the subject's best interest.
- A voluntary decision by the patient to withdraw from the study.
- If the subject was found to have entered the study in violation of the protocol or if the patient was uncooperative during the study.
- Any subject who required the use of an unacceptable concomitant medication—defined as a medication that interfered with the study—will be addressed with justification from the investigator.

3.3.5 Sample Size

Piroxicam 0.5% gel, administered as 5 mg q.i.d. was compared to placebo gel in a double-blind study of the treatment of selected acute soft tissue injuries (ankle or acromioclavicular sprains, supraspinatus, or achilles tendinitis). A total of 200 patients (100 per treatment) were evaluated. Both piroxicam and placebo gels were well tolerated, with 7 piroxicam and 15 placebo patients reporting primarily skin-related adverse effects. This study indicates that piroxicam 0.5% gel, administered as 5 mg q.i.d. is an effective treatment of musculosceletal injuries (sprains and tendinitis), is significantly more effective than placebo, and is well tolerated.[10]

An open, parallel trial was conducted to compare the efficacy and toleration of piroxicam 0.5% gel and diclofenac 1.16% topical gel preparations in the treatment of 173 patients with well-defined, acute sprains and tendinitis of the ankle, shoulder, or elbow. Piroxicam gel was applied to the injured area four times daily by 84 patients and diclofenac gel was similarly applied by 89 patients. The results of this study show that piroxicam 0.5% gel and diclofenac 1.16% gel are equally effective and well tolerated in the treatment of selected acute sprains and tendinitis.[11]

A sample size of 70 patients per treatment group is chosen to provide a power of 80% to detect a statistically significant difference in mean pain intensity on the 0–10 cm VAS if the true difference between treatments is 1.2 points based on previous literature. We calculate that at least 63 patients are required for each patient group to determine the mean difference between delta VAS values as 1.0 with a common standard deviation (SD) of 2.0 (type I error 0.05 and test strength 80%). A 10% dropout was added, and the total sample was rounded to 70 per treatment group.
(Previous literature reference: Predel, Hans-Georg et al. “Efficacy and Safety of Diclofenac + Capsaicin Gel in Patients with Acute Back/Neck Pain: A Multicenter Randomized Controlled Study.” *Pain and therapy* vol. 9,1 (2020): 279-296. doi:10.1007/s40122-020-00161-9).

SAMPLE SIZE			
Group Number	Calculation of Sample size per group	20% Drop Out	Total Subjects
Group 1	63	13	76
Group 2	63	13	76
Total	126	26	152

STUDY PARAMETERS	
Mean, group 1	1.2
Mean, group 2	2.2
Alpha	0.05
Beta	0.2
Power	0.8

$$k = \frac{n_2}{n_1} = 1$$

$$n_1 = \frac{(\sigma_1^2 + \sigma_2^2/K)(z_{1-\alpha/2} + z_{1-\beta})^2}{\Delta^2}$$

$$n_1 = \frac{(2^2 + 2^2/1)(1.96 + 0.84)^2}{1^2}$$

$$n_1 = 63$$

$$n_2 = K * n_1 = 63$$

$\Delta = |\mu_2 - \mu_1|$ = absolute difference between two means
σ_1, σ_2 = variance of mean #1 and #2
n_1 = sample size for group #1
n_2 = sample size for group #2
α = probability of type I error (usually 0.05)
β = probability of type II error (usually 0.2)
z = critical Z value for a given α or β
k = ratio of sample size for group #2 to group #1

3.4 Study Drugs

The specific information about Study Drugs will be described in the Study Drugs Handling Manual.

3.4.1 Test Drug

- Active Ingredients : Piroxicam Plus Counterirritant (Methyl Salicylate, Eugenol and Menthol)
- Brand name : Counterpain® PXM
- Dose :

  Adults : No occlusive dress should be employed. Apply 2-4 g of the gel (refer to dosing card that provided) to the affected area four times daily leaving no residual material on the skin.
  - Apply the gel (2 g) to the each affected hand, wrist, or elbow, 3 times daily.
  - Apply the gel (4 g) to the each affected foot or knee or ankle, 3 times daily.
  - Apply the gel (4 g) to the affected back, 3 times daily.
  - 3 times daily means application one time in morning (06.00 – 11.00), one time in afternoon (11.01 – 17.00), one time in evening (17.01 – 23.00).
  - Aplication of gel will use dosing card that provided in this clinical study.
- Method of administration: Piroxicam Plus is for external use only.

3.4.2 Comparator Drug

- Active Ingredients : Diclofenac Diethylamine 11.6 mg (Diclofenac Sodium 10 mg)
- Brand name : Hotin® DCL
- Dose : No occlusive dress should be employed. Apply 2-4 g of the gel (refer to dosing card that provided) to the affected area four times daily leaving no residual material on the skin.
  - Apply the gel (2 g) to the each affected hand, wrist, or elbow, 3 times daily.
  - Apply the gel (4 g) to the each affected foot or knee or ankle, 3 times daily.
  - Apply the gel (4 g) to the affected back, 3 times daily.
  - 3 times daily means application one time in morning (06.00 – 11.00), one time in afternoon (11.01 – 17.00), one time in evening (17.01 – 23.00)
  - Aplication of gel will use dosing card that provided in this clinical study.

  In the elderly : The lowest dose compatible with adequate safe clinical control should be employed.
- Method of administration: Diclofenac is for external use only.

3.5 Study Drugs Labelling

Even though this clinical study is open-label, a label is needed for the study drug used. The consideration for using a study drug label is that the study drugs used are drugs that are already available on the market and to ensure that subjects use the specific study drug according to the protocol (the correct and same batch number for each study drug), it is given a specific label as a study drug. Specific label and batch number of its Study drugs will be determinded in the Study Drugs Handling Manual.

3.6 Rescue Medication

Rescue medication can be given to patient who have given informed consent. The rescue medication given is only if the subject can not bear the pain and to help reduce pain and per investigator advise. The rescue medication is a drug specifically provided for this study. The use of rescue medication will be recorded. The dosage of rescue medication will be determined by the Investigator.

- Active Ingredients : Paracetamol 600 mg
- Brand name : Sumagesic
- Dose : 1 tablets maximum 3 dose per 24 hours or refer to Investigator advise.
- Method of administration: Oral.

3.7 Storage Method

Please keep under 30° C, protect and avoid direct light. Kept until 1 month after the product opens.

3.8 Dispensing, Storage, Management, and Collection Procedures

The Study Drug Handling Manual will be provided and completed to ensure the study drugs are prepared, shipped, stored, dispensed, and returned to comply with regulations.

It is known that study drugs are drugs that have obtained a marketing authorization number and are circulating in the market. The Sponsor will prepare the provision of study drugs. After the Sponsor ensures the quality of the product, the study drug will be relabeled, which means that this drug is used explicitly for clinical studies.

The sponsor will deliver the study drug from the Technical Operations plant to each research site by courier, where it can monitor the temperature of the study drug delivery below 30°C.

The Study Coordinator from each research site will ensure the storage of study drugs.

During the study, the distribution of study drug subjects will be prescribed by the Investigator based on randomization and dispensed to the subjects by the Sports Therapist during the recovery program. Randomization will be performed by block randomization using and online randomization generator (https://www.graphpad.com/quickcalcs). The patients were randomized into 2 groups – patients receiving piroxicam (group A) or diclofenac (group B, control group). The study is analyzed on an intention-to-treat basis.

At the end of the study period, all study drugs will be returned by the subjects to each site. This return process will be assisted by each Study Coordinator. An then be sent to Technical Operations for destruction.

3.9 Adherence of study drug

The dose of study drugs used during treatment period is checked based on the diary. If AE is occurred to the subject, Investigator can reduce or stop the dose of study drugs.

3.10 Unacceptable Concomitant Medication

As explained in the clinical data and pharmacokinetics and pharmacodynamics of Paracetamol, the drugs mentioned below are known to have interactions with Paracetamol. For this reason, it is not acceptable to get the following treatment:

- Opioid Analgesics
- Oral Non Steroid Anti Inflammation Drugs
  Caution is recommended when analgesic products are used in combination because of possible increases in adverse events (e.g. nephrotoxicity, gastrointestinal lesions, bleeding).
- Alcohol
- Anticoagulants – Oral, Injection: Piroxicam is highly protein bound. There is therefore a possibility of interaction with such drugs as coumarin anticoagulants

3.11 STUDY PLAN

3.11.1 Study Design

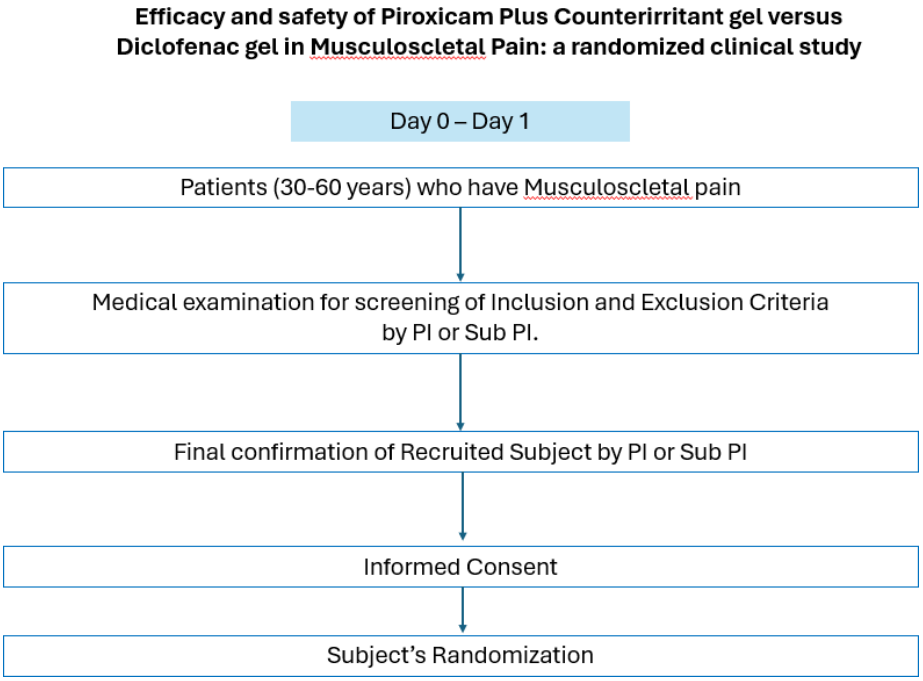
Randomized Control Trial, Open-label, Parallel group at 1 week duration of data collection after topical application to compare the efficacy and safety of standard treatment of musculosceletal pain in adult populations.

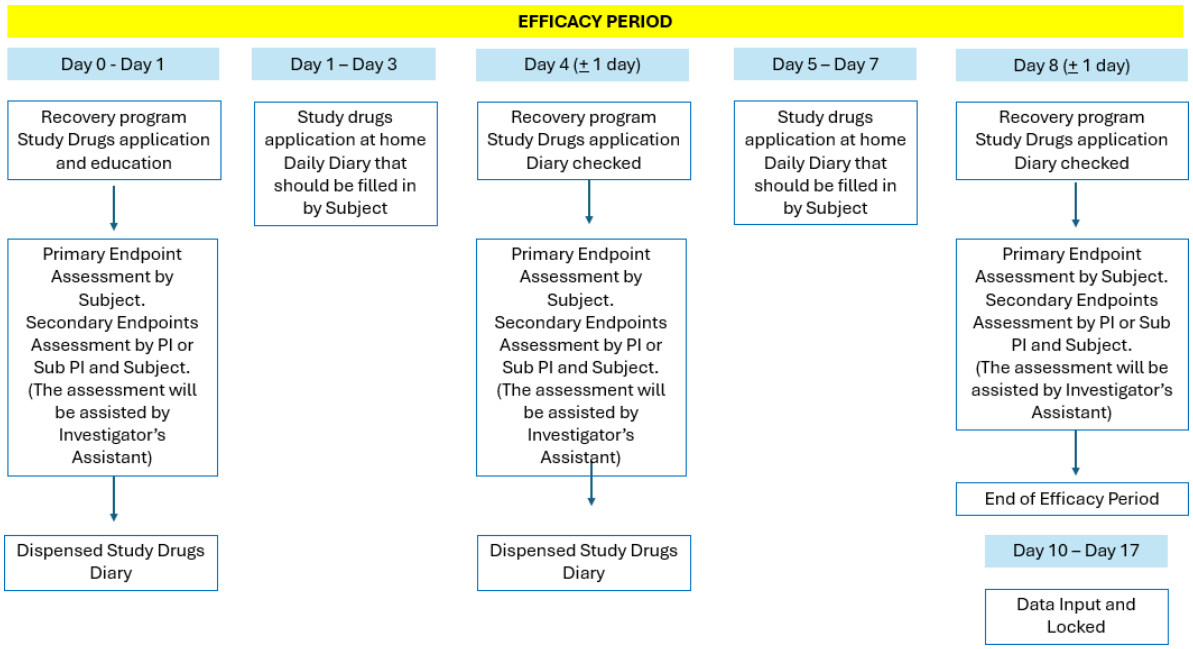
3.11.2 Group Composition

The following 2 groups are examined. The subjects are allocated to these groups at the ratio of 1:1 that will be randomized.

- Test drug group : Piroxicam Plus Counterirritant Gel
- Comparator group : Diclofenac diethylamine Gel

3.11.3 Study period and process





The study period for each subject is defined as "the period from the day of consent to the end of study (the day on which final tests and observation are finished or the day of discontinuation of the study).

The subjects eligibility was confirmed by Principal Investigator (PI) or sub-PI based on the medical assessement, inclusion, exclusion criteria at selection of subject's criteria candidates. After giving consent, the subjects whose eligibility confirmed by the PI or sub-PI are enrolled. At the enrollment, subject will be randomized to prescribe the study drugs. The study drugs assigned to each study site are allocated to each subject in the ascending order of study drug number.

For details of primary and secondary observation items, see " Endpoints."

Data collection in this clinical study is when the subject is coming to have the recovery program in the Efficacy Period that will be collected on Day 0 – Day 1, Day 4 (± 1 day), and Day 8 (± 1 day).

Information of any adverse events regardless related or not related to the investigational product and any concomitant medication or supplementation taken by subject at home would be recorded in subject diary.

The subject need to be returned subject diary and remained Study drugs to the study team during this visit.

3.11.4 Dosage, Administration and Treatment Period

Administration of the study drug after the subject give consent on the informed consent form.
Dosage and Administration, see "Study Drugs".
Application of Study drugs will take around maximum 9 days since subject give consent on the informed consent form.

There are 3 (three) visits that subject need to come to the site after signed the informed consent, Day 0 – Day 1, Day 4 (+ 1 day), and Day 8 (+ 1 day) . In this visit, subject will be checked whether the application of the study drugs is correct or not. Subject also gets the recovery program such as phyisotherapy and exercise program. On the 3rd visit, this is the last visit to check subject's condition and recovery.

3.12 ENDPOINTS

3.12.1 Efficacy Endpoints

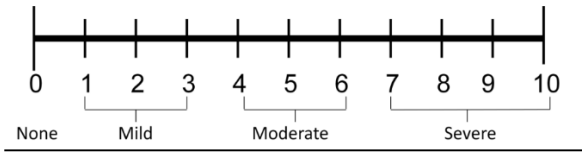
3.12.1.1 Primary Efficacy Endpoint

The primary end-point is the pain reduction of the response to treatment at day 7 or 8 that can be seen through Brief Pain Inventory (BPI). The average result will be captured as the primary efficacy endpoint.

Initial scale of pain	Mid week scale of pain	End of week scle of pain	Difference between initial and mid week scale of pain	Difference between initial and end of week scale of pain

The assessment of pain scale will used some of assessment as follow :

- The Brief Pain Inventory (BPI)
  It is a medical questionnaire that is used to assess pain. It has also been validated for pain assessment chronicle.[12]
  Subjects will be required to complete the Form 1 : Brief Pain Inventory Form.
  The Brief Pain Inventory (BPI) questionnaire has 9 (nine) questions that need to be filled in by the subject itself. Subject needs to scale the pain refer to each question that asked in the BPI (copyright Charles Cleeland, Ph.D. Pain Research Group. 1991) .
  Scale of the numerical rate of pain in the BPI to describe pain as follows:



Score 0 : No Pain
Score 1 – 3 : Mild Pain
Score 4 – 6 : Moderate Pain
Score 7 – 10 : Severe Pain

Study ID# _____ Hospital# _____

Do not write above this line

Date: _____ Time: _____

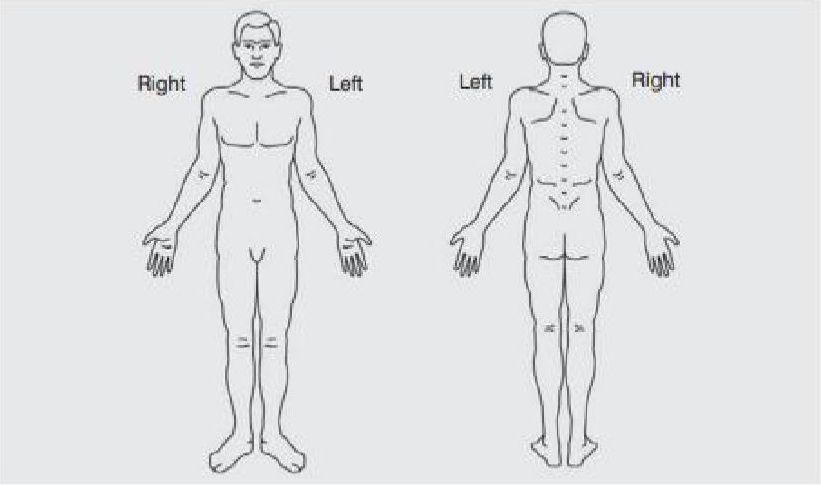
Name: _____

Last First Middle Initial

1) Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

1. Yes 2. No

2) On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3) Please rate your pain by circling the one number that best describes your pain at its WORST in the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

4) Please rate your pain by circling the one number that best describes your pain at its LEAST in the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

5) Please rate your pain by circling the one number that best describes your pain on the AVERAGE.

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

6) Please rate your pain by circling the one number that tells how much pain you have RIGHT NOW.

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

7) What treatments or medications are you receiving for your pain?

8) In the past 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much RELIEF you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No relief										Complete relief

9) Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General activity:

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

B. Mood:

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

C. Walking ability:

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

D. Normal work (includes both work outside the home and housework):

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

E. Relations with other people:

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

F. Sleep:

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

G. Enjoyment of life:

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

3.12.1.2 **Secondary Efficacy Endpoint**

- Initial pain assessment in patients with pain can be helped using assessment initial pain. Investigator or Sub-PI will do the assessment of initial pain using Form No. 2, Initial Pain Assessment (copyright Pasero C, McCaffery M, 2008. As appears in Pasero C, McCaffery M. Pain: Assessment and pharmacologic management, 2011).[12]

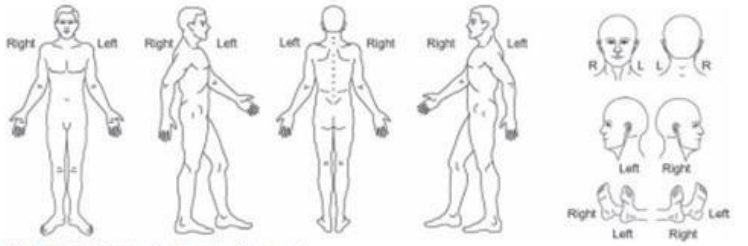
Date _____

Patient's Name _____ Age _____ Room _____

Diagnosis _____ Physician _____

Nurse _____

1. LOCATION: Patient or nurse mark drawing.



2. INTENSITY: Patient rates the pain. Scale used _____

Present pain: _____ Worst pain gets: _____ Best pain gets: _____ Acceptable level of pain: _____

3. IS THIS PAIN CONSTANT? ____ YES; ____ NO IF NOT, HOW OFTEN DOES IT OCCUR? _____

4. QUALITY: (For example: ache, deep, sharp, hot, cold, like sensitive skin, sharp, itchy) _____

5. ONSET, DURATION, VARIATIONS, RHYTHMS: _____

_____

6. MANNER OF EXPRESSING PAIN: _____

_____

7. WHAT RELIEVES PAIN? _____

_____

8. WHAT CAUSES OR INCREASES THE PAIN? _____

_____

9. EFFECTS OF PAIN: (Note decreased function, decreased quality of life.)

Accompanying symptoms (e.g., nausea) _____

Sleep _____

Appetite _____

Physical activity _____

Relationship with others (e.g., irritability) _____

Emotions (e.g., anger, suicidal, crying) _____

Concentration _____

Other _____

10. OTHER COMMENTS: _____

_____

11. PLAN: _____

_____

May be duplicated for use in clinical practice. Copyright Pasero C, McCaffery M, 2008. As appears in Pasero C, McCaffery M. *Pain: Assessment and pharmacologic management*, 2011, Mosby, Inc. Used with permission.

- Point Number 6 : Manner of Expressing Pain will be examined by using the Average Score of Investigator's Checklist Nonverbal Pain Indicators (CNPI).

  The average result will be captured as the primary efficacy endpoint.

Initial CNPI Score	Mid week CNPI Score	End of week CNPI Score	Difference between initial and mid week CNPI Score	Difference between initial and end of week CNPI Score

Investigator or Sub-PI will do the following medical assessment and complete the Form 3 : Checklist Nonverbal Pain Indicators (copyright Feldt KS. The checklist of nonverbal pain indicators (CNPI). Pain Manag Nurs. 2000 Mar;1(1):13-21).
This examination is mainly to ascertain the pain felt by the subject, especially in older subjects where pain assessment in geriatrics requires specificity caused loss neurons of the brain and spinal cord result frequently interpreted changes as abnormal on younger individuals. Conduction speed nerves decrease between 5-10% due to the process aging, this will decrease

the time response and slows transmission impulses, thereby reducing perception touch and pain sensors.[12]

Scoring:

Score a 0 if the behavior was not observed.

Score a 1 if the behavior occurred even briefly during activity or at rest.

The total number of indicators is summed for the behaviors observed at rest, with movement, and overall. There are no clear cutoff scores to indicate severity of pain; instead, the presence of any of the behaviors may be indicative of pain, warranting further investigation, treatment, and monitoring by the practitioner.

Instructions: Observe the patient for the following behaviors both at rest and during movement.

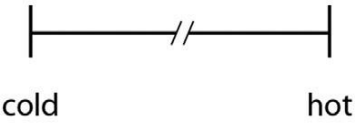
Checklist of Nonverbal Pain Indicators (CNPI)

Behavior	With Movement	At Rest
1. Vocal complaints: nonverbal (Sighs, gasps, moans, groans, cries)		
2. Facial Grimaces/Winces (Furrowed brow, narrowed eyes, clenched teeth, tightened lips, jaw drop, distorted expressions)		
3. Bracing (Clutching or holding onto furniture, equipment, or affected area during movement)		
4. Restlessness (Constant or intermittent shifting of position, rocking, intermittent or constant hand motions, inability to keep still)		
5. Rubbing (Massaging affected area)		
6. Vocal complaints: verbal (Words expressing discomfort or pain [e.g., "ouch," "that hurts"]; cursing during movement; exclamations of protest [e.g., "stop," "that's enough"])		
Subtotal Scores		
Total Score		

- Average on Investigator's assessment on active Range of Motion and Muscle test.
    a) Active Range of Motion
    Improve full of Range of Motion compared to the unaffected site.
    Worsen full of Range of Motion compared to the unaffected site.
    Same range of motion
    b) Muscle test, according to Manual Muscle Testing Oxford Scale
    0 No contraction present
    1 Contraction visible without movement
    2 Movement possible without gravity or incomplete against gravity
    3 Movement possible against gravity into the fullest available range
    4 Movement possible against gravity and an added moderate resistance
    5 Muscle functions normally

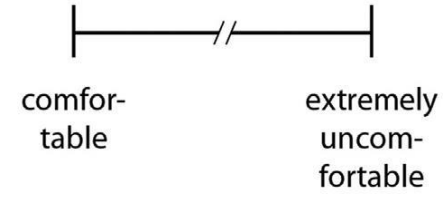
- Assessment to investigate scales on thermal sensation, thermal comfort, and thermal acceptance (ASHRAE 7-point scale) at the end of the week
    a) Thermal sensation scale

A cool
B slightly cool
C neither warm nor cool
D slightly warm
E warm



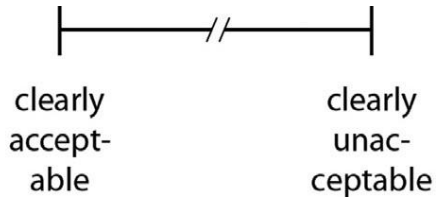
    b) Thermal comfort scale

A slightly uncomfortable
B uncomfortable
C very uncomfortable



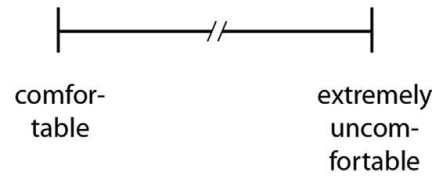
    c) Thermal acceptance

A just acceptable
B just unacceptable



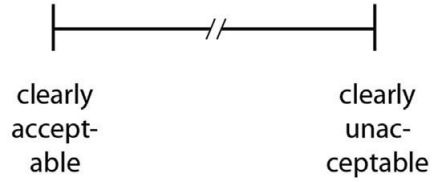
    d) Thermal sensation on thermal comfort

When I feel... :	**...this is:**
A cold	
B cool	
C slightly cool	
D neither warm nor cool	
E slightly warm	
F warm	
G hot	



    e) Thermal sensation on thermal acceptance

When I feel... :	**...this is:**
A cold	
B cool	
C slightly cool	
D neither warm nor cool	
E slightly warm	
F warm	
G hot	



- Average time (in minutes) starting feels the thermal sensation.

- In data related to safety assessment, the number of subjects who experienced adverse events (including serious adverse events) with each symptom present will be recorded and causality of adverse events and serious adverse events assesses with the help of Naranjo's algorithm.

3.12.2 Safety Endpoints – Secondary Endpoint

Safety data collection, safety measurement, review and assessment are applied to all subjects that enrolled in the study.
Measurement of the safety of using this drug is one of the factors measured at the secondary endpoint:

1) AEs, ADRs

The definition of reporting Adverse Events (Aes) and/or Serious Adverse Events (SAEs) in this study applied to subjects who had received oral administration of the study drugs.
If after receiving study drugs the subject has to be hospitalized, an assessment must be carried out whether the condition of hospitalization is related to the study drugs consumed or not. The investigator's assessment is an important factor in assessing safety data related to the consumption of study drugs.

Assessing the causality of adverse events and/or serious adverse events can use the Naranjo Scale which has been described by BPOM-RI, which is an inseparable part of reporting the safety of study drugs.

3.12.2.1 Adverse Events

In this study, "AEs" refer to all untoward medical occurrences in a subject administered a medicinal product. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

The seriousness of AEs is assessed in accordance with

1) Serious
2) Nonserious

Adverse drug reactions (ADR): a response to a medicine which is noxious and unintended, and which occurs at doses normally used in humans.

3.12.2.2 Serious Adverse Events

An adverse event is any undesirable experience associated with the use of a medical product in a subject. The event is serious and should be reported to BPOM-RI when the patient outcome is:
Death **:** Report if you suspect that the death was an outcome of the adverse event, and include the date if known.
Life-threatening **:** Report if suspected that the patient was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient.
Hospitalization (initial or prolonged): Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event.
Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

Disability or Permanent Damage: Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.

Congenital Anomaly/Birth Defect: Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

Required Intervention to Prevent Permanent Impairment or Damage (Devices): Report if you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.

Other Serious (Important Medical Events): Report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic brochospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

3.12.2.3 Evaluation Method and AE Criteria

1) Names of AEs

Names of symptoms, findings, and diseases or names of laboratory or other tests are identified.

2) Onset date

The day on which the AE was observed is specified. Onset day is defined as follows:

Abnormal changes in laboratory test values: the day of the test in which the abnormal change concerned was observed.

When a symptom or sign was observed and its cause was later identified: the day on which the symptom or sign was first observed.

3) Severity

The severity of AEs is decided on the 3-point scale shown in below table. When the severity of AEs was changed, the highest severity is used.

Severity Classification of AEs

Mild	An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
Moderate	An event that is sufficiently discomforting to interfere with normal everyday activities.
Severe	An event that prevents normal everyday activities.

4) Seriousness

The seriousness of AEs is assessed in accordance with definition of Serious AEs.

- Serious
- Nonserious

5) Actions taken for study drugs

Among the following 3 steps of actions taken for study drugs, one that was implemented is entered in case report form.

- None (continued/treatment completed)
- Dose interruption
- Discontinued

6) Treatment of AEs

Treatment of AEs is investigated until the end of treatment of the AEs. Names of all the drugs used or all the therapies used are investigated and entered in case report form. However, this does not apply when the follow-up investigation is terminated based on a medically adequate reason or when follow-up becomes impossible for the reasons including a death that was not caused by the AE, transfer to another clinic or move.

7) Outcome

The course of AEs is classified into 4 categories in accordance with the criteria in table below. When the outcome is "unknown," but evaluation was performed at the time before the follow-up became impossible, the result of the evaluation is also classified. When the outcome is unknown, the reason is entered in case report form.

Recovered	Symptoms or findings disappeared or resolved. Laboratory test values or other data returned to the level within the reference range or the level before the application.
Improving	Symptoms or findings largely disappeared. Laboratory test values show a tendency toward recovery.
Unchanged	No improvement is observed in symptoms, findings, or laboratory test values.
Worse	A part or all symptoms, findings, or laboratory test values cannot be expected to recover or worsened.

8) Date of outcome

The day of outcome is defined as the last day on which the Investigator was able to confirm or classify the outcome directly. Follow-up investigation is performed until the events recover. However, when it was considered unnecessary to follow up on the event until it recovers, the day on which it was determined unnecessary is considered to be the day of the outcome.

When the day of the outcome cannot be accurately determined due to reasons including missed site visits, the day on which the outcome was confirmed or rated over the phone or by letter is considered to be the day of the outcome.

9) A causal relationship with study drugs and definition of ADRs

Causal relationship with study drugs is classified into Naranjo's scale by Investigator.

Source: Naranjo CA et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30

Question	Yes	No	Don't know
Are there previous conclusion reports on this reaction?	+1	0	0
Did the adverse event appear after the suspect drug was administered?	+2	−1	0
Did the AR improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
Did the AR reappear when drug was re-administered?	+2	−1	0
Are there alternate causes [other than the drug] that could solely have caused the reaction?	−1	+2	0
Did the reaction reappear when a placebo was given?	−1	+1	0
Was the drug detected in the blood [or other fluids] in a concentration known to be toxic?	+1	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the adverse event confirmed by objective evidence?	+1	0	0

Scoring for Naranjo algorithm: >9 = definite ADR; 5–8 = probable ADR; 1–4 = possible ADR; 0 = doubtful ADR.

10) Response to Onset of AEs

- When an Investigator notices that medical care for an AE becomes necessary, he or she informs the subject to that effect.

- When an AE occurs, the Investigator ensures the safety of subjects by reducing the dose of study drugs or discontinuing their administration as necessary providing appropriate medical care, and makes efforts to identify the cause.
- The investigator conducts a follow-up investigation until the AE recovers. However, this does not apply when there is medically adequate evidence, as shown in the examples below. In such cases, the reason is entered in case report form.
-

11) Response to Onset of Serious AEs

When serious AEs occur, the following measures are taken.

- When any serious AEs occur, the Principal Investigator promptly notifies the sponsor (monitor) verbally or over the phone, e-mail or fax and reports the details in writing at a later date within 24 hour of their acknowledgement. In this case will also include if the Principal Investigator identifies unexpected ADRs (the characteristics and severity are not consistent with the information in the investigator's brochure) among the serious AEs it should be reported to sponsor.
- When the sponsor and the institutional review board (IRB)/EC request for additional information (autopsy report, medical record of terminal stage, and other necessary information) regarding the reported serious AEs, the Principal Investigator provides this information.
- The sponsor immediately informs all the Principal Investigators involved in this study of all the events that are subject to expedited reporting to the regulatory agency.
- All SAEs, SADRs, and SUSAR (if any) will be reported to the local the institutional review board (IRB)/EC and NADFC according to their reporting guidelines.

3.12.3 Ensuring Safety of Subjects

Basic Points

1) The Principal Investigator is responsible for all the medical decisions related to the study.
2) The Principal Investigator ensures that sufficient medical care for all the AEs related to the study is provided to subjects during their participation in the study and after that.
3) The sponsor is responsible for continuously assessing the safety of study drugs.
4) The sponsor promptly notifies all Principal Investigators involved in the study of the information that may adversely affect the safety of subjects, influence the conduct of the study, or require changes in the approval of the continuation of the study by the institutional review board (IRB)/EC.

3.13 CRITERIA AND PROCEDURE FOR DISCONTINUATION FOR SUBJECTS

3.13.1 Discontinuation Criteria

Investigator discontinues the study when a subject meets the following criteria.

1. When continuation of the study is difficult due to worsening of the target disease of this study or symptoms caused by the target disease

2. When a significant or persisting noncompliance with the protocol that makes it difficult to ensure safety or influences efficacy assessment was detected
3. When a subject is found not to meet the inclusion criteria for subjects of this study or to meet the exclusion criteria
4. When it is difficult to continue the study or a subject requests for discontinuation due to onset of AEs
5. When a subject requests for discontinuation (not in relation to AEs)
6. When a subject stops visiting the site, making it difficult to continue the study
7. Other cases in which Investigator considers it difficult to continue the study

3.13.2 Discontinuation Procedures

When any event corresponding to "Discontinuation Criteria" occurs during the study treatment, Investigator discontinues the administration of study drugs, performs the observation and tests specified in " Schedule and Efficacy and Safety Endpoints," and enter the results, discontinuation day, and reason for discontinuation in case report form.

Appropriate treatment including alternative therapies is provided after discontinuation.

When the study is discontinued due to occurrence of a safety problem in the subject concerned, appropriate measures are taken and the problem is addressed in accordance with " Ensuring Safety of Subjects."

When a subject stops visiting the site, Investigator asks a subject to visit the site and efforts are made to perform the observation and tests specified in "Schedule and Efficacy and Safety Endpoints."

If the designated observation and tests cannot be performed, Investigator promptly conducts follow-up investigation on the course after the latest observation and AEs over the phone, by letter, or other possible methods and enters the result in case report form. When confirmation was made with a person other than the subject for a compelling reason, the reason and the relationship of this person with the subject are entered in case report form.

3.14 STUDY, EFFICACY AND SAFETY ENDPOINTS SCHEDULE

	1st Visit		2nd Visit		3rd Visit	Data Input G Locked	Note
Days	Day 0 - Day 1	Day 1 - Day 3	Day 4 + 1 day	Day 5 - Day 7	Day 8 + 1 day	Day 10 - Day 17	
Medical Assessment for Inclusion and Exclusion Criteria Confirmation	X						PI, Sub PI
Informed consent	X						PI, Subject
Randomization	X						PI
Dispense Study Drugs	X						PI, Sub PI, Study Coordinator 1
Recovery Program : - Aplication of Study Drugs to affected site - Physiotherapy - Exercise program	X		X		X		PI, Sub PI, Study Coordinator 1, Therapist
Primary and Secondary endpoint assessement	X		X		X		Subject assisted by Study Coordinator 1
Application of Study Drugs at home		X		X			Subject
Subject's diary	X	X	X	X	X		Subject
Concomitant medication	X	X	X	X	X		PI, Sub PI, Subject
Rescue medication	X	X	X	X	X		PI, Sub PI, Subject
Adverse events	X	X	X	X	X		PI, Sub PI, Subject
Study drugs and Diary returned					X		PI, Sub PI, Pharmacy
Data input	X		X		X	X	PI, Sub PI, Study Coordinator 2
Data locked						X	PI, Sub PI, Study Coordinator 2
Final CRF					X	X	

3.15 STATISTICAL ANALYSIS

3.15.1 Analysis Sets

In efficacy assessment, “per protocol set” is considered to be the primary analysis set and “full analysis set” the secondary analysis set. In safety assessment, “safety analysis set” is considered to be the analysis set.

Analysis sets are defined as follows.

- Per protocol set (PPS)

PPS is defined as the group of subjects without significant violation of the protocol including violation of inclusion/exclusion criteria who comply with the minimum requirements that should be followed in the protocol, and have available tests and observation results of the primary endpoint.

- Full analysis set (FAS)

FAS is defined as the group of subjects who received the application of the study drug at least once and underwent tests and observation results for efficacy endpoints at least once after the application of the study drug.

- Safety analysis set

Safety analysis set is defined as the group of subjects who received the application of the study drug at least once and underwent tests and observation results for safety endpoints at least once after the application of the study drug.

3.15.2 Statistical Analysis Plan

The person responsible for statistical analysis promptly tabulates and analyzes the data after data finalization in accordance with the following statistical analysis plan.

The following tabulation and analysis are performed for PPS, FAS, and safety analysis set.

For subject characteristics, descriptive statistics of continuous data are calculated for each application group, and the frequency of discrete data is tabulated by application group.

The estimated sample for the study with 90% power at 5% significance level is 70 each arm.

Primary and Secondary Endpoints will be performed as PPS and FAS.

For AEs and ADRs, the frequency is tabulated by application group for site of onset and its total. Similar tabulations are performed by severity and time of onset.

Additionally, each incidence rate of AEs and ADRs are compared between the groups.

For laboratory test values and physical examination values, descriptive statistics of continuous data are calculated for each application group and discrete data are cross-tabulated by application group.

3.16 COMPLIANCE WITH AND DEVIATION FROM PROTOCOL OR CHANGES AND REVISION OF PROTOCOL

3.16.1 Compliance with and Deviation from or Changes in Protocol

Investigator must not deviate from or change the protocol unless the Principal Investigator obtains prior written agreement with the sponsor and written approval by the institutional review board (IRB)/EC. However, this does not apply when the deviation or change is medically inevitable, for example, deviation or change for avoiding urgent risk to subjects, or when the change does not affect the conduct of the study (for example, change in phone numbers).

1) Investigator can deviate from or change the protocol without prior written agreement with the sponsor and prior approval by the institutional review board (IRB)/EC for medically

compelling reasons, for example, to avoid urgent risk to subjects. In such cases, the Principal Investigator notifies the sponsor of the details of the deviation or change and its reason. The Principal Investigator also discusses the revision of the protocol with the sponsor and reaches an agreement. The approval of draft revision by the institutional review board (IRB)/EC is obtained as soon as possible.

2) The Principal Investigator promptly submits the report of all the changes in the study that significantly affect the conduct of the study or increase the risk to subjects to the sponsor and the institutional review board (IRB)/EC.
3) Investigator records all the actions that deviate from the protocol. Among the actions deviate from the protocol, the Principal Investigator prepares the documents that include the reasons, immediately submits them to the sponsor, and retains a copy only for the actions for medically compelling reasons including avoidance of urgent risk to subjects.

3.16.2 Revision of Protocol

The protocol and case report form are revised by the following procedures.

1) When the sponsor considers the revision necessary, the sponsor provides the Principal Investigator the draft revision of the protocol and case report form and other necessary materials and information.
2) The sponsor gives the Principal Investigator time necessary for him or her to sufficiently review the materials and information including the draft revision of the protocol provided in accordance with the previous clause and discuss with the sponsor.
3) After discussing with the Principal Investigator, the sponsor reaches an agreement with the Principal Investigator on the details of the revised protocol and case report form and compliance with the revised protocol. The sponsor and the Principal Investigator each sign, and date the written agreement to prove the above agreement. Similar processes are followed when the protocol and case report form are corrected at the direction of the institutional review board (IRB)/EC, within the range accepted by the sponsor.
4) The sponsor promptly submits the revised protocol and case report form and promptly obtains the approval by the institutional review board (IRB)/EC. For changes in the protocol related to administrative matters (for example, changes in monitors or changes in phone numbers, etc.), addition or deletion of other study sites, and changes in the Principal Investigator or other personnel at other study sites, the sponsor notifies the Principal Investigator of the details of the changes.

3.16.3 Completion or Discontinuation and Interruption of Study

3.16.3.1 Completion of Study

The completion day of the study for each subject is defined as “the day on which observation of all items specified in the protocol is completed or discontinuation day for the subject” and the completion day of the study for each study site as “the latest day among the study completion days for the subjects enrolled at the study site concerned.”

After: the study treatment and observation specified in the protocol were completed for the last subject at the study site concerned, the Principal Investigator promptly notifies the institutional review board (IRB)/EC and the sponsor of the completion of the study in writing and reports the outline of the study results based on the report he or she prepared to the institutional review board (IRB)/EC and the sponsor.

3.16.3.2 **Discontinuation or Interruption of Entire Study**

Criteria for Discontinuation or Interruption of Entire Study

The sponsor promptly discusses the discontinuation or interruption of the study with the medical expert when the following criteria are met and continuation of the study at all the study sites is considered difficult or meaningless.

1) When "unexpected" serious AEs (diseases, disorders, deaths) occur
2) When information indicating that the tendencies in occurrence of "expected" significant AEs including number of incidents, frequency, and conditions for occurrence cannot be predicted based on the investigator's brochure was obtained
3) When information indicating that the tendencies in occurrence of ADRs including number of incidents, frequency, and conditions for occurrence markedly changed for the worse was obtained
4) When information indicating or not indicating the superiority of the test drug to the comparator was obtained
5) When other information affecting the continuation of the study was obtained
    a. Procedures for Discontinuation or Interruption of Entire Study
    b. The entire study is discontinued or interrupted by the following procedures.
6) When the entire study is discontinued or interrupted, the sponsor promptly notifies all the Principal Investigators involved in the study and the regulatory agency to that effect and the detailed reasons in writing.
7) When the sponsor decides the discontinuation or interruption of the entire study and notifies Principal Investigators of the decision, Principal Investigators promptly notifies the institutional review boards (IRB)/EC to that effect in writing and explains the details of the discontinuation or interruption to the institutional review board (IRB)/EC.
8) When the Principal Investigators are notified of the discontinuation or interruption of the entire study, they promptly notify the subjects receiving study treatment to that effect and take appropriate measures including switching to other therapies.

3.16.4 Discontinuation or Interruption at Study Sites

3.16.4.1 **Criteria for Discontinuation or Interruption at Study Sites**

When the following criteria are met, the sponsor assesses whether or not the study can be continued at all or part of the study sites.

1) When the protocol needs to be changed and some study sites cannot respond to the change
2) When the sponsor cannot approve an instruction for correction based on the opinion of the institutional review board (IRB)/EC
3) When the institutional review board (IRB)/EC instructed to discontinue the study
4) When some study sites violated GCP, the protocol, or study contract significantly or continuously

3.16.4.2 **Procedures for Discontinuation or Interruption at Study Sites**

The study is discontinued or interrupted at study sites by the following procedures.

1) When the Principal Investigator discontinued or interrupted the study, he or she promptly explains the discontinuation or interruption in detail in writing to the sponsor and the institutional review board (IRB)/EC.

2) When the institutional review board (IRB)/EC decided discontinuation or interruption of the study and notifies to that effect, the Principal Investigator promptly notifies the sponsor.

3.17 DIRECT ACCESS TO SOURCE DOCUMENTATION

3.17.1 Direct Access to Source Documents, etc.

The Principal Investigator accepts the monitoring and audit by the sponsor and inspection by the institutional review board (IRB)/EC and the regulatory agency and provides all the study-related records including source documents for direct access.

3.17.2 Method of Direct Access

If necessary, the study site and sponsor can have access to clinical study documents. The justification for opening access to clinical study documents will be discussed by the study site and the sponsor. Any access to clinical study documents requires prior Sponsor approval.

3.18 QUALITY CONTROL AND QUALITY ASSURANCE OF STUDY

The sponsor responsibly performs the quality assurance based on the standard operating procedures and maintains quality control system in order to assure that the study is conducted and data are generated, recorded, and reported in compliance with the protocol, the pharmaceutical affairs law, and GCP.

The sponsor will ensure that the reporting of adverse events that occur in this study will be reported to the the institutional review board (IRB)/EC and also BPOM RI in accordance with regulations applied in Indonesia.

3.18.1 Quality Control of Study

The sponsor applies quality control at each step of the handling of data in order to assure the reliability of all the study-related data and their appropriate processing.

The monitors assigned by the sponsor perform monitoring (including direct access to the study-related record such as source documents) according to the standard operating procedures and confirm that the study is being conducted appropriately at study sites in compliance with the protocol, the standard operating procedures, and GCP.

Monitors, the person responsible for quality control system, the person responsible for data management, and the person responsible for statistical analysis perform quality control at each step of the handling of data according to the standard operating procedures specified by the sponsor.

3.18.2 Quality Assurance of Study

The sponsor assures the quality of the study by establishing an audit department that is independent of the department that implements the study. In order to assure the quality of the study, the personnel in charge of audit performs audit at appropriate timing at the sponsor as well as at study sites and other facilities involved in the study as necessary, in accordance with the standard operating procedures of the sponsor.

3.19 ETHICAL IMPLEMENTATION OF STUDY

3.19.1 Review of Study

This study is reviewed by the institutional review board (IRB)/EC selected by each study site as to whether or not its implementation is appropriate from the perspective of ethical, scientific, and medical adequacy.

3.19.2 Continued Review of Study

The adequacy of continued implementation of this study at a particular study site is reviewed once a year or more frequently, or in the following cases.

1) When the sponsor notified the Principal Investigator of serious and unexpected ADRs or other events
2) When the Principal Investigator reported serious AEs or other events
3) When the Principal Investigator reported a revision of consent form and other written information for patients
4) When the Principal Investigator submitted the overview of the current status of the study for the review regarding continuation of the study
5) Other cases in which the Principal Investigator considers that the review regarding continuation of the study is necessary

The Principal Investigator requests the opinion of the institutional review board (IRB)/EC regarding the adequacy of continuation of the study at the study site concerned.

3.19.3 Matters Related to Protection of Privacy and Personal Information of Subjects

In order to protect the privacy and personal information of subjects, subjects are identified by subject IDs.

In the preparation and handling of case report forms and the monitoring, audit, and other tasks performed by the sponsor, as well as when the study results are published, attention is paid to protection of privacy and personal information of subjects.

3.20 STORAGE OF RECORD

3.20.1 Investigator

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor.

3.20.2 Institutional Review Board (IRB)/EC

The institutional review board (IRB) /EC is an independent body constituted of medical, scientific and non- scientific member, whose responsibility is to ensure safeguard the rights, safety, and well-being of all trial subjects.

The institutional review board (IRB) /EC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies).

3.20.3 Sponsor

1) The sponsor specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the sponsor.
2) When the storage of the documents that should be stored by the Principal Investigator or the institutional review board (IRB) /EC becomes unnecessary, the sponsor notifies the institutional review board (IRB) /EC to that effect through Investigator.

3.21 MONETARY PAYMENT

The sponsor pays the cost of this study based on the contract with each study site.

3.22 INSURANCE

The sponsor takes necessary measures including issued guarantee letter in order to compensate for the treatment of health hazards of subjects caused by the study and other losses.

3.23 COMPENSATION FOR HEALTH HAZARDS

1) When any health hazard occurs to a subject in this study, the study site and the sponsor respond to it for the subject or his or her bereaved family in the following manner.
2) The study site makes all possible efforts to treat the health hazard.
3) If neither intention nor negligence of the sponsor was involved and no other parties have liability for the health hazard caused by the study, the sponsor provides compensation based on its compensation system. However, if the health hazard was proven to be the results of the subject's own intention or significant negligence, the compensation is reduced or not provided. If a health hazard that newly occurred is causally unrelated to the study, it is not compensated.
4) If intention or negligence of the sponsor, the study site, a party commissioned by the sponsor or the study site to carry out study-related tasks, or other parties was involved in the health hazard caused by the study, the party that is legally responsible for this health hazard provides the compensation.
5) Adverse event that happened during observation and treatment period will be monitored by investigator and sponsor. The cost for theadverse event related to the study will be compensated by sponsor.

3.24 HANDLING OF PUBLICATION

The sponsor is free to use the information obtained in this study for the purposes including the application for marketing approval related to the test drug.

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