Document Type:	Study Protocol
Official Title:	A Pilot Study Assessing the Treatment Responsiveness of a Novel Osteoarthritis Stiffness Scale
NCT Number:	NCT03570554
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1. Title page

A Pilot Study Assessing the Treatment Responsiveness of a Novel Osteoarthritis Stiffness Scale

Test drugs:	BAY 117031 / Naproxen Sodium		
Study purpose:	Clinical efficacy		
Clinical study phase:	Phase 2	Date:	11-Sep-2018
Registration:	Not Applicable	Version no.:	3.0
IMPACT Number:	19783		
Sponsor:	Bayer HealthCare LLC, Consumer Health 100 Bayer Boulevard Whippany, NJ 07981-0915, USA		
Sponsor's medical expert:	PPD Sr. Associate Director, Global Medical Affairs Bayer HealthCare LLC, Consumer Health		

The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Signature of the sponsor's medically responsible person

The signatory agrees to the content of the final clinical study protocol as presented.

Name: PPD

Role: Sr. Associate Director, Global Medical Affairs

Date: 11 Sept 2018

Signature: PPD

2. Synopsis - amendment 1 and 2

Title	A Pilot Study Assessing the Treatment Responsiveness of a Novel Osteoarthritis Stiffness Scale
IMPACT	19783
Clinical study phase	2
Study objective(s)	To assess the responsiveness of the Brief Arthritis Stiffness Scale (BASS) for detecting treatment effects of common OTC analgesics and a common prescription analgesic in subjects with knee OA
Test drug(s) **Name of active ingredient**	Naproxen sodium
Dose(s)	220 mg (660 mg daily)
Route of administration	Oral
Duration of treatment	4 days
1. Reference drug(s) **Name of active ingredient**	Acetaminophen
Dose(s)	650 mg (3900 mg daily)
Route of administration	Oral
Duration of treatment	4 days
2. Reference drug(s) **Name of active ingredient**	Celecoxib
Dose(s)	100 mg (200 mg daily)
Route of administration	Oral
Duration of treatment	4 days
3. Reference drug(s) **Name of active ingredient**	Placebo
Dose(s)	Not applicable
Route of administration	Oral
Duration of treatment	4 days
Background treatment	Not applicable
Indication	Osteoarthritis of the knee

Diagnosis and main criteria for inclusion /exclusion	Inclusion Criteria - amendment 1 and 2
	• Signed Informed Consent;
	• Ambulatory (as deemed appropriate by the Investigator) male and female subjects between 40 and 80 years of age;
	• Body Mass Index (BMI) between 18 to <40 kg/m^2;
	• Unilateral or bilateral OA of the knee based on the American College of Rheumatology (ACR) clinical criteria: Knee pain plus <u>at least 3</u> of the following:
	  o age >50 years;
	  o less than 30 minutes of morning stiffness;
	  o crepitus on active motion and osteophytes;
	  o bony tenderness;
	  o bony enlargement;
	  o no palpable warmth.
	• Have had diagnostic quality radiography of the target knee performed no more than 1 year prior to baseline showing evidence of OA with Kellgren and Lawrence grade of II or III;
	Note: X-ray of both knees should not be repeated if performed in the previous 12 months, the radiographs are of diagnostic quality and information is available to the investigator.
	• History of analgesic use for ≥4 days/week for past month and willing to discontinue use at least 4 days prior to randomization (low-dose [100 mg or less] aspirin regimen permitted);
	• Joint Stiffness Severity score ≥3 on a 0-10 NRS at Screening;
	• Female subjects of childbearing potential must be using a medically acceptable form of birth control for at least 1 month prior to screening (or 3 months if using oral contraceptives) [e.g., hormonal contraceptives (oral, patch, injectable or vaginal ring), implantable device (implantable rod or intrauterine device), or a double barrier], or in same sex relationship and have a negative pregnancy test at Screening and prior to study drug administration. Female subjects of non-childbearing potential must be amenorrheic for at least two years or have undergone surgical sterilization (e.g., hysterectomy and/or bilateral oophorectomy);
	• Willing to wear an accelerometer during each treatment period of the Treatment Phase. Subjects who decline to wear the accelerometer are still eligible for study participation provided they meet all other required criteria.
	
	For Randomization
	• 48-hour WOMAC pain subscale average score ≥3.0 and/or 24-hour Average Pain Intensity score ≥3 on the 0-10 NRS at Screening;
	• 48-hour WOMAC pain subscale average score ≥4.0 at Visit 2, Treatment Period 1 of 4;
	• 24-hour *Average Pain Intensity* score ≥3 on the 0-10 at Visit 2, Treatment Period 1 of 4;
	• Current pain intensity score ≥4 and ≤9 on the 0-10 NRS at Visit 2, Treatment Period 1 of 4;
	• A Day 1 baseline post-STEPP current pain intensity score ≥5, and ≥1 unit higher than the pre-STEPP current pain score on the 0-10 NRS;
	• Experience knee stiffness at least 5-7 days per week over the past month as reported on the Baseline Stiffness Questionnaire.
	
	Exclusion Criteria - amendment 1
	• History of underlying inflammatory arthropathy, rheumatoid arthritis or fibromyalgia;
	• History of or scheduled for knee replacement surgery (in the target knee) within the next 6 months at screening;

	• Recent injury in the OA affected knee (past 4 months); oral, intra-muscular, intravenous or intra-articular corticosteroid, platelet rich plasma intraarticular knee injections, stem cell therapy or hyaluronic acid injections in either knee within the last 3 months; • Subject reports moderate or severe (score of 2 or 3) pain or tenderness on the 0-3 Regional Pain Scale for any joint or body area other than the target knee and, in the Investigator's opinion, the subject is not able to distinguish pain in the target knee from other painful areas; • Use of any pain medications from the start of the Screening/Washout Phase through trial completion, other than IMP provided by the Sponsor or Rescue Pain medication provided by the study site; • Subject who takes an opioid ≥4 days per week over the past 4 weeks; • Subject is taking more than one antidepressant. Subjects who are on a stable dose of one antidepressant, for at least 1 month, are eligible for enrollment; • Subject is taking more than one anxiolytic medication. Subjects who are on a stable regimen of one anxiolytic for at least 1 month, are eligible for enrollment; • Initiating any new physical therapy for the lower extremities from 4 weeks prior to study start through the duration of the study; • Positive urine drug test for illegal drug substances, non-prescribed controlled substances, or breath/saliva alcohol at screening or Visit 2; **Note:** prescribed marijuana is allowed provided the subject is willing to wash out and not use during the study. • Subject has an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2 times the upper limit of normal; • Subject has a hemoglobin <10.0 g/dL; • Subject has an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m²; • Subject is breast feeding or has a positive pregnancy test at screening or Visit 2; • Kellgren and Lawrence grade of 0, I or IV in the target knee; • Subjects with a medical disorder, condition or history of such that could impair the subject's ability to participate or complete this trial in the opinion of the investigator; • History of hypersensitivity (including but not limited to anaphylactic reactions and serious skin reactions) to naproxen sodium, celecoxib, acetaminophen, NSAIDS, aspirin, similar pharmacological agents or components of the investigational products • History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. • History of allergic-type reactions to sulfonamides; • Current or past history of gastrointestinal bleeding or other bleeding disorder(s); • Prior history of peptic ulcer disease and/or gastro-intestinal bleeding; • Evidence or history of clinically significant (in the judgment of the investigator) hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic diseases, or malignancies within the last 5 years that makes the subject unfit to participate in the trial; • Recent (within the past 1 year) MI or in the peri-operative period surrounding coronary artery bypass graft (CABG) surgery; • Heart failure, advanced renal disease or advanced hepatic disease; • Current participation in any other trials involving investigational or marketed products within 30 days prior to the Screening Visit; • Inability to report pain accurately as assessed at Screening.
Study design	The trial consists of an up to 14 day Screening Phase, a 4 (+3) day Screening Washout Phase and a Treatment Phase consisting of four 4-day treatment periods separated by washout periods lasting several days.

Methodology	A multi-center, randomized, double-blind, 4-period crossover, placebo-controlled pilot trial in male and female adult subjects with pain due to OA of the knee conducted at approximately 3-5 sites in the United States.
Type of control	Active and placebo
Data Monitoring Committee	No
Number of subjects	50 randomized subjects (40 subjects anticipated to complete all visits)
Primary variable(s)	Sum of change from baseline in the Daily BASS score over the 4 day treatment period.
Time point/frame of measurement for primary variable(s)	Morning of Days 1 (baseline), 2, 3 and 4 of each Treatment Period
Plan for statistical analysis	All statistical tests will be 2-sided at the significance level of 5% and no multiplicity adjustment will be made. The primary and secondary efficacy endpoints will be analyzed CCI [redacted]

Table of contents

List of abbreviations - amendment 1

AE	Adverse Event
ACR	American College of Rheumatology
ANOVA	Analysis of Variance
ALT	Alanine Aminotransferase
AP	Anteroposterior
AST	Aspartate Aminotransferase
BASS	Brief Arthritis Stiffness Scale
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
Ca	Calcium
CABG	Coronary Artery Bypass Graft Surgery
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
Cl	Chloride
CO_2	Carbon Dioxide
COX	Cyclooxygenase
CSR	Clinical Study Report
(e)CRF	(electronic) Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ER	Extended Release
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ITT	Intent-to-Treat
IUD	intra-uterine device
K	Potassium
MedDRA	Medical Dictionary for Regulatory Activities
Na	Sodium
NRS	Numerical Rating Scale
NSAID	Nonsteroidal Anti-inflammatory Drug
OA	Osteoarthritis
OTC	Over-the-Counter
PA	Posteroanterior
PGIC (P) / (S)	Patient Global Impression of Change (Pain) / (Symptoms)
PID	Pain Intensity Differences
PP	Per Protocol
QA	Quality Assurance
RBC	Red Blood Cell
RNR	Randomization Number
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SNR	Screening Number
SOC	System Organ Class
SPI	Sum of Pain Intensity

SPID	Summed Pain Intensity Difference
STEPP	Staircase-Evoked Pain Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
US(A)	United States (of America)
WBC	White Blood Cell
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

3. Introduction

Background

Osteoarthritis (OA) is a common, chronic, progressive, skeletal, degenerative disorder that frequently affects several joints such as knee, hip, spine and hands. OA is associated with damage to the cartilage and surrounding tissues and characterized by pain, stiffness, and loss of function. (1) Being a highly prevalent disease and a main form of arthritis, OA is the most common cause of disability in the U.S. In fact, 52.5 million U.S. adults (approximately 1 in 4) aged ≥18 years have self-reported having doctor-diagnosed arthritis according to 2010-2012 data collected by the National Health Interview Survey. (2) The incidence of large joint OA in the U.S., particularly of the knee, is predicted to increase with the aging of the population and obesity epidemic. (3)

Currently, a variety of prescription and over-the-counter (OTC) medications are available. Acetaminophen has been a mainstay of OA pharmacological management for many years and has been tested in many clinical trials although its effectiveness in clinical trials appears limited. (4) An extended release (ER) formulation containing acetaminophen 650 mg in a bilayer form has been shown to be more efficacious than placebo in hip and knee OA. (5) Each caplet contains 650 mg of acetaminophen. The maximum daily dose is 3900 mg.

Aleve®, naproxen sodium, the sodium salt of naproxen, was developed as an analgesic because it is more rapidly absorbed than naproxen. It is available as an OTC analgesic/antipyretic that temporarily reduces fever and relieves minor aches and pains due to: minor pain of arthritis, muscular aches, backache, menstrual cramps, headache, toothache, and the common cold. OTC doses of naproxen sodium have been shown to be efficacious for relieving OA pain. (6, 7, 8) Each tablet contains 220 mg of naproxen sodium with a maximum daily dose of 660 mg.

Celecoxib, a COX-2 selective NSAID, is a commonly used prescription analgesic for OA and its efficacy is supported by a large body of data. (9) For relief of the signs and symptoms of OA the recommended oral dose is 200 mg per day.

Along with pain, stiffness is a frequent symptom of OA. (6) The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), a commonly used patient reported outcome (PRO) instrument for the measurement of OA-related joint pain and physical function includes a 2-item subscale for measuring joint stiffness. (10) However, the WOMAC's 2-item subscale for measuring joint stiffness shows low test-retest reliability. (11) FDA has informed Bayer that the WOMAC stiffness subscale has not been accepted as a stand-alone measure suitable for use as an endpoint.

In order to examine the efficacy of treatments on improving joint stiffness, the Brief Arthritis Stiffness Scale (BASS), a PRO instrument designed specifically to measure stiffness was developed and validated for use in clinical trials. A non-interventional study has previously been conducted to examine the psychometric properties of the BASS. The study provided evidence for the reliability, construct validity, and discriminant validity of both the daily and weekly average BASS score, as well as preliminary responder thresholds. Further evaluation of the BASS to assess the instrument's responsiveness to treatment is needed. A study including an active intervention will provide information to formally evaluate the instrument's ability to detect change and provide utility for the responder definition.

This placebo-controlled clinical trial will assess the effects of naproxen sodium, acetaminophen and celecoxib on stiffness in subjects with OA. Furthermore, data will be

collected to confirm the psychometric evidence supporting the use of the BASS as a patient reported outcome in assessing the effect of treatment in OA.

Benefit-risk assessment

Subjects with OA of the knee who would typically take over-the-counter (OTC) nonsteroidal anti-inflammatory drugs (NSAIDs) for pain relief will be enrolled in this study. The 4 day treatment duration falls within established treatment guidelines. (12)

During the study, subjects will be closely monitored for evidence of adverse events. Potential risks to subjects participating in this study include the risks associated with OTC analgesic use and the risk of inadequate relief in placebo-treated subjects. Subjects will be given the option of taking rescue therapy between each Treatment Period. Given the ability to mitigate risk through close monitoring, this study is considered clinically and ethically acceptable.

4. Study objectives - amendment 1

Primary

- To assess the responsiveness of the Brief Arthritis Stiffness Scale (BASS) for detecting treatment effects of common OTC analgesics and a common prescription analgesic in subjects with knee OA.

Exploratory

- To assess the assay sensitivity of the **ST**aircase-**E**voked **P**ain **P**rocedure (STEPP™) to detect treatment effects of commonly used analgesics compared to placebo and to detect differences between active treatments;

- To determine/identify effect size measurements, determine single dose vs. multi-dose efficacy, identify optimal sample size, and logistical issues for planning comparative analgesic efficacy studies using the STEPP.

- To assess levels of activity captured by the accelerometer between active treatments and placebo during Days 1 (partial), 2 and 3 of the Treatment Phase.

- To evaluate the safety and tolerability of naproxen sodium, celecoxib and acetaminophen ER.

5. Study design

5.1 Design Overview - amendment 1 and 2

This is a multi-center, randomized, double-blind, 4-period crossover, placebo-controlled pilot trial in male and female adult subjects with pain due to OA of the knee. At the completion of Screening and Baseline Phases, eligible subjects will be randomized to a blinded treatment sequence of naproxen sodium, acetaminophen ER, celecoxib and placebo.

The trial consists of an up to 14 day Screening Phase, a 4 (+3) day Screening Washout Phase and a Treatment Phase consisting of four 4-day treatment periods separated by washout periods lasting several days. The study center may schedule screening testing on multiple days as needed provided all screening tests are done within 14 days. Approximately 192 subjects will be screened with 62 eligible to start the Screening Washout Phase. Approximately 12 subjects are anticipated to fail baseline randomization criteria to obtain approximately 50 randomized subjects of whom approximately 10 are anticipated to drop out leaving approximately 40 completed subjects.

Screening Phase Visit 1 - (Day -18 to -5)

Eligible subjects will be selected within a period of up to 14 days prior to the start of the Screening Washout Phase of the trial. Subjects are required to have a diagnosis of OA of the knee based on American College of Rheumatology (ACR) clinical criteria prior to inclusion into the trial. The target knee will need to be identified per inclusion criteria (exam, radiographs and pain scores). In addition, the subject must have an average score of ≥3.0 on the WOMAC pain subscale (0-10 numeric rating scale [NRS] 48-hour recall version) at Screening AND/OR a 24-hour *Average Pain Intensity* score of ≥3 on the 0-10 NRS and a Joint Stiffness Severity score ≥3 on a 0-10 NRS. If OA is present in both knees, the more painful knee will be considered the target knee. Subjects will receive accurate pain reporting training, and training on appropriate expectations for a clinical trial. Additionally, subjects must self-report that they have experienced knee stiffness at least 5-7 days per week over the past month as reported on the Baseline Stiffness Questionnaire.

Subjects will be instructed to discontinue use of all pain medications including supplements and topicals at the start of the Screening Washout phase (Day -4 to -1 +3 days) through trial completion, other than investigational medicinal product (IMP) or rescue medication provided by the study site. Subjects will choose a daily wake-up time to establish a dosing routine that will be entered in a diary. The range for wake-up hours must be between 5:00 am and 9:00 am. Subjects will need to commit to following a consistent wake-up routine for the duration of the trial.

Screening Washout Phase (Day -4 to Day -1+3 days)

Eligible subjects will start a minimum 4-day Screening Washout Phase. Subjects will be required to abstain from taking all pain medications, including topicals, and supplements during the entire 4-day Screening Washout Phase, with the exception noted below.

If needed, subjects can return to the study center up to 3 days after the completion of the Screening Washout Phase provided all current medication restrictions are maintained.

Subjects can take acetaminophen (up to 2000 mg/day) provided by the study site during this Screening Washout Phase, but not within 24 hours of the Randomization visit (Day 1 of Treatment Period 1). No other analgesic medications are permitted.

Start of Treatment Period X of 4 - Visit 2 (Day 1)

Subjects will return to the study center upon completion of the Screening Washout Phase or between-treatment Washout Period. To be eligible for randomization prior to Treatment Period 1, subjects must meet the following randomization criteria: self-reported average score of ≥4 on the WOMAC pain subscale (0-10 NRS, 48-hour recall version) related to OA pain in the target knee; current pain intensity score of ≥4 and ≤9 on the 0-10 NRS; and, a score of ≥4 on the 0-10 NRS for average pain over the past 24-hours. In addition, the Day 1 baseline post-STEPP current pain intensity 0-10 NRS score must be ≥5, and ≥1 unit higher than the pre-STEPP current pain intensity 0-10 NRS score.

Subjects who do not meet all the randomization criteria will be considered a Screening failure and will not be randomized into the study. Subjects who qualify will be asked additional questions related to knee pain, stiffness and function.

Randomized subjects will receive their treatment period specific investigational medicinal product (IMP) or treatment kit that includes study medication at the start of each treatment period. Randomization occurs only once during the start of the first treatment period.

Subjects will take their first dose of IMP from the treatment kit while at the study center and will undergo the STEPP periodically over the next 8 hours to induce knee pain. Subjects will complete pain assessments over 8 hours post-dose, take their afternoon (approximately 4 pm) dose after all assessments are complete, and then will be discharged from the study center. Following discharge from the study center, subjects will take the next two doses of IMP at home approximately as directed for a total of 4 doses on Day 1.

During the completion of Visit 2, subjects will be fitted with an accelerometer to measure the number of steps taken and level of activity (e.g., low, medium, high). Accelerometer data collection will start after completion of the Day 1 activities prior to leaving the study site.

Day 2 and Day 3

The morning following Day 1, subjects will continue with the same blinded treatment. On Day 2 and 3, subjects will be asked to complete the 24-hour BASS assessments and will then take their first (morning) dose of IMP. Subjects will continue to take their IMP as directed for a total of 4 doses per day. Subjects will continue to wear their accelerometer except when showering or bathing.

No rescue therapy will be allowed.

End of Treatment Period X of 4 - Visit 3 (Day 4)

Subjects will return to the study center wearing their accelerometer. They must bring their diary and treatment kit with remaining study medication. The accelerometer will be removed at the study site prior to the pre-dose STEPP. Subjects will complete pain, stiffness and function assessments. Subjects will then take their final remaining IMP morning dose in the (X of 4) treatment sequence. Subjects will undergo the STEPP to induce knee pain periodically over the next 8 hours. Subjects will complete pain assessments hourly over the 8 hours post-dose and then will be discharged from the study center to start the washout period.

Washout between Treatment Periods

Subjects will start a new Washout Period following the completion of Visit 3 (Day 4) of each Treatment Period (except Treatment Period 4). The Washout Period will last from 3 to 7 days after Visit 3. Subjects will not be allowed to take any pain medication not dispensed by the study center. Subjects can take acetaminophen (up to 2000 mg/day) provided by the study site during this Washout Period but not within 24 hours of Day 1 of the next Treatment Period. Subjects will be scheduled to return to the study center to start the next Treatment Period (X of 4) for Day 1, Visit 2.

End of Study (follow up) – after Visit 3, Treatment Period 4 of 4

Subjects will receive a follow up phone call to assess adverse events and document any new concomitant medications. Additionally, subjects will participate in a semi-structured qualitative interview about their experiences in the clinical trial. Upon completion of all trial procedures, subjects will be discharged from the study.

The duration of each subject's participation will be approximately 68 days. For an overview on the trial design and trial procedures see Figure 1.

5.2 Study Methodology

The study is a multi-center double-blind, randomized, crossover, placebo-controlled design with four treatment periods conducted in the United States. Approximately 3-5 sites will be utilized for recruitment.

5.3 Selection of Study Population - amendment 2

All male and female potential subjects 40 to 80 years of age with OA of the knee who would typically take OTC NSAIDs for pain relief may be eligible to participate in the study provided they meet inclusion/exclusion criteria.

Figure 1 – Design Overview - amendment 1 and 2

	Screening Phase	Screening Washout	Treatment Phase (4 arms)					Washout Phase	Follow up Phase
Trial days	**Screening Visit 1 Day -18 to -5**	**Day -4 to -1 (+3 d)**	**Start Treatment Period Visit 2 Day 1**			**Continue Treatment Day 2 & 3**	**End Treatment Period Visit 3 Day 4**	**Between Treatment Periods**	**End of Study**
	Accurate Pain Reporting Training Clinical Trial Expectations Training Baseline Stiffness Questionnaire WOMAC Pain WOMAC Stiffness WOMAC Function Stiffness Severity Question 24-hour average pain (0-10 NRS) STEPP test Regional Pain Scale	Washout before 1st IMP dose	Daily BASS WOMAC Pain ≥4 24-hour average pain ≥4 (0-10 NRS) Current pain ≥4 and ≤9 (0-10 NRS) Post STEPP pain ≥5 and ≥1 unit higher than pre-STEPP pain (0-10 NRS)	✱	WOMAC Stiffness WOMAC Function Daily BASS 1st IMP dose 🚶 ◈ 2nd , 3rd & 4th IMP dose Accelero-meter use after completion of study procedures	Daily BASS prior to 1st IMP dose IMP doses 2, 3 & 4 each day Accelerometer use	Daily BASS WOMAC Pain WOMAC Stiffness WOMAC Function Morning IMP dose 🚶 ◈ PGIC Treatment Preference[a]	3 to 7 days of washout needed before starting the next treatment in the sequence After washout, repeat Treatment Phase for the remaining treatment(s) in the sequence (X of 4)	7-10 days after completion of treatment period 4 of 4 Phone call Qualitative Interview[a]

✱ = Randomized to a 4 arm blinded treatment sequence (only for treatment 1 of 4)

🚶 = Staircase-Evoked Pain Procedure (STEPP) completed pre-dose, and then 2, 4, 6 and 8 hours post-dose

◈ = 0-10 point current pain NRS at pre-dose immediately before and 2-5 minutes after the STEPP, which is also completed at 2, 4, 6 and 8 hours post-dose. Additionally, hourly current pain intensity NRS at 1, 3, 5, and 7 hours post-dose when not completing the STEPP

[a] After Treatment period 4 of 4 or if the subject is withdrawn from the study prior to completion

Justification of the design

The pilot study was designed to capture pain and stiffness data in subjects who could benefit from the administration of an OTC pain reliever. OTC pain relievers are commonly used to treat the pain of OA. The STEPP pain model has been included in multiple studies of new and approved medications to treat pain due to OA of the knee, and is expected to increase treatment effects observed in this study. By including the STEPP in this study, standardized effect sizes can be assessed under short-term use conditions.

Accurate Pain Reporting Training

The Accurate Pain Reporting Program ("*Reporting Your Pain,*" Analgesic Solutions, Wayland, MA) consists of a set of subject and staff educational materials and instructions on how to accurately and reliably report pain scores, and on the proper use of pain intensity scales, with the aim of increasing subjects' pain reporting accuracy. Staff training is conducted prior to the first subject visit. Subjects receive training at the Screening Visit, and at on Day 1 of each of the four Treatment Periods. The training video takes approximately 30 minutes and should be completed prior to pain assessments.

Appropriate Expectations Training

This training ("*Participating in a Research Study, What you need to know,*" Analgesic Solutions, Wayland, MA) also consists of a set of subject and staff educational materials for training on appropriate expectations of personal benefit while participating in a clinical trial. The purpose is to provide subjects truthful information that will neutralize the typically excessive expectations that drive high placebo responses in clinical trials. Subjects receive training at the Screening Visit, and at on Day 1 of each of the four Treatment Periods. The training video takes approximately 30 minutes and should be completed prior to pain assessments.

6. Study population

6.1 Inclusion criteria - amendment 1 and 2

Those who inquire about the trial will be allowed to participate in the study if they meet the following eligibility criteria:

1. Signed Informed Consent;
2. Ambulatory (as deemed appropriate by the Investigator) male and female subjects between 40 and 80 years of age;
3. Body Mass Index (BMI) between 18 to <40 kg/m^2;
4. Unilateral or bilateral OA of the knee based on the American College of Rheumatology (ACR) clinical criteria: Knee pain plus at least 3 of the following:
    - age >50 years;
    - less than 30 minutes of morning stiffness;
    - crepitus on active motion and osteophytes;
    - bony tenderness;
    - bony enlargement;
    - no palpable warmth.
5. Have had diagnostic quality radiography of the target knee performed no more than 1 year prior to baseline showing evidence of OA with Kellgren and Lawrence grade of II or III (see Section 16.2);

    Note: X-ray of both knees should not be repeated if performed in the previous 12 months, the radiographs are of diagnostic quality and information is available to the investigator.
6. History of analgesic use for ≥4 days/week for past month and willing to discontinue use at least 4 days prior to randomization (low-dose [l00 mg or less] aspirin regimen permitted);
7. Joint Stiffness Severity score ≥3 on a 0-10 NRS at Screening;
8. Female subjects of childbearing potential must be using a medically acceptable form of birth control for at least 1 month prior to screening (or 3 months if using oral contraceptives) [e.g., hormonal contraceptives (oral, patch, injectable or vaginal ring), implantable device (implantable rod or intrauterine device), or a double barrier], or in same sex relationship and have a negative pregnancy test at Screening and prior to study drug administration. Female subjects of non-childbearing potential must be amenorrheic for at least two years or have undergone surgical sterilization (e.g., hysterectomy and/or bilateral oophorectomy);
9. Willing to wear an accelerometer during each Treatment Period of the Treatment Phase. Subjects who decline to wear the accelerometer are still eligible for study participation provided they meet all other required criteria.

For Randomization:

10. 48-hour WOMAC pain subscale average score ≥3.0 and/or 24-hour Average Pain Intensity score ≥3 on the 0-10 NRS at Screening;

11. 48-hour WOMAC pain subscale average score ≥4.0 at Visit 2, Treatment Period 1 of 4;
12. 24-hour *Average Pain Intensity* score ≥4 at Visit 2, Treatment Period 1 of 4;
13. Current pain intensity score ≥4 and ≤9 on the 0-10 NRS at Visit 2, Treatment Period 1 of 4;
14. A Day 1 baseline post-STEPP current pain intensity score ≥5, and ≥1 unit higher than the pre-STEPP current pain score on the 0-10 NRS;
15. Experience knee stiffness at least 5-7 days per week over the past month as reported on the Baseline Stiffness Questionnaire at the Screening Visit.

6.2 Exclusion criteria - amendment 1

Subjects presenting with any of the following will not be included in the trial:

1. History of underlying inflammatory arthropathy, rheumatoid arthritis or fibromyalgia;
2. History of or scheduled for knee replacement surgery (in the target knee) within the next 6 months at screening;
3. Recent injury in the OA affected knee (past 4 months); oral, intra-muscular, intravenous or intra-articular corticosteroid, platelet rich plasma intraarticular knee injections, stem cell therapy or hyaluronic acid injections in either knee within the last 3 months;
4. Subject reports moderate or severe (score of 2 or 3) pain or tenderness on the 0-3 Regional Pain Scale for any joint or body area other than the target knee and, in the Investigator's opinion, the subject is not able to distinguish pain in the target knee from other painful areas;
5. Use of any pain medications from the start of the Screening/Washout Phase through trial completion, other than IMP provided by the Sponsor or Rescue Pain medication provided by the study site;
6. Subject who takes an opioid ≥4 days per week over the past 4 weeks;
7. Subject is taking more than one antidepressant. Subjects who are on a stable dose of one antidepressant, for at least 1 month, are eligible for enrollment;
8. Subject is taking more than one anxiolytic medication. Subjects who are on a stable regimen of one anxiolytic for at least 1 month, are eligible for enrollment;
9. Initiating any new physical therapy for the lower extremities from 4 weeks prior to study start through the duration of the study;
10. Positive urine drug test for illegal drug substances, non-prescribed controlled substances, or breath/saliva alcohol at screening or Visit 2;

    Note: prescribed marijuana is allowed provided the subject is willing to wash out and not use during the study.
11. Subject has an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2 times the upper limit of normal;
12. Subject has a hemoglobin <10.0 g/dL;
13. Subject has an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2;
14. Subject is breast feeding or has a positive pregnancy test at screening or Visit 2;

15. Kellgren and Lawrence grade of 0, I or IV in the target knee (see Section 16.2);
16. Subjects with a medical disorder, condition or history of such that could impair the subject's ability to participate or complete this trial in the opinion of the investigator;
17. History of hypersensitivity (including but not limited to anaphylactic reactions and serious skin reactions) to naproxen sodium, celecoxib, acetaminophen, NSAIDS, aspirin, similar pharmacological agents or components of the investigational products
18. History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs.
19. History of allergic-type reactions to sulfonamides;
20. Current or past history of gastrointestinal bleeding or other bleeding disorder(s);
21. Prior history of peptic ulcer disease and/or gastro-intestinal bleeding;
22. Evidence or history of clinically significant (in the judgment of the investigator) hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic diseases, or malignancies within the last 5 years that makes the subject unfit to participate in the trial;
23. Recent (within the past 1 year) MI or in the peri-operative period surrounding coronary artery bypass graft (CABG) surgery;
24. Heart failure, advanced renal disease or advanced hepatic disease;
25. Current participation in any other trials involving investigational or marketed products within 30 days prior to the Screening Visit;
26. Inability to report pain accurately as assessed at Screening;
27. Unwilling or unable to comply with all requirements outlined in the protocol;
28. Member or relative of study staff or the Sponsor directly involved in the study.

In addition to the above stated inclusion/exclusion criteria and restrictions, subject selection in this study is to be made consistent with all the warnings, precautions, and contraindications associated with the use of Aleve®, CCI [redacted] 8 HR Arthritis Pain and celecoxib. The Investigator should review and be familiar with the information available on these marketed products and the information in the package label.

6.3 Justification of selection criteria

The selection criteria are chosen to ensure that subjects with specific risks for administration of the study medication and/or subjects with conditions which may have an impact on the safety of the subject or data integrity during their participation in the study are excluded.

6.4 Withdrawal of subjects from study

6.4.1 Withdrawal

Withdrawal criteria

Subjects *must* be withdrawn from the study if any of the following occurs:

- At their own request or at the request of their legally acceptable representative. At any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.

Subjects *may* be withdrawn from the study if any of the following occurs:

- Serious adverse events;
- If, in the Investigator's opinion, continuation of the study would be harmful to the subject's well-being;
- At the specific request of the Sponsor and in liaison with the Investigator (e.g., obvious non-compliance, safety concerns);
- Protocol violation: if the subject develops conditions which would have prevented entry into the study according to the inclusion/exclusion criteria, the subject must be withdrawn immediately if safety is concerned; in other cases, the investigator will decide whether there is a conflict with the study objectives

Depending on the time point of withdrawal, a withdrawn subject is referred to as either a "*screening failure*" or "*dropout*" as specified below:

Screening failure

A subject who, for any reason (e.g., failure to satisfy the selection criteria), terminates the study prior to randomization is regarded as a "screening failure".

Re-starting the defined set of screening procedures (re-screening) to enable the "screening failure" subject's participation at a later time point is not allowed – with the following exceptions:

- The subject had successfully passed the screening procedures, but could not start subsequent treatment on schedule.
- Initial screening occurred too early to complete the required washout period after prior therapy.
- The in- / exclusion criteria preventing the subject's initial attempt to participate have been changed (via protocol amendment).

- Other situations where the subject had to withdraw consent due to "life circumstances" though they otherwise qualified. These situations will be considered on a case by case basis by the sponsor or sponsor representative in consultation with the investigator.

In any case, the investigator has to ensure that the repeated screening procedures do not expose the subject to an unjustifiable health risk. Also, for re-screening, the subject has to re-sign the informed consent form, even if it was not changed after the subject's previous screening.

Dropout

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject has been randomized and administered at least one dose of study drug.

General procedures

In all cases, the reason for withdrawal must be recorded in the case report form/electronic case report form (CRF/eCRF) data collection system and progress noted in the subject's medical records.

The subject may object to the generation and processing of post-withdrawal data as specified in Section 13.4.

Details for the premature termination of the study as a whole (or components thereof) are provided in Section 12 (Premature termination of the Study).

6.4.2 Replacement

Subjects who prematurely discontinue participation after randomization will not be replaced.

6.5 Subject identification

Each subject is identified by the study site's unique subject identification code. After informed consent procedure every subject is given a screening number (SNR). At the time point of randomization, subjects who meet the entry criteria will be sequentially assigned to a four-digit number in ascending order (randomization number, RNR). See Section 7.3.

7. Treatment(s)

The study center will dispense a blinded treatment sequence after successfully completing screening and baseline assessments. The overencapsulated tablets or capsules (IMP) for each treatment sequence will be dispensed using a computer generated randomization schedule.

7.1 Treatments to be administered - amendment 1

The treatments to be administered during the study are displayed in Sections 7.1 and 7.2.

Table 1: Treatments administered

	Dose Time	Treatment A Naproxen	Treatment B Acetaminophen	Treatment C Celecoxib	Treatment D Placebo
Day 1 Visit 2	8 AM	440 mg	1300 mg	100 mg	Placebo
	4 PM	Placebo	1300 mg	Placebo	Placebo
	8 PM	220 mg	Placebo	100 mg	Placebo
	12 AM	Placebo	1300 mg	Placebo	Placebo
Day 2 At home	8 AM	440 mg	1300 mg	100 mg	Placebo
	4 PM	Placebo	1300 mg	Placebo	Placebo
	8 PM	220 mg	Placebo	100 mg	Placebo
	12 AM	Placebo	1300 mg	Placebo	Placebo
Day 3 At home	8 AM	440 mg	1300 mg	100 mg	Placebo
	4 PM	Placebo	1300 mg	Placebo	Placebo
	8 PM	220 mg	Placebo	100 mg	Placebo
	12 AM	Placebo	1300 mg	Placebo	Placebo
Day 4 Visit 3	8 AM	440 mg	1300 mg	100 mg	Placebo

Subjects will receive study medication 4 times per day on Days 1-3 and one dose of study medication on Day 4. Doses will be administered at approximately 8 AM, 4 PM, 8 PM and 12 AM (midnight) on Days 1-3 with a dosing window of ± 1 hour. At time points when an active treatment is not called for, subjects will receive placebo to ensure that the study can remain blinded.

Note: Number of doses per day are approximate based on subject's dosing times provided the subject doses within the window for each listed time, they will be considered to have met protocol requriements.

7.2 Identity of study treatment

Table 2: Study treatments

Treatment	Treatment A	Treatment B	Treatment C	Treatment D
Dose	Naproxen sodium 660 mg/day	Acetaminophen ER 3900 mg/day	Celecoxib 200 mg/day	Placebo
Pharmaceutical Form	over-encapsulated tablet	over-encapsulated tablet	over-encapsulated capsule	NA
Strength	220 mg	650 mg	100 mg	NA
Formulation	naproxen sodium FD&C blue #2 lake hypromellose magnesium stearate microcrystalline cellulose polyethylene glycol povidone talc titanium dioxide ═══ Swedish orange opaque DBcaps® size AA-el capsules* micro crystalline cellulose*	acetaminophen carnauba wax corn starch hydroxyethyl cellulose hypromellose magnesium stearate microcrystalline cellulose povidone powdered cellulose pre-gelatinized starch sodium starch glycolate titanium dioxide triacetin ═══ Swedish orange opaque DBcaps® size AA-el capsules* micro crystalline cellulose*	celecoxib lactose monohydrate sodium lauryl sulfate povidone croscarmellose sodium magnesium stearate gelatin edible inks ═══ Swedish orange opaque DBcaps® size AA-el capsules* micro crystalline cellulose*	dibasic calcium phosphate dihydrate magnesium stearate ═══ Swedish orange opaque DBcaps® size AA-el capsules* micro crystalline cellulose*
Route of administration / Dosing instructions	orally with a full glass of water	orally with a full glass of water	orally with a full glass of water	orally with a full glass of water
Batch Number	available in the study file	available in the study file	available in the study file	available in the study file
Manufacturer	Bayer Bitterfeld, Germany	Johnson & Johnson Consumer Inc. Fort Washington, PA USA	Greenstone Pepack, NJ USA	Bayer Morristown, NJ USA

*components of the over-encapsulation and filler material.

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.

7.3 Treatment assignment - amendment 1

At the beginning of the first treatment period, 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:

14001XXXX

Whereas the "Xs" will be replaced with a four digit sequentially assigned number as each subject enters the study (e.g., first subject number 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 inclusion and exclusion criteria, subjects enter the Treatment Phase and are randomized into one of four blinded treatment sequences using a Williams design to ensure a balanced stratification. See example below:

A B D C
B C A D
C D B A
D A C B

- Treatment A: Naproxen sodium 660 mg (three tablets of naproxen sodium 220 mg and five tablets of placebo daily); On Days 1, 2 and 3, first dose of two tablets of naproxen in the morning at 8:00 AM ± 1 hour followed by two tablets of placebo 8 hours later at 4:00 PM ± 1 hour, followed by one tablet of naproxen and one tablet of placebo 4 hours later at 8 PM ± 1 hour, followed by two tablets of placebo 4 hours later at 12 AM ± 1 hour;

- Treatment B: Acetaminophen 3900 mg (six tablets of acetaminophen 650 mg and two tablets of placebo daily); On Days 1, 2 and 3, first dose of two tablets of acetaminophen in the morning at 8:00 am ± 1 hour followed by two tablets of acetaminophen 8 hours later at 4:00 PM ± 1 hour followed by two tablets of placebo 4 hours later at 8 PM ± 1 hour followed by two tablets of acetaminophen 8 hours later at 12 AM ± 1 hour;

- Treatment C: Celecoxib 200 mg (two capsules of celecoxib 100 mg and six tablets of placebo daily); On Days 1, 2 and 3, first dose of one capsule of celecoxib and one tablet of placebo in the morning at 8:00 am ± 1 hour followed by two tablets of placebo 8 hours later at 4:00 PM ± 1 hour followed by one capsule of celecoxib and one tablet of placebo 8 hours later at 8:00 PM ± 1 hour 1 followed by two tablets of placebo 8 hours later at 12 AM ± 1 hour;

- Treatment D: Placebo (eight tablets of placebo daily); On Days 1, 2 and 3, first dose of two tablets of placebo in the morning at 8:00 AM ± 1 hour followed by two tablets of

placebo 8 hours later at 4:00 PM ± 1 hour followed by two tablets of placebo 4 hours later at 8 PM ± 1 hour followed by two tablets of placebo 8 hours later at 12AM ± 1 hour.

Note: The Day 4 treatment is a single morning (8 AM) two tablet/capsule dose similar to the morning dosing for Days 1-3.

7.4 Dosage and administration

Subjects will follow the dosing schedule as outlined in Section 7.1. The blister package will be blinded to the specific treatments in the sequence. All subjects will randomly receive one drug treatment (A, B, C or D) during each dosing period. Depending upon which treatment in the sequence, they could be taking naproxen sodium, acetaminophen, celecoxib or placebo. Subjects will administer the drug with a full glass of non-refrigerated, non-carbonated water (about 8 ounces or 240 mL).

The subject will bring their dosing blister package CCI with them to each visit. The CCI blister electronically records the date and time when the subjects depresses the blister to take a dose of IMP. The study center will download and review the dosing data from the CCI blister package for compliance. Any deviations related to dosing outside of the allowable window (± 1 hour) will be documented in the subject's medical record. The study center will counsel all subjects with dosing window deviations.

7.5 Blinding

7.5.1 Blinding measures

Subjects enrolled in the trial, investigators and their staff involved in protocol procedures or data collection analysis will be blinded to the identity of the treatment sequence. The study monitor will conduct product accountability during and after database lock. To preserve the blinding, all investigational products will be over encapsulated and prepackaged according to the randomization schedule.

7.5.2 Unblinding

In the case of a medical emergency, such as serious adverse events (SAE), breaking the blind may become necessary during the trial. Randomization code-break envelopes are securely maintained at the trial site and with the Sponsor.

In compliance with applicable regulations, in the event of a SUSAR related to the blinded treatment, the subject's treatment code will usually be unblinded before reporting to the health authorities, ethic committees and investigators (see Section 9.6.1.4).

7.5.3 Emergency unblinding by the investigator

The investigator will be provided code-break envelopes that can be used to break the blinding of the study drug. Any subject who was unblinded using the code-break envelopes must have the occurrence documented in the subject's medical record. The investigator should notify the sponsor or sponsor medical monitor prior to unblinding if at all possible unless a delay in doing so will deleteriously affect the subject's well being. The investigator must report the

blind break in conjunction with a SAE as defined in Section 9.6.1. Subjects that have been unblinded will not be included in the ITT or PP efficacy analysis.

The Sponsor will collect all code-break envelopes at the end of the study.

7.6 Drug logistics and accountability - amendment 1

The Sponsor will provide sufficient quantity of the investigational medicinal product (IMP) to the study site. All study centers will dispense IMP according to the computer generated randomization schedule.

All study drugs will be stored at the investigational site in accordance with GCP requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate/CRO), and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the Sponsor's study file; the site-relevant elements of this information will be available in the investigator site file. On the day of receipt, the responsible site personnel will confirm receipt of study investigational products in writing. The personnel will use the study investigational products only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study drug must be properly documented according to the sponsor's agreed and specified procedures.

7.7 Treatment compliance

The distribution of the study medication will be supervised by a member of the Investigator's team. Subjects not at the study center will administer IMP at their pre-determined dose time. Dosing performed at the study center will be monitored by the study staff. The study center will monitor used and unused IMP for compliance. Any discrepancies between actual and expected amount of returned study medication must be discussed with the subject at the time of the visit, and any explanation must be documented in the source records.

8. Non-study therapy

8.1 Prior and concomitant therapy - amendment 1

The following treatments are prohibited:

- Use of any pain medications from the start of the Screening Washout Phase through trial completion, other than IMP provided by the Sponsor and rescue pain medication provided by the study site This includes medications such as gabapentin, cannabidiol etc. if prescribed to the subject for the purpose of pain control;
- Taking more than one antidepressant. Subjects who are on a stable dose of one antidepressant, for at least 1 month, are eligible for enrollment;
- Taking more than one anxiolytic medication. Subjects who are on a stable regimen of one anxiolytic for at least 1 month, are eligible for enrollment;
- Fish oil (supplements are permitted if the dose is stable for at least 4 weeks).

From 4 days prior to randomization until the completion of the Treatment Phase (Treatment Period 4 of 4), subjects are not allowed to take pain treatments (including supplements and/or topicals) other than the provided trial treatment (IMP and rescue therapy). Prohibited treatements include:

- Topical capsaicin, NSAIDs, lidocaine, and cannabidiol oil;
- Glucosamine-chondroitin and turmeric (curcumin);
- Supplements intended for pain relief.

If the subject uses an excluded/prohibited medication (analgesic or other medication) after being enrolled into the study, the investigator will use his/her judgement to determine whether the subject is able to continue however, the subject must be discontinued if safety is concerned. In other cases, the subject may be able to continue if the concomitant medication is for short term use and/or is not likely to conflict with the study objectives in subsequent Treatment Periods.

All medications (prescription and nonprescription products, vitamin and herbal products) taken by the subject from 30 days prior to Screening to End of Study (Follow up phone call) will be documented. The reported medications will be reviewed and evaluated by the Principal Investigator or designee to determine if they affect the subject's eligibility to participate in the study.

8.2 Post-study therapy

This a blinded four period, four treatment crossover study for subjects with knee pain due to OA and therefore no additional treatment after the 4th treatment period (treatment period 4 of 4) will be allocated. Subjects will be discharged upon their completion of Follow up phone call.

9. Procedures and variables

9.1 Tabular schedule of evaluations

See flow chart in Section 16.1

Regarding protocol deviations, the processes and responsibilities defined by the Sponsor will be followed. Respective details (e.g., identification and classification of protocol deviations) are described separately.

9.2 Visit description

If not stated otherwise, the measures / actions listed in the following Sections 9.2.1 to 9.2.8 will be performed by or under the supervision of the investigator.

9.2.1 Screening Phase Visit 1 (Day -18 to -5) - amendment 1 and 2

At the Screening visit, the Principal Investigator or appropriate designee will discuss with each subject the nature of the trial, its requirements and its restrictions. Written informed consent will be obtained prior to performance of any protocol-specific procedures.

The Screening Phase will be up to 14 days long. The following will be conducted during the Screening Visit:

- Signed Informed Consent;
- Review Inclusion and Exclusion Criteria;
- Subject demographics;
- Medical history;
- Medication history of all prescription and over-the-counter drugs and other products (including topicals, herbal products, vitamins and nutritional supplements) and investigational drugs, taken within 30 days prior to screening;
- Alcohol breath/saliva test;
- Urine drug screen;
- Urine pregnancy test for female subjects of child bearing potential;
- Blood and urine specimens for safety laboratory tests (hematology, chemistry and urinalysis);
- History of drug, alcohol and tobacco use;
- Height, weight, and Body Mass Index (BMI);
- Physical examination;
- OA assessment of each potentially qualifying knee using ACR criteria;
- Radiograph of each potentially qualifying knee (anteroposterior [AP] or posteroanterior [PA] and lateral projections);
  Note: A historical knee radiograph could be used provided the images were taken within the previous 1 year and can be digitally exported to a central reading lab and are of diagnostic quality.
- Baseline Stiffness Questionnaire of each knee;
- Joint Stiffness Severity rating of each knee;
- Regional Pain Scale (13);
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature after 5 minutes in a sitting position);

- Accurate Pain Reporting Training;
- Appropriate Expectations Training;
- 48-hour recall WOMAC subscales for stiffness, physical function and pain questionnaire to establish the target knee;
- 24-hour *Average Pain Intensity* on 0-10 NRS;
- STEPP test with pre- and post- current pain intensity NRS (confirm understanding and ability to perform the exercise);
- Discuss the procedure to report adverse events;
- Schedule Visit 2 (eligible subjects only).

To qualify for randomization (Day 1), subjects must have an average score ≥3.0 on the 48-hour WOMAC pain subscale AND/OR score ≥3.0 on the 24-hour Average Pain Intensity Scale.

The Principal Investigator or his/her designee must review all screening results before proceeding to the Baseline phase of the study. This includes the radiographic interpretation of the knee radiographs using the Kellgren and Lawrence scale as well as safety laboratory values. Subjects will be reminded once screening criteria have been met, to discontinue use of all pain medications, including topicals, and supplements until they return for Visit 2. Subjects can take acetaminophen (up to 2000 mg/day), for knee pain but not within 24 hours of the Randomization visit. The rescue therapy will be provided by the study site. Subjects will record a diary entry with the day and time of each dose of rescue analgesic used.

An external centralized vendor chosen by the sponsor will read/ interpret the knee radiographs and communicate the findings to the study center. Subjects that do not meet qualification after leaving the test site at Visit 1, will not be required to return their paper diary.

9.2.2 Screening Washout Phase (Day -4 to Day -1 +3 days)

Eligible subjects will abstain from taking <u>any</u> pain medications, including topicals, and supplements during the Screening Washout Phase, except acetaminophen as noted below. This is necessary so that subjects can accurately document their untreated baseline pain and stiffness prior to treatment randomization. If needed, subjects can take acetaminophen (up to 2000 mg/day) during the Screening Washout Phase, but not within 24 hours of the Randomization visit.

Subjects can return to the study center <u>up to 3 days after the 4th day</u> of the Screening Washout Phase provided medication restrictions are maintained. The study center will contact the subject to remind them of their Visit 2 appointment.

9.2.3 Visit 2 (Day 1, Start Treatment Period) - amendment 1 and 2

Visit 2 will occur 4 to 7 days after starting the Screening Washout Phase (within 21 days of the initial screening visit). The following activities will be completed:

- Review inclusion and exclusion criteria;
- Concomitant medication review;
- Review changes in the subject's medical/medication history since previous visit;
- Vital signs (blood pressure and heart rate after 5 minutes in a sitting position);
- Accurate Pain Reporting Training;

- Appropriate Expectations Training;
- Alcohol breath/saliva test;
- Urine drug screen;
- Urine pregnancy test for female subjects of child bearing potential;
- 48-hour recall WOMAC (0-10 NRS version) subscales for stiffness, physical function and pain questionnaires;
- 24-hour *Average Pain Intensity* assessment (0-10 NRS);
- Daily BASS assessment;
- Adverse Event assessment;
- Subjects will report the current pain intensity for their target knee on the 0-10 NRS;
- Immediately thereafter, subjects will perform the STEPP pre-dose (time 0). Subjects will report the current pain intensity for their target knee on the 0-10 NRS 2-5 minutes after performance of the STEPP.

Randomization Criteria:
Subjects must self-report the following pain ratings in order to be randomized and start Treatment Period 1 of 4:

- An average score of ≥4.0 on WOMAC pain subscale summation score (0-10 NRS, 48-hour recall version);
- 24-hour *Average Pain Intensity* score of ≥4 on the 0-10 NRS;
- Current pain intensity score of ≥4 and ≤9 on the 0-10 NRS;
- Day 1 baseline post -STEPP current pain intensity score ≥5 and ≥1 unit higher than the pre-STEPP current pain intensity score on the 0-10 NRS.

Subjects who do not meet all of the randomization criteria will not be randomized. Upon successful completion of all remaining inclusion and exclusion criteria, subjects enter the Treatment Phase and are randomized into one of four blinded treatment sequences (see Section 7.3).

Subjects will perform the STEPP pre-dose (time 0) and at 2, 4, 6 and 8 hours post-dose. Subjects will report the current pain intensity for their target knee on the 0-10 NRS immediately before and 2-5 minutes after each performance of the STEPP.

In addition, subjects will self-report the current pain intensity of their target knee on the 0-10 NRS at post-dose hours 1, 3, 5, and 7.

Subjects will take their first (morning) dose at the direction of the study staff. Their second dose in the afternoon of Day 1 will be taken after completing all of the hour 8 activities and prior to leaving the study site. Their 3rd dose in the evening and their 4th dose in the late evening (around midnight) will be taken at home. Subjects will be reminded of their selected wake up time and encouraged to keep this schedule for the duration of the trial. Subjects will be fitted with an accelerometer on their lower leg (ankle) area on Day 1, directly after completion of the 8 hour activities. Subjects will wear the accelerometer at the completion of the clinic visit. Subjects will be trained to wear the accelerometer during the treatment periods. Subjects will be scheduled for Visit 3 and reminded to bring their diary, treatment kit for review and wear their accelerometer which will be removed at the study site prior to performing any study related procedures.

Note: subjects will wear the accelerometer on the ankle for Days 1 (at the conclusion of the clinic visit), 2 and 3 of each Treatment Period without removal except when showering or bathing. The accelerometer cannot be used in conjunction with any swimming or watersport activity. The accelerometer may be removed for sleep. The subject may request to use the opposite ankle for placement of the accelerometer during the trial.

9.2.4 Day 2 and 3 (Continue Treatment Period) - amendment 1

Subjects will rate their knee joint stiffness using the Daily BASS assessments in their diary before taking their first (approximately 8 AM) dose of two capsules or tablets. Subjects will follow the dosing instructions provided for the remaining doses to be taken each day. Subjects will continue to wear their accelerometer as instructed.

Subjects cannot use any rescue therapy at this time.

9.2.5 Visit 3 (Day 4, End of Treatment Period X of 4) - amendment 1 and 2

Subjects will return to the study center (wearing their accelerometer) for final assessments of the Treatment Period (X of 4). Subjects must take the morning (approximately 8 AM) dose of study medication at the study center. The following activities will be performed prior to dosing:

- Review inclusion and exclusion criteria;
- Concomitant medication review;
- Remove accelerometer from subject (prior to pre-dose STEPP);
- Accelerometer data download and battery charging (~1 hour);
- Vital signs (blood pressure, heart rate, after 5 minutes in a sitting position);
- Daily BASS assessment;
- 24-hour *Average Pain Intensity* on 0-10 NRS assessment;
- Current pain intensity on 0-10 NRS (immediately prior to the pre-dose STEPP);
- 48-hour recall WOMAC (0-10 NRS version) subscales for stiffness, physical function and pain questionnaires; Adverse Event assessment.

Subjects will perform the STEPP pre-dose (time 0) and at 2, 4, 6 and 8 hours post-dose. Subjects will report the current pain intensity for their target knee on the 0-10 NRS immediately before and 2-5 minutes after each performance of the STEPP.

In addition, subjects will self-report the current pain intensity of their target knee on the 0-10 NRS at post-dose hours 1, 3, 5, and 7.

- Approximately 8 hours after dosing, prior to leaving the study center on Day 4 of each Treatment Period, subjects will complete two Patient Global Impression of Change (PGIC) scales: the PGIC for OA Pain, and the PGIC for OA Symptoms

Upon completion of data download and re-charge (~1 hour), the accelerometer will be stored at the clinic until the next Visit 2 of the next Treatment Period occurs.

9.2.6 Washout between Treatment Periods (3 to 7 days after Visit 3)

After the completion of Visit 3, subjects will start a new Washout Period of at least 3 days before returning to the study center for their next Visit 2 (i.e., the start of the next Treatment

Period). The use of rescue therapy (up to 2000 mg of acetaminophen per day) provided by the study site is allowed, but not within 24 hours of returning to the study center for the start of the next Treatment Period.
Subjects are required to return to the study site to start the next treatment in the sequence provided at randomization. Subjects will repeat the ***Treatment Period*** of study until all 4 blinded treatments have been dosed. Subjects will follow the treatment sequence in numeric order (1 of 4, 2 of 4, 3 of 4 and 4 of 4) and not deviate in order.

9.2.7 Visit 3 (Day 4, End of Treatment Period 4 of 4)

Subjects will complete the Treatment Preference rating and the accelerometer will be removed from the subject and the data downloaded.

9.2.8 End of Study (7 to 10 days after Visit 3, Treatment Period 4 of 4)

At the completion of the final treatment/visit in the sequence (4 of 4) or if the subject withdraws prior to the last treatment visit, subjects will receive a phone call from the study site to review concomitant medications and assess adverse events. Additionally, subjects will participate in a semi-structured qualitative interview about their experiences in the clinical trial (see Section 16.2).

9.2.9 Rescue therapy

Rescue analgesic therapy will be available for subjects during the Screening Washout Phase and washout between Treatment Periods. The Study Site will provide subjects with acetaminophen 500 mg tablets. The total daily dosage must not exceed 2000 mg. Rescue therapy is **not allowed** 24 hours prior to Day 1 pre-treatment assessments and it is not allowed from Day 1 through Day 4 assessments of each Treatment Period.

The amount of rescue therapy dispensed will be recorded. Subjects will record the amount and date and time of all rescue therapy doses used in their diary. At the start of all Treatment Periods, subjects will return all unused rescue therapy and the study center will account for the amount used against the subject's record.

Subjects will be queried in a nonspecific fashion for any adverse events (e.g., "Have you had any changes in health?"). Any reported AEs will be collected and recorded on the CRF/e-CRF data collection system. The information recorded will be based on signs and symptoms reported by the subject or observed by the research coordinator during the clinical evaluation.

9.3 Population characteristics

9.3.1 Demographic

For basic subject assessment prior to screening, some demographic information may be collected before obtaining written informed consent:

- Year of birth (approximate age);
- Native language.

Collection of demographic information is subject to all applicable local regulations.

9.3.2 Medical history

Medical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected as available to the investigator:

- Start before signing of the informed consent;
- Considered relevant for the subject's study eligibility.

Detailed instructions on the differentiation between (i) medical history and (ii) adverse events can be found in Section 9.6.1.1.

9.3.3 Other baseline characteristics

Information on smoking (including e-cigarettes), as well as drug and alcohol consumption will be collected.

9.4 Efficacy analysis

CCI

[redacted]

9.4.1 Primary efficacy endpoint

All efficacy analyses will be based on the PP population.

- Sum of change from baseline (Day 1 of the Treatment Period) in BASS score over the 4 day treatment period.

9.4.2 Secondary efficacy endpoints

The secondary efficacy endpoints related to the primary objective include:

- Absolute BASS score at each time point.
- Day 4 change from baseline (Day 1 of the treatment period) in BASS score.

Note: Key pairwise comparisons of absolute BASS score and change from baseline BASS score will be assessed, including, but not limited to: naproxen versus placebo, celecoxib versus placebo, acetaminophen versus placebo, naproxen versus acetaminophen and naproxen versus celecoxib.

9.4.3 Exploratory efficacy endpoints - amendment 1 and 2

- Day 1 and Day 4 post-STEPP sum of pain intensity difference (SPID) at 4, 6, and 8 hours post-dose, based on 0-10 NRS;
- Day 1 and Day 4 post-STEPP sum of pain intensity (SPI) at 4, 6, and 8 hours post-dose, based on 0-10 NRS;
- Day 1 and Day 4 post-STEPP pain intensity difference (PID) from baseline at 2, 4, 6 and 8 hours post-dose, based on 0-10 NRS;

- Day 1 and Day 4 post-STEPP pain intensity (PI) at 2, 4, 6, and 8 hours post-dose, based on 0-10 NRS;
- Current hourly PI using the 0–10 NRS pre-dose, and from 1 to 8 hours post-dose;
- Mean change from baseline (Day 1 of the Treatment Period) to end of Treatment Period on the Western Ontario and McMaster Universities Arthritis (WOMAC) pain subscale, 48-hour recall version, assessed on Day 1 and Day 4, including an assessment of all key pairwise comparisons;
- Mean change from baseline to end of treatment period on WOMAC stiffness subscale, 48-hour recall version, assessed on Day 1 and Day 4, including an assessment of all key pairwise comparisons;
- Absolute WOMAC stiffness subscale scores, 48-hour recall version, for each study treatment at each time point;
- Physical activity level outcomes during Days 1 (partial), 2 and 3 as measured by the accelerometer;
- Change from baseline to end of treatment period on WOMAC function subscale, 48-hour recall version, assessed on Day 1 and Day 4, including an assessment of all key pairwise comparisons;
- Patient Global Impression of Change (PGIC) on Day 4 of each Treatment Period, including PGIC for OA Pain (PGIC-P) and PGIC for OA Symptoms (PGIC-S);
- Subject preference for treatment assessed at the end of the study;
- Qualitative (semi-structured) interview to assess subjects' experience with treatments, and experience with the STEPP, relevance to their disease status, how to improve it, etc. (see Section 16.2).

9.4.4 Safety analysis - amendment 1

The following laboratory tests will be performed at screening:

- Hematology (Hemoglobin, Hematocrit, RBC count, Platelet count, WBC count),
- Serum Chemistry (BUN, Creatinine, Glucose, Ca++, Na+, K+, Cl-, Total CO2 (Bicarbonate), AST, ALT, Total Bilirubin, Alkaline phosphatase, Albumin, Total protein)
- Urinalysis (Specific gravity, pH, Glucose (qual), Protein (qual), Blood (qual), Ketones, Leukocyte Esterase, Nitrite, Bilirubin, Urobilinogen)

Adverse events will be collected throughout the treatment and safety follow-up periods and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Only treatment-emergent AEs will be included, i.e., AEs that begin or worsen after the first dose of the investigational products in the Treatment Phase. The number and percent of subjects who experience any event, by System Organ Class (SOC), and by Preferred Term will be displayed by treatment group. Tables will also be produced by severity and relationship to investigational product. Seriousness, severity, relationship to investigational product, duration, and outcome will also be listed.

9.5 Pharmacokinetics / pharmacodynamics

Not applicable

9.5.1 Pharmacodynamics

Not applicable

9.6 Safety

9.6.1 Adverse events

9.6.1.1 Definitions

Definition of adverse event (AE)

In a clinical study, an AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the subject should not be recorded as an AE (however, the condition for which the surgery is required may be an AE).

In the following differentiation between medical history and AEs, the term "condition" may include abnormal e.g., physical examination findings, symptoms, diseases.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g., seasonal allergy without acute complaints);
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at *unchanged intensity*, are recorded as medical history (e.g., allergic pollinosis);
- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events. This includes intercurrent illnesses.

Definition of serious adverse event (SAE)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death

b. Is life-threatening

   The term 'life-threatening' in the definition refers to an event in which the subject 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

A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours
- The admission is pre-planned
  (e.g., elective or scheduled surgery arranged prior to the start of the study; admission is part of the study procedures as described in Section 9.2)
- The admission is not associated with an AE
  (e.g., social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

e. Is a congenital anomaly / birth defect

f. Is another serious or important medical event as judged by the investigator

9.6.1.2 Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

9.6.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 9.6.1.1.

9.6.1.2.2 Intensity

The intensity of an AE is classified according to the following categories:

- Mild: Presents with signs and symptoms easily tolerated, does not need treatment, or prolonged hospitalization and does not necessarily require stopping the drug;
- Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant;
- Severe: A type of adverse event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects clinical status. The event possesses a significant risk of harm to the research participant and hospitalization may be required.

9.6.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a decision to be made by the investigator, who is a qualified physician, based on all information available at the time of the completion of the CRF/eCRF data collection system.

The assessment is based on the question whether there was a “reasonable causal relationship” to the study treatment in question.

Possible answers are “yes” or “no”

An assessment of “no” would include:

1. The existence of a highly likely alternative explanation, e.g., mechanical bleeding at surgical site.

or

2. Non-plausibility, e.g., the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of “yes” indicates that that the AE is reasonably associated with the use of the study treatment.

Important factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge): Subject’s response after de-challenge or re-challenge should be considered in view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment:
  The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might have caused the event in question.

- Known response pattern for this class of drug: Clinical/preclinical
- Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event
- The pharmacology and pharmacokinetics of the study treatment:
  The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject's pharmacodynamics should be considered.
- The assessment is not possible

Causal relationship to protocol-required procedure(s)

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a "reasonable causal relationship" to protocol-required procedure(s).

Possible answers are "yes" or "no"

9.6.1.2.4 Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

The study treatment action should be recorded separately for each study treatment as detailed in the CRF/eCRF data collection system.

- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Dose increased
- Not applicable
- Unknown

9.6.1.2.5 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other

9.6.1.2.6 Outcome

The outcome of the AE is to be documented as follows:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

9.6.1.3 Assessments and documentation of adverse events

AEs observed, mentioned upon open questioning by a member of the investigator's team or spontaneously reported by the subject will be documented. The observation phase for AEs will start with signing the informed consent form and will end in general with the last visit of follow-up. After the end of follow-up there is no requirement to actively collect AEs.

In case of ongoing AEs after the last follow-up visit – especially when related to treatment with the study medication – the respective AE will be followed until resolution, if possible. The type of information that should be assessed and recorded by the investigator for each AE is listed in Section 9.6.1.2.

For all SAEs the sponsor has to carry out a separate assessment for expectedness, seriousness and causal relationship to treatment with the study medication.

The investigator has to record on the respective CRF/eCRF data collection system all adverse events occurring in the period between the signing of the informed consent and the end of the Follow-up Visit, there is no requirement to actively collect AEs including deaths. The type of information that should be assessed and recorded by the investigator for each AE is listed in Section 9.6.1.2.

"Death" should not be recorded as an AE on the AE page. Instead, "death" is the outcome of underlying AE(s).

For all serious adverse events (SAEs) the sponsor has to carry out a separate assessment for expectedness, seriousness and causal relationship to study drug.

9.6.1.4 Reporting of serious adverse events and pregnancy

The definition of serious adverse events (SAEs) is given in Section 9.6.1.1. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

Investigator's notification of the sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

The investigator must report immediately (within 24 hours of the investigator's awareness) all SAEs occurring during the observation period defined in Section 9.6.1.3 to the recipient

detailed in the instructions for SAE reporting included in the Investigator File. For this, an AE page in the CRF/eCRF data collection system as well as the complementary pages provided in the Investigator File must be completed for each SAE.

Pregnancy occurring during a clinical investigation, although not considered a serious adverse event, must be reported to Bayer within the same timelines as a serious adverse event on a Pregnancy Monitoring Form. The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother or the child should be reported. This also applies to pregnancies following the administration of the investigational product to the father prior to sexual intercourse. Send the completed SAE or pregnancy forms to:

CCI [redacted] or Fax: CCI [redacted] (in the USA)

SAEs occurring after the protocol-defined observation period will be processed by the sponsor according to all applicable regulations.

Notification of the IRB

Notification of the Institutional Review Board (IRB) about all relevant events (e.g., SAEs, suspected, unexpected, serious adverse reactions [SUSARs]) will be performed by the sponsor and/or by the investigator according to all applicable regulations.

Notification of the authorities

The processing and reporting of all relevant events (e.g., SAEs, SUSARs) to the authorities will be done by the sponsor according to all applicable regulations.

Sponsor's notification of the investigational site

The sponsor will inform the investigational site about reported relevant events (e.g., SUSARs) according to all applicable regulations.

9.6.1.5 Expected adverse events

For this study, the applicable reference document is the most current version of the package insert or Investigator Brochure for naproxen, acetaminophen and celecoxib. If relevant new safety information is identified, the information will be integrated into an update of the safety information and distributed to all participating sites.

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

9.6.2 Pregnancies

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.

For all reports, the forms provided are to be used. The investigator should submit them within the same timelines as an SAE (see Section 9.6.1.4.). Send the completed pregnancy forms to:

CCI [redacted] or Fax: CCI [redacted] (in the USA)

9.6.3 Safety Examinations

The following safety examinations will be performed at the time points specified in the study flowchart, see Section 16.1.

- **Physical examination**

The physical examination (by means of inspection, palpation, auscultation) will be performed by a physician (or appropriately licensened designee) at the study site covering at least the organs of the cardiovascular, respiratory, and abdominal systems.

Abnormal physical examination findings are recorded either as medical history or as adverse events (see Section 9.6.1.1).

- **Body weight and height, BMI**

Body weight will be measured by a member of the investigator's team under the following conditions:

  – Subject without shoes after having emptied his or her bladder

  – Physician scale, measurement units 0.1 kg

The subject's height will be measured (without shoes) to calculate the BMI.

- **Blood pressure / heart rate**

Systolic and diastolic blood pressure and heart rate will be measured by a member of the investigator's team under the following conditions:

  – Systolic blood pressure (after resting for at least 5 min in sitting position)

  – Diastolic blood pressure (after resting for at least 5 min in sitting position)

  – Heart rate (after resting for at least 5 min in sitting position)

  – Measuring site: cuff to be placed on the right / left upper arm (if possible, the same arm will be used for all measurements in one subject); cuff location will be documented

  – Method: oscillometric by automatic or manual measurement device

- **Laboratory examinations**

Urine samples will be collected to assess for illicit drugs at Screening Visit 1 and Visit 2. Safety laboratory examination will collected at Screening.

Table 3: Urine drug screen panel

Test Panel	Parameter
Urine Drug Screen	Methamphetamines, Amphetamines, cannabinoids, cocaine, opiates, benzodiazepines, barbiturates, Methylenedioxymethamphetamine, Methadone, Oxycodone, Adulterants

Table 4: Safety laboratory evaluations - amendment 1

Hematology	Hemoglobin, Hematocrit, RBC count, Platelet count, WBC count
Chemistry	BUN, Creatinine, Glucose, Ca++, Na+, K+, Cl-, Total

	CO2 (Bicarbonate), AST, ALT, Total Bilirubin, Alkaline phosphatase, Albumin, Total protein
Urinalysis	Specific gravity, pH, Glucose (qual), Protein (qual), Blood (qual), Ketones, Leukocyte Esterase, Nitrite, Bilirubin, Urobilinogen

9.7 Other procedures and variables - amendment 1 and 2

STEPP

The STEPP consists of stepping fully up and down on a standardized stair that will be provided to the sites. Pain measures are performed immediately before and 2-5 minutes after the exercise using a 0-10 pain intensity NRS. Details about the STEPP will be provided in the STEPP Manual.

0-10 point pain intensity NRS

The 0-10 point current pain intensity NRS will be assessed at the Screening Visit before and after one performance of the STEPP, and at Visits 2 and 3 of each Treatment Period before and after the STEPP performed pre-dose and at 2, 4, 6, and 8 hours post-dose. It will also be assessed at 1, 3, 5, and 7 hours post-dose when not completing the STEPP. The 0-10 point average pain intensity over the last 24 hours NRS will be assessed at the Screening Visit and at Visits 2 and 3 of each Treatment Period.

WOMAC (0-10 NRS version; version 3.1)

WOMAC Pain, Stiffness and Physical Function subscales (0-10 NRS, 48-hour recall version) will be measured at the Screening Visit, and Visits 2 and 3 of each Treatment Phase.

Baseline Stiffness Questionnaire

The Baseline Stiffness questionnaire will be assessed at the Screening Visit. It is used to characterize the subjects knee stiffness over the past month.

Joint Stiffness Severity Rating

The Joint Stiffness Severity rating will be assessed at the Screening Visit. It is a subjective rating of joint stiffness severity on a typical day.

Daily BASS

The Daily BASS is a PRO instrument measuring of the severity of OA-related stiffness in the target knee joint.

The Daily BASS will be assessed daily during each Treatment Period. Subjects will report their Daily BASS score in-clinic at Visits 2 and 3 (Days 1 and 4), and at home in diaries during Days 2 and 3.

PGIC for OA Pain

A question that rates the effects of the investigational product on OA pain is asked at Visit 3 for each Treatment Period.

PGIC for OA Symptoms

A question that rates the effects of the investigational product on OA symptoms is asked at Visit 3 for each Treatment Period.

Treatment Preference

A question that asks which treatment gave the most pain relief is asked at Visit 3 for Treatment Period 4 of 4.

Qualitative Interview – amended

Mixed-methods research, which combines quantitative methods with qualitative methods, is becoming more common in all areas of human subjects research, including clinical trials.(14,15,16) Quantitative research, in which subjects answer questions on fixed forms, is limited by the imagination and assumptions of the researchers. Patients often have helpful observations about their experiences that may trigger hypotheses about the medications being studied, the assessments used in the study, and the patient experience with logistical and other aspects of study conduct that may improve subsequent clinical trials. Therefore this study will include a semi-structured interview to provide subjects the opportunity to share their perspectives on these issues with investigators. The qualitative interview will be conducted after Visit 3 of Treatment Period 4 of 4 (during the follow up phone call) or if the subject is withdrawn prior to study completion.

Accelerometer Data Collection (new for amendment 1)

Subjects will wear an accelerometer on their lower leg during each Treatment Period of the Treatment Phase. The accelerometer [redacted] will measure physical activity level outcomes captured during Days 1 (partial), 2 and 3 of the Treatment Phase.

Subjects will wear the accelerometer on the lower leg area (ankle) for each Treatment Period without removal except when showering or bathing. The accelerometer cannot be used in conjunction with any swimming or watersport activity. The accelerometer may be removed for sleep. The subject may request to use the opposite ankle for placement of the accelerometer during the trial.

9.8 Appropriateness of procedures / measurements

All efficacy and safety parameters, as well as the methods to measure them, are standard variables / methods in clinical studies and / or clinical practice. They are widely used and generally recognized as reliable, accurate and relevant.

10. Statistical methods and determination of sample size

10.1 General considerations

Statistical analysis will be performed using Statistical Analysis Software (SAS) 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.

10.2 Analysis sets

Three sets will be identified in this trial.

Safety Population (Set):

All subjects who take at least one dose of IMP (regardless of their randomization status). Safety measures will be analyzed for all subjects in the safety population.

Intent to Treat (ITT) Population (Set):

All randomized subjects who have taken at least one dose of IMP.

Per Protocol (PP) Population (Set):

The Per Protocol set will include all subjects in ITT who do not have any major protocol violations that could affect the evaluability of the primary efficacy parameter. 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 efficacy endpoints to assess the robustness of the results based on PP Population.

10.3 Variables and planned statistical analyses

10.3.1 Primary endpoint

The primary efficacy endpoint is:

- Sum of change from baseline (Day 1 of the Treatment Period) in BASS score over the 4 day treatment period

10.3.2 Secondary endpoints

The secondary efficacy endpoints include:

- Absolute BASS score at each time point
- Day 4 change from baseline in BASS score

10.3.3 Exploratory endpoints - amendment 1 and 2

- Day 1 and Day 4 post-STEPP sum of pain intensity difference (SPID) at 4, 6, and 8 hours post-dose, based on 0-10 NRS;
- Day 1 and Day 4 post-STEPP sum of pain intensity (SPI) at 4, 6, and 8 hours post-dose, based on 0-10 NRS;
- Day 1 and Day 4 post-STEPP pain intensity difference (PID) from baseline at 2, 4, 6 and 8 hours post-dose, based on 0-10 NRS;
- Day 1 and Day 4 post-STEPP pain intensity (PI) at 2, 4, 6, and 8 hours post-dose, based on 0-10 NRS;
- Current hourly PI using the 0–10 NRS pre-dose, and from 1 to 8 hours post-dose;
- Mean change from baseline (Day 1 of the Treatment Period) to end of Treatment Period on the Western Ontario and McMaster Universities Arthritis (WOMAC) pain subscale, 48-hour recall version, assessed on Day 1 and Day 4;
- Mean change from baseline to end of treatment period on WOMAC stiffness subscale, 48-hour recall version, assessed on Day 1 and Day 4;
- Absolute WOMAC stiffness subscale scores, 48-hour recall version, at each time point;
- Mean change from baseline to end of treatment period on WOMAC function subscale, 48-hour recall version, assessed on Day 1 and Day 4;
- Patient Global Impression of Change (PGIC) on Day 4 of each Treatment Period, including PGIC for OA Pain (PGIC-P) and PGIC for OA Symptoms (PGIC-S);
- Subject preference for treatment assessed at the end of the study;
- Qualitative (semi-structured) interview to assess subjects' experience with treatments, and experience with the STEPP relevance to their disease status, how to improve it, etc. (see Section 16.2);
- Level of activities during Days 1 (partial), 2 and 3 as measured by the accelerometer CCI [redacted]).
    - Number of steps per day
    - Total distance
    - Minutes active vs. inactive per day
    - Percent time in low, medium or high activity
    - Peak performance of the day (30 minutes)
    - Maximum performance (1, 5, 20, 60 minutes)
    - Stride velocity
    - Stride length
    - Cadence

10.3.4 Efficacy analysis

CCI [redacted]

CCI [redacted]

10.3.5 Safety and Tolerability

AEs will be collected from screening throughout the Treatment Phase and Follow-up Phase and will be coded using the Medical Dictionary for Regulatory Activities. Only treatment-emergent AEs will be included, i.e., AEs that begin or worsen after the first dose of the investigational medicinal product (IMP) in the Treatment Phase. 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 period and treatment group. Tables will also be produced by severity and relationship to each IMP. Seriousness, severity, relationship to each IMP duration, and outcome will also be listed.

Quantitative data for blood pressure, heart rate will be described by summary statistics for the original data as well as for the differences to baseline. Frequency tables will be provided for qualitative data. Laboratory data outside the reference range will be listed and highlighted with 'L' for low and 'H' for high. An additional table with all abnormal values will be presented.

Listings of individual subject data (e.g., vital signs) will be provided.

10.4 Determination of sample size

Because there are no reference data on the impact of naproxen, acetaminophen and placebo on stiffness with the utilization of the BASS scale, an estimated 50 subjects randomized to achieve approximately 40 subjects completing the study are considered adequate for this pilot study. Screening will continue until 50 subjects are randomized in the study.

10.5 Planned interim analyses

No interim analysis is planned for this study.

11. Data handling and quality assurance

11.1 Data recording - amendment 1

Data collection and storage

The data collection tool for this study will be a validated electronic data capture system to be used at the study site. Subject data necessary for analysis and reporting will be provided to the Sponsor in CDISC (Clinical Data Interchange Standards Consortium) standards.

Interface to local laboratory

Laboratory and/or Radiology test results will be received as electronic data files or results/reports from the local laboratory. For easy access and tracking by the investigator, the results will be additionally provided in printed form. Test results originating directly from the site (e.g., urine drug screen) will be entered into the CRF/eCRF data collection system by designated site personnel.

Source documentation

Entries made in the CRF/eCRF data collection system must be either verifiable against source documents, or have been directly entered into the CRF/eCRF data collection system, in which case the entry in the CRF/eCRF data collection system will be considered as the source data (e.g., time points of blood sampling). The site has to ensure the availability of all required documentation.

Data recorded from screening failures

Data of 'only screened subjects' will be recorded at least as source data, as far as the reason for the premature discontinuation is identifiable. At minimum, the following data should be recorded in the screening log:

- Demographic information (subject number; year of birth or age, sex);
- Date of informed consent;
- Reason for premature discontinuation;
- Date of last visit.

For screening failures with an SAE, the following data should be collected in the CRF/eCRF data collection system in addition to the data specified above:

- All information related to the SAE such as:
  - Concomitant medication
  - Medical history
  - Other information needed for SAE complementary page

11.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's/CRO's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor/designee will monitor the site activity to verify that the:

- Data are authentic, accurate and complete.
  Supporting data may be requested (example: blood glucose readings to support a diagnosis of diabetes);
- Safety and rights of subjects are being protected;
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol);
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

11.3 Data processing

Data will be collected as described in Section 11.1. 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, ECG).

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

11.4 Missing data

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

11.5 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 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.

11.6 Archiving

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

Study subject files will be archived according to local regulations and in accordance with the maximum period of time permitted by the study site. 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 (e.g., 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.

12. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g., treatment arms; dose steps; centers]) at any time, which may be due but not limited to the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g., SAEs)
  - Results of any interim analysis
  - Results of parallel clinical studies
  - Results of parallel animal studies
    (on e.g., toxicity, teratogenicity, carcinogenicity or reproduction toxicity);
- If the study conduct (e.g., recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The investigator has the right to close his/her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing;
- All affected institutions (e.g., IRB(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law;
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification is given by the sponsor for destruction;
- In the event of a partial study closure, ongoing subjects, including those in post study follow-up, must be taken care of in an ethical manner.

Details for individual subject's withdrawal can be found in Section 6.4.1.

13. Ethical and legal aspects

13.1 Investigator(s) and other study personnel

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's investigator site file.

Whenever the term 'investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained and delegated individual of the investigational site.

The principal investigator of each center must sign the protocol signature page and must receive all required external approvals (e.g., health authority, ethics committee, sponsor) before subject recruitment may start at the respective center. Likewise, all amendments to the protocol must be signed by the principal investigator and must have received all required external approvals before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor's study file.

The global sponsor of this study is identified on the title page of this protocol. If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

13.2 Funding and financial disclosure

Funding

This study will be funded by its sponsor.

Financial disclosure

Each investigator (including principal and/or any sub investigators) who is directly involved in the treatment or evaluation of research subjects has to provide a financial disclosure according to all applicable legal requirements. All relevant documentation will be filed in the trial master file.

13.3 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by Good Clinical Practice (GCP) guidelines and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IRBs will be obtained for all participating centers/countries before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IRB approval must be obtained and also forwarded to the sponsor. The responsible unit (e.g., IRB, head of

the study center/medical institution) must supply to the sponsor, upon request, a list of the EC/IRB members involved in the vote and a statement to confirm that the IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IRB/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IRB/head of medical institution/sponsor. Any deviations from the protocol must be explained and documented by the investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 12.

13.4 Subject information and consent

All relevant information on the study will be summarized in an integrated subject information sheet and informed consent form provided by the sponsor or the study center. A sample subject information and informed consent form is provided as a document separate to this protocol.

Based on this subject information sheet, the investigator or designee will explain all relevant aspects of the study to each subject prior to her entry into the study (i.e. before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The investigator will also mention that written approval of the IRB has been obtained.

Each subject will be informed about the following aspects of premature withdrawal:

- Each subject has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision;
- The subject's consent covers End of Study tasks as specified in the visit description described in Section 9.2.7 to be conducted after withdrawal of consent;
- The subject's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the statistical analysis plan;
- Subject-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 subject 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 subject's oral objection may be documented in the subject's source data.

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

Only if the subject 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 subject will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the subject's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject´s clinical record must clearly show that informed consent was obtained prior to these procedures.

The informed consent form and any other written information provided to subjects will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written informed consent form. The investigator will inform the subject of changes in a timely manner and will ask the subject to confirm 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.

13.5 Publication policy and use of data

The sponsor will make the information regarding the study 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.

The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator, whilst free to utilize study data derived from his/her center for scientific purposes, must obtain written consent of the sponsor on the intended publication manuscript before its submission. To this end, the investigator must send a draft of the publication manuscript to the sponsor within a time period specified in the contract. The sponsor will review the manuscript promptly and will discuss its content with the investigator to reach a mutually agreeable final manuscript.

13.6 Compensation for health damage of subjects / 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.

13.7 Confidentiality

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

Subject names will not be supplied to the sponsor. Only the subject numbers (SNR and RNR) will be recorded in the CRF/eCRF data collection system, and if the subject 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 subjects 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 subject's identity will remain confidential.

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

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15. Protocol amendments

15.1 Amendment 2 (11-Sep-2018)

15.1.1 Overview of changes to the study

The protocol was amended from version 2.0 to modify I/E critiera, screening and randomization requirements to enhance recruitment. Other changes include removing the Investigator signature page and updating the WOMAC NRS to the licensed version.

The following sections have been modified for Amendment 2:

- Section 2.0 (Synopsis, Inclusion/Exclusion Criteria only)
- Section 5.1 (Design Overview)
- Section 5.3 (Selection of Study Population)
- Figure 1 (Design Overview)
- Section 6.1 (Inclusion Criteria)
- Section 9.2.1 (Screening Phase Visit 1)
- Section 9.2.3 (Visit 2)
- Section 9.2.5 (Visit 3)
- Section 9.4.3 (Exploratory efficacy endpoints)
- Section 9.7 (Other procedures and variables)
- Section 10.3.3 (Exploratory endpoints)
- Section 16.1 (Study Flow Chart)
- WOMAC Osteoarthritis Index NRS 3.1

15.1.2 Changes to the protocol text

Section 2.0 (Synopsis, Inclusion/Exclusion Criteria only)

Changes are identified in Sections 6.1 and 6.2 of the amendment.

Section 5.1 (Design Overview)

Screening Phase Visit 1 - (Day -18 to -5)

The target knee will need to be identified per inclusion criteria (exam, radiographs and pain scores). In addition, the subject must have an average score of ≥~~4~~**3**.0 on the WOMAC pain subscale (0-10 numeric rating scale [NRS] ~~24~~**48**-hour recall version) at Screening~~,~~ **AND/OR** a 24-hour *Average Pain Intensity* score of ≥~~4~~**3** on the 0-10 NRS and a Joint Stiffness Severity score ≥3 on a 0-10 NRS.

Start of Treatment Period X of 4 - Visit 2 (Day 1)

Subjects will return to the study center upon completion of the Screening Washout Phase or between-treatment Washout Period. To be eligible for randomization prior to Treatment Period 1, subjects must meet the following randomization criteria: self-reported average score of ≥~~5~~**4** on the WOMAC pain subscale (0-10 NRS, ~~24~~**48**-hour recall version) related to OA pain in the target knee; current pain intensity score of ≥4 and ≤9 on the 0-10 NRS; and, a score of ≥~~5~~**4** on the 0-10 NRS for average pain over the past 24-hours. In addition, the Day 1 baseline post-STEPP current pain intensity 0-10 NRS score must be ≥~~6~~**5**, and ≥1 unit higher than the pre-STEPP current pain intensity 0-10 NRS score.

Section 5.3 (Selection of Study Population)

All male and female potential subjects 40 to ~~75~~ **80** years of age with OA of the knee who would typically take OTC NSAIDs for pain relief may be eligible to participate in the study provided they meet inclusion/exclusion criteria.

Figure 1 (Design Overview)

Start of Treatment Period, Visit 2, Day 1

WOMAC Pain ≥~~5~~**4**	24-hour average pain ≥~~5~~**4**	Post STEPP pain ≥~~6~~**5** and ≥1 unit higher than pre-STEPP pain (0-10 NRS)

Section 6.1 (Inclusion Criteria)

2. Ambulatory (as deemed appropriate by the Investigator) male and female subjects between 40 and ~~75~~**80** years of age;
3. Body Mass Index (BMI) between 18~~-35~~**to <40** kg/m^2;

For Randomization:

10. **48-hour WOMAC pain subscale average score ≥3.0 and/or 24-hour Average Pain Intensity score ≥3 on the 0-10 NRS at Screening**;
11. ~~24~~**48**-hour WOMAC pain subscale average score ≥~~4~~**3**.0 at Screening and ≥~~5~~**4**.0 at Visit 2, Treatment Period 1 of 4;
12. 24-hour *Average Pain Intensity* score ≥~~4~~**3** on the 0-10 NRS at Screening and ≥~~5~~**4** at Visit 2, Treatment Period 1 of 4;
14. A Day 1 baseline post-STEPP current pain intensity score ≥~~6~~**5**, and ≥1 unit higher than the pre-STEPP current pain score on the 0-10 NRS;

Section 9.2.1 (Screening Phase Visit 1)

- ~~24~~**48**-hour recall WOMAC subscales for stiffness, physical function and pain questionnaire to establish the target knee;

To qualify for randomization (Day 1), subjects must have either an average score ≥3.0 on the 48-hour WOMAC pain subscale OR score ≥3.0 on the 24-hour Average Pain Intensity Scale.

Section 9.2.3 (Visit 2)

- ~~24~~**48**-hour recall WOMAC (0-10 NRS version) subscales for stiffness, physical function and pain questionnaires;

Randomization Criteria:
Subjects must self-report the following pain ratings in order to be randomized and start Treatment Period 1 of 4:

- An average score of ≥~~5~~**4**.0 on WOMAC pain subscale summation score (0-10 NRS, ~~24~~**48**-hour recall version);
- 24-hour *Average Pain Intensity* score of ≥~~5~~**4** on the 0-10 NRS;
- Day 1 baseline post -STEPP current pain intensity score ≥~~6~~**5** and ≥1 unit higher than the pre-STEPP current pain intensity score on the 0-10 NRS.

Section 9.2.5 (Visit 3)

- ~~24~~**48**-hour recall WOMAC (0-10 NRS version) subscales for stiffness, physical function and pain questionnaires; Adverse Event assessment.

Section 9.4.3 (Exploratory efficacy endpoints)

- Mean change from baseline (Day 1 of the Treatment Period) to end of Treatment Period on the Western Ontario and McMaster Universities Arthritis (WOMAC) pain subscale, ~~24~~**48**-hour recall version, assessed on Day 1 and Day 4, including an assessment of all key pairwise comparisons;
- Mean change from baseline to end of treatment period on WOMAC stiffness subscale, ~~24~~**48**-hour recall version, assessed on Day 1 and Day 4, including an assessment of all key pairwise comparisons;
- Absolute WOMAC stiffness subscale scores, ~~24~~**48**-hour recall version, for each study treatment at each time point;
- Physical activity level outcomes during Days 1 (partial), 2 and 3 as measured by the accelerometer;
- Change from baseline to end of treatment period on WOMAC function subscale, ~~24~~**48**-hour recall version, assessed on Day 1 and Day 4, including an assessment of all key pairwise comparisons;

Section 9.7 (Other procedures and variables)

WOMAC (0-10 NRS version; version 3.1)

WOMAC Pain, Stiffness and Physical Function subscales (0-10 NRS, ~~24~~**48**-hour recall version) will be measured at the Screening Visit, and Visits 2 and 3 of each Treatment Phase.

Section 10.3.3 (Exploratory endpoints)

- Mean change from baseline (Day 1 of the Treatment Period) to end of Treatment Period on the Western Ontario and McMaster Universities Arthritis (WOMAC) pain subscale, ~~24~~**48**-hour recall version, assessed on Day 1 and Day 4;
- Mean change from baseline to end of treatment period on WOMAC stiffness subscale, ~~24~~**48**-hour recall version, assessed on Day 1 and Day 4;
- Absolute WOMAC stiffness subscale scores, ~~24~~**48**-hour recall version, at each time point;
- Mean change from baseline to end of treatment period on WOMAC function subscale, ~~24~~**48**-hour recall version, assessed on Day 1 and Day 4;

Section 16.1 (Study Flow Chart)

The table was amended to correctly reflect the WOMAC under Trial Procedures.

~~24~~**48** hour WOMAC Pain
~~24~~**48** hour WOMAC Stiffness
~~24~~**48** hour WOMAC Function

footnote b - WOMAC pain subscale average score must be ≥~~5~~**4**.0 on 0-10 scale to be eligible for Randomization on Day 1 of Treatment Period 1 of 4

WOMAC Osteoarthritis Index NRS 3.1

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (0-10 NRS, ~~24~~48-hour recall version) - amendment 2
Examples ~~only and not representative~~ of the licensed version.

The licensed version was copied into the protocol.

15.2 Amendment 1 (13-Apr-2018)

15.2.1 Overview of changes to the study

The protocol was amended from version 1.0 to include the use of accelerometers. These devices will be worn by each subject starting at the conclusion of Visit 2 (Day 1) after 8 hours of study procedures and for all awake times for Days 2 and 3 of the Treatment Phase. The data from the accelerometer will be downloaded at the completion of each Visit 3. The purpose is to collect data regarding activity levels in a treatment scenario that could be used to further investigate in future studies with naproxen. Additional changes to the protocol are moving the Qualitative Interview from Visit 3 of Treatment Period 4 to the follow up phone call or if the subject withdraws from the study prior to completing Visit 3 of Treatment Period 4. Safety labs were added to the Screening Visit. Other changes constituted text changes to clarify inclusion/exclusion criteria, prohibited medications as well as minor text changes in other sections of the protocol.

The following sections have been modified for Amendment 1:

- Section 2.0 (Synopsis, Inclusion/Exclusion Criteria only)
- List of Abbreviations
- Section 4.0 (Study Objectives)
- Section 5.1 (Design Overview)
- Section 5.3 (Selection of Study Population)
- Figure 1 (Design Overview)
- Section 6.1 (Inclusion Criteria)
- Section 6.2 (Exclusion Criteria)
- Section 7.1 (Treatments to be Administered)
- Section 7.3 (Treatment Assignment)

- Section 7.6 (Drug Logistics and accountability)
- Section 8.1 (Prior and Concomitant Therapy)
- Section 9.2.1 (Screening Phase Visit 1)
- Section 9.2.3 (Visit 2)
- Section 9.2.4 (Day 2 and 3)
- Section 9.2.5 (Visit 3, Day 4, End of Treatment Period X of 4)
- Section 9.2.7 (Visit 3, Day 4, End of Treatment Period 4 or 4)
- Section 9.2.8 (End of Study)
- Section 9.2.9 (Rescue Therapy)
- Section 9.4.3 (Exploratory Endpoints)
- Section 9.4.4 (Safety Analysis)
- Section 9.6.3 (Safety Examinations)
- Section 9.7 (Other Procedures and Variables)
- Section 10.3.3 (Exploratory Endpoints)
- Section 11.1 (Data Recording)
- Section 15 (Protocol Amendments)
- Section 16.1 (Study Flow Chart)
- Section 16.2 (Subjective Assessments)

15.2.2 Changes to the protocol text

List of Abbreviations

The following abbreviations were added to the table:

ALT Alanine Aminotransferase

AP Anteroposterior

AST Aspartate Aminotransferase

BUN Blood Urea Nitrogen

Ca Calcium

Cl Chloride

CO2 Carbon Dioxide

eGFR Estimated Glomerular Filtration Rate

K Potassium

Na Sodium

PA Posteroanterior

RBC Red Blood Cell

WBC White Blood Cell

Section 2.0 (Synopsis, Inclusion/Exclusion Criteria only)

Changes are identified in Sections 6.1 and 6.2 of the amendment.

Section 4.0 (Study Objectives)

Exploratory

- To determine/identify effect size measurements, determine single dose vs. multi-dose efficacy, identify optimal sample size, and logistical issues for planning comparative analgesic efficacy studies using the STEPP.
- **To assess levels of activity captured by the accelerometer between active treatments and placebo during Days 1 (partial), 2 and 3 of the Treatment Phase.**
- To evaluate the safety and tolerability of naproxen sodium, celecoxib and acetaminophen ER.

Section 5.1 (Design Overview)

Screening Phase Visit 1 - (Day -18 to -5)

In addition, the subject must have an average score of ≥4.0 on the WOMAC pain subscale (0-10 numeric rating scale [NRS] 24-hour recall version) at Screening, a 24-hour *Average Pain Intensity* score of ≥4 on the 0-10 NRS and a Joint Stiffness Severity score ≥~~4~~**3** on a 0-10 NRS.

Start of Treatment Period X of 4 - Visit 2 (Day 1)

During the completion of Visit 2, subjects will be fitted with an accelerometer to measure the number of steps taken and level of activity (e.g., low, medium, high). Accelerometer data collection will start after completion of the Day 1 activities prior to leaving the study site.

Day 2 and Day 3

Subjects will continue to take their IMP as directed for a total of 4 doses per day. **Subjects will continue to wear their accelerometer except when showering or bathing.**

End of Treatment Period X of 4 - Visit 3 (Day 4)

Subjects will return to the study center **wearing their accelerometer**. **They must bring** their diary and treatment kit with remaining study medication. **The accelerometer will be removed at the study site prior to the pre-dose STEPP.**

End of Treatment Period X of 4 - Visit 3 (Day 4)

Subjects will return to the study center **wearing their accelerometer**. **They must bring** their diary and treatment kit with remaining study medication. **The accelerometer will be removed at the study site prior to the pre-dose STEPP.**

End of Study (follow up) – after Visit 3, Treatment Period 4 of 4

Subjects will receive a follow up phone call to assess adverse events and document any new concomitant medications. **Additionally, subjects will participate in a semi-structured qualitative interview about their experiences in the clinical trial.** Upon completion of all trial procedures, subjects will be discharged from the study.

Figure 1 (Design Overview)

The addition of accelerometer use on Visit 1, Day 1 and Days 2 and 3 of the Treatment Phase. The Qualitative Interview was moved from Visit 3 to the Follow up Phase.

Footnote a - **After** Treatment period 4 of 4 ~~only~~ **or if the subject is withdrawn from the study prior to completion**

Section 5.3 (Selection of Study Population)

Accurate Pain Reporting Training

Staff training is conducted prior to the first subject visit. Subjects receive training at the Screening Visit, and at on Day 1 of each of the four Treatment Periods**. The training video takes approximately 30 minutes and should be completed prior to pain assessments.**

Appropriate Expectations Training

Subjects receive training at the Screening Visit, and at on Day 1 of each of the four Treatment Periods. **The training video takes approximately 30 minutes and should be completed prior to pain assessments.**

Section 6.1 (Inclusion Criteria)

8. Female subjects of childbearing potential must be using a medically acceptable form of birth control for at least 1 month prior to screening (or 3 months if using oral contraceptives) [e.g., hormonal contraceptives (oral, patch, injectable or vaginal ring), implantable device (implantable rod or intrauterine device), or a double barrier], or in same sex relationship and have a negative pregnancy test at Screening and prior to study drug administration. Female subjects of non-childbearing potential must be amenorrheic for at least two years or have undergone surgical sterilization (e.g., hysterectomy and/or bilateral oophorectomy);

9. Willing to wear an accelerometer during each Treatment Period of the Treatment Phase. Subjects who decline to wear the accelerometer are still eligible for study participation provided they meet all other required criteria.

Section 6.2 (Exclusion Criteria)

3. Recent injury in the OA affected knee (past 4 months); **oral, intra-muscular, intravenous or** intra-articular corticosteroid, **platelet rich plasma intraarticular knee injections, stem cell therapy** or hyaluronic acid injections in either knee within the last 3 months;
5. Use of any pain medications from the start of the ~~Baseline~~ **Screening/Washout** Phase through trial completion, other than IMP provided by the Sponsor or Rescue Pain medication provided by the study site;

9. Initiating any new physical therapy for the lower extremities from 4 weeks prior to study start through the duration of the study;

10. Positive urine drug test for illegal drug substances, non-prescribed controlled substances, or breath/saliva alcohol at screening or Visit 2;

Note: prescribed marijuana is allowed provided the subject is willing to wash out and not use during the study.

11.Subject has an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2 times the upper limit of normal;

12.Subject has a hemoglobin <10.0 g/dL;

13.Subject has an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m²;

15.Kellgren and Lawrence grade of 0, I or IV **in the target knee** (see Section 16.2);

23.Recent **(within the past 1 year)** MI or in the peri-operative period surrounding coronary artery bypass graft (CABG) surgery;

Section 7.1 (Treatments to be Administered)

Note: Number of doses per day are approximate based on subject's dosing times provided the subject doses within the window for each listed time, they will be considered to have met protocol requriements.

Section 7.3 (Treatment Assignment)

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

- Treatment D: Placebo (eight tablets of placebo daily); On Days 1, 2 and 3, first dose of two tablets of placebo in the morning at 8:00 AM ± 1 hour followed by two tablets of placebo 8 hours later at 4:00 PM ± 1 hour followed by two tablets of placebo 4 hours later at 8 PM ± 1 hour followed by two tablets of placebo 8 hours later at 12AM ± 1 hour.

Note: The Day 4 treatment is ~~only~~ **a** single morning (8 AM) two tablet/capsule dose similar to the morning dosing for Days 1-3.

Section 7.6 (Drug Logistics and accountability)

All study drugs will be stored at the investigational site in accordance with GCP ~~and GMP~~ requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate/CRO), and will be inaccessible to unauthorized personnel.

Section 8.1 (Prior and Concomitant Therapy)

The following treatments are prohibited:

- Use of any pain medications from the start of the Screening Washout Phase through trial completion, other than IMP provided by the Sponsor and rescue pain medication provided by the study site **This includes medications such as gabapentin, cannabidiol etc. if prescribed to the subject for the purpose of pain control;**
- Taking more than one antidepressant. Subjects who are on a stable dose of one antidepressant, for at least 1 month, are eligible for enrollment;

- Taking more than one anxiolytic medication. Subjects who are on a stable regimen of one anxiolytic for at least 1 month, are eligible for enrollment;
- **Fish oil (supplements are permitted if the dose is stable for at least 4 weeks).**

From 4 days prior to randomization until the completion of the Treatment Phase (Treatment Period 4 of 4), subjects are not allowed to take pain treatments (including supplements and/or topicals) other than the provided trial treatment (IMP and rescue therapy). **Prohibited treatements include:**

- **Topical capsaicin, NSAIDs, lidocaine, and cannabidiol oil;**
- **Glucosamine-chondroitin and turmeric (curcumin);**
- **Supplements intended for pain relief.**

If the subject uses an excluded/prohibited medication (analgesic or other medication) after being enrolled into the study, the investigator will use his/her judgement to determine whether the subject is able to continue however, the subject must be discontinued if safety is concerned. In other cases, the subject may be able to continue if the concomitant medication is for short term use and/or is not likely to conflict with the study objectives in subsequent Treatment Periods.

Section 9.2.1 (Screening Phase Visit 1)

The Screening Phase will be up to 14 days long. The following will be conducted during the Screening Visit:

- Signed Informed Consent;
- Review Inclusion and Exclusion Criteria;
- Subject demographics;
- Medical history;
- Medication history of all prescription and over-the-counter drugs and other products (including topicals, herbal products, vitamins and nutritional supplements) and investigational drugs, taken within 30 days prior to screening;
- **Alcohol breath/saliva test;**
- **Urine drug screen;**
- **Urine pregnancy test for female subjects of child bearing potential;**
- **Blood and urine specimens for safety laboratory tests (hematology, chemistry and urinalysis);**
- History of drug, alcohol and tobacco use;
- Height, weight, and Body Mass Index (BMI);
- Physical examination;
- OA assessment of ~~the~~ **each potentially qualifying** knee using ACR criteria;
- Radiograph of ~~the target~~ **each potentially qualifying** knee (anteri~~o~~posterior [AP] **or posteroanterior [PA]** and lateral projections);
  Note: A historical knee radiograph could be used provided the images were taken within the previous 1 year and can be digitally exported to a central reading lab and are of diagnostic quality.
- Baseline Stiffness Questionnaire **of each knee**;
- Joint Stiffness Severity rating **of each knee**;
- Regional Pain Scale (13);

- ~~Alcohol breath/saliva test;~~
- ~~Urine drug screen;~~
- ~~Urine pregnancy test for female subjects of child bearing potential;~~
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature after 5 minutes in a sitting position);

This includes the radiographic interpretation of the knee radiographs using the Kellgren and Lawrence scale **as well as safety laboratory values**. Subjects will be reminded **once screening criteria have been met,** to discontinue use of all pain medications, including topicals, and supplements until they return for Visit 2. Subjects can take acetaminophen (up to 2000 mg/day), for knee pain but not within 24 hours of the Randomization visit.

An external centralized vendor chosen by the sponsor will read/ interpret the knee radiographs and communicate the findings to the study center. **Subjects that do not meet qualification after leaving the test site at Visit 1, will not be required to return their paper diary.**

Section 9.2.3 (Visit 2)

Visit 2 will occur 4 to 7 days after starting the Screening Washout Phase (within 21 days of the initial screening visit). The following activities will be completed:

- Review inclusion and exclusion criteria;
- Concomitant medication review;
- Review changes in the subject's medical/medication history since previous visit;
- Vital signs (blood pressure and heart rate after 5 minutes in a sitting position);
- **Accurate Pain Reporting Training;**
- **Appropriate Expectations Training;**

Subjects will be reminded of their selected wake up time and encouraged to keep this schedule for the duration of the trial. **Subjects will be fitted with an accelerometer on their lower leg (ankle) area on Day 1, directly after completion of the 8 hour activities. Subjects will wear the accelerometer at the completion of the clinic visit. Subjects will be trained to wear the accelerometer during the treatment periods.** Subjects will be scheduled for Visit 3 and reminded to bring their diary**,** ~~and~~ treatment kit for review **and wear their accelerometer which will be removed at the study site prior to performing any study related procedures**.

Note: subjects will wear the accelerometer on the ankle for Days 1 (at the conclusion of the clinic visit), 2 and 3 of each Treatment Period without removal except when showering or bathing. The accelerometer cannot be used in conjunction with any swimming or watersport activity. The accelerometer may be removed for sleep. The subject may request to use the opposite ankle for placement of the accelerometer during the trial.

Section 9.2.4 (Day 2 and 3)

Subjects will follow the dosing instructions provided for the remaining doses to be taken each day. **Subjects will continue to wear their accelerometer as instructed.**

Section 9.2.5 (Visit 3, Day 4, End of Treatment Period X of 4)

Subjects will return to the study center **(wearing their accelerometer)** for final assessments of the Treatment Period (X of 4). Subjects must take the morning (approximately 8 AM) dose of study medication at the study center. The following activities will be performed prior to dosing:

- Review inclusion and exclusion criteria;
- Concomitant medication review;
- **Remove accelerometer from subject (prior to pre-dose STEPP);**
- **Accelerometer data download and battery charging (~1 hour);**
- Vital signs (blood pressure, heart rate, after 5 minutes in a sitting position);

In addition, subjects will self-report the current pain intensity of their target knee on the 0-10 NRS at post-dose hours 1, 3, 5, and 7.

- Approximately 8 hours after dosing, prior to leaving the study center on Day 4 of each Treatment Period, subjects will complete two Patient Global Impression of Change (PGIC) scales: the PGIC for OA Pain, and the PGIC for OA Symptoms

Upon completion of data download and re-charge (~1 hour), the accelerometer will be stored at the clinic until the next Visit 2 of the next Treatment Period occurs.

Section 9.2.7 (Visit 3, Day 4, End of Treatment Period 4 or 4)

Subjects will complete the Treatment Preference rating and ~~participate in a semi-structured qualitative interview about their experiences in the clinical trial (see Section 16.2).~~ **The accelerometer will be removed from the subject and the data downloaded.**

Section 9.2.8 (End of Study)

At the completion of the final treatment/visit in the sequence (4 of 4) **or if the subject withdraws prior to the last treatment visit**, subjects will receive a phone call from the study site to review concomitant medications and assess adverse events. **Additionally, subjects will participate in a semi-structured qualitative interview about their experiences in the clinical trial (see Section 16.2).**

Section 9.2.9 (Rescue Therapy)

Rescue therapy is not allowed 24 hours prior to Day 1 **pre-treatment assessments** and it is not allowed from Day 1 through Day 4 **assessments** of each Treatment Period.

Subjects will be queried in a nonspecific fashion for any adverse events **(e.g., "Have you had any changes in health?")**. Any reported AEs will be collected and recorded on the CRF/e-CRF data collection system.

Section 9.4.3 (Exploratory Endpoints)

- **Physical activity level outcomes during Days 1 (partial), 2 and 3 as measured by the accelerometer;**

- ~~Mean change~~ **Change** from baseline to end of treatment period on WOMAC function subscale, 24-hour recall version, assessed on Day 1 and Day 4, including an assessment of all key pairwise comparisons;

Section 9.4.4 (Safety Analysis)

The following laboratory tests will be performed at screening:

- **Hematology (Hemoglobin, Hematocrit, RBC count, Platelet count, WBC count),**
- **Serum Chemistry (BUN, Creatinine, Glucose, Ca++, Na+, K+, Cl-, Total CO2 (Bicarbonate), AST, ALT, Total Bilirubin, Alkaline phosphatase, Albumin, Total protein)**
- **Urinalysis (Specific gravity, pH, Glucose (qual), Protein (qual), Blood (qual), Ketones, Leukocyte Esterase, Nitrite, Bilirubin, Urobilinogen)**

~~Safety measures will be analyzed for all subjects in the safety population.~~

Section 9.6.3 (Safety Examinations)

The physical examination (by means of inspection, palpation, auscultation) will be performed by a physician **(or appropriately licensened designee)** at the study site covering at least the organs of the cardiovascular, respiratory, and abdominal systems.

Urine samples will be collected to assess for illicit drugs at Screening Visit 1 and Visit 2.
Safety laboratory examination will collected at Screening.

Table 4: Safety laboratory evaluations

Hematology	**Hemoglobin, Hematocrit, RBC count, Platelet count, WBC count**
Chemistry	**BUN, Creatinine, Glucose, Ca++, Na+, K+, Cl-, Total CO2 (Bicarbonate), AST, ALT, Total Bilirubin, Alkaline phosphatase, Albumin, Total protein**
Urinalysis	**Specific gravity, pH, Glucose (qual), Protein (qual), Blood (qual), Ketones, Leukocyte Esterase, Nitrite, Bilirubin, Urobilinogen**

Section 9.7 (Other Procedures and Variables)

The qualitative interview will be conducted ~~at~~ **after** Visit 3 of Treatment Period 4 of 4 **(during the follow up phone call) or if the subject is withdrawn prior to study completion**.

Accelerometer Data Collection (new for amendment 1)

Subjects will wear an accelerometer on their lower leg during each Treatment Period of the Treatment Phase. The accelerometer CCI [redacted] **) will measure physical activity level outcomes captured during Days 1 (partial), 2 and 3 of the Treatment Phase.**

Subjects will wear the accelerometer on the lower leg area (ankle) for each Treatment Period without removal except when showering or bathing. The accelerometer cannot be used in conjunction with any swimming or watersport activity. The accelerometer may be removed for sleep. The subject may request to use the opposite ankle for placement of the accelerometer during the trial.

Section 10.3.3 (Exploratory Endpoints)

- Qualitative (semi-structured) interview to assess subjects' experience with treatments, and experience with the STEPP relevance to their disease status, how to improve it, etc. (see Section 16.2)**;**
- **Level of activities during Days 1 (partial), 2 and 3 as measured by the accelerometer** CCI [redacted] **).**
    - **Number of steps per day**
    - **Total distance**
    - **Minutes active vs. inactive per day**
    - **Percent time in low, medium or high activity**
    - **Peak performance of the day (30 minutes)**
    - **Maximum performance (1, 5, 20, 60 minutes)**
    - **Stride velocity**
    - **Stride length**
    - **Cadence**

Section 11.1 (Data Recording)

Laboratory and/or Radiology test results will be received as electronic data files **or results/reports** from the local laboratory. ~~They will be transferred to the clinical study database at the study site.~~ For easy access and tracking by the investigator, the results will be additionally provided in printed form.

Section 16.1 (Study Flow Chart)

The table was amended to include Clinical Laboratory Testing at the Screening Visit, Accelerometer setup, use, data download and battery charging. The Qualitative Interview was moved from Visit 3 to the Follow up phone call.

Footnote i - Completed ~~at~~**after** Visit 3, Treatment Period 4 of 4 ~~only~~ **or if the subject is withdrawn prior to completion**

Section 16.2 (Subjective Assessments)

0-10 Point Numerical Rating Scale (NRS)

Location (check one)

☐ Left Knee ☐ Right Knee

Qualitative Interview

The qualitative interview will consist of a series of open-ended questions administered by a trained interviewer in one-on-one interviews with study subjects **during the follow up phone call** ~~at the conclusion of Treatment 4 of 4~~**or if withdrawn prior to completion**. The primary purpose of the qualitative interview is to provide additional data to augment the quantitative data collected from instruments such as the BASS, WOMAC, and NRS.

The qualitative interview will take approximately 30-60 minutes to complete, and will consist of ~~15-20~~ **approximately 30** questions designed to collect information about: 1) subjects' experiences on the study treatments, to determine if there are any advantages of naproxen sodium (Aleve) that were not discovered using the quantitative instruments; 2) subjects' experiences with the STEPP, to determine if the procedure can be optimized to elicit OA pain and stiffness to a greater degree, which would increase assay sensitivity in trials of new treatments for pain due to OA of the knee; and, 3) subjects' perspectives on factors to optimize recruitment and retention in future OA studies conducted by Bayer.

16. Appendices

16.1 Study Flow Chart - amendment 1 and 2

Table 5: Study schema

Trial Procedure	Visit 1 Screening	Screening Washout Phase	Treatment Phase These events are repeated during each of the 4 Treatment Periods. Treatment Periods will be separated by a washout of 3 to 7 days						End of Study (Phone call)
			Visit 2 Start of Treatment Period		Continue Treatment Period Outpatient	Visit 3 End of Treatment Period			
	Day -18 to -5	Day -4 to -1 (+3 d)	Day 1	2, 4, 6, 8 hrs	Day 2-3	Day 4	2, 4, 6 hrs	8 hrs	7-10 days after Treatment Period 4 of 4
Signed Informed Consent	X								
Inclusion/Exclusion criteria review	X		X			X			
Subject demographics	X								
Medical history	X								
Prior/Concomitant medications	X		X			X			X
History of drug, alcohol and tobacco use	X								
Body weight, height and BMI	X								
Physical examination	X								
OA assessment of the knee (includes radiograph)	X								
Vital signs[a]	X		X			X			
Clinical Laboratory Tests (hematology, chemistry, urinalysis)	X								
Alcohol breath/saliva test	X		X						
Urine drug screen	X		X						
Urine pregnancy test (if applicable)	X		X						
Accurate pain reporting training	X		X						
Appropriate expectations training	X		X						
Regional Pain Scale	X								
48 hour WOMAC Pain	X		X[b]			X			
48 hour WOMAC Stiffness	X		X			X			
48 hour WOMAC Function	X		X			X			
24 hour Average Pain Intensity NRS	X		X			X			
Baseline Stiffness questionnaire	X								
Joint Stiffness Severity NRS	X								
Washout from analgesic medications		X						X[d]	
Daily BASS			X		X	X			
Accelerometer Setup				X					
Accelerometer Use				X	X				
Accelerometer Data Download						X			
Accelerometer Battery Charge						X			
Current Pain Intensity NRS			X[e]			X[e]			
STEPP →10 point pain NRS	X[c]		X[f]	X[f]		X[f]	X[f]	X[f]	
Randomization			X[g]						
IMP self-administration			X		X	X[h]			
IMP compliance review			X			X			
Patient Global Impression of Change								X	
Subject treatment preference								X[i]	
Qualitative interview									X[i]
Adverse events			X	X	X	X	X	X	X

[a] Vital signs (blood pressure, respiratory rate, heart rate and body temperature after 5 minutes of rest in a sitting position). After the screening assessment, vital signs assessments will consist of heart rate and blood pressure

[b] WOMAC pain subscale average score must be ≥4.0 on 0-10 scale to be eligible for Randomization on Day 1 of Treatment Period 1 of 4

[c] Screening STEPP is to confirm subject is capable of performing the exercise and completing the pre-STEPP and post-STEPP NRS

[d] A washout period of 3 to 7 days will occur at the start of Treatment Periods: 2 of 4, 3 of 4, and 4 of 4. During each washout, only acetaminophen will be allowed as rescue therapy (as needed up to 2000 mg/day)

[e] Current pain intensity performed immediately prior to the pre-dose STEPP and hourly at 1, 3, 5 and 7 hours after dosing

[f] Subjects will complete the 0-10-point NRS pain scale pre-dose (time 0) and immediately before (at rest) and then 2-5 minutes after completing the STEPP at 2, 4, 6 and 8 hours post-dose. Additionally, subjects will complete hourly current pain intensity rating 1, 3, 5, and 7 hours post-dose when not completing the STEPP

[g] Subjects will be randomized to a treatment sequence at Treatment Period 1 of 4

[h] Subjects will only take the 8 AM dose that day

[i] Completed after Visit 3, Treatment Period 4 of 4 or if the subject is withdrawn prior to completion

16.2 Subjective Assessments - amendment 1 and 2

Regional Pain Scale

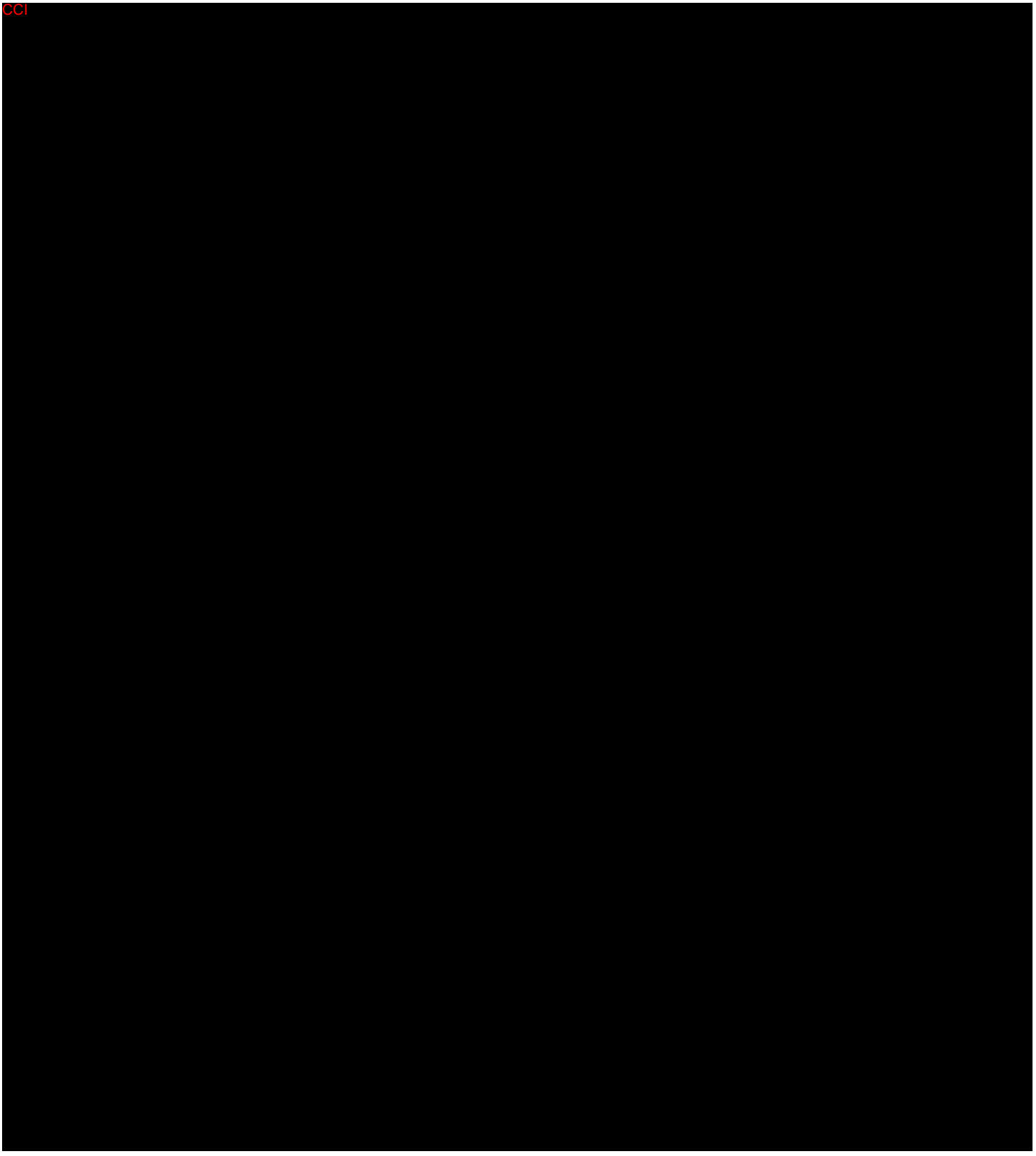
Please indicate below the amount of pain and/or tenderness you have had over THE PAST 7 DAYS in each of the joint and body areas listed below. Please make an X in the box that best describes your pain or tenderness. Be sure to mark both right side and left side separately. If you have had no pain or tenderness in a particular joint or body part, mark "None." There should be an answer for every joint or body part listed. (13)

JOINTS	None	Mild	Mod	Severe
Shoulder, Lt.	☐	☐	☐	☐
Shoulder, Rt.	☐	☐	☐	☐
Elbow, Lt.	☐	☐	☐	☐
Elbow, Rt.	☐	☐	☐	☐
Wrist, Lt.	☐	☐	☐	☐
Wrist, Rt.	☐	☐	☐	☐
Hand knuckles, Lt.	☐	☐	☐	☐
Hand knuckles, Rt.	☐	☐	☐	☐
Finger knuckles, Lt.	☐	☐	☐	☐
Finger knuckles, Rt.	☐	☐	☐	☐
Hip, Lt.	☐	☐	☐	☐
Hip, Rt.	☐	☐	☐	☐
Knee, Lt.	☐	☐	☐	☐
Knee, Rt.	☐	☐	☐	☐
Ankle, Lt.	☐	☐	☐	☐
Ankle, Rt.	☐	☐	☐	☐
Ball of foot, Lt.	☐	☐	☐	☐
Ball of foot, Rt.	☐	☐	☐	☐
Heel, Lt.	☐	☐	☐	☐
Heel, Rt.	☐	☐	☐	☐
Foot arch, Lt.	☐	☐	☐	☐
Foot arch, Rt.	☐	☐	☐	☐

OTHER BODY AREAS	None	Mild	Mod	Severe
Jaw, Lt.	☐	☐	☐	☐
Jaw, Rt.	☐	☐	☐	☐
Lower Back	☐	☐	☐	☐
Upper Back	☐	☐	☐	☐
Neck	☐	☐	☐	☐
Upper arms, Lt.	☐	☐	☐	☐
Upper arms, Rt.	☐	☐	☐	☐
Lower arms, Lt.	☐	☐	☐	☐
Lower arms, Rt.	☐	☐	☐	☐
Upper leg, Lt.	☐	☐	☐	☐
Upper leg, Rt.	☐	☐	☐	☐
Lower leg, Lt.	☐	☐	☐	☐
Lower leg, Rt.	☐	☐	☐	☐
Head	☐	☐	☐	☐
Chest	☐	☐	☐	☐
Abdomen	☐	☐	☐	☐

Baseline Stiffness Questionnaire

CCI



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[redacted]

0-10 Point Numerical Rating Scale (NRS)

Location (check one)

☐ **Left Knee** ☐ **Right Knee**

Current Pain Assessment

How would you rate the pain in your KNEE right now?

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst possible pain

Average Pain Intensity

How would you rate the average pain in your KNEE over the last 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst possible pain

Patient Global Impression of Change – Pain and Symptoms Due to OA of the Knee

PGIC in PAIN (PGIC-P):

Completed at the end of Day 4 of each Treatment Period:

√ (Check) the box you feel most closely describes how the pain in your knee has changed since you began this four-day treatment period. Please rate only your pain and not any other symptoms related to your index knee.

Choose only ONE response.

- ☐ Very Much Better
- ☐ Much Better
- ☐ Minimally Better
- ☐ No Change
- ☐ Minimally Worse
- ☐ Much Worse
- ☐ Very Much Worse

PGIC in SYMPTOMS (PGIC-S):

Completed at the end of Day 4 of each Treatment Period:

√ (Check) the box you feel most closely describes how all of the symptoms related to your index knee have changed since you began this four-day treatment period. Please include pain, stiffness, ability to function, and all other symptoms related to your index knee.

Choose only ONE response.

- ☐ Very Much Better
- ☐ Much Better
- ☐ Minimally Better
- ☐ No Change
- ☐ Minimally Worse
- ☐ Much Worse
- ☐ Very Much Worse

Treatment Preference

Which treatment was the *most effective* for relief of your knee pain?

- ☐ **Treatment Period 1**
- ☐ **Treatment Period 2**
- ☐ **Treatment Period 3**
- ☐ **Treatment Period 4**

Qualitative Interview - amendment 1

The qualitative interview will consist of a series of open-ended questions administered by a trained interviewer in one-on-one interviews with study subjects during the follow up phone call or if withdrawn prior to completion. The primary purpose of the qualitative interview is to provide additional data to augment the quantitative data collected from instruments such as the BASS, WOMAC, and NRS. It is anticipated that subjects will provide additional details not revealed through the quantitative instruments used to assess pain and stiffness, such as their perception regarding the clinical trial experience (e.g., pros and cons), additional details about the impact of each treatment on their daily function and quality of life, and information that may be useful to optimize the STEPP for inducing experimental pain in clinical studies.

The qualitative interview will take approximately 30-60 minutes to complete, and will consist of approximately 30 questions designed to collect information about: 1) subjects' experiences on the study treatments, to determine if there are any advantages of naproxen sodium (Aleve) that were not discovered using the quantitative instruments; 2) subjects' experiences with the STEPP, to determine if the procedure can be optimized to elicit OA pain and stiffness to a greater degree, which would increase assay sensitivity in trials of new treatments for pain due to OA of the knee; and, 3) subjects' perspectives on factors to optimize recruitment and retention in future OA studies conducted by Bayer.

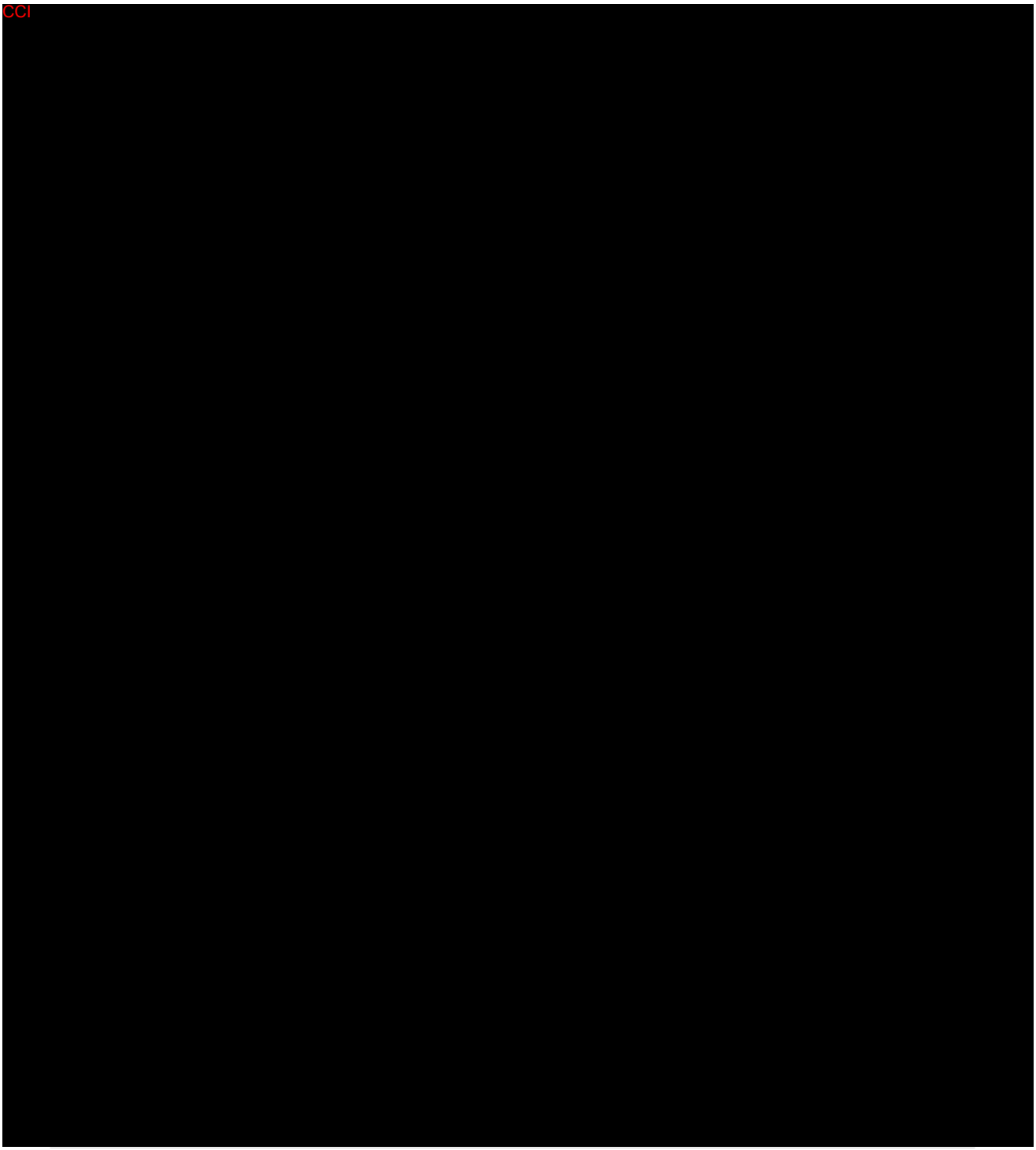
Audio from each interview will be recorded, transcribed, and analyzed using qualitative data analysis software[CCI] The specific procedures related to interviewer training, interview script, audio data collection, data analysis and reporting of results will be documented separately outside of the protocol.

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (0-10 NRS, 48-hour recall version) - amendment 2

Examples of the licensed version.

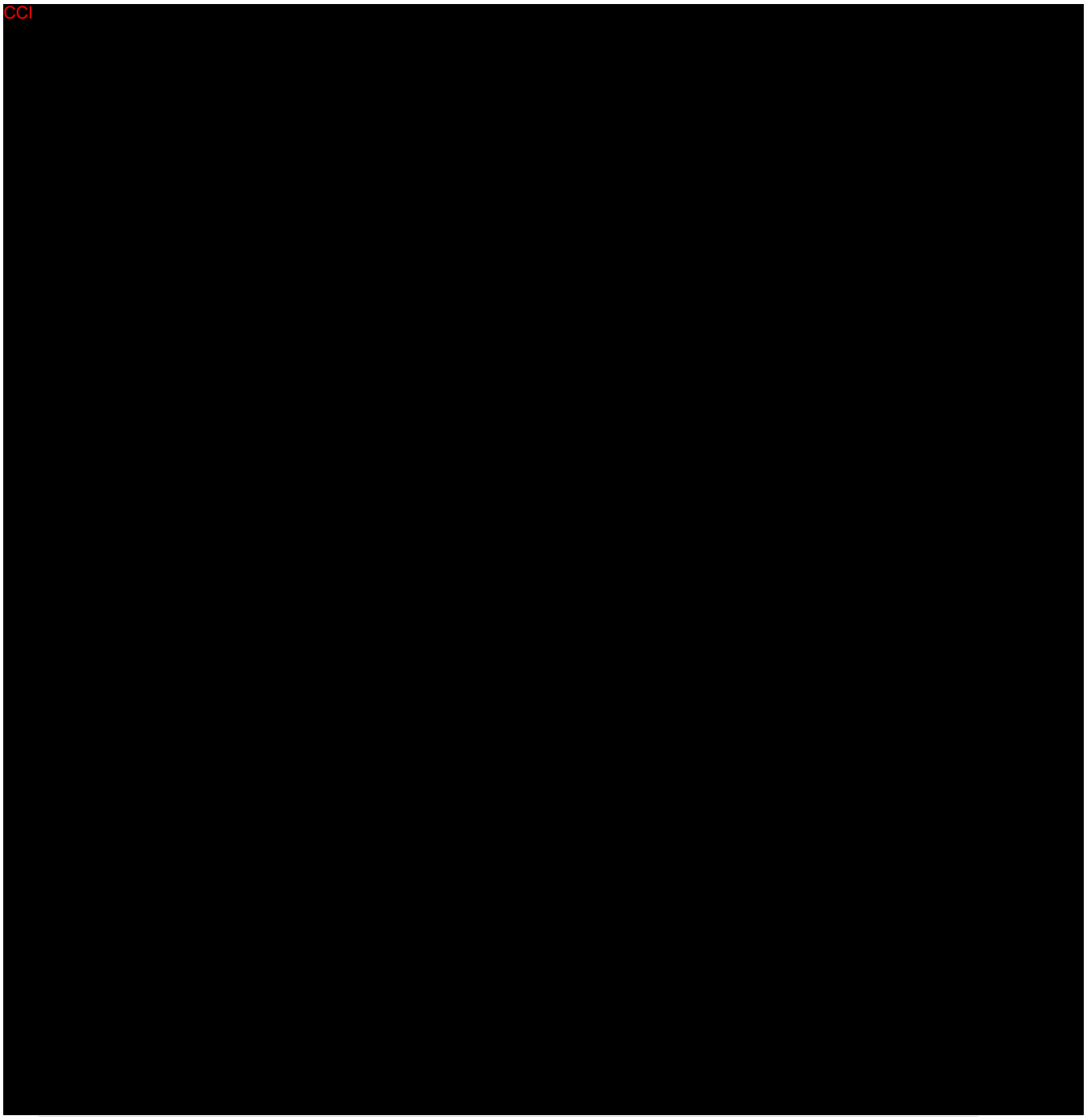
WOMAC Osteoarthritis Index NRS3.1

CCI

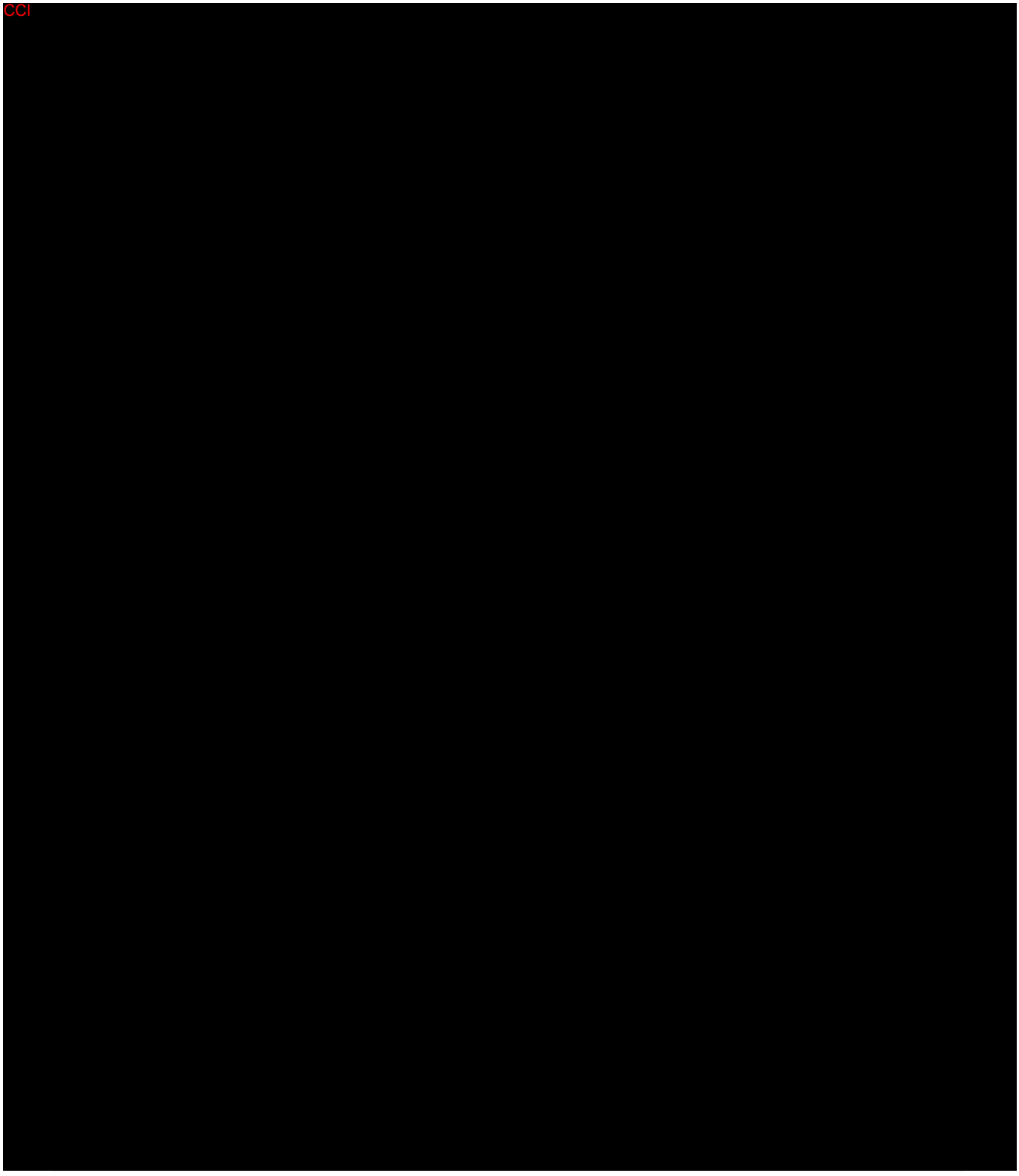


WOMAC NRS 3.1 – English for USA – V5 Page 2 of 6

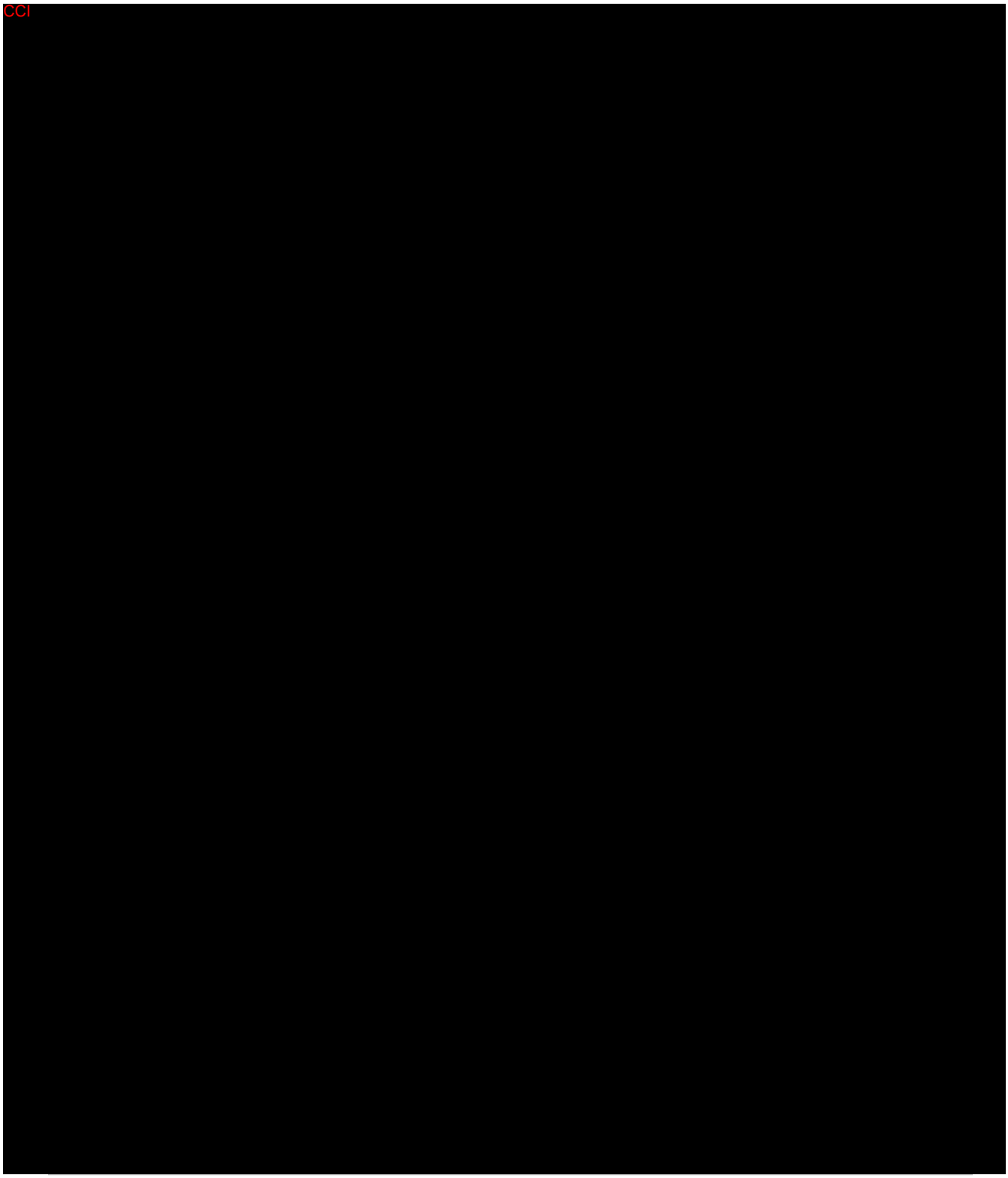
WOMAC Osteoarthritis Index NRS3.1

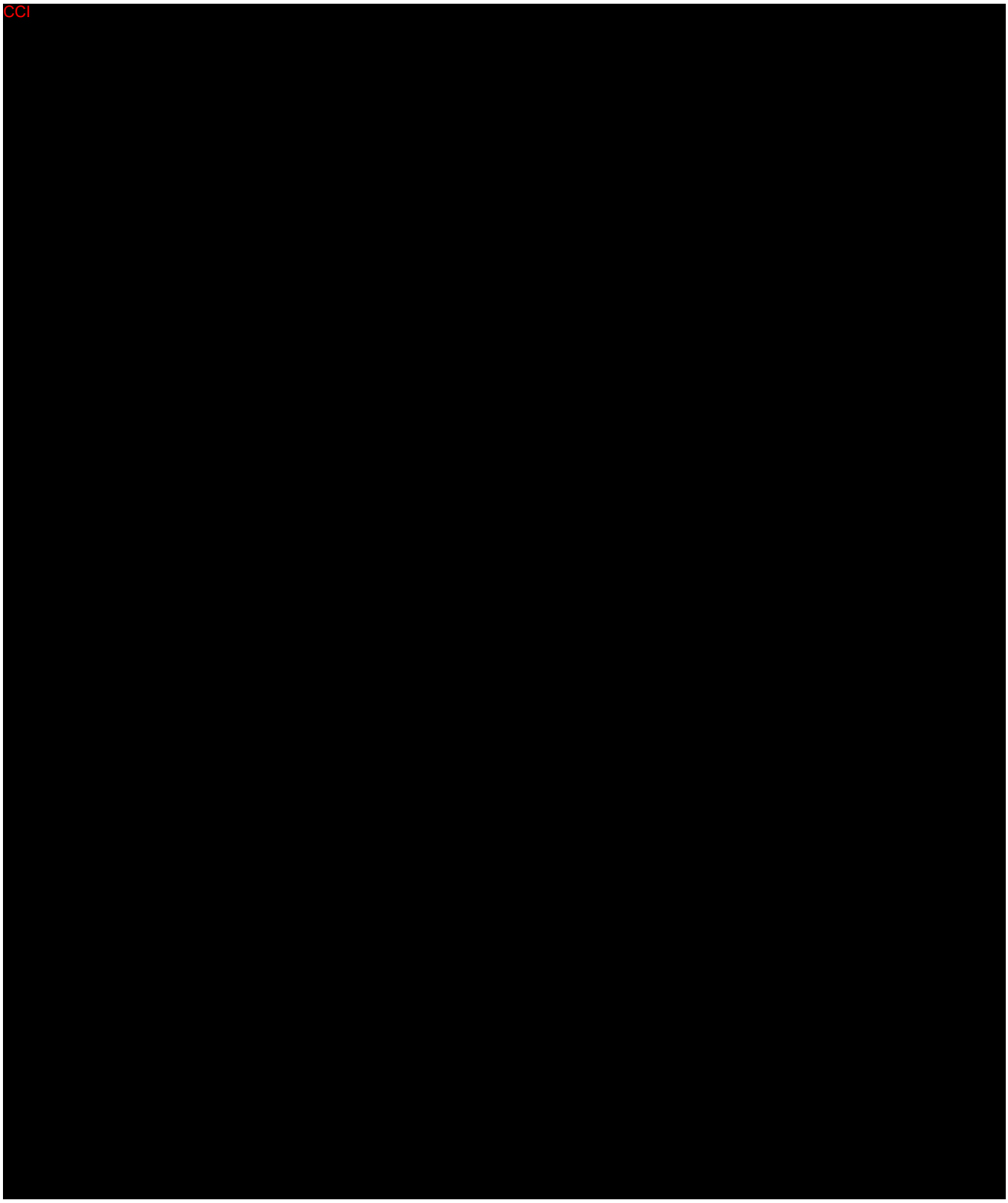


WOMAC Osteoarthritis Index NRS3.1



WOMAC Osteoarthritis Index NRS3.1

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Joint Stiffness Severity

Daily Brief Arthritis Stiffness Scale

The questions in this diary are designed to measure the severity of any STIFFNESS you have experienced in your [STUDY JOINT] over the past 24 hours.

While you may also experience pain related to your osteoarthritis, please be sure to think only about STIFFNESS in your [STUDY JOINT] when answering these questions.
Please complete the diary **before your morning dose of study medication.**

CCI

Kellgren and Lawrence Scale

Criteria for Radiologic Diagnosis of Osteoarthritis according to the Kellgren and Lawrence Criteria*

Grading	Interpretation
Grade 0	Normal
Grade I	Doubtful narrowing of joint space and possible osteophytic lipping
Grade II	Definite osteophytes and possible narrowing of joint space
Grade III	Moderate multiple osteophytes, definite narrowing of joint space, some sclerosis, and possible deformity of bone contour
Grade IV	Large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity of bone contour

*The Epidemiology of Chronic Rheumatism: Atlas of Standard Radiographs, Vol. 2, Oxford Scientific Publishers, 1963.