1 TITLE PAGE

Protocol Number:	VAN2001
Title:	A Phase 2a, Multicenter, Randomized, Double-blind, Placebo-controlled and Active-controlled, Parallel-group Study Evaluating the Analgesic Efficacy and Safety of V120083 in Subjects with Moderate to Severe Chronic Pain Due to Osteoarthritis of the Knee
Sponsor:	Purdue Pharma L.P. One Stamford Forum Stamford, CT 06901-3431 USA
Test Drug:	V120083
Phase:	Phase 2a
Version Date:	Version 2, 17-Feb-2017
Approval Date:	16-Feb-2017
GCP Statement:	This study is to be performed in compliance with the International Council for Harmonisation (ICH) and all applicable Good Clinical Practices (GCPs) and federal and local regulations.
Confidentiality:	This document is confidential. It contains proprietary information of Purdue Pharma L.P. Any viewing or disclosure of such information that is not authorized in writing by the sponsor (or designee) is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 SYNOPSIS

Synopsis

Name of Company: Purdue Pharma LP		**Protocol Number:** VAN2001
Name of Finished Product: V120083 capsules	**Name of Active Ingredient:** V120083	
US IND/EUDRACT No.: [redacted]		
Full Title of the Study: A Phase 2a, Multicenter, Randomized, Double-blind, Placebo-controlled and Active-controlled, Parallel-group Study Evaluating the Analgesic Efficacy and Safety of V120083 in Subjects with Moderate to Severe Chronic Pain Due to Osteoarthritis of the Knee		
Investigator(s)/Center(s): Approximately 30		
Planned First Subject First Visit: Q1 2017	**Phase of Development:** Phase 2a	

Objectives:

Primary:

- The primary objective of this study is to evaluate the analgesic efficacy of V120083 twice daily (bid) compared to placebo in subjects with moderate to severe chronic pain due to osteoarthritis of the knee using the "average pain over the last 24 hours" score from the modified Brief Pain Inventory – short form (mBPI-SF) pain severity subscale at week 4 of the double-blind period.

Secondary:

The secondary objectives of this study are to:

- Evaluate the safety and tolerability (including adverse event [AE] reporting, clinical laboratory parameters, and physical examination) of 2 dose levels of V120083
- Evaluate the efficacy of V120083 on pain, stiffness, physical function, and overall disability using the Western Ontario and McMaster Osteoarthritis Index (WOMAC) subscale and total scores
- Evaluate the efficacy of V120083 on pain intensity due to OA using numerical rating scale (NRS) pain scores from the mBPI-SF pain severity subscale
- Evaluate the impact of V120083 on pain-related quality of life/function using the mBPI-SF pain interference subscale
- Evaluate the effect of V120083 on pain severity and pain interference overall using the mBPI-SF total score
- Evaluate the impact of V120083 on subjects' health state (as defined by mobility, self-care, daily activities, pain/discomfort, and anxiety/depression) using the EuroQol-5D (EQ-5D)
- Evaluate the impact of V120083 on subjects' functional health and well-being using the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36)
- Evaluate subject global impression of treatments using the Patient Global Impression of Change (PGIC) questionnaire
- Evaluate the impact of V120083 on mood (anxiety and depression) using the Hospital Anxiety and Depression Scale (HADS)

- Evaluate the efficacy of naproxen vs. placebo for assay sensitivity using the primary and secondary endpoints indicated above.
- Determine plasma levels of V120083 in subjects under clinical use conditions.
- [redacted]
- Evaluate supplemental analgesic medication use
- Evaluate treatment response
- Evaluate the occurrence of treatment-emergent suicidal ideation or behavior using the Columbia – Suicide Severity Rating Scale (C-SSRS)

Study Design (Methodology):

This is a phase 2a, double-blind, double-dummy, placebo- and active-controlled, parallel-group, multicenter study to evaluate the analgesic efficacy and safety of V120083 vs placebo in subjects with moderate to severe chronic pain due to osteoarthritis (OA) of the knee (Figure 1). The total duration of the study for a given subject is up to 56 days, inclusive of a 21 day screening period; a 28 day double blind treatment period; and a 7 day follow up period. Naproxen 500 mg bid will be used as an active control to determine the assay sensitivity of the study.

During the screening period, subjects will be assessed for their eligibility and those who are qualified to continue in the study will be randomized at visit 2 in equal ratios to receive 1 of the following 4 treatments in the double-blind period: V120083 30 mg bid, V120083 60 mg bid, naproxen 500 mg bid, or placebo. Clinic visits during the double-blind period will occur at week 1 (visit 3), week 2 (visit 4), and week 4 (visit 5/end-of-study visit).

Blood samples for pharmacokinetic (PK) analysis will be collected at visits 2, 3, 4, and 5. The PK evaluation will involve two components: intense PK sampling and sparse PK sampling. Sparse PK sampling will be conducted for all subjects enrolled (276 subjects), with samples collected at visits 3 (predose, 1 and 2 hours postdose), 4 (predose or postdose), and 5 (predose or postdose) during the treatment period. Intense PK sampling will be conducted for 24 subjects, consisting of the sparse PK schedule and visit 2 predose sample and postdose sampling at 1, 2, 4, 6, and 8 hours (day 1 of dosing). The study will include pharmacogenomics (PG) sampling that will be optional for all subjects.

Starting at screening, subjects may take their own supplemental analgesic medication, ie, 500 mg acetaminophen (APAP) which can be taken as needed up to 2 g/ 24 hours for breakthrough pain, but is not to be taken within 24 hours of visit 2. Acetaminophen 500 mg will be provided as supplemental analgesic medication during the double-blind period. Subjects may take no more than 4 tablets of APAP/acetaminophen 500 mg per 24 hours (ie, no more than 2 g/24 hours) and no more than 2 tablets of APAP/acetaminophen 500 mg at any one time for breakthrough pain. All subjects must refrain from taking any supplemental analgesic medications for at least 24 hours prior to the clinic visits during the double-blind period (ie, no supplemental analgesic medication is allowed during the 24 hour period before the week 1 [visit 3], week 2 [visit 4], and week 4 [visit 5] visits during the double-blind period).

An interim analysis may be performed for futility when approximately 50% of randomized subjects have completed the study. An independent Data Monitoring Committee (DMC) will review all unblinded safety and efficacy data from the analysis and make recommendations, as necessary, for plans for additional studies in the clinical program.

Study Design:

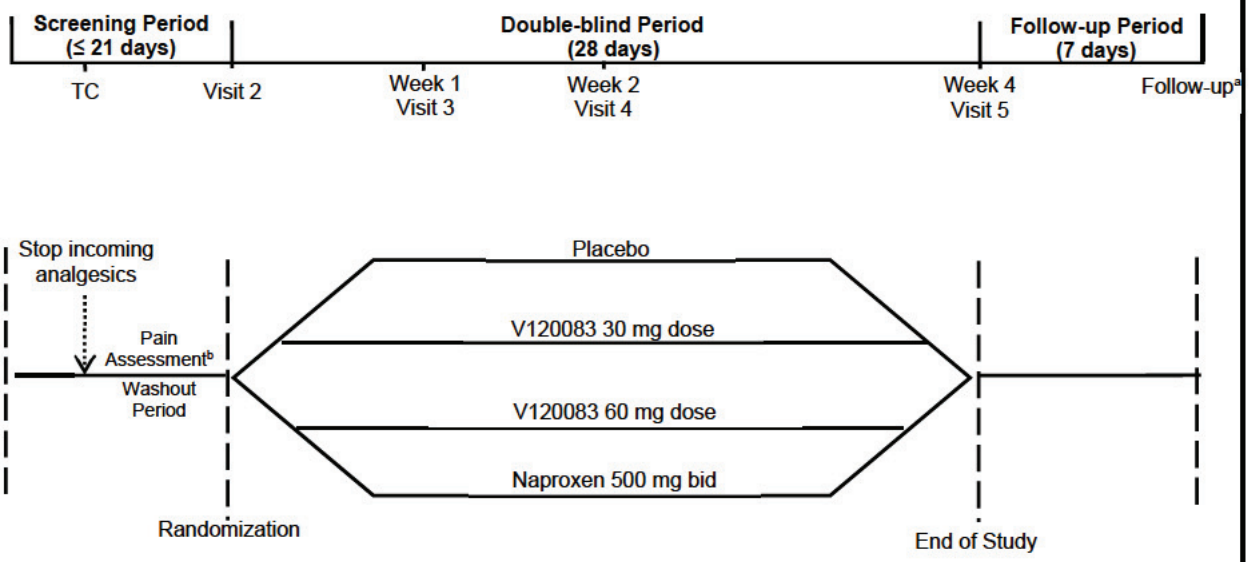

Figure 1 Study Design

Approximately 69 subjects/treatment arm
TC = telephone contact to instruct subjects meeting initial enrollment criteria to stop all incoming analgesics in accordance with acceptable medical practice and begin washout period (where applicable).
[a] The follow-up visit may be conducted via a telephone contact or at a clinic visit.
[b] Subjects who do not take any medications for pain will record their "average pain over last 24 hours" scores for 3 to 7 days. Subjects who take medications for pain will record their "average pain over last 24 hours" scores for 3 to 9 days after all incoming pain medications have been stopped. All subjects may return to the study clinic for visit 2 as soon as they recorded "average pain over last 24 hours" scores ≥ 4 and ≤ 9 for ≥ 3 consecutive days. All subjects must return to the study clinic for visit 2 within 96 hours of the latest qualifying pain score entry within the pain assessment period.

Planned Number of Subjects (including sample size rationale):

Approximately 69 subjects are planned for each treatment arm of the study. The planned total number of randomized subjects is approximately 276.

The analgesic effect size of V120083 is unknown. Therefore, the sample size calculation is based on a clinically important difference for OA pain reduction of 1 unit on an 11-point NRS (0 to 10). [redacted] This study may provide appropriate information for the data variability in the sample size calculations. The standard deviation (SD) for average pain over last the 24 hours, an individual question of the mBPI-SF at week 4, was approximately 2.34. With a fixed sample size study design, the sample size needed for 80% power to detect this difference with a significance level of 0.05 (1-sided) is 69 subjects per arm, assuming a 1:1 randomization ratio of each active arm to placebo. The sample size calculation was performed with nQuery+nTerim 3.0.

Indication:

Osteoarthritis pain of the knee

Criteria for Inclusion/Exclusion:

Inclusion Criteria:

1. Males and females ≥ 40 and ≤ 80 years of age with moderate to severe chronic OA pain of the knee (lasting several hours daily) as their predominant pain condition for at least 6 months prior to screening;
2. Diagnostic criteria for primary pain condition (American College of Rheumatology [ACR] clinical and radiographic criteria):
   - At least 1 of the following in addition to knee pain: age >50, morning stiffness <30 min, crepitus on active motion, and
   - Kellgren-Lawrence (K-L) grade 2 or 3 radiographic evidence at the screening visit as determined by a local radiologist or rheumatologist. If a radiograph is not available, one must be taken and the diagnostic criteria must be confirmed before visit 2. Note that K-L grades 2-3 require the presence of osteophytes, which is required to meet ACR clinical and radiographic criteria for knee OA;
3. Subjects with body mass index (BMI) ranging from 18.0 to 38.0 (kg/m^2), inclusive;
4. Subjects whose OA pain of the index knee is not adequately treated prior to the screening visit:
   - Subjects must have a self-reported average pain intensity rating of moderate or severe on a verbal rating scale (ie none, mild, moderate, and severe) over the 7 days prior to the screening visit
5. The subjects must have "average pain over the last 24 hours" scores ≥ 4 and ≤ 9 on an 11-point NRS for the index knee on ≥ 3 consecutive days during the pain assessment period and come in for visit 2 within 96 hours after the latest qualifying pain score entry
6. For subjects receiving adjunct therapy for chronic pain, such as physical therapy, exercise, chiropractic therapy, acupuncture therapy, TENS unit, or herbal and other complementary therapy, such treatment should be either stopped at screening or remain unchanged during the entire study; Adjunct therapies, glucosamine and chondroitin initiated at least 1 month before screening can be continued at stable dose/regimen (should not be initiated during the study); elastic support and other braces applied to either knee should be used during the study in the same manner as at screening;
7. If either female of childbearing potential (ie, not medically or surgically sterilized or not postmenopausal more than 1 year) or non-surgically sterilized male with sexual partner of childbearing potential, be willing to use adequate and reliable contraception throughout the study (eg, abstinence or barrier with additional spermicidal foam or jelly, or the use of intrauterine device or hormonal contraception by female subjects and partners of male subjects);
8. Subjects who are willing and able to stop taking any/all analgesic medications, including over-the-counter pain medications, opioids, marijuana, and topical analgesics for OA pain for the duration of the study, with the exception of study-specific rescue medication;
9. Subjects who are willing and able to be compliant with the protocol, are capable of subjective evaluation, are able to read and understand questionnaires, and are able to read, understand, and sign the written informed consent.

Exclusion Criteria:

1. Subjects with radiographic evidence of OA with Kellgren-Lawrence (K-L) grade 0, 1 or 4;
2. Females who are pregnant (positive serum/urine test) or lactating or planning to become pregnant during the study;
3. Subjects with chronic pain conditions other than OA of the knee as their predominant pain condition, including gout, pseudogout, psoriatic arthritis, active Lyme disease, rheumatoid arthritis or any other inflammatory arthritis, fibromyalgia, neuropathic pain conditions, bursitis, or acute injury or signs of active infection in the target pain area;
4. Subjects scheduled for surgical interventions of the disease site or any other major surgery during the study conduct period;

5. Subjects with a history of a prior joint replacement of the index knee;
6. Subjects who have had arthroscopy on either knee or hip within 6 months of entering the study, or open surgery on either knee or hip within 12 months of entering the study;
7. Subjects with a palpable effusion in either knee;
8. Subjects with a history of significant trauma to a knee, hip or shoulder within the previous year;
9. Subjects who have significant pain, other than or more than knee pain, including significant hip, back pain, that may confound the analgesic efficacy assessments of this study;
10. Subjects who used immunosuppressive drugs, anti-depressants other than Selective Serotonin Reuptake Inhibitors (SSRIs for depression), warfarin or anticoagulants, cyclosporine (except ophthalmic emulsion), aspirin except for 81 mg daily dose for cardiovascular prophylaxis, diuretics with unstable cardiac diseases, or methotrexate within 30 days of study randomization;
11. Subjects who initiated, or received an increase in the dose of, oral corticosteroids within 6 weeks prior to entering the study or who anticipate a change in oral corticosteroid therapy during the study period;
12. Subjects who have used any investigational medication within 30 days or five half-lives, whichever is longer, prior to the first dose of study medication;
13. Subjects with a history of seizures within the past 5 years;
14. Subjects with evidence of current major depression or other clinically significant psychiatric disorder that in the opinion of the investigator would interfere with the subject's ability to participate in the study. Subjects with history of a psychotic disorder or psychosis, bipolar disorder, or post-traumatic stress disorder should be excluded. Subjects with major depression in remission or other psychiatric disorder must be on a stable medication (SSRI) for > 3 months to participate in the study;
15. Subjects with HADS score over 10 on either subscale at visit 1;
16. Subject answers "yes" to "suicidal ideation" in prior 24 months to any items 1 through 5 on the C-SSRS;
17. Subject answers "yes" to any lifetime "suicidal behavior" item on the C-SSRS;
18. Subjects with any history of alcohol or other substance abuse or addiction within the past 5 years;
19. Subjects who use immediate release/short-acting opioids at a daily dose exceeding 15mg daily morphine equivalent more than 4 days per week;
20. Subjects who have used any extended-release/long acting opioids in the 30 days prior to screening;
21. Subjects who have a positive urine drug test for illicit drugs, cannabinoids, non-prescribed opioids;
22. Subjects taking strong CYP3A inhibitors, inducers, sensitive substrates, substrates with narrow therapeutic range, or p-gp substrates (see Appendix Q);
23. Subjects taking moderate CYP3A inhibitors if the dose has not been stable for at least 1 month prior to start of study drug dosing (see Appendix Q);
24. Subjects for whom it is anticipated that therapy with a moderate to strong CYP3A inhibitor, or CYP3A inducers, sensitive substrates, substrates with narrow therapeutic range, or P-gp substrates will be initiated during the study, after the screening visit;
25. Subjects with clinically unstable medical conditions, including cardiac disease (unstable atrial fibrillation, any symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia), uncontrolled hypertension, respiratory disease, biliary tract disease, hypothyroidism, renal disease, adrenal cortical insufficiency, or any other medical condition that, in the investigator's opinion, is inadequately treated and precludes entry into the study;
26. Subjects with myocardial infarction, stroke, or other thrombotic events in the past 5 years; and/or any history of coronary artery bypass graft;

27. Subjects with a screening electrocardiogram (ECG) showing a QTcF value (QT data corrected for heart rate using the Fridericia formula) of ≥ 470 milliseconds (msec) or other ECG findings that, in the investigator's opinion, would preclude participation in the study;
28. Subjects with any clinically significant abnormal laboratory value, including evidence of impaired liver function (values ≥ 3 times the upper limit of normal for aspartate transaminase [AST/SGOT] or alanine transaminase [ALT/SGPT], or bilirubin ≥ 1.5 mg/dL), or impaired kidney function (eGFR < 60 mL/min);
29. Subjects with positive hepatitis B, hepatitis C or HIV test results indicative of current infection;
30. Subjects with a history of malignancy within the past 5 years, with exception of basal cell carcinoma that has been successfully treated;
31. Subjects with an ongoing or resolved worker's compensation claim and/or litigation related to their pain disorder;
32. Subjects who, in the opinion of the investigator, are unsuitable to participate in this study for any other reason;
33. Pain-condition-specific exclusions: Subjects who received local pain-control procedures, including intra-articular steroid injection in the index knee or intramuscular steroid injection at any site, joint lavage, or other invasive therapies within 6 weeks of entering the study or hyaluronate injection in the index knee within 12 weeks of entering the study, or for whom such therapies are planned within the study period.
34. Subjects with a history of bleeding disorders or history of documented gastrointestinal ulcer disease.
35. Subjects who are allergic to or cannot tolerate aspirin, other NSAIDS (including naproxen), or acetaminophen, including history of NSAID-induced asthma, or nasal polyps
36. Subjects who have received TRPV1 antagonist previously

Test Treatment, Dose, and Mode of Administration:

- **V120083 30 mg, bid, po:** supplied as blinded capsules with each capsule containing 30 mg V120083.
    - Subjects assigned to V120083 30 mg will take 1 capsule containing V120083 30 mg, 1-V120083 placebo capsule, and 1 active comparator placebo capsule.
- **V120083 60 mg, bid, po** supplied as blinded capsules with each capsule containing 30 mg V120083.
    - Subjects assigned to V120083 60 mg will take 2 capsules containing V120083 30 mg and 1 active comparator placebo capsule.

During the double-blind treatment period (days 1 through 28), subjects will self-administer orally (po) study drug bid, except on the first day of the double-blind treatment period, when the study personnel will provide the first dose at the site. Supplemental analgesic medication should not be taken during the 24 hours prior to clinic visits. Study drugs will be supplied in blister packages to be provided to subjects at each clinic visit. All subjects will take 3 capsules bid as outlined in the synopsis and Section 9.4.

Reference Treatment, Dose, and Mode of Administration:

- **Active comparator, bid, po:** Naproxen supplied as blinded capsules with each dose consisting of one 500-mg capsule.
    - Subjects assigned to naproxen 500 mg bid will take 1 capsule containing naproxen 500 mg and 2 capsules containing V120083 placebo
- **V120083 placebo, bid, po:** Capsules that match both 30- and 60-mg doses supplied as blinded capsules; to be taken po bid by subject's assigned to 30 mg V120083, active comparator, or placebo.
    - Subjects assigned to placebo will take two V120083 placebo capsules and 1 active comparator placebo
- **Active comparator placebo, bid, po:** Capsules that match active comparator supplied as blinded capsules; to be taken by subjects assigned to V120083 (30 or 60 mg) or placebo.

Supplemental Medication:

Supplemental analgesic medication is acetaminophen (APAP) 500 mg. No more than 4 tablets per 24 hours (ie, no more than 2 g per 24 hours), and no more than 2 tablets (1 g) per dose, as needed, will be permitted during the double-blind period. All subjects will be instructed to refrain from taking any supplemental analgesic medication for at least 24 hours prior to the weeks 1, 2, and 4 visits (visits 3, 4, and 5, respectively) of the double-blind period.

Concomitant Medication:

All medications used for chronic pain, other than the study drugs and supplemental analgesic medication, are prohibited during the study. Medication used for chronic pain includes opioids, NSAIDs (other than the study drug), cyclooxygenase-2 (COX-2) inhibitors, aspirin, gabapentin, antiepileptics, and antidepressants (eg, tricyclics and selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors).

Other prohibited concomitant treatments include benzodiazepines, monoclonal antibodies for osteoporosis, methotrexate, any local OA treatments for the knee(s), including topical anesthetics or NSAIDs; topical, intra-articular, or systemic corticosteroids; or any OA injection in the knee(s), anti-depressants (other than SSRIs, serotonin norepinephrine reuptake inhibitors [SNRIs] for depression), warfarin or anti-coagulants, and cyclosporine (except ophthalmic emulsion).

Based on in vitro data, V120083 is a CYP3A4/5 substrate and has the potential to inhibit P-gp and CYP3A4/5. Concomitant administration of CYP3A inhibitors, inducers, substrates, and P-gp substrates are restricted as follows:

- *Subjects taking strong CYP3A inhibitors will be excluded from the study due to potential increases in plasma levels of V120083 when co-administered with V120083. Subjects who initiate these medications during the study will be discontinued from the study.*
- *Subjects taking moderate CYP3A inhibitors will be excluded if the dose has not been stable for at least one month prior to start of study drug dosing (see Appendix Q for a representative list of moderate and strong CYP3A inhibitors). Subjects who discontinue therapy with moderate CYP3A inhibitors during the study will be permitted to continue on the study*
- *If the subject is taking multiple moderate CYP3A inhibitor(s) or the category is unknown, the investigator should contact the medical monitor and subjects are to be carefully monitored.*
- *Subjects taking CYP3A Inducers will be excluded from the study due to potential decrease in plasma levels of V120083. Subjects who initiate these medications during the study will be discontinued from the study.*
- *Subjects taking CYP3A sensitive substrates and substrates with narrow therapeutic range, or P-gp substrates will be excluded from the study due to potential increases in plasma levels of such medications when co-administered with V120083. Subjects who initiate these medications during the study will be discontinued from the study. (See Appendix Q for a list of inducers and substrates)*

APAP/acetaminophen may be used intermittently for headache, fever, or acute pain up to the 2 g per 24 hour maximum amount; low-dose aspirin (81mg daily) for cardiovascular disease prophylaxis is allowed. Note: Subjects will be requested not to take any APAP/acetaminophen for at least 24 hours before each clinic visit.

Duration of Treatment and Study Duration

Total study duration is up to 56 days.

The screening period is up to 21 days; the double-blind period is 4 weeks; the follow-up period is 7 days.

Study Procedures:

Screening Period (up to 21 days)

Visit 1

At visit 1, after written informed consent is obtained, the subject will undergo a complete evaluation for study eligibility. To qualify for the study, subjects must meet all initial study entry criteria, including a self-reported average pain intensity rating of moderate or severe on a verbal rating scale (ie, none, mild, moderate, severe) over the 7 days prior to the screening visit. For subjects with OA pain at both knees, the investigator will identify the more painful knee joint to serve as the index knee for the study. Subjects will be instructed to record all pain assessments based on the index knee.

Telephone Contact and Washout Period

As soon as the laboratory results, ECG results, and radiograph results are available, the site staff will contact the subjects by telephone to inform them of the results and whether they are qualified to continue in the study. Subjects who do not meet the initial entry criteria will be considered screen failures. For subjects who meet the initial entry criteria and:

- Who do not take any analgesic medications for their pain, the site staff will instruct them to record in the diary their "average pain over the last 24 hours" scores for their index knee at approximately 8 PM every evening for 3 to 7 days. These subjects may return to the study clinic for visit 2 as soon as they have "average pain over the last 24 hours" scores ≥ 4 and ≤ 9 for ≥ 3 consecutive days. All subjects must return to the study clinic for visit 2 within 96 hours of the latest qualifying pain score entry within the pain assessment period.
- Who are on topical and/or oral analgesics (including NSAIDs, opioids, antidepressants, anticonvulsants, or other medications for OA), the site staff will instruct them to discontinue from these medications in accordance with accepted medical practice. Once all medications used for pain have been discontinued, the subjects will undergo an analgesic washout period of up to 9 days. During this period, the subjects will record in the diary their "average pain over the last 24 hours" scores for the index knee at approximately 8 PM every evening for 3 to 9 days. These subjects may return to the study clinic for visit 2 as soon as they reported "average pain over the last 24 hours" scores of ≥ 4 and ≤ 9 for ≥ 3 consecutive days. All subjects must return to the study clinic for visit 2 within 96 hours of the latest qualifying pain score entry within the pain assessment period.
- Subject's own supplemental analgesic medication, ie, APAP/acetaminophen, is permitted to be taken during the washout period as needed (PRN) up to 2 g/24 hours. Supplemental analgesic medication is not to be taken within 24 hours of visit 2.

Concomitant medications and AEs will be documented during this telephone contact.

Rescreening of subjects who previously failed screening is allowed only with the permission of the medical monitor on a case by case basis.

Subjects may be considered for rescreening if they failed screening previously due to eligibility criteria that are now allowed under the current amended protocol; delay of acquiring records; out of window issues (eg, lost or delayed labs); timing of exclusionary procedures; or other reasons approved by the medical monitor.

Subjects with positive hepatitis B, hepatitis C, or human immunodeficiency results, subjects with a positive urine drug test (UDT) for illicit drugs or non-prescribed opioids; and/or subjects who previously received study drug in a V120083 trial will not be permitted to be rescreened.

X-rays for rescreened subjects do not need to be repeated provided they were originally collected as part of this study and occurred within 1 month of rescreening.

All rescreening must be approved in advance by the medical monitor.

Double-blind Period (4 weeks)

The double-blind period is 4 weeks.

Prior to entering the double-blind period, the subjects' "average pain over the last 24 hours" scores will be assessed to determine the subjects' eligibility to continue in the double-blind period. To qualify for entry into the double-blind period, subjects must have "average pain over the last 24 hours" scores of ≥ 4 and ≤ 9 for ≥ 3 consecutive days during the pain assessment period. Subjects who do not qualify for the double-blind period will be discontinued from the study as screen failures.

Subjects who are eligible for the double-blind period will have visit 2 (Day 1) scheduled in the morning. At this visit, all qualified subjects will be randomized to receive the double-blind treatments. The first dose of study drug will be administered at the study clinic. For subjects in the intensive PK subgroup, blood samples for pharmacokinetic (PK) analysis will be collected predose and postdose at 1, 2, 4, 6, and 8 hours. These subjects will remain at the study clinic until the PK samples are collected.

Clinic visits during the double-blind period will occur at week 1 (visit 3), week 2 (visit 4), and week 4 (visit 5) visits. All clinic visits should occur in the morning. During these visits, PK samples will be collected at visits 3 (predose, 1 and 2 hours postdose), 4 (predose or postdose), and 5 (predose or postdose) during the treatment period. Supplemental analgesic medication is APAP/acetaminophen 500 mg. No more than 4 tablets/24 hours (ie, no more than 2 g/24 hours), as needed, will be permitted during the double-blind period. All subjects will be instructed to refrain from taking any supplemental analgesic medication for at least 24 hours prior to the weeks 1, 2, and 4 visits (visits 3, 4, and 5, respectively) of the double-blind period and to refrain from taking study drug dose on the morning of clinic visits to allow for predose PK sampling.

Subjects are allowed a ±1 day window for visit 3, and a ±2 day window for visits 4 and 5. All scheduled visits in the double-blind period will be anchored to the day of randomization (visit 2). Subjects who discontinued treatment early will be instructed to return to study clinic for an early discontinuation visit (visit 5). After the end of the study or early discontinuation, subjects will be converted to a pain regimen as deemed medically appropriate by the investigator/designee.

Follow-up Period (7 days)

Subjects will receive a telephone call approximately 1 week after the end-of-study visit to assess subject status and documentation of AEs and concomitant medications.

Criteria and Methods for Evaluation:

Efficacy Variables/Endpoints:

Primary Efficacy Variable:

The primary efficacy variable in this study is the "average pain over the last 24 hours" score from the mBPI-SF pain severity subscale at week 4 of the double-blind period.

Secondary Efficacy Variables/Endpoints:

The secondary efficacy variable/endpoints are:

- Weekly "average pain over the last 24 hours" collected by e-diary
- Average daily "pain right now" collected by e-diary
- WOMAC total scores
- WOMAC pain subscale
- WOMAC physical function subscale
- WOMAC stiffness subscale
- mBPI-SF total scores (all parts of question 6)
- mBPI-SF pain severity subscale
- mBPI-SF pain interference subscale
- Responder to treatment
- SF-36

- EQ-5D
- PGIC at the end of double-blind period (week 4)
- Supplemental analgesic medication use
- Evaluate the occurrence of treatment-emergent suicidal ideation or behavior using the Columbia – Suicide Severity Rating Scale (C-SSRS)

Other Variables

Evaluation of taste disturbance using the Chemotherapy-induced Taste Alteration Scale (CiTAS) will be performed at prespecified times.

Drug Concentration Measurements:

Blood samples for pharmacokinetic (PK) analysis will be collected at visits 2, 3, 4, and 5. The PK evaluation will involve two components: intense PK sampling and sparse PK sampling. Sparse PK sampling will be conducted for all subjects enrolled (276 subjects), with samples collected at visits 3 (predose, 1 and 2 hours postdose), 4 (predose or postdose), and 5 (predose or postdose) during the treatment period. Intense PK sampling will be conducted for 24 subjects, consisting of the sparse PK schedule and visit 2 predose sample and postdose sampling at 1, 2, 4, 6, and 8 hours (day 1 of dosing). A single sample of blood (6 mL) will be taken for each time point. The date and time of dosing and sampling will be documented on the case report forms (CRFs).

Analytical Methodology:

Plasma concentrations of V120083 and possibly its metabolites will be quantified by a validated bioanalytical method.

Safety Variables:

Safety will be assessed using adverse events (including SAEs), clinical laboratory results, vital sign measurements, physical examinations, ECGs, C-SSRS, and results from the Hospital Anxiety and Depression Scale (HADS)

Pharmacogenomic Sampling:

The study will include PGx sampling that will be optional for all subjects.

Statistical Methods:

Analysis Populations:

The enrolled population consists of all individuals who sign the informed consent form.

The safety population is the group of subjects who are randomized and receive at least 1 dose of the double-blind study drug.

The full analysis population (FAP) is the group of subjects who are randomized, receive at least 1 dose of double- blind study drug, and have at least 1 efficacy assessment.

The per-protocol population is a subset of the full analysis population and consists of all subjects in the full analysis population (FAP) who do not have major protocol violations.

The Pharmacokinetics (PK) population consists of all individuals who are randomized and receive at least 1 dose of the V120083 and have at least 1 valid, quantifiable PK blood sample

Efficacy Analysis:

Primary efficacy analysis is based on the “average pain over 24 hours” score in the mBPI-SF pain severity subscale at week 4 and the analysis will be performed using a mixed-effect general linear model with repeated measures (MMRM). The MMRM will include treatment (4 levels: V120083 30 mg bid, V120083 60 mg bid, naproxen 500 mg bid, and placebo) and time (3 levels for weeks 1, 2 and 4) as fixed effects; the baseline pain subscale will be incorporated as fixed covariates, and subject will be a random effect. Restricted maximum likelihood (REML) will be used to estimate the parameters in the model. While data from the entire double-blind period will be used to fit the linear model to get a better estimate of the variance-covariance matrix, the primary

comparison between groups will be based on estimates/contrasts for the pain score over the last 24 hours at week 4 means.

Secondary Efficacy Analysis:

The PGIC rating score (obtained at the week 4 or end-of-study visit) will be measured on a 7-point scale in which 1 = very much improved and 7 = very much worse. The categories will be compared between treatment group and placebo using the Chi-squared test. Further analysis will be conducted on collapsed categories (very much improved/much improved vs improved/no change/worse/much worse/very much worse) using Fisher's exact test.

Other continuous longitudinal variables will be analyzed similarly to the primary efficacy method, using an MMRM.

All hypothesis tests will be 1-sided and conducted at the 5% level of significance.

Pharmacokinetic Analyses:

Pharmacokinetic parameters of V120083 will be calculated based on the plasma concentrations of V120083 by using non-compartmental analysis for intense PK sampling component.

A population PK analysis may be performed and will be reported in a separate report from the clinical study report.

Interim Analysis:

All interim analysis may be performed by the independent statistician/independent programmer and communicated to the independent (DMC. At the interim analysis, the following procedures will be performed:

- Safety evaluation for early termination may be performed when 50% of subjects have completed the study. The independent statistician /programmer will provide safety data listings and summary tables by unblinded treatment arms. The DMC members will review the safety data, including AEs and clinical laboratory values. The decision to stop 1 or more treatment arms due to safety issues will be made based on clinical judgment. The arm will be stopped if there is significant physical toxicity or evidence of impending risk of physiologic harm or extremely abnormal laboratory findings related to treatment.
- Efficacy evaluation for V120083 treatment arms may be performed by the independent statistician/programmer when 50% of subjects have completed the study. The 50% interim analysis will be performed to evaluate the efficacy of each dose of study drug in the study population. The DMC will review the results of the analysis and make recommendations, as appropriate, regarding plans for further studies.

Lan et al (1982) introduced stochastic curtailment to stop a trial if, given current data, it is likely to predict the outcome of the trial with high probability. [32]The conditional power at the scheduled end of the study, given the observed data at the interim evaluation, will be calculated with a stochastic curtailment approach to support the decision of early stop for futility. The conditional power is based on the formula given by Cui et al (1999, p. 854) and Emerson et al (2005, p. 13). [33,34]

Safety Analysis:

Safety analyses will include vital signs, physical examinations, clinical laboratory parameters, AEs, ECGs, and C-SSRS results. AEs will be displayed by body system and preferred term using the Medical Dictionary for Regulatory Activities®, and summarized in terms of severity and relationship to study drug. Vital signs analysis will include the mean, standard deviation, and range at baseline and at the end of the double-blind treatment period, and the change from baseline to the end of the double-blind treatment period. Laboratory parameters will be summarized for the randomized safety population by presenting summary statistics (n, mean, standard deviation, median, and range) at the baseline and end of double-blind treatment, and change from baseline values to end of double-blind treatment for each treatment group. Within-treatment comparisons during the double-blind period will be based on shift tables (3 by 3: low, normal, high classification [LNH]) for a particular laboratory test and will compare the baseline LNH to the end-of-double-blind LNH. ECG findings at each time point will be tabulated.

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

µ	mu (also symbol for micro)
ACR	American College of Rheumatology
AE	adverse event
ALT	alanine aminotransferase (alanine transaminase; also SGPT)
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
APAP	acetaminophen
AST	aspartate aminotransferase (aspartate transaminase; also SGOT)
ATC	anatomical therapeutic chemical
AUC	area under the plasma concentration-time curve
bid	twice daily
BMI	body mass index
BP	bodily pain
Bpm	beats per minute
C	Celsius or centigrade
CFR	Code of Federal Regulations
CiTAS	Chemotherapy-induced Taste Alteration Scale
Cmax	Maximum Concentration
COX-2	cyclo-oxygenase 2
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CSPC	clinical supply product complaint
C-SSRS	Columbia-Suicide Severity Rating Scale
dL	deciliter
DMC	data monitoring committee
DO	Doctor of Osteopathic Medicine
ECG	electrocardiogram
EQ-5D	EuroQol-5D
EQ-5D-5L	5-level scale EQ-5D
F	Fahrenheit
FAP	full analysis population
FDA	Food and Drug Administration
g	gram
GCP(s)	Good Clinical Practice(s)
GEE	generalized estimating equation
GGT	gamma-glutamyltransferase
GH	general health
HADS	Hospital Anxiety and Depression Scale
HBV	hepatitis B

HCV	hepatitis C
HIV	human immunodeficiency virus
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethic Committee
IRB	Institutional Review Board
IVRS	interactive voice response system
IWRS	interactive web response system
Kg	kilogram
K-L	Kellgren-Lawrence
L	liter
L.P.	Limited Partnership
LAH	left anterior hemiblock
LBBB	left bundle branch block
LDH	lactate dehydrogenase
LFT	liver function test
LLN	lower limit of the laboratory reference range
LNH	low, normal, high (relative to the laboratory reference range)
MAD	multiple ascending dose
mBPI-SF	modified Brief Pain Inventory – Short Form
MedDRA	Medical Dictionary for Regulatory Activities
mEq	milliequivalent
mg	milligram
MH	mental health
MI	myocardial infarction
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
MMRM	mixed-effect general linear model with repeated measures
mmol	millimole
msec	millisecond
NP	Nurse Practitioner
NOAEL	no-observed-adverse-event-level
NRS	numerical rating scale
NSAID	nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
PA	Physician Assistant
PF	physical functioning
PG	pharmacogenomics
PGIC	Patient Global Impression of Change

PI	principal investigator
PK	pharmacokinetic(s)
po	oral route of administration
PP	per-protocol population
PPLP	Purdue Pharma Limited Partnership
PR	PR interval (ECG)
QRS	QRS interval (ECG)
QT	QT interval (ECG)
QTc	QT data corrected for heart rate
QTcB	QT data corrected for heart rate using the Bazett formula
QTcF	QT data corrected for heart rate using the Fridericia formula
RBC	red blood cell (count)
RE	role-emotional
RP	role-physical
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SF	social functioning
SF-36	Medical Outcomes Study 36-Item Short Form Health Survey
SGOT	serum glutamic-oxaloacetic transaminase (also AST)
SGPT	serum glutamate pyruvate transaminase (also ALT)
SI	international system of units for clinical laboratory values
SOC	System Organ Class
SOP	standard operating procedure
SSRI	selective serotonin reuptake inhibitors
SNRI	serotonin norepinephrine reuptake inhibitors
ST	ST interval (ECG)
TEAE	treatment-emergent adverse event
TENS	Transcutaneous Electrical Nerve Stimulation
TESS	treatment-emergent sign or symptom
Tmax	time to maximum plasma concentration
TRPV1	transient receptor potential vanilloid subfamily, member 1
UA	urinalysis
ULN	upper limit of the laboratory reference range
US	United States
v	versus
VAS	ED-5Q visual analogue scale
VT	vitality
WBC	white blood cell (count)
WOMAC	Western Ontario and McMaster Osteoarthritis Index

5 ETHICS

5.1 Institutional Review Board or Independent Ethics Committee

The protocol, any protocol amendments, and the informed consent form (ICF) will be reviewed and approved by each study center's Institutional Review Board (IRB)/Independent Ethics Committee (IEC) before subjects are screened for entry. Verification of the IRB's/IEC's unconditional approval of the protocol will be transmitted to the sponsor (or designee) prior to the site(s) being initiated. The investigator(s) will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per International Council for Harmonisation (ICH) guidelines and local IRB standards of practice.

A list of IRB(s)/IEC(s) that approved this study will be included in the clinical study report.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating practices (SOPs) of the sponsor (or designee) to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:

- Declaration of Helsinki, 1964 ("Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects"), and all its accepted amendments to date concerning medical research in humans
- ICH E6 Guideline for Good Clinical Practice (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, and ICH of Pharmaceuticals for Human Use
- US Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR, including, but not limited to, parts 11, 50, 54, 56, and 312 concerning electronic records/signatures, Informed Consent, Financial Disclosures, IRB/IEC and Investigational New Drug Application regulations).

5.3 Subject Information and Consent

The principal investigator (or designee) will explain the nature of the study and the action of the test product. The subjects will be informed that participation is voluntary and that they can withdraw from the study at any time.

In accordance with ICH E6 (section 4.8) and 21 CFR 50, informed consent shall be documented by the use of a written ICF approved by the IRB prior to protocol-specific procedures being performed.

The subject or their guardians/legally authorized representatives will be given a signed copy of the consent, and the original will be maintained with the subject's records.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Purdue Pharma Limited Partnership (PPLP) at multiple sites in the United States.

The contract research organization (CRO) [redacted] has been retained by PPLP to implement and manage the study, including management of subcontracted vendors, and is referred to henceforth in this protocol as the sponsor's designee.

The name of the Medical Monitor, along with the telephone and fax numbers of the other contact persons at the CRO, will be listed in the regulatory binder provided to each site.

The names of clinical site personnel trained for this study must appear on the delegation log.

7 INTRODUCTION

Chronic pain is estimated to affect approximately 100 million adults in the United States (US) alone.[1] Osteoarthritis (OA), a common form of joint disease, results in long-term pain and prolonged disability. In the US, OA affects approximately 27 million patients of all ages.[2] Pain, joint stiffness, and reduced motion lead to disability and loss of independence among patients with OA. An effective cure for OA remains elusive and analgesics provide the primary treatments. Current standard of care therapies for OA pain include use of traditional nonsteroidal anti-inflammatory drugs (NSAIDs), which can cause serious and sometimes life-threatening adverse effects associated with long-term use. Management of chronic pain, especially for OA patients, is in need of novel therapeutic options.

Purdue Pharma, L.P. is developing V120083 for the management of pain due to OA. V120083 is a potent and selective TRPV1 receptor antagonist which was discovered in the collaborative research [redacted].

TRPV1 (transient receptor potential vanilloid subfamily, member 1) is an ion channel located mainly on peripheral sensory neurons. TRPV1 plays a significant and unique role in the pain pathway because it is a polymodal initiator of pain signaling. Direct blockade of this channel is expected to interrupt the start of neuronal transmission of pain producing signals. TRPV1 is activated by a broad range of mechanical, thermal, or chemical stimuli including factors often associated with infection, inflammation or ischemia such as heat, low pH, nitric oxide, and lipoxygenase metabolite formation[3, 4]. TRPV1 expression on sensory neurons is also known to be increased in the presence of persistent inflammation. The hyperalgesia associated with the inflammatory process is related to this increase. The ultimate result is channel sensitization, which manifests as a potentiation of thermal, capsaicin, and pH responses in TRPV1 channels.[3, 4]

There are many published examples of novel TRPV1 antagonists that produce significant antihyperalgesia against thermal and mechanical endpoints in standard models of pain-like behavior in rodents. A number of these TRPV1 antagonists are currently in various stages of clinical development. Contact activation, tissue and/or cellular injury, and inflammation are each capable of direct and indirect modulation of the TRPV1 channel via multiple mechanisms. The mechanistic convergence of initiators and potentiators of the TRPV1 channel provide the conceptual basis for believing that TRPV1 antagonism might be an effective approach to treating pain associated with inflammation and nerve injury [3, 4].

V120083 has an analgesic effect, not only in rodent inflammatory pain models but also in rodent neuropathic pain models. These pharmacological profiles suggest an analgesic effect on chronic pain and various other pain mechanisms.

In metabolism studies, *in vivo* metabolites in rats, dogs and humans and *in vitro* metabolites in cryopreserved human hepatocytes were identified. In rat and dog studies, V120083 mainly existed in an unchanged form in the plasma and the majority of V120083 was excreted as metabolites in the urine, the feces, and in bile. The major metabolic pathway of V120083 in the human plasma and cryopreserved human hepatocytes appears to be oxidation followed by glucuronidation and the formation of 5-methyl-2-oxoimidazolidinyl acetic acid (OAA), 2-oxoimidazolidinyl propanoic acid (OPA).

In the 1 month repeated dose toxicity study in dogs, vomiting and low body weight accompanied with decreased food consumption were observed in both sexes treated at 600 mg/kg/day during dosing period. In the 3 month repeated dose toxicity study in dogs, these findings were also noted at the high dose of 500 mg/kg/day.

In both the dog 3 month and rat 6 month repeat dose toxicology studies, the presence of study test article (V120083) manifested as crystal formation and deposition was observed in the lamina propria of the small intestine and/or mesenteric lymph node in the majority of animals in the high dose group in rats (1,000 mg/kg/day) and dogs (500 mg/kg/day). Crystals were also observed in mandibular lymph nodes and the lamina propria of several other organs in a smaller number of rats in the high dose group. The crystal deposition was identified as unchanged V120083 based on analytical identification and likely related to limitation in the solubility in body fluid including plasma.

V120083 was negative in the following genotoxicity studies: *in vitro* bacterial reverse mutation test, mouse lymphoma assay, and *in vivo* micronucleus test with rat bone marrow cells. Potential genotoxicity of S189A6, an impurity of V120083, has been also evaluated. S189A6 was negative in *in vitro* micronucleus test and *in vivo* combination study of micronucleus and comet assays in rats, while S189A6 was concluded to be positive in the reverse mutation test with bacteria.

[redacted]

[redacted]

Some investigational TRPV1 antagonists have demonstrated deficits in thermosensory function, placing patients at risk for inadvertent cutaneous and oral burns[6]. These issues have not been seen in prior studies with V120083. Subjects will receive additional instructions on how to avoid thermal injury.

[redacted]

This present study, VAN2001, is the first efficacy study planned for V120083. Osteoarthritis (OA) has been chosen as a chronic pain model of choice to demonstrate efficacy. OA is a leading cause of pain, loss of function, and disability in Western populations, and radiographic evidence of OA is present in the majority of adults by the age of 65 years [7]. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as naproxen, are the most frequently used analgesics for the treatment of mild to moderate OA pain [8], and thus naproxen is being used in this study as a positive control.

Although efficacious, NSAIDs are associated with significant gastrointestinal side effects and a potential increased risk of adverse cardiovascular events. Therefore, alternatives for the chronic treatment of OA pain are needed.

Expression of the TRPV1 receptor is upregulated in animal models of OA[9]. In patients with OA, injection of the TRPV1 agonist capsaicin into affected joints relieves pain, presumably by desensitizing the TRPV1 receptor[10]. Thus, antagonism of the TRPV1 receptor may be useful in the treatment of OA pain.

Additional information pertaining to V120083, including its physicochemical properties in *in vitro* and *in vivo* nonclinical studies specifically its pharmacology, pharmacokinetics, and toxicology, are presented in the Investigator's Brochure [5].

Refer to the V120083 Investigator's Brochure for additional product information. Refer to Appendix E for naproxen product information.

7.1 Potential Risks and Benefits

The safety assessments of V120083 rely on data accumulated during product development and data on other drugs in the class. Based on the preclinical and clinical data available to date, the conduct of the trial is regarded as justifiable at the planned doses and duration.
V120083 is being considered as a new option for the treatment of pain due to osteoarthritis of the knee. No identified risks or new potential risks have emerged from the phase I clinical studies performed. V120083 was safe and generally well tolerated by healthy human volunteers at single doses up to 1000 mg and at multiple doses up to 300 mg bid administered for up to 14 days. The dose of V120083 (30 mg or 60 mg) selected for the proposed trial is within the dose ranges studied in the phase I trials.

Important potential risks to subjects are based on nonclinical safety data of V120083 and the phase 1 clinical studies. The most common TEAEs reported in the MAD study were feeling cold and feeling hot, reported in subjects receiving higher doses (100 mg and 300 mg) of V120083. No subjects in the 30 mg dose group experienced these events and only 1 AE each of feeling cold and feeling hot were reported by placebo-treated subjects. These AEs were expected due to the mechanism of action of V120083; no clinically significant changes in body temperature were observed.

One subject, who received multiple doses of 300 mg V120083, experienced an SAE of pleural effusion. This SAE was considered not related to study drug.

V120083, like other TRPV1 antagonists, may attenuate response to noxious heat stimuli. Therefore, subjects receiving V120083 should be cautioned to take measures to avoid the occurrence of burn injury. Such measures include keeping the hot water thermostat ≤ 120 degrees Fahrenheit (F), checking water temperature, using potholders or oven mitts when handling cookware, and taking care when eating hot foods or drinking hot beverages.

Risk minimization measures include a data monitoring committee (DMC) to review available safety and tolerability data and will be mandated to make decisions regarding the conduct of the trial according to the DMC charter and interim analysis criteria. Additionally, the sponsor or representatives will review blinded safety data throughout the trial. The DMC members will review the safety data, including but not limited to AEs and clinical laboratory values. The DMC recommendations will include: 1) Continue the study without modification; 2) Continue the study and amend the protocol, as specified; 3) Pause enrollment, pending resolution of a specified issue; 4) Terminate the study.

The decision to stop 1 or more treatment groups due to safety issues will be made based on review and recommendation by the DMC.

Placebos are used in this trial to conceal whether a treatment is being given or not and hence to control for the psychosomatic effects of offering treatment. Randomization will be used in this trial to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown patient attributes (eg, demographics and baseline characteristics) are evenly balanced across treatment groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

Taking the above information into account, benefit-risk considerations support conduct of the proposed clinical trial VAN2001 in patients with OA pain of the knee.

For full details, refer to the latest IB for further information about the nonclinical and clinical programs and Guidance for the Investigator.

This clinical trial will be conducted in compliance with the clinical trial protocol, ICH GCP guidelines, and any additional applicable regulatory requirements.

8 STUDY OBJECTIVES

The primary objective of this study is:

- To evaluate the analgesic efficacy of V120083 bid compared with placebo in subjects with moderate to severe chronic pain due to OA of the knee using the "average pain over the last 24 hours" score from the modified Brief Pain Inventory – short form (mBPI-SF) pain severity subscale at week 4 of the double blind period.

The secondary objectives of this study are:

- Evaluate the safety and tolerability (including adverse event [AE] reporting, clinical laboratory parameters, and physical examination) of 2 dose levels of V120083
- Evaluate the efficacy of V120083 on pain, stiffness, physical function, and overall disability using the Western Ontario and McMaster Osteoarthritis Index (WOMAC) subscale and total scores
- Evaluate the efficacy of V120083 on pain intensity due to OA using numerical rating scale (NRS) pain scores from the mBPI-SF pain severity subscale
- Evaluate the impact of V120083 on pain-related quality of life/function using the mBPI-SF pain interference subscale
- Evaluate the effect of V120083 on pain severity and pain interference overall using the mBPI-SF total score
- Evaluate the impact of V120083 on subjects' health state (as defined by mobility, self-care, daily activities, pain/discomfort, and anxiety/depression) using the EuroQol-5D (EQ-5D)
- Evaluate the impact of V120083 on subjects' functional health and well-being using the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36)
- Evaluate subject global impression of treatments using the Patient Global Impression of Change (PGIC) questionnaire
- Evaluate the impact of V120083 on mood (anxiety and depression) using the Hospital Anxiety and Depression Scale (HADS)
- Evaluate the efficacy of naproxen vs. placebo for assay sensitivity using the primary and secondary endpoints indicated above.
- Determine plasma levels of V120083 in subjects under clinical use conditions.

[redacted]

- Evaluate supplemental analgesic medication use

- Evaluate treatment response
- Evaluate the occurrence of treatment-emergent suicidal ideation or behavior using the Columbia-Suicide Severity Rating Scale (C-SSRS)

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan Description

This is a phase 2a, double-blind, placebo- and active-controlled, parallel group, multicenter study to evaluate the analgesic efficacy and safety of V120083 vs. placebo in subjects with moderate to severe chronic pain due to OA of the knee. It is planned that approximately 69 subjects will be randomized into each treatment group. Subjects will be enrolled at approximately 30 sites in the United States.

The study design is presented in Figure 1.

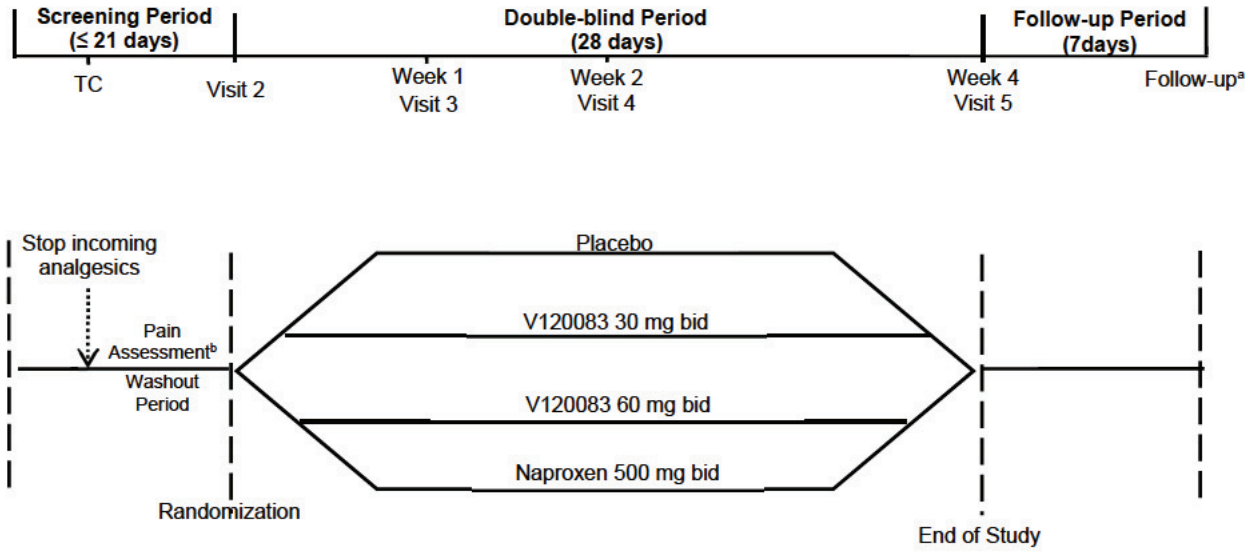

Figure 1 Study Design

TC = telephone contact to instruct subjects meeting initial enrollment criteria to stop all incoming analgesics in accordance with acceptable medical practice and begin washout period (where applicable).

[a] The follow-up visit may be conducted via a telephone contact or at a clinic visit.

[b] Subjects who do not take any medications for pain will record their "average pain over last 24 hours" scores for 3 to 7 days. Subjects who take medications for pain will record their "average pain over last 24 hours" scores for 3 to 9 days after all incoming pain medications have been stopped. All subjects may return to the study clinic for visit 2 as soon as they recorded "average pain over last 24 hours" scores ≥ 4 and ≤ 9 for ≥ 3 consecutive days. All subjects must return for visit 2 within 96 hours of the latest qualifying pain score entry within the pain assessment period.

Note: Approximately 69 subjects/treatment group will be randomized.

Efficacy and safety evaluation for V120083 treatment groups may be performed by the DMC when 50% of subjects have completed the study.

The total duration of the study for a given subject is up to 56 days, inclusive of a 21-day screening period; a 28-day double-blind treatment period; and a 7-day follow-up period. Naproxen 500 mg bid will be used as an active control to determine the assay sensitivity of the study.

During the screening period, subjects will be assessed to determine eligibility for enrollment into the trial. As soon as the laboratory, ECG, and radiograph results are available, the site staff will contact the subjects by telephone to inform them of the results and whether they are qualified to continue in the study. Subjects who do not meet the initial entry criteria will be considered screen failures. For subjects who meet the initial entry criteria and:

- Who do not take any analgesic medications for their pain, the site staff will instruct them to record in the diary their "average pain over the last 24 hours" scores (Appendix N) for their index knee at approximately 8 PM every day for 3 to 7 days; these subjects may return to the study clinic for visit 2 as soon as they have "average pain over the last 24 hours" scores ≥ 4 and ≤ 9 for ≥ 3 consecutive days. All subjects must return to the study clinic for visit 2 within 96 hours of the latest qualifying pain score entry within the pain assessment period.
- Who take medication for their chronic pain (including any topical and/or oral analgesics, antidepressants, anticonvulsant, and other medication used for pain), the site staff instruct them to:
  - Discontinue use of all medication for pain (including any topical and/or oral analgesics, antidepressants, anticonvulsant and other medication used for pain) in accordance with accepted medical practice and,
  - As soon as all medication used for pain is stopped, record in the diary their "average pain over the last 24 hours" scores for their index knee at approximately 8 PM every day for 3 to 9 days; these subjects may return to the study clinic for visit 2 as soon as they reported "average pain over the last 24 hours" scores of ≥ 4 and ≤ 9 for ≥ 3 consecutive days. All subjects must return to the study clinic for visit 2 within 96 hours of the latest qualifying pain score entry within the pain assessment period.

Prior to entering the double-blind period, the subjects' "average pain over the last 24 hours" scores will be assessed to determine the subjects' eligibility to continue in the double-blind period. To qualify for entry into the double-blind period, subjects must have "average pain over the last 24 hours" scores of ≥ 4 and ≤ 9 for ≥ 3 consecutive days during the pain assessment period. Subjects who do not qualify for the double-blind period will be discontinued from the study as screening failures.

Rescreening of subjects who previously failed screening is allowed only with the permission of the medical monitor on a case by case basis.

Subjects may be considered for rescreening if they failed screening previously due to eligibility criteria that are now allowed under the current amended protocol; delay of acquiring records; out of window issues (eg, lost or delayed labs); timing of exclusionary procedures; or other reasons approved by the medical monitor.

Subjects with positive hepatitis B, hepatitis C, or human immunodeficiency results, subjects with a positive urine drug test (UDT) for illicit drugs or non-prescribed opioids; and/or subjects who previously received study drug in a V120083 trial will not be permitted to be rescreened.

X-rays for rescreened subjects do not need to be repeated provided they were originally collected as part of this study and occurred within 1 month of rescreening.

All rescreening must be approved in advance by the medical monitor.

Subjects who are eligible for the double-blind period will have visit 2 scheduled in the morning. After meeting eligibility requirements, approximately 276 subjects will be stratified for randomization in a 1:1:1:1 fashion according to the baseline severity of pain score (mBPI-SF average pain) and study site at visit 2 to receive 1 of the following 4 treatments in the double blind period: V120083 30 mg bid, V120083 60 mg bid, naproxen 500 mg bid, or placebo. The first dose of study drug will be administered at the study clinic.

Blood samples for pharmacokinetic (PK) analysis will be collected at visits 2, 3, 4, and 5. The PK evaluation will involve two components: intense PK sampling and sparse PK sampling. Sparse PK sampling will be conducted for all subjects enrolled (276 subjects), with samples collected at visits 3 (predose, 1 and 2 hours postdose), 4 (predose or postdose), and 5 (predose or postdose) during the treatment period. Intense PK sampling will be conducted for 24 subjects, consisting of the sparse PK schedule and visit 2 predose sample and postdose sampling at 1, 2, 4, 6, and 8 hours (day 1 of dosing). The study will include pharmacogenomics (PG) sampling that will be optional for all subjects.

Clinic visits during the double-blind period will occur at week 1 (visit 3), week 2 (visit 4), and week 4 (visit 5). All clinic visits must occur in the morning. During these visits, blood samples for PK analysis will be collected as outlined in the Schedule of Activities (Table 3). The study will also include pharmacogenomics (PG) sampling that will be optional for all subjects.

Starting at screening phone call visit, subjects may take their own supplemental analgesic medication, ie, 500 mg acetaminophen (APAP), which can be taken as needed up to 2 g/24 hours for breakthrough pain, but it is not to be taken within 24 hours of visit 2. Supplemental analgesic medication, APAP/acetaminophen 500 mg, will be provided during the double-blind period. No more than 4 tablets/24 hours (ie, no more than 2 g/24 hours), as needed, will be permitted during the double-blind period. All subjects will be instructed to refrain from taking any supplemental analgesic medication for at least 24 hours prior to the weeks 1, 2, and 4 (visits 3, 4, and 5, respectively) of the double-blind period.

Subjects are allowed a ±1 day window for visit 3, and a ±2 day window for visits 4 and 5, from baseline. All scheduled visits will be anchored to the day of randomization (visit 2). Subjects who discontinued treatment early will be instructed to return to study clinic for an early discontinuation visit (visit 5). After the end of the study/early discontinuation visit, all subjects will be converted to a pain regimen as deemed medically appropriate by the investigator/designee.

An interim analysis may be performed for futility when approximately 50% of randomized subjects have completed the study. An independent DMC will review all unblinded safety and efficacy data from the interim analysis and make recommendations as necessary.

Follow-up Period (7 days)
Subjects will receive a telephone call approximately 7 days after the end of the study/ study discontinuation visit to assess subject status and documentation of AEs and concomitant medications.

A study flow chart describing the schedule of activities for this study is presented in Table 3.

9.2 Discussion of Study Design, Including the Choice of Control Groups

The analgesic effect of V120083 is currently unknown. This is a proof-of-concept study designed to evaluate the efficacy of V120083 30 mg bid and 60 mg bid compared with placebo in subjects with chronic moderate to severe OA pain of the knee.

This study will employ a double-blind, parallel-group design. This method is selected because it is the most efficient and nonbiased design to demonstrate the efficacy and safety of V120083 versus (*v*) placebo. The duration of the double-blind period will be 28 days. This treatment duration was selected as this length of time was sufficient to demonstrate the onset of analgesic activity for a drug that may require repeated use for efficacy and for establishing maintenance of analgesic activity for chronic pain conditions such as OA.

Naproxen 500 mg bid will be used in this study as active control. Naproxen is selected for this study because it has shown to be efficacious in treating subjects with OA pain of the knee in previous proof-of-concept studies conducted by PPLP. In this study, naproxen will be used to determine assay sensitivity for a successful study regardless of efficacy of the study drug.

The purpose of the placebo group is to account for the placebo effect, that is, effects from treatment that do not depend on the treatment itself. Such factors include knowing one is receiving a treatment, attention from health care professionals, and the expectations of a treatment's effectiveness by those running the research study. Without a placebo group to compare against, it is not possible to know whether the treatment itself had any effect.

The study population was chosen for study as it represents significant numbers of subjects who are suboptimally treated with currently available standard-of-care therapies. Only those subjects who meet protocol-specified criteria for inadequate analgesia will be eligible to enter the double-blind period. During the study, subjects will be asked to stop all incoming analgesic medications and other medications used for chronic pain and instead receive only the study drugs to manage their OA pain of the knee. Subjects are permitted to take supplemental analgesic medication throughout the double-blind period in order to maintain subjects in the study for the 4-week time course (except for 24 hours prior to the weeks 1, 2, and 4 visits).

Randomization will be used in this study to avoid bias in the assignment of subjects to study treatments, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

9.3 Selection of Study Population

Subjects meeting all the inclusion criteria and none of the exclusion criteria may be entered into the study. Subjects who do not fulfill the inclusion or exclusion criteria may be allowed to enter the study only after discussion with the sponsor (or designee). In such instances, documentation will be filed at the clinical site and with the sponsor (or designee).

9.3.1 Inclusion Criteria

Subjects who meet the following criteria will be included in the study:

1. Males and females ≥ 40 and ≤ 80 years of age with moderate to severe chronic OA pain of the knee (lasting several hours daily) as their predominant pain condition for at least 6 months prior to screening;
2. Diagnostic criteria for primary pain condition (American College of Rheumatology [ACR] clinical and radiographic criteria):
    - At least 1 of the following in addition to knee pain: age > 50, morning stiffness < 30 min, crepitus on active motion, and
    - Kellgren-Lawrence (K-L) grade 2 or 3 radiographic evidence at the screening visit as determined by a local radiologist or rheumatologist. If a radiograph is not available, one must be taken and the diagnostic criteria must be confirmed before visit 2. Note that K-L grades 2-3 require the presence of osteophytes, which is required to meet ACR clinical and radiographic criteria for knee OA;
3. Subjects with body mass index (BMI) ranging from 18.0 to 38.0 (kg/m^2), inclusive;
4. Subjects whose OA pain of the index knee is not adequately treated prior to the screening visit:
    - Subjects must have a self-reported average pain intensity rating of moderate or severe on a verbal rating scale (ie none, mild, moderate, and severe) over the 7 days prior to the screening visit
5. The subjects must have “average pain over the last 24 hours” scores ≥ 4 and ≤ 9 on an 11-point NRS for the index knee on $\geq$ 3 consecutive days during the pain assessment period and come in for visit 2 within 96 hours after the latest qualifying pain score entry.
6. For subjects receiving adjunct therapy for chronic pain, such as physical therapy, exercise, chiropractic therapy, acupuncture therapy, TENS unit, or herbal and other complementary therapy, such treatment should be either stopped at screening or remain unchanged during the entire study; Adjunct therapies, glucosamine and chondroitin initiated at least 1 month before screening can be continued at stable dose/regimen (should not be initiated during the study); elastic support and other braces applied to either knee should be used during the study in the same manner as at screening;
7. If either female of childbearing potential (ie, not medically or surgically sterilized or not postmenopausal more than 1 year) or non-surgically sterilized male with sexual partner of childbearing potential, be willing to use adequate and reliable contraception throughout the study (eg, abstinence or barrier with additional spermicidal foam or jelly, or the use of intrauterine device or hormonal contraception by female subjects and partners of male subjects);

8. Subjects who are willing and able to stop taking any/all analgesic medications, including over-the-counter pain medications, opioids, marijuana, and topical analgesics for OA pain for the duration of the study, with the exception of study-specific rescue medication;
9. Subjects who are willing and able to be compliant with the protocol, are capable of subjective evaluation, are able to read and understand questionnaires, and are able to read, understand, and sign the written informed consent.

9.3.2 Exclusion Criteria

1. Subjects with radiographic evidence of OA with Kellgren-Lawrence (K-L) grade 0, 1 or 4;
2. Females who are pregnant (positive serum/urine test) or lactating or planning to become pregnant during the study;
3. Subjects with chronic pain conditions other than OA of the knee as their predominant pain condition, including gout, pseudogout, psoriatic arthritis, active Lyme disease, rheumatoid arthritis or any other inflammatory arthritis, fibromyalgia, neuropathic pain conditions, bursitis, or acute injury or signs of active infection in the target pain area;
4. Subjects scheduled for surgical interventions of the disease site or any other major surgery during the study conduct period;
5. Subjects with a history of a prior joint replacement of the index knee;
6. Subjects who have had arthroscopy on either knee or hip within 6 months of entering the study, or open surgery on either knee or hip within 12 months of entering the study;
7. Subjects with a palpable effusion in either knee;
8. Subjects with a history of significant trauma to a knee, hip or shoulder within the previous year;
9. Subjects who have significant pain, other than or more than knee pain, including significant hip, back pain, that may confound the analgesic efficacy assessments of this study;
10. Subjects who used immunosuppressive drugs, anti-depressants other than Selective Serotonin Reuptake Inhibitors (SSRIs for depression), warfarin or anticoagulants, cyclosporine (except ophthalmic emulsion), aspirin except for 81 mg daily dose for cardiovascular prophylaxis, diuretics with unstable cardiac diseases, or methotrexate within 30 days of study randomization;
11. Subjects who initiated, or received an increase in the dose of, oral corticosteroids within 6 weeks prior to entering the study or who anticipate a change in oral corticosteroid therapy during the study period;
12. Subjects who have used any investigational medication within 30 days or five half-lives, whichever is longer, prior to the first dose of study medication;
13. Subjects with a history of seizures within the past 5 years;
14. Subjects with evidence of current major depression or other clinically significant psychiatric disorder that in the opinion of the investigator would interfere with the subject's ability to participate in the study. Subjects with history of a psychotic disorder or psychosis, bipolar disorder, or post-traumatic stress disorder should be excluded. Subjects with major depression in remission or other psychiatric disorder must be on a stable medication (SSRI) for > 3 months to participate in the study;

15. Subjects with HADS score over 10 on either subscale at visit 1;
16. Subject answers “yes” to “suicidal ideation” in prior 24 months to any items 1 through 5 on the C-SSRS;
17. Subject answers “yes” to any lifetime “suicidal behavior” item on the C-SSRS;
18. Subjects with any history of alcohol or other substance abuse or addiction within the past 5 years;
19. Subjects who use immediate release/short acting opioids at a daily dose exceeding 15 mg daily morphine equivalent more than 4 days per week;
20. Subjects who have used any extended-release/long acting opioids in the 30 days prior to the screening visit;
21. Subjects who have a positive urine drug test for illicit drugs, cannabinoids, or non-prescribed opioids;
22. Subjects taking strong CYP3A inhibitors, inducers, sensitive substrates, substrates with narrow therapeutic range, or P-gp substrates (see Appendix Q);
23. Subjects taking moderate CYP3A inhibitors if the dose has not been stable for at least 1 month prior to start of study drug dosing (see Appendix Q);
24. Subjects for whom it is anticipated that therapy with a moderate to strong CYP3A inhibitor, or CYP3A inducers, sensitive substrates, substrates with narrow therapeutic range, or P-gp substrates will be initiated during the study, after the screening visit;
25. Subjects with clinically unstable medical conditions, including cardiac disease (unstable atrial fibrillation, any symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia), uncontrolled hypertension, respiratory disease, biliary tract disease, hypothyroidism, renal disease, adrenal cortical insufficiency, or any other medical condition that, in the investigator’s opinion, is inadequately treated and precludes entry into the study;
26. Subjects with myocardial infarction, stroke, or other thrombotic events in the past 5 years; and/or any history of coronary artery bypass graft;
27. Subjects with a screening ECG showing a QTcF value (QT data corrected for heart rate using the Fridericia formula) of ≥ 470 msec or other ECG findings that, in the investigator’s opinion, would preclude participation in the study;
28. Subjects with any clinically significant abnormal laboratory value, including evidence of impaired liver function (values ≥ 3 times the upper limit of normal for aspartate transaminase [AST/SGOT] or alanine transaminase [ALT/SGPT], or bilirubin ≥ 1.5 mg/dL), or impaired kidney function (eGFR < 60 mL/min);
29. Subjects with positive hepatitis B, hepatitis C or HIV test results indicative of current infection;
30. Subjects with a history of malignancy within the past 5 years, with exception of basal cell carcinoma that has been successfully treated;
31. Subjects with an ongoing or resolved worker’s compensation claim and/or litigation related to their pain disorder;

32. Subjects who, in the opinion of the investigator, are unsuitable to participate in this study for any other reason;
33. Pain-condition-specific exclusions:
    - Subjects who received local pain-control procedures, including intra-articular steroid injection in the index knee or intramuscular steroid injection at any site, joint lavage, or other invasive therapies within 6 weeks of entering the study or hyaluronate injection in the index knee within 12 weeks of entering the study, or for whom such therapies are planned within the study period;
34. Subjects with a history of bleeding disorders or history of documented gastrointestinal ulcer disease;
35. Subjects who are allergic to or cannot tolerate aspirin, other NSAIDS (including naproxen), or acetaminophen, including history of NSAID-induced asthma, or nasal polyps;
36. Subjects who have received TRPV1 antagonist previously.

9.3.3 Removal of Subjects from Study Participation

Subjects will be informed that they are free to discontinue from the study at any time and for any reason. The investigator may remove a subject from the study if, in the investigator's opinion, it is not in the best interest of the subject to continue in the study. Subjects may be discontinued due to a change in compliance with inclusion/exclusion criteria that is clinically relevant and affects subject safety, occurrence of AEs, or ingestion of protocol-prohibited concomitant medication that might affect subject safety or study assessments/objectives. In case of premature discontinuation of study participation, every effort will be made to perform all end-of-study assessments. All subjects who prematurely discontinue will be followed for ongoing and newly occurring AEs as described in section 10.

For subjects who discontinue the study prematurely due to an AE, per FDA's Guidance for Industry - Premarketing Risk Assessment (March 2005)[11], copies of relevant hospital records, autopsy reports, biopsy reports and radiological reports related to the event should be obtained, when feasible.

Reasons for screen/randomization failure consist of the following:

- The subject does not meet all the inclusion or meets any exclusion criteria – the criteria will be recorded; or
- Subject's choice (the subject chooses for personal reasons to withdraw from the study, eg, family emergency precluding the subject from continuing in the study, relocation of the subject, or a new work schedule which precludes the subject from further study participation); or
- Lost-to-follow-up (the study clinic personnel lose contact with the subject); or
- AE or SAE, (if an AE or SAE causes a subject to withdraw from the study); or
- Administrative reason (the subject discontinues from the study early for any logistical, nonmedical reason that is associated with either the clinical site or sponsor, eg, the sponsor stops the study or the clinical site is no longer able or is no longer approved to conduct the study).

Reasons for discontinuation from the study and study drug at the same time during the double-blind period consist of the following:

- Adverse event (if an AE causes a subject to withdraw from the study),
  - Note: worsening of the condition for which the subject qualifies for study entry (ie, OA pain in the index knee) will not be considered an AE; for these subjects, the reason for discontinuation should be recorded as lack of therapeutic effect (see below), or
- Subject's choice (the subject chooses for personal reasons, to withdraw from the study, eg, family emergency precluding the subject from continuing in the study, relocation of the subject, or a new work schedule which precludes the subject from further study participation), or
- Lost-to-follow-up (the study clinic personnel lose contact with the subject). Once suspecting the subject is lost-to-follow-up, the study clinic must attempt to contact the subject by phone, making at least 3 documented attempts, each at least 1 week apart. Additionally, 1 registered letter must have been sent with a copy on file. The study clinic should only deem the subject as lost-to-follow-up no less than 30 days following the first documented phone call attempt, unless circumstances preclude this (eg, phone service has been discontinued, or there is other evidence that contact is not feasible), or
- Lack of therapeutic effect (the subject chooses to withdraw from the study because he/she does not feel the study drug is effectively treating his/her condition under study or the investigator/medically qualified designee chooses to discontinue the subject from the study because, in his/her opinion, the study drug is not effectively treating the subject's condition under study. The study clinic should confirm that worsening of OA pain in the index knee, not worsening of other pain, is in fact the cause for discontinuation, or
- Confirmed or suspected diversion, or
- Administrative reason (the subject discontinues from study early for any logistical, nonmedical reason that is associated with either the clinical site or sponsor, eg, the sponsor stops the study or the clinical site is no longer able or no longer approved to conduct the study).

If the subject discontinues due to subject's choice, administrative, or lost to follow-up reasons, the specific circumstances surrounding the discontinuation must be recorded.

The investigator/designee should document instances of inability to tolerate treatment as discontinuations due to AE and record the specific symptom(s) and/or sign(s) (eg, nausea, vomiting). Instances of inadequate pain control in the index knee should be documented as lack of therapeutic effect.

Dosing must be permanently discontinued for a study subject if he/she develops any of the following:

1. QTcF values > 500 msec or > 480 msec with a concurrent increase in QTcF > 60 msec from the mean screening value
2. Answers "yes" to "suicidal ideation" to items 1 through 5 or "yes" to any "suicidal behavior" on the C-SSRS

9.4 Treatments

9.4.1 Treatments administered

The first dose of the study drug will be administered by study personnel at the study clinic.

For the remainder of the double-blind treatment period, subjects will self-administer the study drugs orally bid, in the morning and evening at consistent time intervals.

Between the screening phone call visit and visit 2, subjects may take their own supplemental analgesic medication, ie, APAP/acetaminophen, which can be taken as needed up to 2 g/day for breakthrough pain, but it is not to be taken within 24 hours of visit 2. Acetaminophen 500 mg will be provided in bottles to subjects at visits 2, 3, and 4 of the study, as needed. The supplemental medication is to be taken only, as needed, for breakthrough pain. Subjects are permitted to take one to two 500 mg tablets of acetaminophen at a time as needed for breakthrough pain, not to exceed 2 grams total in 24 hours. Subjects will be instructed that no more than 4 tablets of APAP/acetaminophen 500 mg per 24 hours (ie, no more than 2 g/24 hours) are allowed. All subjects will be instructed to refrain from taking any supplemental analgesic medication for at least 24 hours prior to each scheduled visit.

At visit 5, study drugs and supplemental medication will not be dispensed to subjects, and subjects will be instructed to return to taking their prestudy medications.

9.4.2 Identity of Investigational Product(s)

Study drugs will be supplied as blinded materials in blister cards and dispensed to subjects at visits 2 through 4 during the study. Each subject will take 3 capsules at each dosing time po, bid.

All study drugs should be stored at 25°C (77°F); excursions permitted between 15°to 30°C (59°to 86°F) and protected from light.

All study drug will be labeled as V120083 30 mg, naproxen 500 mg and/or placebo capsules.

The sponsor (or designee) will provide the principal investigator (PI) with study drugs according to Table 1 and Table 2.

Table 1 Test Treatment

Name	V120083
Dosage Form	Capsules
Dosage Regimen	bid
Route	Oral
Strength	30 mg
Supplier	Purdue Pharma L.P.

bid=twice daily, L.P.=limited partnership

Table 2 Reference Treatments

Name	Naproxen	V120083 Placebo	Active Comparator Placebo
Dosage Form	Capsules	Capsules	Capsules
Dosage Regimen	bid	bid	bid
Route	Oral	Oral	oral
Strength	500 mg	n/a	n/a
Supplier	Purdue Pharma L.P.	Purdue Pharma L.P.	Purdue Pharma L.P.

Refer to Appendix D for naproxen comparator product formulations.
bid=twice daily, L.P.=limited partnership, n/a=not applicable

Dosage and Administration:

- **V120083 30 mg, bid, po,** supplied as blinded capsules with each capsule containing 30 mg V120083. Subjects assigned to V120083 30 mg will take 1 capsule containing V120083 30 mg, 1 V120083 placebo capsule, and 1 active comparator placebo capsule bid during the double blind period (days 1 to 28).
- **V120083 60 mg, bid, po** supplied as blinded capsules with each capsule containing 30 mg V120083. Subjects assigned to V120083 60 mg will take 2 capsules containing V120083 30 mg and 1 active comparator placebo capsule bid during the double blind period (days 1 to 28).

- **Active comparator, Naproxen, bid, po,** supplied as blinded capsules with each dose consisting of one 500-mg capsule. Subjects assigned to naproxen 500 mg bid will take 1 capsule containing naproxen 500 mg and 2 capsules containing V120083 placebo bid during the double blind period (days 1 to 28).

- **V120083 placebo, bid, po:** Capsules that match both 30- and 60-mg doses supplied as blinded capsules; to be taken po bid by subjects assigned to 30 mg V120083 active comparator or placebo during the double blind period (days 1 to 28). Subjects assigned to placebo will take two V120083 placebo capsules and 1 active comparator placebo bid during the double blind period (days 1 to 28).

- **Active comparator placebo, bid, po:** Capsules that match active comparator supplied as blinded capsules; to be taken po bid by subjects assigned V120083 (30 or 60 mg) or placebo during the double blind period (days 1 to 28).

Supplemental Analgesic Medication:

Between the screening phone call visit and visit 2, subjects may take their own supplemental analgesic medication, 500 mg APAP/acetaminophen, which can be taken as needed up to 2 g/24 hours for breakthrough pain, but is not to be taken within 24 hours of visit 2. Supplemental analgesic medication (subject's own) will be recorded in the subject diary. The sites may dispense 500 mg APAP/acetaminophen at the screening visit as needed.

Acetaminophen, 500 mg, will be procured by the sites and provided to subjects at visits 2, 3, and 4, as needed.

Dosage and Administration:

Subjects will be instructed to take supplemental medication, as needed, for breakthrough pain only, no more than 2 tablets at a time (ie, no more than 1000 mg/dose) and no more than 4 tablets per 24 hours (ie, no more than 2 g/24 hours). Subjects will also be instructed not to take any supplemental medication for at least 24 hours before any scheduled clinic visit during the double-blind period. Supplemental medication is not considered a concomitant medication and will be recorded separately from concomitant medications.

Drug Supplies Instructions:

Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. All other protocol-required treatments as identified in Table 1 and Table 2 and acetaminophen are not considered concomitant medications and will be recorded separately from concomitant medications.

The study drug identification numbers (Med identification #) will be provided to the clinical site on the packing list with the study drug shipment.

9.4.3 Drug Accountability

The PI and study staff will be responsible for the accountability of all clinical supplies (dispensing, inventory, and record keeping) following sponsor (or designee) instructions and adhering to GCP guidelines as well as municipal, state, and federal regulations.

Under no circumstances will the PI and study staff allow the study drug to be used other than as directed by this protocol. Clinical supplies will not be dispensed to any individual who is not enrolled in the study.

An accurate and timely record of clinical supplies must be maintained. This includes, but may not be limited to: (a) documentation of receipt and condition of clinical supplies, (b) documentation of study drug dispensing/return, (c) documentation of clinical supply product complaints, if any, (section 9.6.6 Clinical Supplies Product Complaints), (d) documentation of return of clinical supplies to sponsor (or designee), and (e) all shipping service receipts. All forms will be provided by the sponsor (or designee). The clinical site may use comparable forms to comply with any institutional SOPs.

The supplies and inventory records must be made available, upon request, for inspection by designated representatives of the sponsor (or designee), representatives of the FDA, and representatives of US (including state or local) or international health authorities. All

undispensed study drug and empty containers are to be returned by the PI and/or study staff and ultimately to the sponsor (or designee) at the conclusion of the study, unless provision is made by the sponsor (or designee). Upon completion of drug accountability and reconciliation procedures by clinical site personnel and by sponsor (or designee) personnel, study drug that is to be returned to the sponsor (or designee) must be sealed with tamper-evident seals and shipped back to the sponsor (or designee) following all local regulatory and shipment laws.

9.4.4 Method of Assigning Subjects to Treatment Groups

Subjects will be randomized at visit 2 by Interactive Web Response System/Interactive Voice Response System (IWRS/IVRS) to receive 1 of the 4 treatment groups according to a randomization schedule generated by sponsor (or designee) and will be assigned a unique randomization number.

9.4.5 Selection of Doses in the Study

The doses selected for this study are based on the safety, tolerability, and PK profiles established from two phase 1 studies in healthy human subjects. In these studies, single doses of V120083 up to 1000mg and multiple doses up to 300mg bid for up to 14 days were safe and generally well tolerated.

In this phase 2a, proof-of-concept study, the near maximal safe and tolerated dose of V120083 60 mg bid was selected as the highest dose level to maximize the chances to demonstrate efficacy. Additionally, V120083 30 mg bid will be evaluated to establish the therapeutic dose range of the study drug.

9.4.6 Selection and Timing of Dose for Each Patient

The dosing frequency of bid dosing for this study was selected on the basis of multiple-dose PK data generated in a phase 1 clinical study. For the doses selected in this study, bid administration of V120083 is estimated to provide plasma concentrations sufficient to achieve efficacy for subjects in studies and is expected to yield a trough concentration at 12 hours after V120083 dosing higher than the trough observed for nonclinical efficacious dose.

9.4.7 Blinding

During the double-blind period of the study, the subject and all personnel involved with the conduct, analysis, and the interpretation of the study, including the investigators, clinical site personnel, and the sponsor (or designee) staff, will be blinded to the medication codes.

The randomization schedule will be kept strictly confidential, filed securely by the sponsor (or designee), and accessible only to authorized persons per sponsor's (or designee)'s SOPs until the time of unblinding.

Unblinding a subject should only be done in emergency situations for reasons of subject safety.

At the initiation of the study, the clinical sites will receive instructions for unblinding a subject.

In the event that an emergency unblinding is required, the investigator/medically qualified designee should make every attempt to contact the sponsor's Medical Monitor or designee before breaking the blind.

When the blinding code is broken, the date, time of unblinding, and reason(s) must be fully documented in the source documentation. If not already done, the sponsor's Medical Monitor or designee must be contacted as soon as possible to notify him/her of the unblinding and to discuss the reason(s) for unblinding.

In the event that an emergency unblinding is required, authorized IWRS users at the clinical sites and the sponsor or designee, will have the ability to retrieve the subject's treatment group assignment through IVRS/IWRS.

If not already done, the sponsor's Medical Monitor or designee must be contacted as soon as possible to notify him/her of the unblinding and to discuss the reason(s) for unblinding.

9.4.8 Prior and Concomitant Therapy

At the screening visit, study staff will record all medications, including analgesics, used by the subject during the 30 days prior to screening. At all subsequent visits, including the post-treatment follow-up period, study staff will record concomitant therapy taken by a subject during the study; the reason for its use will be recorded.

Prior and concomitant therapy is defined to include all medications (over-the-counter and/or prescription, including analgesics), procedures, and significant nonpharmacological therapies that are used to treat the subject, including those used in response to an AE/SAE, during the time periods relevant to study conduct.

Prohibited concomitant medications:

All medications used for chronic pain, other than the study drugs and supplemental analgesic medication, are prohibited during the study. Prohibited medication used for chronic pain includes all opioids, NSAIDs (other than the study drug), cyclooxygenase-2 (COX-2) inhibitors, aspirin, gabapentin, antiepileptics, and antidepressants used for chronic pain (eg, tricyclics, selective serotonin /norepinephrine re-uptake inhibitors [SSRIs,SNRIs])

Muscle relaxants (eg cyclobenzaprine, methocarbamol) are prohibited. Muscle relaxants cannot be initiated during the study.

Other prohibited concomitant treatments include benzodiazepines, monoclonal antibodies for osteoporosis, methotrexate, any local OA treatments for the knee(s), including topical anesthetics or NSAIDs; topical, intra-articular, or systemic corticosteroids (other than inhalers); or any OA injection in the knee(s), antidepressants (other than SSRIs used for depression), warfarin or anticoagulants, cyclosporine (except ophthalmic emulsion), and marijuana.

Based on in vitro data, V120083 is a CYP3A4/5 substrate and has the potential to inhibit P-gp and CYP3A4/5. Concomitant administration of CYP3A inhibitors, inducers, substrates, and P-gp substrates are restricted as follows:

- Subjects taking strong CYP3A inhibitors will be excluded from the study due to potential increases in plasma levels of V120083 when co-administered with V120083. Subjects who initiate these medications during the study will be discontinued from the study.

- Subjects taking moderate CYP3A inhibitors will be excluded if the dose has not been stable for at least one month prior to start of study drug dosing. See Appendix Q for a

representative list of moderate and strong CYP3A inhibitors). Subjects who discontinue therapy with moderate CYP3A inhibitors during the study will be permitted to continue on the study

- If the subject is taking multiple moderate CYP3A inhibitor(s) or the category is unknown, the investigator should contact the medical monitor and subjects are to be carefully monitored.

- Subjects taking CYP3A inducers will be excluded from the study due to potential decrease in plasma levels of V120083. Subjects who initiate these medications during the study will be discontinued from the study.

- Subjects taking CYP3A sensitive substrates and substrates with narrow therapeutic range, or P-gp substrates will be excluded from the study due to potential increases in plasma levels of such medications when co-administered with V120083. Subjects who initiate these medications during the study will be discontinued from the study. (See Appendix Q for a representative list of inducers and substrates).

- The investigator should contact the medical monitor if there are any questions or concerns.

APAP/acetaminophen may be used intermittently for headache, fever, or acute pain up to the 1 gram maximum per dose and 2 g per 24 hour maximum amount; low-dose aspirin (81 mg daily) for cardiovascular disease prophylaxis is allowed. Note: Subjects will be requested not to take any APAP/acetaminophen for at least 24 hours before each clinic visit.

Aspirin dose of 81 mg per day is allowed to be taken for cardiovascular disease prophylaxis.

9.4.9 Treatment Compliance

Records of study drug and doses administered, including supplemental analgesic medication (ie, acetaminophen), will be kept during the study. The site monitor will review drug accountability records during site visits and at the completion of the study.

Site personnel will evaluate clinical supplies returned and acetaminophen at each subject visit in accordance with section 9.4.3. In addition, as each subject completes the study, site personnel will review the records of all clinical supplies returned by the subject (including evaluation for possible trends, eg, 5% of drug missing at 3 subject visits) in accordance with section 9.4.3.

9.5 Study Procedures

9.5.1 Schedule of Activities

The Schedule of Activities for the study is presented in Table 3.

Table 3 Schedule of Activities

Protocol Activity	Screening			Double-blind Period				Follow-up
	Visit 1	Phone Call	Pain Assessment /Washout[a]	Visit 2 (Rand)	Visit 3	Visit 4	Visit 5 or discontinuation (EOS)	Phone Call or Clinic Visit
Study day	Days -21 to -1			Day 1	Week 1	Week 2	Week 4	7 after the last dose
Days from Baseline	-			-	6-8	12-16	25-31	
Informed consent form (ICF)	X							
Contact IVRS/IWRS	X	X[b]		X	X	X	X	
Inclusion/exclusion criteria	X			X				
Demography	X							
Medical history and current medical condition	X							
Pain history/ACR criteria	X							
Vital Signs	X			X	X	X	X	
HADS	X						X	
Columbia-Suicide Severity Rating Scale (C-SSRS)[o]	X			X	X	X	X	X[p]
Physical examination	X			X	X	X	X	
Height, weight, and BMI[d]	X						X	
Bilateral X-ray of the knees	X						X	
Kellgren-Lawrence classification[q]	X						X	
Identify index knee	X							
Average pain over the last 7 days	X							
Electrocardiogram[e]	X					X	X	X[r]
Virus screen (HBV, HCV, and HIV)	X							

Protocol Activity	Screening			Double-blind Period				Follow-up
	Visit 1	Phone Call	Pain Assessment /Washout[a]	Visit 2 (Rand)	Visit 3	Visit 4	Visit 5 or discontinuation (EOS)	Phone Call or Clinic Visit
Study day	Days -21 to -1			Day 1	Week 1	Week 2	Week 4	7 after the last dose
Days from Baseline	-			-	6-8	12-16	25-31	
Laboratory evaluations (chemistry, hematology, and urinalysis)	X					X	X	X[r]
Serum pregnancy test[f]	X						X	
Urine pregnancy test				X	X	X		
Urine drug test	X							
Chemotherapy-induced Taste Alteration Scale (CiTAS)				X	X	X	X	
mBPI-SF – entire scale				X	X	X	X	
WOMAC				X	X	X	X	
EQ-5D				X	X	X	X	
SF-36				X	X	X	X	
PGIC							X	
Randomization				X				
Dispense study drug as instructed by IWRS				X	X	X		
Dispense supplemental analgesic medication	X[g]			X	X[h]	X[h]		
Adverse events	←						→	
Prior and concomitant therapies	←						→	
Distribute subject diary	X							
Collect subject diary		X[b]	X[c]				X[i]	
Review subject's diary				X	X	X	X[i]	
Diary entries								
Study medication dosing information (date/time/amount taken)				←		→		
Indicate if meal eaten within ± 2 hours of dosing					←		→	
Supplemental analgesic use (time/date/amount taken)			←			→		

Protocol Activity	Screening			Double-blind Period				Follow-up
	Visit 1	Phone Call	Pain Assessment /Washout[a]	Visit 2 (Rand)	Visit 3	Visit 4	Visit 5 or discontinuation (EOS)	Phone Call or Clinic Visit
Study day	Days -21 to -1			Day 1	Week 1	Week 2	Week 4	7 after the last dose
Days from Baseline	-			-	6-8	12-16	25-31	
"Pain right now" scores				←	—	—	→	
Daily "average pain over the last 24 hours" scores			←	—	—	—	→	
Collect unused study drug and conduct drug accountability					X	X	X	
Washout of prohibited analgesics			X					
Collect sample(s) for PK analysis				X[j]	X[k]	X[k]	X[k]	
Collect sample for PG analysis[l]				X			X	
Telephone contacts				X[m]	X[m]	X[m]	X[m]	X[n]

Abbreviations: ACR = American College of Rheumatology, BMI = body mass index; C-SSRS = Columbia-Suicide Severity Rating Scale; EQ-5D = EuroQol-5D; HADS = Hospital Anxiety and Depression Scale; HBV = hepatitis B; HCV = hepatitis C; HIV = human immunodeficiency virus; ICF = informed consent form; IVRS/IWRS = interactive voice response system/interactive web response system; mBPI-SF = Modified Brief Pain Inventory – Short Form; PG = pharmacogenomics; PGIC = Patient Global Impression of Change; PK = pharmacokinetic; Rand = randomization; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; WOMAC = Western Ontario and McMaster Osteoarthritis Index.

a The washout period is required only for subjects who take analgesic medications for pain. Subjects who do not take any medications for pain will record their "average pain over last 24 hours" scores for 3 to 7 days. Subjects who take medications for pain will record their "average pain over last 24 hours" scores for at least 3 days once all medication used for pain has been discontinued in accordance with acceptable medical practice. Subjects may return to the study clinic for visit 2 as soon as they recorded "average pain over last 24 hours" scores ≥ 4 and ≤ 9 for ≥ 3 consecutive days. All subjects must return to the study clinic for visit 2 within 96 hours of the latest qualifying pain score entry within the pain assessment period.

b Applicable only to screen failure subjects who do NOT meet the study inclusion criteria or who meet ANY of the exclusion criteria for clinical laboratory results, radiograph results, and/or ECG results.

c Applicable only to randomization failure subjects who do NOT meet the randomization criteria, the subject diary will be collected at the end of the pain assessment visit.

d Body weight and BMI will be assessed at screening and visit 5 (end-of-study). Height will be assessed at screening only.

e Subjects with a screening ECG showing a QTcF value (QT data corrected for heart rate using the Fridericia formula) of ≥ 470 msec or other ECG findings that, in the investigator's opinion, would preclude participation in the study. *If subsequent QTcF values exceed 500 msec or 480 msec with a concurrent QTcF change of > 60 msec from baseline, the subject must discontinue study drug and the reason for study drug discontinuation will be recorded as AE (see section 10).*

f Serum pregnancy test to be included for female subjects who are premenopausal or postmenopausal for less than 1 year and who are not surgically sterile.

g Supplemental analgesic medication is to be dispensed as needed at the screening visit

h Supplemental analgesic medication will be dispensed at visits 2, 3, and 4 of the study, as needed.

I Subject diary will be collected at last visit.

J For subjects in the intense PK sampling population, PK samples will be collected at Visit 2 (6 time points; predose and 1, 2 [+/- 10 min], 4, 6 and 8 hrs [+/- 20 min] postdose). The actual time of dosing and sampling should be recorded.

k For all subjects, PK samples will be collected at visit 3 (predose, 1 and 2 hours postdose); visit 4 (predose or postdose) and 5 (predose or postdose). The actual time of dosing and sampling should be recorded.

[l] PG samples will be collected for DNA and protein at visit 2 predose and at visit 5 postdose.
[m] At approximately 1 to 2 days prior to each scheduled visits, the site personnel will contact the subject to remind subjects to:
Refrain from taking any supplemental analgesic medications for at least 24 hours prior to the clinic visit (applicable to visits 3, 4 and 5 only) and to hold morning dose of study drug on the day of the clinic visit for predose PK sampling
[n] Follow-up visit could be by telephone contact or by a clinic visit.
[o] At screening visit, use C-SSRS Baseline/Screening Assessment. For randomization visit and subsequent scheduled or unscheduled visits, use C-SSRS Since Last Visit Assessment. Positive scores on the C-SSRS may result in discontinuation and/or referral to a specialist for evaluation as outlined in the protocol
[p] C-SSRS should be completed at all visits that include clinical assessments
[q] K-L grade should be determined by a local radiologist or rheumatologist.
[r] Subjects who require follow-up of clinical laboratory or ECG assessments must return to the clinical site for this visit.

9.5.2 Screening

9.5.2.1 Visit 1 (Screening Visit)

Each subject will be assigned a unique subject number at screening. Subject numbers will be used on all study documentation.

The following information will be obtained and procedures performed for all potential subjects at a screening visit conducted within 7 to 14 days after the ICF is signed:

- Obtain ICF
- Obtain PG consent form (optional)
- Obtain intense PK consent form (optional)
- Contact IVRS/IWRS to obtain subject number which will be retained throughout the study. Instructions for contacting the IWRS are provided in the study manual
- Review inclusion/exclusion criteria
- Record the subject's demographic information
- Record the subject's medical history and current medical conditions

  If the subject is a referral, the site should make every effort (eg, collect medical records released at screening visits and make at least 2 attempts) to obtain subject's medical records to verify eligibility.
- Record the subject's pain history/ACR criteria
- Collect any spontaneously reported AEs/SAEs prior to recording vital sign measurements
- Record the subject's vital signs as outlined in section 9.6.4.3 (sitting after 5 minutes' rest)
- Administer the HADS questionnaire

  Note: Subjects with HADS score over 10 on either subscale will be excluded from the study.
- Administer C-SSRS Baseline/Screening questionnaire
  - *Note: Subjects who answer "yes" to "suicidal ideation" to any item 1 through 5 (past 24 months) or "yes" to any suicidal behavior, current or history of, will be excluded from the study. The Principal Investigator must evaluate positive responses on the C-SSRS and take appropriate action in consideration of medical judgement and the training and certification process for administering the test. It is the responsibility of the PI to review the results in all subjects and determine if any result constitutes an adverse event and/or requires evaluation by a mental health professional.*
- Perform a physical examination (including measurement of height, weight, and BMI) and examination of the index knee
- Perform X-ray of both knees in standing position

- K-L grade
- Identify the index knee
    - Note: The Investigator or his/her staff must identify and record which knee is chosen as the primary OA site (index knee). The same site must be used for all pain assessments throughout the study.
- Have the subject record his/her 'average pain over the last 7 days' for the index knee on the verbal rating scale
- Record all prior medications, including the subject's incoming analgesic medications and other medications used for chronic pain (if applicable), and non-drug therapies used over the last 30 days
- Collect any AEs that occur during the visit

For subjects NOT meeting inclusion/exclusion criteria evaluated at the screening visit, complete the following screen failure procedures:

- Discontinue the subject
- Record reason for discontinuation
- Provide each subject with post-study instructions as deemed medically appropriate
- Contact IWRS to indicate that the subject discontinued from the study.

For subjects meeting all Inclusion/Exclusion Criteria evaluated at the screening visit, the visit continues as follows:

- Perform a 12-lead ECG after 5 minutes' rest, and verify QTcF value.

  Note: Subjects with any clinically significant findings as well as QTcF > 470 msec will be excluded from the study.

    - Transmit all electronic ECG data immediately to the central ECG provider for interpretation. Retain a copy of all electronic ECG data obtained during the study in the subject's file;

- ECG reports from the central ECG provider will be sent to the clinical site within 72 hours of receipt of ECG transmission. The investigator/designee must review and sign the ECG report from the central ECG provider.

  Note: to be eligible for this study, the Fridericia-Corrected QT (QTcF) value must be ≤ 470 msec. Subjects will proceed with the screening visit if the ECG readings at the clinical site meet these criteria. However, a confirmation from the central ECG provider is needed before the subject is permitted to continue in the double-blind period. The subject will be <u>discontinued</u> if the QTcF value is > 470 msec (based on reports generated by the central ECG provider).

- Collect samples for clinical laboratory tests (hematology, chemistry, and urinalysis)
- Collect samples for viral serology (hepatitis B and C and HIV)

- Collect sample for serum pregnancy test to be included for female subjects who are premenopausal or postmenopausal for less than 1 year and who are not surgically sterile
- Collect sample for a urine drug test
- Dispense subject diary and provide instructions for diary completion
- As needed, dispense supplemental analgesic medication:
  - Instruct the subject to take supplemental analgesic medication (acetaminophen 500 mg), as needed, for OA pain of the knee only. No more than 1000 mg (ie, 1- 2 tablets) at a time and no more than 2 g (ie, 4 tablets) per 24 hours is allowed
  - Instruct the subject to refrain from taking any supplemental analgesic medication for at least 24 hours prior to the next scheduled visit.
  - Instruct the subject to avoid other acetaminophen-containing over the counter products (eg, cold and flu products). Subject should consult with investigator if there is any question or doubt as to whether an over-the-counter medication contains acetaminophen labelled for uses other than pain (eg, cold and flu remedies/products)
- The Investigator or a medically qualified designee will discuss with the subject which pain medications will need to be discontinued when he/she is contacted by telephone.

Rescreening of subjects who previously failed screening is allowed only with the permission of the medical monitor on a case by case basis.

Subjects may be considered for rescreening if they failed screening previously due to eligibility criteria that are now allowed under the current amended protocol; delay of acquiring records; out of window issues (eg, lost or delayed labs); timing of exclusionary procedures; or other reasons approved by the medical monitor.

Subjects with a positive hepatitis B, hepatitis C, or human immunodeficiency virus test results; subjects with positive urine drug test (UDT) for illicit drugs or non-prescribed opioids and/or subjects who previously received study drug in a V120083 trial will not be permitted to be rescreened.

All rescreening must be approved in advance by the medical monitor.

9.5.2.2 Telephone Contact/Washout Period

When results for laboratory assessments (eg, pregnancy tests, hematology, serum chemistry, and urinalysis, urine drug screen), ECG, and radiograph results are available:

- The investigator/medically qualified designee will review the results against all relevant inclusion/exclusion criteria to determine whether it is appropriate for the subject to enter into the double-blind period
  - All results must be signed by the investigator/medically qualified designee upon review
- The clinical site personnel will contact subjects by telephone to inform them of the results and whether they qualify to continue in the study.

If results from the central ECG provider, radiograph, and/or clinical laboratory assessment do not meet the study entry criteria:

- Record reason for discontinuation
- Provide each subject with post-study instructions as deemed medically appropriate
- Contact the IWRS to indicate the subject is a screen failure.

If the subject's results from the central ECG provider, clinical laboratory assessment and radiograph all meet the study entry criteria:

- Record AEs
- Record concomitant medication and therapies
- If the subject is taking medications for pain - instruct subjects to discontinue all analgesic medications (with the exception of supplemental analgesic medication) in accordance with accepted medical practice
- Subject's own supplemental analgesic medication, ie, APAP, is permitted to be taken as needed up to 2 g/day (limited to maximum of 1g/dose). Supplemental analgesic medication is not to be taken within 24 hours of visit 2/randomization.
- Instruct the subject to record his/her daily "average pain over the last 24 hours" scores for the index knee at approximately 8 PM every day for:
  - Up to 7 days (or until instructed to stop) if the subject is not taking any medications for pain
  - Up to 9 days (or until instructed to stop) after all analgesic medications have been discontinued (applicable only to subjects taking medications for pain)
- During the remaining screening period, the site personnel will monitor daily the subjects' daily "average pain over the last 24 hours" scores in the diaries. The subjects may return to the study clinic as soon as he/she recorded "average pain over the last 24 hours" scores of ≥ 4 and ≤ 9 for ≥ 3 consecutive days or until the pain score recording period (7 days for subjects not taking any medications; 9 days for subjects who were on pain medication prior to screening) is completed. All subjects must return for visit 2 within 96 hours of the latest qualifying pain score entry within the pain assessment period.

If the subject's daily "average pain over the last 24 hours" scores do not meet the study entry criteria (see sections 9.3.1 and 9.3.2) – contact the subject via telephone to:

- Discontinue the subject
- Instruct the subject to return his/her diary to the study clinic
- Record reason for discontinuation
- Provide each subject with poststudy instructions as deemed medically appropriate
- Contact the IWRS/IVRS to indicate the subject is a screen failure.

If the subject's daily "average pain over the last 24 hours" scores do meet the study entry criteria (see sections 9.3.1 and 9.3.2) – contact the subject via telephone to:

- Record AEs
- Record concomitant medication
- Schedule visit 2 to occur in the morning as soon as possible (within 96 hours of the latest qualifying score within the pain assessment period)
- Instruct the subject to refrain from taking any medications used for chronic pain

9.5.3 Visit 2 – Randomization

At approximately 1 to 2 days before visit 2, the study clinic personnel will contact the subjects to:

- Instruct the subject to keep refraining from taking any medications used for chronic pain

The following procedures will be performed at visit 2:

- Record AEs
- Perform a physical examination and examination of the index knee
- Record concomitant medication and therapies
- Record the subject's vital signs (to be performed prior to any venipuncture/blood testing) as outlined in section 9.6.4.3
- Administer C-SSRS Since Last Visit questionnaire
    - *Note: Subjects who answer "yes" to "suicidal ideation" to any item 1 through 5 or "yes" to any suicidal behavior must be discontinued from the study. The Principal Investigator must evaluate positive responses on the C-SSRS and take appropriate action in consideration of medical judgement and the training and certification process for administering the test. It is the responsibility of the PI to review the results in all subjects and determine if any result constitutes an adverse event and/or requires evaluation by a mental health professional. Any new suicidal ideation or behavior must be discussed with the Medical Monitor.*
- For women of childbearing potential, conduct urine pregnancy test

Note: Subjects with a positive urine pregnancy test will be discontinued from the study.

- Review the subject diary
- Review subject eligibility for randomization

Subjects are eligible to be randomized if he/she:

- Reported "average pain over the last 24 hours" scores of ≥ 4 or ≤ 9 for ≥ 3 consecutive days
- Continues to forgo all incoming analgesic medications, and other medications used for chronic pain (if applicable)
- Does not use any concomitant medication prohibited by the protocol

- Continues to meet all criteria for study continuation
- Has a negative urine pregnancy test (applicable only to women of childbearing potential)

The following randomization failure procedures will be performed for subjects who do not qualify for continuing in the study:

- Record reason for discontinuation
- Provide each subject with post-study instructions as deemed medically appropriate
- Contact the IWRS to indicate the subject is a randomization failure.

The following procedures will be performed for subjects who are eligible for randomization:

- Contact IVRS/IWRS to indicate that the subject is entering the double-blind period.
- Have the subject record his/her responses to the mBPI-SF WOMAC, EQ-5D, and SF-36
- Perform CiTAS rating
- Collect optional PG sample (for subjects who provide additional consent)
- Collect optional PK sample (for subject who provide additional consent)
- Dispense study drug as instructed by IWRS
- Instruct the subject to take the first dose of the study drug at the study clinic
- For subsequent doses, instruct the subject to take 3 capsules bid
- Instruct the subject to record the following information in the diary during the study:
  - Study drug dosing information (date/time/amount taken)
  - Supplemental analgesic medication dosing information (date/time/amount taken)
  - Indicate if meal eaten within ± 2 hours of dosing
  - The "pain right now" scores for the index knee immediately prior to taking supplemental analgesic medication (Appendix N).
- Dispense supplemental analgesic medication
  - Instruct the subject to take supplemental analgesic medication (acetaminophen 500 mg), as needed, for OA pain of the knee only. No more than 1000 mg (ie, 1-2 tablets) at a time and no more than 2 g (ie, 4 tablets) per 24 hours is allowed
  - Instruct the subject to refrain from taking any supplemental analgesic medication for at least 24 hours prior to the next scheduled visit.
  - Instruct the subject to avoid other acetaminophen-containing over the counter products (eg, cold and flu products). Subject should consult with investigator if there is any question or doubt as to whether an over-the-counter medication contains acetaminophen labelled for uses other than pain (eg, cold and flu remedies/products)

- Instruct the subject to record his/her daily "average pain over the last 24 hours" scores for the index knee at approximately 8 PM every day
- For subjects in the intensive PK subgroup, collect PK blood samples for pharmacokinetic (PK) analysis at the following time points and record time of collection:
    - Predose and 1, 2, 4, 6, and 8 hours after the first dose of the study drug
- Schedule the next visit to occur in the morning approximately 1 week later
- Telephone contact 1 to 2 days prior to next scheduled visit for reminders.

9.5.4 Visits 3 (week 1) and 4 (week 2) - Double-blind Period

At approximately 1 to 2 days before the scheduled clinic visits, the site personnel will contact the subject to remind subjects to refrain from taking any supplemental analgesic medications for at least 24 hours prior to the clinic visit. Remind subject to hold morning dose of study drug to allow for predose PK sampling during clinic visits.

The following procedures will be performed at visit 3 (week 1) and 4 (week 2):

- Administer C-SSRS Since Last Visit questionnaire
    - *Note: Subjects who answer "yes" to "suicidal ideation" to any item 1 through 5 or "yes" to any suicidal behavior must be discontinued from the study. The Principal Investigator must evaluate positive responses on the C-SSRS and take appropriate action in consideration of medical judgement and the training and certification process for administering the test. It is the responsibility of the PI to review the results in all subjects and determine if any result constitutes an adverse event and/or requires evaluation by a mental health professional. Any new suicidal ideation or behavior must be discussed with the Medical Monitor.*
- Have the subject record his/her responses to the mBPI-SF, WOMAC, EQ-5D, and SF-36
- Perform CiTAS rating
- Record AEs
- Record the subject's vital signs (to be performed prior to any venipuncture/blood testing) as outlined in section 9.6.4.3
- Perform a physical examination and examination of the index knee
- Record concomitant medication and therapies
- For women of childbearing potential, conduct urine pregnancy test
    - Note: Subjects with a positive urine pregnancy test will be discontinued from the study.

- At visit 4 only,
    - Perform a 12-lead ECG after 5 minutes' rest [prior to predose or postdose PK sampling]

  - Transmit all electronic ECG data immediately to the central ECG provider for interpretation. Retain a copy of all electronic ECG data obtained during the study in the subject's file. ECG reports from the central ECG provider will be sent to the clinical site within 72 hours of receipt of ECG transmission
  - The investigator/designee must review and sign the ECG report from the central ECG provider
  - For any subjects with any QTcF values > 500 msec or > 480 msec with a concurrent increase in QTcF > 60 msec from the mean screening value, record an AE as "QTcF prolonged (QTcF values > 500 msec)" or "QTcF prolonged > 480 msec with a concurrent increase in QTcF value > 60 msec)", and instruct the subject to return to the clinical site at the follow-up visit for a repeat ECG.

- At visit 4 only,
  - Collect samples for clinical laboratory tests (hematology, chemistry, and urinalysis)
- Collect predose PK sample at visit 3, noting time of sample collection [at visit 4, conduct the ECG prior to any PK sampling and PK sample could be pre- or postdose]
- Advise subject to take morning dose of study drug at the study clinic
  - Record the study drug dosing information in the diary
- Collect all unused double-blind medication and supplemental analgesic medication, as required
- Review subject diary for the following information to ensure continual compliance. Educate the subject as necessary:
  - Double-blind study medication dosing information (time/date/amount of taken)
  - Supplemental pain medication dosing information (time/date/amount of taken) with corresponding "pain right now" scores.
  - Instruct the subject to complete last missed diary(ies) if not completed.
- Perform drug accountability review
- Dispense study drug as instructed by IWRS
  - Remind the subject to take 3 capsules bid
- Dispense supplemental analgesic medication;
  - Instruct the subject to take supplemental analgesic medication (acetaminophen 500 mg), as needed, for OA pain of the knee only. No more than 1000 mg (ie, 1-2 tablets) at a time and no more than 2 g (ie, 4 tablets) per 24 hours is allowed
  - Instruct the subject to refrain from taking any supplemental analgesic medication for at least 24 hours prior to the next scheduled visit.

  - Instruct the subject to avoid other acetaminophen-containing over the counter products (eg, cold and flu products). Subject should consult with investigator if there is any question or doubt as to whether an over-the-counter medication contains acetaminophen labelled for uses other than pain (eg, cold and flu remedies/products)

- Remind the subject to record the following information in the diary:
  - Study drug dosing information (date/time/amount taken)
  - Supplemental analgesic medication dosing information (date/time/amount taken)
  - Indicate if meal eaten within ± 2 hours of dosing
  - The "pain right now" scores for the index knee immediately prior to taking supplemental analgesic medication (Appendix N)
- Instruct the subject to record his/her daily "average pain over the last 24 hours" scores for the index knee at approximately 8 PM every day
- At visit 3 only, collect PK blood sample at predose and at 1 and 2 hours postdose, noting time of sample collection. Collect pre- or postdose sample at visit 4.
- Schedule the next visit
- Telephone contact 1 to 2 days prior to next scheduled visit for reminders.

9.5.5 Visit 5 - End of Study or Early Discontinuation

At approximately 1 to 2 days before the scheduled clinic visits, the site personnel will contact the subject to remind subjects to refrain from taking any supplemental analgesic medications for at least 24 hours prior to the clinic visit. Remind subject to hold morning dose of study drug to allow for predose PK sampling during clinic visit (if taking pre-dose sample).

The following procedures will be performed at the clinical site for all subjects at the end of study or early discontinuation visit:

- Record AEs
- Administer C-SSRS Since Last Visit questionnaire
  - *Note: Subjects who answer "yes" to "suicidal ideation" to any item 1 through 5 or "yes" to any suicidal behavior must be discontinued from the study. The Principal Investigator must evaluate positive responses on the C-SSRS and take appropriate action in consideration of medical judgement and the training and certification process for administering the test. It is the responsibility of the PI to review the results in all subjects and determine if any result constitutes an adverse event and/or requires evaluation by a mental health professional. Any new suicidal ideation or behavior must be discussed with the Medical Monitor.*
- Have the subject record his/her responses to the mBPI-SF, WOMAC, EQ-5D, SF-36, HADS, and Patient's Global Impression of Change (PGIC)
- Perform CiTAS rating
- Record the subject's vital sign measurements

- Record concomitant medication and therapies
- Collect samples for clinical laboratory tests (hematology, chemistry, and urinalysis)
- Collect predose or postdose PK blood sample and record time of collection
- Collect optional PG sample (for subjects who provide additional consent)
- Collect sample for serum pregnancy test to be included for female subjects who are premenopausal or postmenopausal for less than 1 year and who are not surgically sterile
- Instruct subject to take study drug at the study clinic (if taking predose PK);
    - Record the study drug dosing information in the diary
- Collect all unused double-blind medication and supplemental analgesics medication
- Collect subject diary
- Review subject diary for the following information to ensure continual compliance.
    - Double-blind study medication dosing information (time/date/amount of taken)
    - Indicate if meal eaten within ± 2 hours of dosing
    - Supplemental pain medication dosing information (time/date/amount of taken) with corresponding "pain right now" scores
    - Instruct the subject to complete last missed diary(ies) if not completed.
- Perform drug accountability review
- Perform X-ray of both knees in standing position
- K-L grade
- Perform a physical examination (measurements for weight and BMI) and examination of the index knee.
- Perform a 12-lead ECG after 5 minutes' rest
    - Transmit all electronic ECG data immediately to the central ECG provider for interpretation. Retain a copy of all electronic ECG data obtained during the study in the subject's file. ECG reports from the central ECG provider will be sent to the clinical site within 72 hours of receipt of ECG transmission
    - The investigator/designee must review and sign the ECG report from the central ECG provider
    - For any subjects with any QTcF values > 500 msec or > 480 msec with a concurrent increase in QTcF > 60 msec from the mean screening value, record an AE as "QTcF prolonged (QTcF values > 500 msec)" or "QTcF prolonged > 480 msec with a concurrent increase in QTcF value > 60 msec)", and instruct the subject to return to the clinical site at the follow-up visit for a repeat ECG.
- Discontinue the subject

- Confirm that the subject has completed the double-blind period or record the reason for discontinuation from the double-blind period
- Convert the subject to his/her own pain regimen and provide poststudy instructions as deemed medically appropriate

Note: Before releasing the subject from the clinical site, it is the responsibility of the investigator/designee (medically qualified designee) to use his/her clinical judgment to assess the subject's continuing pain medication needs.

- Contact IWRS to indicate that the subject has completed/discontinued from the double-blind period
- Schedule a telephone contact or clinic visit to occur in 7 days for the follow-up visit Schedule the follow-up telephone contact or visit
- Telephone contact 1 to 2 days prior to next scheduled visit for reminders (for subjects required to visit study site for follow-up visit)
- The investigator/medically qualified designee will review and sign upon receipt, all radiograph results, all clinical laboratory results from the central laboratory, and all ECG reports from the central ECG provider
    - For any subjects with any QTcF values > 500 msec or an QTcF > 480 msec with a concurrent increase in QTcF value > 60 msec from the mean screening value, instruct the subject to return to the clinical site for a follow-up ECG during the follow-up visit
    - For subjects with abnormal clinical laboratory assessments that require further follow-up, instruct the subject to return to the clinical site for a follow-up assessment during the follow-up visit.

9.5.6 Unscheduled Visits

At the investigator's discretion, a subject may have an unscheduled visit, eg, to discuss safety. If any clinical assessments are performed during an unscheduled visit, the C-SSRS Since Last Visit questionnaire should be administered.

9.5.7 Follow-up

The follow-up phase is designed to evaluate the proper conversion from the study drug to the subject's individual pain regimen upon completion of or discontinuation from the study drug.

The follow-up evaluation is performed 7 days after the last dose via a telephone call or at the study clinic by the investigator/designee if the investigator deems necessary. However, subjects who require follow-up clinical laboratory or ECG assessments must return to the clinical site for this visit. The C-SSRS should be administered if any clinical assessments are conducted.

The following procedures will be performed for all subjects via telephone contact or at the study clinic:

- Record information for all concomitant medications and nondrug therapies

- Record all adverse events, including outcomes of previously reported unresolved adverse events
- If any SAEs or AESIs are reported at 7 days follow-up, a clinical visit must be scheduled and the full AE assessment must be performed; If the subject has their 7 day assessment at the clinic and an SAE or AESI is reported, the full AE assessment must be performed.

9.6 Efficacy Variables, Drug Concentration, Safety and Other Variables

9.6.1 Appropriateness of Measurements

All assessments are standard, widely used, and generally recognized as reliable, accurate, and relevant.

- **Kellgren-Lawrence Classification**

The K-L criteria are the most widely used method of classifying the severity of knee osteoarthritis (OA; Appendix G). It consists of 5 grades (ranging from grade 0 = no radiographic features of OA to grade 4 = severe OA with large osteophytes, marked narrowing of the joint space, severe sclerosis, and definite deformity of the bone ends).[12] According to a review conducted by Schiphof et al, a cutoff of ≥ 2 is sufficient to distinguish definite/mild osteoarthritis from none/possible osteoarthritis.[13] The K-L criteria will be used to evaluate subjects at the screening visit. Subjects meeting K-L criteria 0, 1, or 4 do not qualify for this study.

- **Columbia-Suicide Severity Rating Score (C-SSRS)**

Suicidality will be monitored throughout the study using the C-SSRS (Appendix O). The C-SSRS scale consists of a baseline/screening evaluation that assesses the lifetime and prior 24 month experience of the subject with suicide events and suicidal ideation and a post baseline/"Since Last Visit" evaluation that focuses on suicidality since the last study visit. The C-SSRS is a prospective assessment instrument that directly classifies suicidal ideation and behavior into categories. The C-SSRS involves a series of probing questions to inquire about possible suicidal thinking and behavior.

Hospital Anxiety and Depression Scale (HADS)

The HADS is a self-screening questionnaire that is commonly used by physicians and therapists to assess levels of anxiety and depression (Appendix H). The HADS is a self-reported 14-item instrument that measures the presence and severity of anxiety and depression based on the subject's experience over the past week.[14] It consists of 2 subscales, each having 7 items: an anxiety subscale (HADS-A) and a depression subscale (HADS-D). The 2 subscales, anxiety and depression, have been found to be independent measures. The score for each subscale ranges from 0 (no anxiety or depression) to 21, with a score of 11 or higher indicating the probable presence of the mood disorder. The questionnaire will be administered at visit 1 (screening) and visit 5 (end-of-study/study discontinuation).

Subjects with scores > 10 at the screening visit do not qualify for this study.

- **Modified Brief Pain Inventory-Short Form (mBPI-SF)**

The mBPI-SF is a self-administered questionnaire used to assess the severity of pain, and the interference of pain on daily functions (Appendix I). It has been validated in numerous trials and

for use in patients with OA.[17] It consists of 6 questions: 4 questions ask the subjects to rate their pain on a 0 to 10 NRS for worst pain, average pain, least pain, and current pain; 1 question asks subjects to rate their pain relief over the past 24 hours; 1 question with 7 parts that ask subjects to rate the impact of their pain on mood and everyday activities. The mBPI-SF questionnaire will be completed at each clinic visit from visit 2 to the last visit during the double-blind period. The questionnaire takes less than 5 minutes to complete.

The question daily "average pain over the last 24 hours" scores will be administered daily during the screening visits (Appendix N). The full questionnaire will be administered at visits 2 through 5 (end of study/early discontinuation).

- **Western Ontario and McMaster OA Index (WOMAC)**

The WOMAC is a self-administered questionnaire used to assess subjects with OA of the hip or knee (see Appendix J). The WOMAC was validated in 1988 and is the leading outcome measure in clinical trials for knee and hip OA.[18-23] The 24-hour, 0 to 4 categorical version (LK3.1) will be administered at each visit (excluding the follow-up visit), and it will be used to monitor the course of the disease or to determine the effectiveness of medications. The following 3 subscales will be calculated and analyzed:

Pain Subscale (5 items: walking; stair climbing; nocturnal; at rest; weight bearing): the pain subscale score can be 0 to 20.

Stiffness Subscale (2 items: morning stiffness; stiffness occurring later in the day): the stiffness subscale score can be 0 to 8.

Physical Function Subscale (17 items: descending stairs; ascending stairs; rising from sitting; standing; bending to floor; walking on flat surface; getting into or out of car; going shopping; putting on socks; rising from bed; taking off socks; lying in bed; sitting; getting into or out of the bathtub; getting on or off the toilet; heavy domestic duties; light domestic duties): the physical function subscale score can be 0 to 68.

The questionnaire will be administered at visits 2 through 5 (end of study/early discontinuation).

- **EQ-5D**

EQ-5D is a standardized generic measure of health status for clinical and economic appraisal (see Appendix K).[24-29] It is based on a descriptive system that defines health in terms of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels of severity (no problems, slight problems, moderate problems, severe problems, and extreme problems/unable to). It is a valid, reliable, and widely used instrument. The questionnaire will be administered at visits 2 through 5 (end of study/early discontinuation). It takes a few minutes to complete.

- **Medical Outcomes Study 36-item Short-Form Health Survey (SF-36)**

The SF-36 is a generic health survey with 36 items that measure functional health and well-being from the subject's perspective (Appendix L).[28] The 36 questions are grouped into 11 sections. Some of the sections consist of multiple questions. The survey is summarized into 8 dimensions/scales: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH). From the 8 health dimensions, a physical component summary and mental component

summary measure are derived. The questionnaire will be administered at visits 2 through 5 (end of study/early discontinuation). The SF-36 questionnaire takes 5 to 10 minutes to complete.

- **Patient Global Impression of Change (PGIC)**

The Patient Global Impression of Change (PGIC; Appendix M) is an ordinal scale of global evaluation which assesses the change in overall status relative to the start of the study. The scale has only1 item that measures global change of overall status (improvement or worsening) by the subject on a 7-point scale from 1 to 7, where 1 = very much improved and 7 = very much worse. It is a valid, reliable, and widely used instrument and has shown a high degree of correlation with a subject's self-reported pain score. The PGIC will be administered at visit 5 (end-of-study/early discontinuation).

9.6.2 Efficacy Variables

9.6.2.1 Primary Efficacy Variable

The primary efficacy assessment is the daily "average pain over the last 24 hours" score (on an 11-point NRS scale where 0 = no pain, 10 = pain as bad as you can imagine) from the mBPI-SF pain severity subscale at week 4 of the double-blind period.

9.6.2.2 Secondary Efficacy Variable(s)

- Weekly "average pain over the last 24 hours" collected by e-Diary
- Average daily "pain right now" collected by e-Diary
- WOMAC total scores
- WOMAC pain severity subscale
- WOMAC physical function subscale
- WOMAC stiffness subscale
- mBPI-SF total scores (all parts of 6 questions)
- mBPI-SF pain severity subscale
- mBPI-SF pain interference subscale
- SF-36
- EQ-5D
- PGIC at the end of double-blind period (week 4)
- Supplemental analgesic medication use
- Responder to treatment

9.6.3 Drug Concentration Measurements

Samples of blood will be taken to determine plasma concentrations of V120083 in this study. For subjects in the intensive PK subgroup, blood samples will be collected at visit 2 (day 1 of

dosing) predose and postdose at 1, 2, 4, 6, and 8 hours. All subjects will have PK samples collected a visit 3 (week 1; predose, 1 and 2 hours postdose); visit 4 (week 2; predose or postdose); and visit 5 (week 4; predose or postdose). The site will obtain one (6 mL) blood sample during the visit and confirm the time of the subject's last 2 doses of study drug. The actual time when the samples are taken should be recorded. See Appendix C for information on collection, processing, storage, and shipment of PK samples.

9.6.3.1 Analytical Methodology

Plasma concentrations of V120083 will be quantified by a validated liquid chromatography tandem mass spectrometric method.

9.6.4 Safety Variable(s)

9.6.4.1 Adverse Events (AEs)

AEs will be collected as described in the schedule of assessments in section 9.5.1. Details of AE data collection are described in section 10.

9.6.4.2 Clinical Laboratory Evaluations

Blood and urine samples will be collected for chemistry, hematology, and urinalysis evaluation (Appendix A). The clinical laboratory evaluations will be conducted by a central laboratory.

Some of blood/plasma and urine samples collected during the study may be used for future exploratory investigative studies, if and as necessary.

A serum pregnancy test will be performed for female subjects who are premenopausal or postmenopausal for less than 1 year and who are not surgically sterile at screening, and at end of study or early discontinuation as applicable. A urine pregnancy test will be performed for all female subjects of childbearing potential prior to the first dose of the study drug and as indicated in Table 3.

Laboratory results will be evaluated. The investigator will assess whether any values reflect AEs and if so, report them as described in section 10.

Appendix B represents the criteria (ie, upper limit, lower limit criteria for each laboratory parameter) that will be used to identify subjects with alert laboratory values.

The Schedule of Activities (section 9.5.1) shows the time points at which blood will be collected for clinical laboratory tests, and urine will be collected for urinalysis.

9.6.4.3 Vital Signs

Height, weight, and BMI will be measured at visit 1.

Vital signs will be collected at the visits designated on the Schedule of Activities (section 9.5.1).

Vital signs to be collected are the following: systolic/diastolic blood pressure, heart rate, respiration rate (after subject has been seated for at least 5 minutes), and temperature. When vital signs are scheduled at the same time that blood samples are obtained, the vital signs will be obtained before and as close to the scheduled blood sample as possible.

All vital sign abnormalities, including clinically notable vital sign abnormalities (Table 5), will be evaluated using appropriate medical judgment to determine whether they represent AEs. Vital sign abnormalities that require medical intervention (beyond confirmatory vital sign collection) are AEs.

Reference ranges for the vital sign values are presented in Table 4. For values outside the reference range, the measurements will be repeated at the investigator's discretion.

Table 4 Reference Range for Vital Sign Values

Vital Sign Parameter	Range
Systolic blood pressure	100–140 mm Hg
Diastolic blood pressure	60–90 mm Hg
Heart Rate	60–100 bpm
Respiratory rate	12–20 breaths per minute
Temperature	36.8°C–38.3°C

Table 5 Criteria Used to Identify Clinically Notable Vital Sign Abnormalities

Vital Sign Parameter	Value	Change From Baseline[a]
Systolic blood pressure	≥ 180 mm Hg	Increase of ≥ 20 mm Hg
	≤ 90 mm Hg	Decrease of ≥ 20 mm Hg
Diastolic blood pressure	≥ 105 mm Hg	Increase of ≥ 15 mm Hg
	≤ 50 mm Hg	Decrease of ≥ 15 mm Hg
Heart rate	≥ 120 bpm	Increase of ≥ 15 bpm
	≤ 50 bpm	Decrease of ≥ 15 bpm
Respiratory rate	< 12 breaths per minute	—
	> 20 breaths per minute	—

[a] Both value and change from baseline criteria must be met to qualify as a clinically notable abnormality.

9.6.4.4 Electrocardiograms (ECGs)

ECG results from 12-lead ECG will be transmitted to the central ECG provider for interpretation and will be evaluated by the investigator for clinical significance. The investigator will assess whether any findings reflect AEs and if so, report them as described in section 10, Adverse Events.

In order for subjects to enter the study, the baseline QTcF value obtained at the screening visit (visit 1) should not exceed 470 msec. To remain in the study, QTcF values for ECG tracings in each visit subsequent to screening should not exceed 500 msec or 480 msec with a concurrent QTcF change of > 60 msec from baseline. If QTcF values exceed 500 msec or 480 msec with a concurrent QTcF change of > 60 msec from baseline, the subject must discontinue study drug and the reason for study drug discontinuation will be recorded as AE (section 10).

All ECG abnormalities, including clinically notable abnormalities (

Table **6**), will be evaluated using appropriate medical judgment to determine whether they represent AEs. Abnormalities that require medical intervention are AEs.

Table 6 Criteria Used to Identify Clinically Notable ECG Values

ECG Parameter	Value	Change From Baseline[a]
Heart rate	≥ 100 bpm	Increase of ≥ 15 bpm
	≤ 50 bpm	Decrease of ≥ 15 bpm
QTcF – Screening	> 470	
QTcF – During study	> 480	With increase of 60 msec from baseline

[a] Value or change from baseline criteria may be met to qualify as a clinically notable abnormality.

9.6.4.5 Physical Examination

The physical examination must be performed by the investigator or a medically qualified designee (MD, DO, PA, NP).

Findings from physical examinations will be evaluated by the investigator. Findings at the screening visit will be considered medical history. The investigator will assess whether any changes from the baseline physical examination reflect AEs and if so, report them as described in section 10, Adverse Events.

9.6.4.6 Other Safety Variables

Other safety variables will include:

- HADS scores
- C-SSRS
- K-L scores

9.6.5 Other Variables

9.6.5.1 Chemotherapy-induced Taste Alteration Scale (CiTAS)

Subjects will be asked to rate their evaluation of taste alterations for the 18 items and 5 subscales on the CiTAS, a 5-point Likert-type scale.[31] All results will be reviewed by the staff for accuracy and completeness at the time the questionnaire is administered (Appendix P).

9.6.5.2 Pharmacogenomics

Subjects will be asked if they are interested in participating in an optional exploratory pharmacogenomic portion of the study following their written informed consent for the trial. Not participating in this exploratory PG portion of the study will not affect their participation in the trial. This will involve collecting additional blood samples which may be used for future exploratory PG analysis. In general, collection of these additional blood samples will be scheduled to occur at times when blood samples are already being collected for the study.

Three samples of blood, totaling approximately 20 mL, will be collected from each subject during the treatment period:

- 1 sample for DNA at visit 2 predose
- 2 samples for protein: 1 sample at visit 2 predose, and 1 sample at visit 5.

Pharmacogenomic Samples

Informed consent specific for PG sampling, must be obtained prior to blood collection.

To obtain sufficient DNA for PG studies, a single blood sample will be drawn at the time point specified in Table 3 into the appropriate tubes provided by the sponsor [redacted].

Privacy of information collected from samples obtained for storage and future analysis will be maintained. PPLP has developed secure policies and procedures to maintain subject privacy. At the clinical site, unique codes will be placed on each PG blood sample for transfer to the sponsor designated/approved storage facility. Each code is a unique random number used only to identify each biosample of each subject.

Subjects may withdraw consent for banking samples at any time by contacting the investigator responsible for administering their initial informed consent. After withdrawal of consent, no future samples will be collected and any samples with subject identification will be removed from the biorepository and their destruction documented in the repository database. Any analyses performed or data obtained from the samples prior to the subject withdrawing consent will not be deleted.

Data generated from processed samples remain confidential and will be retained by PPLP for an indefinite period. Specimens will be maintained for potential analysis for up to approximately 20 years following their acquisition. Samples will be destroyed according to PPLP policies and procedures and this destruction will be documented in the repository database.

[redacted]

9.6.6 Clinical Supplies Product Complaints

9.6.6.1 Types of CSPCs

Clinical Supplies Product Complaints (CSPCs) of study drug(s) consist of any issues involving:

- Supply quality, quantity, packaging
- Supply shipping
- Supply storage
- Suspected or known theft or diversion by non-subjects

9.6.6.2 Reporting of CSPCs to Sponsor or Designee

All CSPCs must be reported to the sponsor (or designee) by completing the CSPC Report Form and faxing within 24 hours of first knowledge of the issue. Follow-up information, or new

information available after the initial report, should be actively sought and reported by faxed follow-up reports to the sponsor (or designee) as it becomes available. In cases of confirmed or suspected diversion, the signature of the investigator / medically qualified designee is required on the CSPC Report Form.

9.6.7 Subject Drug Discrepancies

Site personnel will evaluate the study drugs dispensed / used by each subject at each visit and upon subject completion or discontinuation of the subject for any reason. All study drugs should be accounted for. Site personnel will consult the subject regarding any discrepancies of what is expected to be returned vs. what is actually returned. This discussion and its outcome should be documented in the source on the individual subject. Questions regarding the event may be referred to the Medical Monitor.

Any study drug discrepancy will be reported in the Electronic Data Capture system. The discrepancy may be categorized into the following:

- Subject lost drug
- Subject's drug was stolen
- Subject took more than expected
- Other (subject related) (any other situation which does not fall into the above categories).

9.6.8 Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Clinical site audits will be conducted periodically by the sponsor's (or designee's) qualified compliance auditing team, which is an independent function from the study conduct team.

9.6.9 Data Collection

Electronic Data Capture will be used to record case report form (CRF) data.

Electronic diaries will be used for this study.

Investigators/designees will enter the information required by the protocol onto the appropriate source documents, and in CRFs in accordance with the accompanying CRF completion instructions. The CRFs will be reviewed for completeness and accuracy against the source documents by the CRAs who will periodically visit each clinical site. Any discrepancies found between the source documents and the completed CRFs will be noted, and the CRAs will ensure that appropriate clinical site personnel address the discrepancies.

The investigator/medically qualified designee must verify that the data are complete and accurate via signature in the CRF as required.

Subjects will enter self-reported information into their diaries and/or directly into an electronic device or on paper at the clinical site. Investigators/designees will review the diary data on an ongoing basis and periodically with the subject.

9.6.10 Clinical Data Management

Clinical data will be entered into the clinical database in accordance with data management procedures. Programmed and manual review of the clinical database will be performed according to data validation procedures. Clinical sites will be notified of any discrepancies and will be requested to address them. The database will be 'locked' by clinical data management once the database has been appropriately updated in accordance with the clinical site responses.

CRF data will be stored in a clinical database as specified in data management processes. External data (eg, laboratory data, diary, and ECG data) will be received from third party vendors and processed per the data management procedures. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

9.6.11 Data Quality Assurance

In accordance with the data management plan, the clinical database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be documented and sent to the clinical site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail. Quality checks will be performed per the data management procedures.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

All data analyses will be performed by sponsor's (or designee's) statistical and programming personnel. Statistical programming and analyses will be performed using SAS® and/or other validated statistical software as required.

This section describes the statistical analyses of safety, efficacy, and other data collected. The statistical analyses described in this section will be performed as further outlined in the statistical analysis plan (SAP). The final SAP will take into account any amendment to the protocol.

The data described in the sections below will be listed by subject.

9.7.1 Analysis Populations

The **enrolled population** consists of all individuals who sign the ICF.

The **safety population** is the group of subjects who are randomized and receive at least 1 dose of the double-blind study drug.

The **full analysis population** (FAP) is the group of subjects who are randomized, receive at least 1 dose of double-blind study drug, and have at least 1 efficacy assessment.

The **per-protocol population** (PP) is a subset of the full analysis population and consists of all subjects in the full analysis population who do not have major protocol violations.

The **pharmacokinetics** (PK) population consists of all individuals who are randomized and receive at least 1 dose of V120083 and have at least 1 valid, quantifiable PK blood sample.

9.7.2 Summary of Study Population Characteristics

9.7.2.1 Demographics and Baseline Characteristics

The continuous demographic/baseline variables (eg, age [years], weight), will be summarized using mean, standard deviation (SD), minimum, and maximum values. For categorical (nominal) variables (eg, gender, race), the number and percentage of subjects will be used. Demographic/baseline variables will be summarized for all subjects in the safety population.

A listing will be provided for the enrolled population and the safety population.

9.7.2.2 Subject Disposition

Subject disposition will be summarized by treatment groups for the double-blind period. The number and percent of subjects who completed and the number and percent of subjects who discontinued along with the distribution of the reasons for discontinuation will be presented. The number and percent of subjects in each analysis population will be presented. Subject disposition and reasons for discontinuation during screening period will be presented for the enrolled population. A listing will be provided for the enrolled population and the safety population.

9.7.2.3 Dosing and Extent of Exposure

Dosing and extent of exposure will be summarized by treatment groups for the double-blind period.

The double-blind period begins on the day the first double-blind study drug is administered. The number and percentage of subjects exposed to double-blind treatment for overlapping time intervals (eg, any exposure, ≥ 1 week, ≥ 2 weeks, ≥ 4 weeks) in the double-blind period will be calculated by treatment group for the safety population. Descriptive statistics (mean, SD/standard error, median, minimum, and maximum) will be provided to summarize the length of exposure (in days) to each treatment.

A data listing of the study drug dosage administered to each subject during the double-blind period will be provided.

9.7.2.4 Prior and Concomitant Therapy

Prior and concomitant therapies will be coded to World Health Organization Drug Dictionary terms. A dictionary listing of all unique concomitant medications used in the study will be provided, sorting medications by drug class and preferred drug name.

Concomitant therapy use during the double-blind period will be summarized by treatment group for the safety population. In each of these summary tables, the number of subjects taking each therapy will be presented by anatomical therapeutic chemical (ATC) codes (levels 1, 2, and 3). In addition, prior medications used for OA will be summarized using ATC codes by treatment group for the safety population.

A data listing for all prior and concomitant therapy will be provided for the safety population.

9.7.2.5 Medical History

Medical history will be coded to Medical Dictionary for Regulatory Activities Terminology (MedDRA) terms. Coded medical history terms will be summarized for all subjects in the safety population.

9.7.3 Efficacy Analysis

All efficacy analyses will be conducted on the full analysis population. An analysis of the primary efficacy variable for the per-protocol population may be performed if more than 20% of the subjects in the FAP have major protocol deviations that would affect the evaluation of efficacy. The primary hypothesis test will be 1 sided with a 5% significance level. For each of the following primary and secondary analyses, the primary contrasts will be those between placebo and each dose of study drug. The placebo and the active control will be compared to assess assay sensitivity.

9.7.3.1 Primary Efficacy Variable(s)

Primary efficacy analysis is based on the daily “average pain over the last 24 hours” score from the mBPI-SF pain severity subscale at week 4 of the double-blind period. The analysis will be performed using a mixed-effect general linear model with repeated measures (MMRM). The MMRM will include treatment (4 levels: 60 mg bid or 30 mg bid of V120083, 500 mg bid naproxen, and placebo) and time (3 levels for weeks, 1, 2, and 4) as fixed effects; the baseline pain scale will be incorporated as fixed covariates, and subject will be a random effect. The treatment by time interaction effect will also be investigated. The restricted maximum likelihood approach will be used to estimate the parameters in the model. While data from the entire double-blind period will be used to fit the linear model to get a better estimate of the variance-covariance matrix (based on Akaike information criteria), the primary comparison between groups will be based on estimates/contrasts for the week 4 means. Reported results of primary analysis from MMRM will include least-squares mean (LSM) estimates, standard errors for each treatment group, the p-value for testing the differences between placebo/naproxen and each dose of V120083, and the corresponding confidence interval (90% and 95%) for the difference in LSMs.

9.7.3.2 Secondary Efficacy Variable(s)

Weekly “average pain over the last 24 hours” collected by e-Diary

The weekly “average pain over the last 24 hours” collected by e-Diary will be analyzed in a similar manner as for the primary endpoint.

Average daily “pain right now” collected by e-Diary

Summary statistics (mean, SD, median, and range) for the average daily “pain right now” scores will be provided by weeks and treatment group for all subjects in the full analysis population. The weekly average of daily “pain right now” scores will be defined as the sum of nonmissing daily “pain right now” scores reported during that week (days 1 to 7, days 8 to 14, days 15 to 21, and days 21 to 28) divided by the number of days with nonmissing scores for that week. If a subject reports fewer than 3 days of pain scores during a week, the weekly mean “pain right

now" score will be set to missing. If there are > 1 "pain right now" scores reported on the same day, then the average "pain right now" score on the day will be used to calculate weekly mean "pain right now" scores. All observed data will be used. Associated 95% CIs for the treatment group means will be calculated and presented.

WOMAC

The WOMAC total score, pain subscale, stiffness subscale and physical function subscale will be analyzed in a similar manner as for the primary endpoint.

mBPI-SF

The 2 components (severity and interference of pain) of the mBPI-SF will be analyzed in a similar manner as for the primary endpoint.

SF-36

There are 8 dimensions/scales: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH). Special transformations are applied to the sum of the scores for a dimension in order to standardize the scales. The detailed algorithm for computing the scores for the scales will be described in the Statistical Analysis Plan for the study.

In addition to the 8 scales, 2 summary measures will be derived:

Physical component summary (PCS) measure (aggregate of PF, RP, BP, and GH scales); and

Mental component summary (MCS) measure (aggregate of VT, SF, RE, and MH scales).

EQ-5D

The 5-level scale EQ-5D (EQ-5D-5L) is a generic instrument that can be used in the clinical and economic evaluation of health care, and to collect data on quality of life and preferences/utility. The instrument comprises questions on mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and a visual analogue scale (VAS) from 0 ("Worst imaginable health state") to 100 ("Best imaginable health state").

The U.S. population-based index values based on crosswalk value sets for EQ-5D-5L developed by EuroQoL Research Fundation (van Hout B et al. 2012) and VAS will be analyzed in a similar manner as for the primary endpoint. In addition, responses from each of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) will be converted into binary outcomes ('No problems' vs 'Problems') based on EQ-5D-5L User Guide and the binary outcomes from each of 5 dimensions will be analyzed using a generalized estimating equation (GEE).

Responder to treatment

A subject's response to treatment will be defined as the percentage reduction from the baseline mean "average pain over the last 24 hours" score to the week 4 pain score from the mBPI-SF pain severity subscale. For each subject, percentage reduction in pain from baseline through double-blind treatment will be calculated as:

% reduction = 100* (bslpain – wk4) / bslpain,

Where, bslpain = baseline **mean** pain score
wk4 = week 4 pain intensity score.

All subjects who discontinue study drug prior to week 4 will be considered nonresponders and will be assigned a 0% reduction in pain.

The proportion of subjects with a response to treatment at week 4 will be compared using a logistic regression model with “responder” (yes/no) as dependent variable, treatment and screening mean pain score as covariate.

A graph of the observed cumulative percentage of subjects *v* percentage reduction in pain from screening mean pain score will be generated by treatment group. Based on this graph, estimates of percentage of responders for the following cutoffs: (<0, 0, > 0, ≥ 10%, ≥ 20%, ≥ 30%, ≥ 40%, ≥ 50%, ≥ 60%, ≥ 70%, ≥ 80%, ≥ 90%, and = 100%) for each treatment group will be computed and graphed.

PGIC

The PGIC rating score obtained at week 4 or end-of-study visit of the double-blind period will be measured on a 7-point scale in which 1 = very much improved and 7 = very much worse. The categories will be compared between treatment group and placebo using the Chi-Squared test. Further analysis will be conducted on collapsed categories (very much improved/much improved *v* minimally improved/no change/minimally worse/much worse/very much worse) using Fisher’s exact test. Changes from baseline values will be analyzed by treatment group separately using analysis of covariance (ANCOVA), with baseline adjusted as a covariate.

Supplemental Medication

The percentage of subjects who require no supplemental analgesic medication usage will be calculated for each treatment group. Ninety-five percent confidence intervals for the proportion of subjects in each treatment group who do not require any supplemental analgesic medication will be constructed using the normal approximation to the binomial distribution and a correction for continuity. The average daily number of supplemental acetaminophen 500 mg will be summarized for each treatment group weekly and over 28 days. For each visit (time point), the total number of tablets taken will be calculated as the number of tablets given minus the number of tablets returned. The average daily number of tablets will be calculated by dividing the total number of tablets taken during the time interval by the number of days in the interval.

Descriptive statistics (*n*, mean, SD, median, minimum, and maximum) will be presented by treatment group. Due to the nature of the data, supplemental pain medication for OA tends to have a large proportion of zeros (contributed by subjects who do not take any supplemental pain medication) followed by continuous distribution of nonzero values. Therefore, the supplemental pain medication for OA will also be summarized categorically. Preliminarily, the categories will be (1) no supplemental acetaminophen tablets, (2) 0 to ≤ 0.5 tablets, (3) > 0.5 to ≤ 1.0 tablets, (4) > 1.0 to ≤ 2.0 tablets, and (5) > 2.0 tablets. Upon review of the blinded data prior to database lock, the categories will be reviewed and if any adjustments to the categories are deemed necessary, the rationale and new categories will be documented in the SAP prior to database lock.

Other continuous secondary variables (see section 9.6.2.2) will be analyzed similarly to the primary efficacy method, using an MMRM.

9.7.4 Pharmacokinetic Analysis

9.7.4.1 Pharmacokinetic Variable(s)

Plasma V120083 concentrations, sampling times, dosing histories, and individual-specific demographics, including age and weight, will be collected. For intense PK sampling component, time to maximum plasma concentration (Tmax), maximum observed plasma concentration (Cmax), and area under the plasma concentration-time curve from time zero to the time of the last sampling after dosing (AUC_{0-8}) will be calculated.

9.7.4.2 Pharmacokinetic Statistical Analysis

All individual subject plasma concentration data will be listed.

Descriptive statistics (mean, standard deviation, coefficient of variation, geometric mean, coefficient of variation for geometric mean, median, minimum, and maximum) will be tabulated by treatment and visit for predose individual plasma concentrations (troughs), which are sampled at 12 ± 1 hours postdose at visit 3, 4, and 5.

For intense PK sampling component, descriptive statistics for plasma concentrations at visit 2 will be tabulated by treatment and nominal sampling time. The time course of individual and mean plasma concentrations will be graphically presented. Pharmacokinetic parameters of V120083 will be calculated based on the plasma concentrations of V120083 by using non-compartmental analysis for intense PK sampling component. The actual elapsed sampling times will be used in the PK metrics calculations. Descriptive statistics for PK metrics will be tabulated by treatment.

A population PK analysis may be performed and will be reported in a separate report from the clinical study report.

9.7.5 Statistical / Analytical Issues

9.7.5.1 Adjustments for Covariates

Details of adjustments for covariates for the efficacy variables and the definition of these covariates are contained in section 9.7.3. For each primary and secondary efficacy variable analyzed using MMRM, the baseline values will be included as covariate in the model.

Exploratory/subgroup analyses with adjustment for covariates may be performed for further scientific interest in order to look for explanatory variables related to the occurrence of primary safety and efficacy endpoints. Models predicting study endpoints may be developed with potential covariates inclusion in the analysis. The covariates will be chosen and pre-specified from among the baseline and demographic variables.

9.7.5.2 Handling of Dropouts or Missing Data

The distribution of prognostic factors between subjects with complete data and those who discontinue study drug early will be examined to evaluate any potential sources of bias. In the

absence of any apparent systematic loss, data will be analyzed assuming that these observations are missing at random.

mBPI-SF

If more than half of the items in either the severity of pain subscale or the interference of pain subscale are missing, then the resulting subscale score will be treated as missing. Otherwise, if half the items or less in a particular subscale are missing, then for the purpose of computing the subscale score, the item's scoring value will be imputed by the mean score from the other items within the subscale.

WOMAC

The pain subscale of the WOMAC at week 4, will be obtained by adding the responses to questions 1 through 5. A mean score will also be computed for the 3 subscales and composite scale by averaging the response to the questions instead of summing them.

- Pain Subscale: calculated by averaging items 1 to 5. If 2 or more pain scores are missing, then the pain subscale will be set to missing; otherwise, the average of the nonmissing pain scores will be used for the missing pain scores.
- Stiffness Subscale: calculated by averaging items 6 to 7. If both stiffness scores are missing, then the stiffness subscale will be set to missing. If 1 stiffness score is missing, then the nonmissing stiffness score will be used in the analysis.
- Physical Function Subscale: calculated by averaging items 8 to 24. If 4 or more physical functioning scores are missing, then the physical functioning subscale will be set to missing; otherwise, the average of the nonmissing physical function scores will be used for the missing physical functioning scores.
- Composite Scale: calculated by averaging 3 subscale averages: (pain subscale + stiffness subscale + physical functioning subscales)/3. If 1 or more of the subscales is missing, then the composite scale will be set to missing.

PGIC and other efficacy endpoints

No imputation will be done for the PGIC or other efficacy endpoints.

9.7.5.3 Interim Analyses and Data Monitoring

An interim analysis may be conducted when approximately 50% of randomized subjects have completed the end-of-study visit. The unblinded interim analyses and data review will be performed by an independent committee consisting of a statistician, clinician, and programmer not associated with the study team. Additional data reviews may be conducted as deemed necessary. The sponsor may request additional (ad hoc) DMC recommendations throughout the study. Details will be further pre-specified in the DMC and corresponding interim analysis statistical analysis plan documents.

At the interim analysis, the following procedures will be performed:

- Safety evaluation for early termination will be performed when 50% of subjects have completed the study. The independent statistician/programmer will provide safety data listing and summary tables by unblinded treatment groups. The DMC members will review the safety data, including but not limited to AEs and clinical laboratory values.

The decision to stop 1 or more treatment groups due to safety issues will be made based on clinical judgment. The arm will be stopped if there is significant physical toxicity or evidence of impending risk of physiologic harm or extremely abnormal laboratory findings related to treatment.

- Efficacy evaluation for V120083 treatment groups may be performed by the independent statistician/programmer when 50% of subjects have completed the study. The 50% interim analysis may be performed to evaluate the efficacy of each dose of study drug in the study population. The DMC will review the results of the analysis and make recommendations, as appropriate, regarding plans for further studies.

Lan et al[32] introduce stochastic curtailment to stop a trial if, given current data, it is likely to predict the outcome of the trial with high probability. The conditional power at the scheduled end of the study, given the observed data at the interim evaluation, will be calculated with a stochastic curtailment approach to support the decision of early termination for futility.
SAS 9.2 PROC SEQTEST will be used to calculate the conditional power based on the formula given by Cui et al[33] and Emerson et al[34]Additional info will be pre-specified in the DMC charter.

9.7.5.4 Homogeneity Across Clinical Sites

Although subjects will be assigned unique subject numbers sequentially within sites, there is no plan currently to include site as a factor in the statistical models as a main effect because of the large number of sites that are expected to be used for the study. In addition, enrollment at some sites will be very small. Per ICH guidance (E9 section 3.2), a graphical exploration of the homogeneity of treatment effects across sites will be provided for the primary efficacy variable if appropriate.

9.7.5.5 Multiple Comparisons / Multiplicity

No multiplicity adjustment will be performed for this study.

9.7.5.6 Examination of Subgroups

No formal subgroup analyses are planned for efficacy and safety variables.

9.7.6 Safety Analyses

Evaluation of safety will be performed for all subjects in the safety population.

9.7.6.1 Adverse Events (AEs)

AEs will be coded to MedDRA terms (version 18.1). A listing sorted by MedDRA System Organ Class (SOC) and Preferred Term will include all lower level terms and verbatim descriptions associated with the Preferred Terms.

Data for AEs will be analyzed using the treatment-emergent signs and symptoms (TESS) philosophy. Treatment-emergent signs and symptoms are defined as AEs that:

- Emerge during treatment, having been absent at pretreatment; or
- Re-emerge during treatment, having been present at pretreatment but stopped prior to treatment; or
- Worsen in severity during treatment relative to the pretreatment state, when the AE is continuous.

Treatment emergent AEs (TEAEs) will be assigned to study drug according to their onset date. AEs that start after a subject's last dose but within 7 days of dosing will be considered TEAEs and will be assigned to the last treatment administered. AEs that start more than 7 days after the last dose of study drug will be considered non-TEAEs.

Only TEAEs will be included in summary tables. However, all AEs will be included in a by-subject AE listing. The incidence of TEAEs will be summarized by SOC, MedDRA Preferred Term and treatment (if appropriate) by presenting the number and percentage of subjects with an AE. A subject will be counted only once in the incidence count for a specific MedDRA Preferred Term, although a MedDRA Preferred Term might be reported more than once for a particular subject. Separate summaries will be provided for TEAEs by maximum severity (mild, moderate, severe) and relationship (yes, no) to study drug. A TEAE will be considered related to study drug if the investigator reported the event to be "definitely, probably, possibly, or unlikely" related to treatment. In addition, a table of TEAEs occurring in ≥ 5% of the subjects in at least 1 treatment group will be presented.

- Individual subject listings of AEs that resulted in death, of other SAEs and of AEs that led to treatment discontinuation, dose interruption, or dose reduction will be generated. These listings will include the treatment group and dose (if applicable) at the time of AE onset, start and stop dates of the AE, days on study, and days on treatment. Summary tables (eg, incidence of TEAEs leading to treatment discontinuation) may be generated depending upon the incidence of these significant AEs.
- Summaries of TEAEs occurring in the double-blind period will be generated by treatment group for subjects in the safety population.

Adverse events of special interest (AESIs) will be summarized as well. A list of AESIs are defined in section 10.3.2.

9.7.6.2 Laboratory Values

Clinical laboratory values will be evaluated for each laboratory parameter by subject. For each laboratory test, abnormal values will be identified as those outside (above or below) the reference range, and will be flagged in the by-subject listings.

Reference (normal) ranges for laboratory parameters will be included in the clinical study report for this protocol.

Laboratory test results will be assigned an LNH classification according to whether the value is below (L), within (N), or above (H) the laboratory parameter's reference range. Within treatment comparisons during the double-blind period will be based on 3 by 3 tables (shift tables) that, for a particular laboratory test, compare the prerandomization LNH classification to the LNH classification at the end of double-blind treatment.

Summary statistics (n, mean, SD, minimum, maximum, and median values) for end of double-blind (EODB) and change from baseline to EODB values of continuous laboratory parameters will be produced by treatment group for subjects in the safety population.

All clinical laboratory results will be evaluated for markedly abnormal values, see Table 7. A listing of all subjects in the safety population with at least 1 markedly abnormal laboratory value will be prepared; for a given subject, in addition to the flagged markedly abnormal laboratory parameters, the listing will present the results of all scheduled and unscheduled study evaluations of the same laboratory parameter whether or not they are markedly abnormal. The incidence of markedly abnormal laboratory tests will be summarized by treatment group for subjects in the safety population. For these calculations, each subject may be counted once in

the laboratory parameter value high and in the laboratory parameter low categories, as applicable.

Table 7 Laboratory Ranges Used to Identify Markedly Abnormal Laboratory Values

	Markedly Abnormal Range[a]	
Laboratory Parameter	**Lower Limit[a]**	**Upper Limit[a]**
Hematology		
Hemoglobin	< 10 g/dL or 100 g/L	——
Platelets	< 75.0 × 10^9/L or < 75000/mm^3	——
Leukocytes	< 3.0 × 10^9/L or < 3000/mm^3	——
Lymphocytes	<800/mm^3 or <0.8 × 10^9/L	——
Neutrophils	< 1500 × 10^6/L or < 1500/mm^3	——
Clinical Chemistry		
Electrolytes		
Sodium	< LLN	> 150 mmol/L
Potassium	< LLN	> 5.5 mmol/L
Bicarbonate (HCO_3)	<16 mmol/L or <16 mEq/dL[b]	——
Liver Function Tests		
Alkaline phosphatase	——	>2.5 × ULN
Aspartate aminotransferase (AST)	——	> 3 × ULN
Alanine aminotransferase (ALT)	——	> 3 × ULN
Gamma glutamyl transferase (GGTP)	——	> 2.5 × ULN
Total bilirubin	——	> 1.5 × ULN
Renal Function Tests		
Creatinine	——	> 1.5 × baseline or > 1.5 × ULN
eGFR	≤ 59 ml/min/1.73 m^2	
Other Chemistry		
Calcium corrected	< 8 mg/dL or < 2.0 mmol/L	> 11.5 mg/dL or > 2.9 mmol/L
Phosphorus	< 2.5 mg/dL or < 0.8 mmol/L	—
Glucose	< 55 mg/dL or < 3.0 mmol/L	Fasted > 160 mg/dL or > 8.9 mmol/L
Uric acid	——	> ULN
Cholesterol	——	> 300 mg/dL or > 7.75 mmol/L
Triglycerides	——	> 2.5 × ULN
Albumin	< 3 g/dL or 30 g/L	——

Abbreviations: LLN = lower limit of the laboratory reference (normal) range; ULN = upper limit of the laboratory reference (normal) range.

[a] Common Terminology Criteria for Adverse Events version 4.03 June 2010, Grade 2 limits , *unless otherwise specified*.
[b] Common Terminology Criteria for Adverse Events version 3.0 Aug 2006, Grade 2 limit.

Additional analyses of liver function tests (AST, ALT, and total bilirubin) will be conducted by generating shift tables using the categories presented in Table 8 below.

For liver function tests, shift summaries will be generated comparing screening values to end of double-blind values.

Table 8 Categories for Shift Analysis of AST, ALT, and Total Bilirubin

AST/ALT	Total Bilirubin
≤ 1 × ULN	1 × ULN
> 1 - ≤ 3 × ULN	> 1 – 1.5 × ULN
> 3 - ≤ 5 × ULN	> 1.5 – 2.0 × ULN
> 5 - ≤ 10 × ULN	> 2.0 × ULN
> 10 - ≤ 20 × ULN	—
> 20 × ULN	—

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of the laboratory reference (normal) range.

A listing of all subjects in the safety population with liver function test results for AST and ALT >3 × ULN or total bilirubin > 1.5 × ULN will be generated:

For all laboratory listings and summaries described in this section, the following definitions will be applied to each laboratory test:

Screening value = the last scheduled or unscheduled (repeat) test result obtained prior to the first dose of study drug in the double-blind period.

End of double-blind value = the last scheduled test result obtained during treatment with double-blind study drug.

Laboratory evaluations occurring ≥ 7 days after the last dose of study drug will not be included in the calculations listed above.

All laboratory test results will be reported in SI units.

9.7.6.3 Vital Signs

Vital sign listings will include all subjects in the safety population. Vital sign summary tables will be presented by treatment group for subjects in the safety population.

Vital sign values will be evaluated on an individual basis by subject. Abnormal vital sign values will be identified as those outside (above or below) the reference ranges defined in Table 4.

For each continuous vital sign parameter descriptive summary statistics (n, mean, standard deviation/standard error, median, and range) will be prepared for values observed. Summary statistics for the change from baseline to the end of the double-blind will also be presented.

Vital sign abnormalities that meet or exceed the “clinically notable vital sign” values (Table 5) will be listed. The incidence of clinically notable vital signs during the double-blind period will be presented by treatment for all subjects in the safety population.

9.7.6.4 Electrocardiograms

ECG parameters collected include: heart rate (bpm), PR interval (msec), RR interval (msec), QRS interval (msec), uncorrected QT interval (msec), QTcB (Bazett’s correction) interval (msec), and QTcF (Fridericia’s correction) interval (msec).

All summaries described in this section will be generated by period. Summaries of ECG evaluations performed during the double-blind period will be generated by randomized treatment group for subjects in the safety population. In addition, certain summary tables may be generated for ECGs collected during exposure to the study drugs across the double-blind period.

The following listings and summary tables will be generated:

1. Summary statistics (n, mean, SD, minimum, and maximum) of the baseline value, the value at each scheduled evaluation, and the corresponding change from baseline for each continuous ECG parameter.
2. Count (%) of subjects with a change from baseline in QT, QTcB, or QTcF intervals > 30 but ≤ 60 milliseconds, and with a change > 60 milliseconds at each scheduled postbaseline evaluation.
3. Listing of subjects with a change from baseline in QT, QTcB, or QTcF intervals > 30 but ≤ 60 milliseconds, and with a change > 60 milliseconds at each scheduled postbaseline evaluation.
4. Count (%) of subjects, for each ECG parameter, with at least 1 outlier value observed during the phase or period of interest.
5. Listing of subjects with at least 1 outlier ECG parameter postbaseline
6. For each selected ECG morphology finding, the count (%) of subjects with the specific finding absent or present at baseline vs. end of phase (eg, end of run-in period, end of double-blind period).
7. Listing of subjects with treatment-emergent ECG morphology findings.

For these analyses, the following rules will apply:

- The baseline value of each ECG parameter will be defined as the average of all ECG values collected prior to the start of study drug.
- In listings summaries 1 through 3 above, the value of the ECG parameters at each scheduled post-baseline evaluation will be calculated as the average of the tracing results collected at that time.
- For listings 4 through 7, every ECG tracing will be evaluated (ie, no average will be calculated).
- For listings 6 and 7, a subject will be categorized as having a specific morphology finding present at baseline if the finding is observed in at least 1 ECG tracing obtained prior to the start of study drug. A specific ECG morphology finding will be considered present at the end of a phase/period if it is observed in at least 1 ECG tracing collected during that phase/period.
- For listing 7, an ECG morphology finding will be considered treatment emergent if it is observed in at least 1 postbaseline ECG tracing but is absent from all screening baseline tracings.

Outliers (display 5 above) are defined as follows:

- Heart rate: a value for a subject is considered to be an outlier at a postscreening time point if the heart rate measurement at that time point is < 50 bpm and at least a 25% decrease from the subject's baseline mean heart rate (ie, a bradycardia

event), or if the heart rate measurement at the postscreening time point is > 100 bpm and at least a 25% increase from the baseline mean heart rate (ie, a tachycardia event).

- PR interval: a value for a subject is considered to be an outlier at a postscreening time point if the PR interval from the ECG at the postscreening time point is > 200 msec and at least a 25% increase from the subject's baseline mean PR interval.
- QRS interval: a value for a subject is considered to be an outlier at a postscreening time point if the QRS interval from the ECG at the postscreening time point is > 100 msec and at least a 25% increase from the subject's baseline mean QRS interval.
- QT interval: a value for a subject is considered to be an outlier at a postscreening time point if the QT interval from the ECG at the postscreening time point is > 450 msec, and the subject's baseline mean QT interval is > 450 msec.
- QTcF: a value for a subject is considered to be an outlier at a postscreening time point if the QTcF interval from the ECG at the postscreening time point is > 450 msec, and the subject's baseline mean QTcF interval is ≤ 450 msec.

For display 7 listed above, the specific ECG morphology findings consist of the following:

- Abnormal U wave
- Atrial fibrillation
- Right bundle branch block (RBBB)
- Left bundle branch block (LBBB)
- Left anterior hemiblock (LAH)
- Myocardial infarction (MI)
- ST depression
- T wave (biphasic and/or inverted).

For each of the of the findings listed above, a subject will be categorized as having the specific treatment-emergent ECG abnormality if it is observed in at least 1 postscreening period ECG morphologic determination, but is absent from all screening baseline results. The final list of abnormalities will be defined in the statistical analysis plan based on a blinded data review.

9.7.6.5 Physical Examination

Any observed changes in physical examinations from before treatment to after treatment will be listed and described.

9.7.6.6 Other Safety Variables

Descriptive statistics will be presented by treatment group for the HADS, C-SSRS, and K-L scores using the safety population. Changes from baseline values will be analyzed by treatment group separately for both the anxiety and depression scores using ANCOVA, with baseline adjusted as a covariate.

9.7.7 Other variable analysis

CiTAS scores will be listed and summarized descriptively using the safety population.

For the assessment of the CiTAS, scores received from each subscale will be evaluated rather than the total score received from the entire scale. The subscale scores will be obtained by dividing the number of the items into the sum of scores of those items as follows:

- Decline in basic taste: Add up score from question 2 to question 6, and divide it by 5.
- Discomfort: Add up score from question 13 to question 18, and divide it by 6.
- Phantogeusia and parageusia: Add up score from question 10 to question 12, and divide it by 3.
- General taste alterations: Add up score from question 1 and question 7 to question 9, and divide it by 4.

The maximum score is 5 points, whereas the minimum score is 1 point that can be received from subscales.

9.7.8 Other Analyses

[redacted]

9.7.9 Determination of sample size

A total of up to 276 subjects is planned to be randomized to the double-blind period of this study using a 1:1:1:1 randomization ratio; ie, approximately 69 subjects are to be randomized to each of the 4 treatment groups (V120083 [60 mg or 30 mg], naproxen [active comparator], or placebo). The actual number of subjects treated will depend on the outcome of the interim analysis.

The analgesic effect size of V120083 is unknown. Therefore, the sample size calculation is based on a clinically important difference for OA pain reduction of 1 unit on an 11-point NRS (0 to 10). [redacted] This study may provide appropriate information for the data variability in the sample size calculations. The standard deviation (SD) for average pain over last the 24 hours, an individual question of the Summary of Modified Brief Pain Inventory Short Form (mBPI-SF) at week 4, was approximately 2.34. With a fixed sample size study design, the sample size needed for 80% power to detect this difference with a significance level of 0.05 (1-sided) is 69 subjects per arm, assuming a 1:1 randomization ratio of each active arm to placebo. The sample size calculation was performed with nQuery+nTerim 3.0.

10 ADVERSE EVENTS

10.1 Definition

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject, regardless of whether administered any pharmaceutical product or placebo. An AE does not necessarily have a causal relationship with treatment.

An AE can be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the investigational product.
- Any new disease or exacerbation of an existing disease.
- Recurrence of an intermittent medical condition (eg, headache) not present at baseline.
- Any case of abuse of alcohol, illicit drugs, or prescription drugs; abuse of study drug(s) or protocol -specified drug(s); addiction.
- A pregnancy that occurs or becomes confirmed during a clinical study (see section 10.3.1).
- Abnormal laboratory values or other clinical tests (eg, ECG or X-ray) that results in symptoms, a change in treatment, discontinuation from study drug, or are considered to be medically significant.
    - All laboratory abnormalities should be evaluated by the investigator to determine if indicative of an adverse event.

10.2 Assessment

10.2.1 Criteria for Assessing Severity

The investigator/medically qualified designee will evaluate the comments of the subject and the response to treatment in order that he/she may judge the true nature and severity of the AE. Severity refers to the accumulated intensity of discomfort / impairment of health since the last recording of AEs and will be assessed according to the following criteria:

Mild: Awareness of sign, symptom, or event, but easily tolerated.

Moderate: Enough discomfort to interfere with usual activity and may warrant intervention.

Severe: Incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention.

The criteria for assessing severity are different from those used for seriousness (see section 10.2.3 for the definition of SAE).

10.2.2 Criteria for Assessing Causality

The question of the relationship of an AE to study drug should be determined by the investigator/medically qualified designee after thorough consideration of all facts that are available.

Assessment of causality is based on considering associative connections (time or place), pharmacological explanations, previous knowledge of the drug, presence of characteristic clinical or pathological phenomena, exclusion of other causes, and/or absence of alternative explanations. The causal relationship of an AE to study drug will be assessed according to the following criteria:

Reasonable possibility: There is evidence to suggest a causal relationship between the drug and the adverse event [21CFR312.32].

No reasonable possibility: The evidence does not suggest a causal relationship between the drug and the adverse event.

10.2.3 Criteria for Assessing Seriousness

All AEs must be evaluated as potential SAEs. An SAE is any untoward medical occurrence that at any dose:

- Results in a fatality
- Is life-threatening, ie, the subject was at immediate risk of fatality from the AE as it occurred. (This does not include an event that, had it occurred in a more severe form or was allowed to continue, might have been fatal.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
    - The following types of hospitalizations are not considered SAEs for regulatory reporting purposes:
        - Hospitalization(s) for planned (pre-scheduled) medical procedures known at the time of screening
        - Protocol-specific hospital admission
        - Respite care
        - Admission for the treatment of pre-existing condition (known at the time of screening) not associated with the development of a new adverse event or with the worsening of the pre-existing condition
        - Observation/same day/ambulatory procedures.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)
- Is a medically important event or reaction.
    - Other important medical events that may not be immediately life-threatening or result in fatality or hospitalization but may, based on appropriate medical judgment, jeopardize the subject or require intervention to prevent one of the outcomes in the definition of SAE listed above, should also be considered SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse.

Cases of abuse, addiction, or substance dependence involving study drug(s) or protocol-specified drug(s) AND cases of abuse, addiction, or substance dependence involving alcohol or other drug(s) occurring after the initiation of protocol-specified drug(s) or study drug(s) for which there is no relevant history must be reported as SAEs (see section 10.3.3). Subjects involved in suspected or known abuse must be discontinued from the study.

10.3 Adverse Events – Reporting

All AEs will be reported starting from the time informed consent for study participation is provided.

A cluster of signs and symptoms that results from a single cause should be reported as a single AE (eg, fever, elevated white blood cell count, cough, abnormal chest X-ray, etc. can all be reported as “pneumonia”).

AEs assessed as non-serious will be reported through the 7 days following the subject’s last study drug dose or until the last study visit, whichever is later. Nonserious AEs that are ongoing at the subject’s last study visit must be followed until resolution or for 30 days after the subject’s last study drug dose, whichever comes first.

AEs assessed as SAEs will be reported as per section 10.3.3.

10.3.1 Additional Reporting Requirements for Pregnancies

A pregnancy is not by definition an AE, but it is handled as an AE because it is not a condition that should occur during the clinical trial, requires the subject to be discontinued from the study, and requires ongoing monitoring of the pregnancy by the investigator. A pregnancy that occurs or becomes confirmed during a clinical study must be recorded as an AE on the AE CRF and submitted electronically to the sponsor. The pregnancy must also be reported to the sponsor (or designee) using the Notification of Pregnancy Form within 24 hours of first knowledge of the pregnancy to Sponsor.

- The investigator/medically qualified designee should discuss every pregnancy (either subject or subject’s partner) with the Medical Monitor.
- The investigator/medically qualified designee will follow up with the subject or subject’s partner every 3 months throughout the pregnancy and report to the sponsor (or designee) using the Notification of Pregnancy Form.
- Following the estimated date of delivery, the investigator/medically qualified designee will follow up with the subject or subject’s partner and report to the sponsor (or designee) using the Pregnancy Outcome Questionnaire.

While pregnancy itself is not considered an SAE, any SAEs related to the pregnancy of the subject (see below) or occurring in a subject during the subject’s pregnancy or after delivery, must be documented using the SAE CRF. SAEs occurring in the child (ie, congenital anomalies or other conditions present at birth, whether genetically inherited or occurring in utero) must be documented and reported to the sponsor (or designee) on a separate SAE CRF (see section 10.3.3 for SAE reporting procedures).

Reportable SAEs associated with pregnancy include, but are not limited to:

- Pregnancy losses (eg, spontaneous abortion, late fetal fatality, elective termination)
- Life-threatening developments (eg, placental abruption, fetal distress)
- Congenital anomalies
- Neonatal fatality, or
- Any event resulting in maternal hospitalization/prolonged hospitalization or maternal fatality.

10.3.2 Additional Reporting Requirements for Adverse Events of Special Interest

The following AESIs will be recorded and reported via the AE of Special Interest Notification Form:

- Disturbances in thermal sensation, which may include:
    - inhibition of thermal sensation and associated AEs such as thermal burns
    - heat sensitivity
- Taste disturbance

AESIs must be reported to the sponsor (or designee) as soon as possible of first knowledge. AESIs that also meet criteria of SAEs (see section 10.2.3) must additionally be reported via the SAE CRF Data Form (see section 10.3.3).

Criteria for placing the study on clinical hold and temporarily halting dosing is outlined in section 7.1 Potential Risks and Benefits.

10.3.3 Additional Reporting Requirements for Serious Adverse Events

Additional Reporting Requirements for Serious Adverse Events

All SAEs must be reported starting from the time informed consent for study participation is provided. If the investigator becomes aware of an SAE within 30 days after the subject's last dose of study drug, or protocol-specified drug, or standard treatment, or within 30 days after the last study visit or follow-up phone call, the SAE must be reported. SAEs must be followed until the event resolves, the event or sequelae stabilize, or it is unlikely that additional information can be obtained after demonstration of due diligence with follow-up efforts (ie, the subject or health care practitioner is unable to provide additional information, or the subject is lost to follow-up).

All SAEs must be reported to the sponsor (or designee) within 24 hours of first knowledge of the SAE following the SAE CRF Completion Instructions. In the initial report, all available information should be provided. The SAE CRF must be signed by the investigator/medically qualified designee (must be MD or DO). The investigator or sponsor (or designee), depending on local regulations, must inform the IRB about such AEs in accordance with ICH guidelines and the practices of the governing IRBs. Follow-up information, or new information available after the initial report, should be actively sought and reported to the sponsor (or designee) as it becomes available following the SAE CRF Completion Instructions

SAE CRFs should contain the following information, at a minimum:

- The reportable event
- Study drug (if known)
- Protocol number
- Subject number
- Investigator name

- Investigator/medically qualified designee (must be MD or DO) causality assessment for each SAE.

All documents that will be submitted to the sponsor (or designee) that contain information regarding the SAE (including but not limited to, ancillary source document(s), medical or hospital charts, notes) must be redacted (blacked out) for protected health information, including subject initials. The assigned subject number should be recorded on each of the documents submitted to the sponsor. These documents should be faxed to [redacted].

The investigator/medically qualified designee (must be MD or DO) must notify the sponsor's (or designee's) medical monitor by telephone immediately if:

- The SAE CRFs cannot be completed to meet the 24-hour reporting requirement due to business hours (or other plausible reason) or,
- An SAE is being reported during weekend hours (beginning at 5 PM Eastern Time Friday through 12 AM Eastern Time Monday) or,
- An SAE is reported on a holiday (beginning at 5 PM Eastern Time of the business day before the holiday through 12 AM Eastern Time of the next business day).

All available information should be provided in the phone contact including:

- Protocol number.
- Investigator name.
- Subject number.
- AE with serious criterion.
- Investigator/medically qualified designee (must be MD or DO) causality assessment(s) for each SAE.

The SAE must be reported to the sponsor (or designee) as soon as possible upon reopening for business following the SAE Case Report Form Completion Instructions.

See section 9.4.7 for description of the emergency unblinding procedure.

11 ADMINISTRATIVE ASPECTS

11.1 Changes to Protocol

Any change to the protocol will be in the form of a written protocol amendment or administrative change document that will be issued by the sponsor or designee.

Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRB(s)/IEC(s) of all clinical sites.

The protocol requirements should in no way prevent any immediate action from being taken by the investigator/medically qualified designee, or by the sponsor (or designee), in the interest of preserving the safety of subjects included in the study. If an immediate change to the protocol

is deemed by the investigator /medically qualified designee to be necessary for safety reasons, the sponsor's Medical Monitor (or designee) must be notified promptly and the IRB/IEC for the site must be informed according to the IRBs/IECs documented process.

Changes affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval, but the IRB/IEC must be kept informed of such changes. Therefore the clinical site will send the administrative change document to the IRB/IEC according to the IRBs/IECs documented process.

11.2 Discontinuation of Study

The sponsor reserves the right to discontinue the study for safety or administrative reasons at any time. A written statement fully documenting the reasons for discontinuing the study will be provided to the clinical site(s) and IRB/IEC.

Criteria for placing the study on clinical hold and temporarily halting dosing is outlined in section 7.1 Potential Risks and Benefits. If, in the opinion of the investigator, the clinical observations in the study suggest that it may be unwise to continue, the investigator may discontinue their participation in the study or part of the study. A written statement fully documenting the reasons for discontinuation will be provided to the sponsor (or designee) and IRB.

11.3 Disclosure and Confidentiality

This protocol will be registered and maintained on ClinicalTrials.gov in accordance with federal and local regulations.

The contents of this protocol and any amendments and results obtained during the course of this study will be kept confidential by the investigator, the investigator's staff, and IRB/IEC and will not be disclosed in whole or in part to others or used for any purpose other than reviewing or performing the study without the written consent of the sponsor. Accordingly, the investigator is prohibited from publishing any data collected or results obtained during the course of this study without the prior written approval of the sponsor. These obligations of confidentiality and nonuse shall in no way diminish such obligations as set forth in the Confidentiality Agreement between the sponsor and the investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in the Confidentiality Agreement between the investigator and sponsor or designee.

11.4 Monitoring Procedures

The CRA will visit the study clinic at suitable intervals and be in frequent contact with the site through verbal and written communication. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP. The investigator and staff are expected to cooperate with the CRA, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

It is essential that the CRA have access to all study and subject related documents at any time these are requested. The CRFs and corresponding original subject source documents are to be fully available for review by the CRA to verify data accuracy and adherence to study protocol. The CRA will adhere to all requirements for subject confidentiality.

11.5 Records Retention

The investigator has the responsibility to retain all study documents, including but not limited to the protocol, site source documents, copies of CRFs, Investigator's Brochure, regulatory documents (eg, FDA 1572 form, ICFs, and IRB/IEC correspondence) in accordance with ICH E6 (4.9.5) and 21 CFR 312.62(c).

In addition, if applicable the sponsor (or designee) will send a list of treatment codes by study subject to the investigator after the clinical database for this study has been unblinded. The clinical site should plan on retaining study documents per the site contract.

11.6 Inspection Procedures

A government regulatory authority may conduct an inspection during the study or after its completion. If an inspection is requested by a regulatory authority the investigator or designee must immediately inform the sponsor that a request has been made.

11.7 Publication of Results

Any formal presentation or publication of data collected as a direct or indirect result of this trial will be considered as a joint publication by the investigator(s) and the appropriate personnel at the sponsor's site. Authorship will be determined by mutual agreement. For multicenter studies, it is mandatory that the first publication is based on data obtained from all analyzed subjects as stipulated in the protocol by the sponsor's statisticians, and not by the investigators themselves. Investigators participating in multicenter studies must agree not to present data gathered individually or by a subgroup of centers prior to the full, initial publication, unless this has been agreed to by all other investigators and the sponsor.

The sponsor must receive copies of any intended communication at least 30 working days in advance for an abstract or oral presentation and 60 days in advance for a manuscript. This is to allow the sponsor to review the communication for accuracy (thus avoiding potential discrepancies with submissions to regulatory authorities), to verify that confidential information is not being inadvertently divulged, to allow for the filing of additional patent protection, to provide any relevant supplementary information, and to allow establishment of co-authorship. The authorship of communications arising from pooled data will include selected members from clinical sites as well as sponsor personnel.

12 SIGNATURE PAGE FOR INVESTIGATORS

Protocol Number: VAN2001

Version: Version 2, 17-Feb-2017

Title: A Phase 2a, Multicenter, Randomized, Double-blind, Placebo-controlled and Active-controlled, Parallel-group Study Evaluating the Analgesic Efficacy and Safety of V120083 in Subjects with Moderate to Severe Chronic Pain Due to Osteoarthritis of the Knee

Test Drug: V120083

I have read this protocol and agree to conduct this trial in accordance with the protocol and in accordance with ICH and Good Clinical Practices and local and federal regulations. It will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and relevant amendments to date.

Investigator	Signature	Date

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14 APPENDICES

Appendix A: Clinical Laboratory Evaluations

Category	Parameters
Hematology	RBC counts, Hemoglobin, Hematocrit, Platelets, and WBC count with differential (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils) in percentages (%) and absolute counts
Clinical Chemistry	
Electrolytes	Sodium, Potassium, Chloride, Calcium Corrected, Magnesium, Bicarbonate
Liver function tests	Alkaline Phosphatase, Aspartate Aminotransferase (AST/SGOT), Alanine Aminotransferase (ALT/SGPT), Total Bilirubin, Direct Bilirubin, gamma-glutamyl transferase (GGT)
Renal function parameters	Blood Urea/Blood Urea Nitrogen, Creatinine, eGFR
Other	Glucose, Albumin, Cholesterol, Triglycerides, Phosphorus, Lactate Dehydrogenase (LDH), Total Protein, Globulin, Uric Acid
Urinalysis	pH, Protein, Glucose, Ketone, Occult Blood, RBC, WBC, Epithelial Cells, Bacteria, Casts, Crystals, Specific Gravity
Urine drug test	Urine screen includes: Amphetamines, Cannabinoids, Opiates, Cocaine Metabolites, Benzodiazepines, Barbiturates; Phencyclidine, Methadone, Propoxphene
Serum pregnancy test	Human Chorionic Gonadotropin (Choriogonadotropin Beta)
Urine pregnancy test	Human Chorionic Gonadotropin (Choriogonadotropin Beta)
Virus screen	Hepatitis B, Hepatitis C, Human Immunodeficiency Virus

RBC = red blood cells, WBC = white blood cells

Appendix B: Critical Alert Laboratory Values

Critical Laboratory Ranges Used to Identify Alert Range Values

Laboratory Parameter		Alert Laboratory Range[a] Low	High
Hematology			
	Hemoglobin	< 8.0 g/dL or < 80 g/L	——
	Platelets	< 50,000mm^3 or < 50 × 10^9/L	——
	Leukocytes (total WBC)	< 2,000/mm^3 or < 2.0 × 10^9/L	——
	Absolute Neutrophil Count	< 1,000/mm^3 or < 1.0 × 10^9/L	——
Chemistry			
Electrolytes			
	Sodium	< 130 mmol/L	> 155 mmol/L
	Potassium	< 3.0 mmol/L	> 6.0 mmol/L
	Magnesium	< 0.9 mg/dL or < 0.4 mmol/L	> 3.0 mg/dL or > 1.23 mmol/L
	Bicarbonate (HCO_3)	<11 mEq/dL or < 11 mmol/L[b]	——
Liver Function			
	Alkaline phosphatase	——	> 5 × ULN
	Aspartate aminotransferase (AST)	——	> 5 × ULN
	Alanine aminotransferase (ALT)	——	>5 × ULN
	Total Bilirubin	——	>3 × ULN
	Total Bilirubin (Screening only)	——	>ULN [c]
Renal Function			
	Creatinine	——	> 3 × baseline or > 3 × ULN
	eGFR	<29 ml/min/1.73m^2	
Other Chemistry			
	Calcium Corrected	< 7.0 mg/dL or < 1.75 mmol/L	> 12.5 mg/dL or > 3.1 mmol/L
	Glucose	< 40 mg/dL or < 2.2 mmol/L	> 250 mg/dL or> 13.9 mmol/L
	Albumin	< 2 g/dL or < 20 g/L	——
	Bilirubin and Liver Function Test	——	Bilirubin > 34 µmol/L **and** any LFT > 3.0 × ULN[d]

ULN = upper limit of the laboratory reference (normal) range; WBC = white blood cells (count).
[a] Common Terminology Criteria for Adverse Events version 4.03 June 2010, Grade 3 limits, unless otherwise specified.
[b] Common Terminology Criteria for Adverse Events version 3.0 Aug 2006, Grade 3 limit.
[c] Common Terminology Criteria for Adverse Events version 4.03 June 2010, Grade 1 limit.
[d] Sponsor defined alert value, based on Hy's Law.

Appendix C: Pharmacokinetic Sample Collection, Processing, Storage, and Shipment

Detailed instructions are provided in the study-specific Pharmacokinetic Sample Collection Manual (PK Manual) which will be provided separately to the clinical site.

Collect PK blood samples to analyze V120083 concentrations in plasma using labeled 4 mL-draw K_2EDTA Vacutainer® evacuated collection tubes.

After obtaining the PK blood sample, mix collection tube thoroughly by slowly inverting the collection tube several times.

Place the collection tube in an ice/water bath immediately after collection and inversion.

Within 30 minutes of blood sample collection, centrifuge the blood samples in a refrigerated centrifuge set at approximately 3000 rpm for 15 minutes at approximately 4°C.

Transfer clear supernatant (plasma), using clean disposable pipettes, split equally into appropriately prelabeled cryotubes (primary and back-up).

Within 60 minutes of blood sample collection, store plasma samples in a freezer set to maintain a temperature of -20°C.

At times agreed upon by the sponsor and the clinical site, one set of samples (primary) will be packed in sufficient dry ice and shipped to the sponsor designated bioanalytical laboratory as per the Sample Shipment schedule. The second set (back-up samples) will be shipped separately to the sponsor designated bioanalytical laboratory as per the Sample Shipment schedule.

On the day of shipment, clinical site staff will notify (via telephone or email) the contact person at the bioanalytical laboratory about the shipment and provide the tracking number of the pending shipment.

Appendix D: Naproxen Capsules 500 mg Comparator Product Formulations

Description:
Commercially available naproxen 500 mg tablets will be over-encapsulated with Swedish Orange opaque gelatin capsules (Double-blind Size 00) so they cannot be identified.

Route of Administration:
The intended route of administration is oral.

Appendix E: Naproxen Product Information

Full product prescribing information available at
http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/017581s112,018164s062,020067s019lbl.pdf

EC-NAPROSYN® (naproxen delayed-release tablets)
NAPROSYN® (naproxen tablets)
ANAPROX®/ANAPROX® DS (naproxen sodium tablets)

R_x only

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use (*see WARNINGS).***
- **NAPROSYN, EC-NAPROSYN, ANAPROX and ANAPROX DS are contraindicated in the setting of coronary artery bypass graft (CABG) surgery *(see CONTRAINDICATIONS, WARNINGS).***

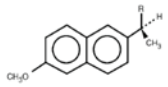
Gastrointestinal Bleeding, Ulceration, and Perforation

- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events *(see WARNINGS).***

DESCRIPTION

Naproxen is a propionic acid derivative related to the arylacetic acid group of nonsteroidal anti-inflammatory drugs.

The chemical names for naproxen and naproxen sodium are (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid and (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid, sodium salt, respectively. Naproxen and naproxen sodium have the following structures, respectively:



naproxen (R=COOH) $C_{14}H_{14}O_3$ mol wt 230.26
naproxen sodium (R=COONa) $C_{14}H_{13}NaO_3$ mol wt 252.23

Naproxen has a molecular weight of 230.26 and a molecular formula of $C_{14}H_{14}O_3$. Naproxen sodium has a molecular weight of 252.23 and a molecular formula of $C_{14}H_{13}NaO_3$.

Naproxen is an odorless, white to off-white crystalline substance. It is lipid-soluble, practically insoluble in water at low pH and freely soluble in water at high pH. The octanol/water partition coefficient of naproxen at pH 7.4 is 1.6 to 1.8. Naproxen sodium is a white to creamy white, crystalline solid, freely soluble in water at neutral pH.

NAPROSYN (naproxen tablets) is available as yellow tablets containing 250 mg of naproxen, pink tablets containing 375 mg of naproxen and yellow tablets containing 500

mg of naproxen for oral administration. The inactive ingredients are croscarmellose sodium, iron oxides, povidone and magnesium stearate.

EC-NAPROSYN (naproxen delayed-release tablets) is available as enteric-coated white tablets containing 375 mg of naproxen and 500 mg of naproxen for oral administration. The inactive ingredients are croscarmellose sodium, povidone and magnesium stearate. The enteric coating dispersion contains methacrylic acid copolymer, talc, triethyl citrate, sodium hydroxide and purified water. The dissolution of this enteric-coated naproxen tablet is pH dependent with rapid dissolution above pH 6. There is no dissolution below pH 4.

ANAPROX (naproxen sodium tablets) is available as blue tablets containing 275 mg of naproxen sodium and ANAPROX DS (naproxen sodium tablets) is available as dark blue tablets containing 550 mg of naproxen sodium for oral administration. The inactive ingredients are magnesium stearate, microcrystalline cellulose, povidone and talc. The coating suspension for the ANAPROX 275 mg tablet may contain hydroxypropyl methylcellulose 2910, Opaspray K-1-4210A, polyethylene glycol 8000 or Opadry YS-1-4215. The coating suspension for the ANAPROX DS 550 mg tablet may contain hydroxypropyl methylcellulose 2910, Opaspray K-1-4227, polyethylene glycol 8000 or Opadry YS-1-4216.

CLINICAL PHARMACOLOGY

Mechanism of Action

Naproxen has analgesic, anti-inflammatory, and antipyretic properties. The sodium salt of naproxen has been developed as a more rapidly absorbed formulation of naproxen for use as an analgesic.

The mechanism of action of the naproxen, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Naproxen is a potent inhibitor of prostaglandin synthesis in vitro. Naproxen concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because naproxen is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

Pharmacokinetics

Naproxen and naproxen sodium are rapidly and completely absorbed from the gastrointestinal tract with an in vivo bioavailability of 95%. The different dosage forms of NAPROSYN are bioequivalent in terms of extent of absorption (AUC) and peak concentration (C_{max}); however, the products do differ in their pattern of absorption. These differences between naproxen products are related to both the chemical form of naproxen used and its formulation. Even with the observed differences in pattern of absorption, the elimination half-life of naproxen is unchanged across products ranging from 12 to 17 hours. Steady-state levels of naproxen are reached in 4 to 5 days, and the degree of

naproxen accumulation is consistent with this half-life. This suggests that the differences in pattern of release play only a negligible role in the attainment of steady-state plasma levels.

Absorption

NAPROSYN

After administration of NAPROSYN tablets, peak plasma levels are attained in 2 to 4 hours. After oral administration of ANAPROX, peak plasma levels are attained in 1 to 2 hours. The difference in rates between the two products is due to the increased aqueous solubility of the sodium salt of naproxen used in ANAPROX. Peak plasma levels of naproxen given as NAPROSYN Suspension are attained in 1 to 4 hours.

EC-NAPROSYN

EC-NAPROSYN is designed with a pH-sensitive coating to provide a barrier to disintegration in the acidic environment of the stomach and to lose integrity in the more neutral environment of the small intestine. The enteric polymer coating selected for EC-NAPROSYN dissolves above pH 6. When EC-NAPROSYN was given to fasted subjects, peak plasma levels were attained about 4 to 6 hours following the first dose (range: 2 to 12 hours). An in vivo study in man using radiolabeled EC-NAPROSYN tablets demonstrated that EC-NAPROSYN dissolves primarily in the small intestine rather than in the stomach, so the absorption of the drug is delayed until the stomach is emptied.

When EC-NAPROSYN and NAPROSYN were given to fasted subjects (n=24) in a crossover study following 1 week of dosing, differences in time to peak plasma levels (T_{max}) were observed, but there were no differences in total absorption as measured by C_{max} and AUC:

	EC-NAPROSYN* 500 mg bid	**NAPROSYN* 500 mg bid**
C_{max} (µg/mL)	94.9 (18%)	97.4 (13%)
T_{max} (hours)	4 (39%)	1.9 (61%)
$AUC_{0-12\ hr}$ (µg·hr/mL)	845 (20%)	767 (15%)

*Mean value (coefficient of variation)

Antacid Effects

When EC-NAPROSYN was given as a single dose with antacid (54 mEq buffering capacity), the peak plasma levels of naproxen were unchanged, but the time to peak was reduced (mean T_{max} fasted 5.6 hours, mean T_{max} with antacid 5 hours), although not significantly *(see PRECAUTIONS; Drug Interactions)*.

Food Effects

When EC-NAPROSYN was given as a single dose with food, peak plasma levels in most subjects were achieved in about 12 hours (range: 4 to 24 hours). Residence time in the small intestine until disintegration was independent of food intake. The presence of food prolonged the time the tablets remained in the stomach, time to first detectable serum

naproxen levels, and time to maximal naproxen levels (T_{max}), but did not affect peak naproxen levels (C_{max}).

Distribution

Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels naproxen is greater than 99% albumin-bound. At doses of naproxen greater than 500 mg/day there is less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses (average trough C_{ss} 36.5, 49.2 and 56.4 mg/L with 500, 1000 and 1500 mg daily doses of naproxen, respectively). The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma *(see PRECAUTIONS; Nursing Mothers*).

Elimination

Metabolism

Naproxen is extensively metabolized in the liver to 6-0-desmethyl naproxen, and both parent and metabolites do not induce metabolizing enzymes. Both naproxen and 6-0-desmethyl naproxen are further metabolized to their respective acylglucuronide conjugated metabolites.

Excretion

The clearance of naproxen is 0.13 mL/min/kg. Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (<1%), 6-0-desmethyl naproxen (<1%) or their conjugates (66% to 92%). The plasma half-life of the naproxen anion in humans ranges from 12 to 17 hours. The corresponding half-lives of both naproxen's metabolites and conjugates are shorter than 12 hours, and their rates of excretion have been found to coincide closely with the rate of naproxen disappearance from the plasma. Small amounts, 3% or less of the administered dose, are excreted in the feces. In patients with renal failure metabolites may accumulate (*see WARNINGS; Renal Toxicity and Hyperkalemia)*).

Special Populations

Pediatric Patients

In pediatric patients aged 5 to 16 years with arthritis, plasma naproxen levels following a 5 mg/kg single dose of naproxen suspension (see **DOSAGE AND ADMINISTRATION**) were found to be similar to those found in normal adults following a 500 mg dose. The terminal half-life appears to be similar in pediatric and adult patients. Pharmacokinetic studies of naproxen were not performed in pediatric patients younger than 5 years of age. Pharmacokinetic parameters appear to be similar following administration of naproxen suspension or tablets in pediatric patients. EC-NAPROSYN has not been studied in subjects under the age of 18.

Geriatric Patients

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly, although the unbound

fraction is <1% of the total naproxen concentration. Unbound trough naproxen concentrations in elderly subjects have been reported to range from 0.12% to 0.19% of total naproxen concentration, compared with 0.05% to 0.075% in younger subjects. The clinical significance of this finding is unclear, although it is possible that the increase in free naproxen concentration could be associated with an increase in the rate of adverse events per a given dosage in some elderly patients.

Race

Pharmacokinetic differences due to race have not been studied.

Hepatic Impairment

Naproxen pharmacokinetics has not been determined in subjects with hepatic insufficiency.

Chronic alcoholic liver disease and probably other diseases with decreased or abnormal plasma proteins (albumin) reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. Caution is advised when high doses are required and some adjustment of dosage may be required in these patients. It is prudent to use the lowest effective dose.

Renal Impairment

Naproxen pharmacokinetics has not been determined in subjects with renal insufficiency. Given that naproxen, its metabolites and conjugates are primarily excreted by the kidney, the potential exists for naproxen metabolites to accumulate in the presence of renal insufficiency. Elimination of naproxen is decreased in patients with severe renal impairment. Naproxen-containing products are not recommended for use in patients with moderate to severe and severe renal impairment (creatinine clearance <30 mL/min) (*see WARNINGS; Renal Toxicity and Hyperkalemia*).

Drug Interaction Studies

Aspirin: When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known. See Table 1 for clinically significant drug interactions of NSAIDs with aspirin (*see PRECAUTIONS; Drug Interactions*).

CLINICAL STUDIES

General Information

Naproxen has been studied in patients with rheumatoid arthritis, osteoarthritis, juvenile arthritis, ankylosing spondylitis, tendonitis and bursitis, and acute gout. Improvement in patients treated for rheumatoid arthritis was demonstrated by a reduction in joint swelling, a reduction in duration of morning stiffness, a reduction in disease activity as assessed by both the investigator and patient, and by increased mobility as demonstrated by a reduction in walking time. Generally, response to naproxen has not been found to be dependent on age, sex, severity or duration of rheumatoid arthritis.

EC-NAPROSYN® (naproxen delayed-release tablets), NAPROSYN® (naproxen tablets), ANAPROX®/ANAPROX® DS (naproxen sodium tablets)

In patients with osteoarthritis, the therapeutic action of naproxen has been shown by a reduction in joint pain or tenderness, an increase in range of motion in knee joints, increased mobility as demonstrated by a reduction in walking time, and improvement in capacity to perform activities of daily living impaired by the disease.

In a clinical trial comparing standard formulations of naproxen 375 mg twice a day (750 mg a day) vs 750 mg twice a day (1500 mg/day), 9 patients in the 750 mg group terminated prematurely because of adverse events. Nineteen patients in the 1500 mg group terminated prematurely because of adverse events. Most of these adverse events were gastrointestinal events.

In clinical studies in patients with rheumatoid arthritis, osteoarthritis, and juvenile arthritis, naproxen has been shown to be comparable to aspirin and indomethacin in controlling the aforementioned measures of disease activity, but the frequency and severity of the milder gastrointestinal adverse effects (nausea, dyspepsia, heartburn) and nervous system adverse effects (tinnitus, dizziness, lightheadedness) were less in naproxen-treated patients than in those treated with aspirin or indomethacin.

In patients with ankylosing spondylitis, naproxen has been shown to decrease night pain, morning stiffness and pain at rest. In double-blind studies the drug was shown to be as effective as aspirin, but with fewer side effects.

In patients with acute gout, a favorable response to naproxen was shown by significant clearing of inflammatory changes (e.g., decrease in swelling, heat) within 24 to 48 hours, as well as by relief of pain and tenderness.

Naproxen has been studied in patients with mild to moderate pain secondary to postoperative, orthopedic, postpartum episiotomy and uterine contraction pain and dysmenorrhea. Onset of pain relief can begin within 1 hour in patients taking naproxen and within 30 minutes in patients taking naproxen sodium. Analgesic effect was shown by such measures as reduction of pain intensity scores, increase in pain relief scores, decrease in numbers of patients requiring additional analgesic medication, and delay in time to remedication. The analgesic effect has been found to last for up to 12 hours.

Naproxen may be used safely in combination with gold salts and/or corticosteroids; however, in controlled clinical trials, when added to the regimen of patients receiving corticosteroids, it did not appear to cause greater improvement over that seen with corticosteroids alone. Whether naproxen has a "steroid-sparing" effect has not been adequately studied. When added to the regimen of patients receiving gold salts, naproxen did result in greater improvement. Its use in combination with salicylates is not recommended because there is evidence that aspirin increases the rate of excretion of naproxen and data are inadequate to demonstrate that naproxen and aspirin produce greater improvement over that achieved with aspirin alone. In addition, as with other NSAIDs, the combination may result in higher frequency of adverse events than demonstrated for either product alone.

In ^{51}Cr blood loss and gastroscopy studies with normal volunteers, daily administration of 1000 mg of naproxen as 1000 mg of NAPROSYN (naproxen) or 1100 mg of ANAPROX

(naproxen sodium) has been demonstrated to cause statistically significantly less gastric bleeding and erosion than 3250 mg of aspirin.

Three 6-week, double-blind, multicenter studies with EC-NAPROSYN (naproxen) (375 or 500 mg twice a day, n=385) and NAPROSYN (375 or 500 mg twice a day, n=279) were conducted comparing EC-NAPROSYN with NAPROSYN, including 355 rheumatoid arthritis and osteoarthritis patients who had a recent history of NSAID-related GI symptoms. These studies indicated that EC-NAPROSYN and NAPROSYN showed no significant differences in efficacy or safety and had similar prevalence of minor GI complaints. Individual patients, however, may find one formulation preferable to the other.

Five hundred and fifty-three patients received EC-NAPROSYN during long-term open-label trials (mean length of treatment was 159 days). The rates for clinically-diagnosed peptic ulcers and GI bleeds were similar to what has been historically reported for long-term NSAID use.

Geriatric Patients

The hepatic and renal tolerability of long-term naproxen administration was studied in two double-blind clinical trials involving 586 patients. Of the patients studied, 98 patients were age 65 and older and 10 of the 98 patients were age 75 and older. Naproxen was administered at doses of 375 mg twice daily or 750 mg twice daily for up to 6 months. Transient abnormalities of laboratory tests assessing hepatic and renal function were noted in some patients, although there were no differences noted in the occurrence of abnormal values among different age groups.

INDICATIONS AND USAGE

Carefully consider the potential benefits and risks of NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS and other treatment options before deciding to use NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (*see WARNINGS: Gastrointestinal Bleeding, Ulceration, and Perforation*).

Naproxen as NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS is indicated:

- For the relief of the signs and symptoms of rheumatoid arthritis
- For the relief of the signs and symptoms of osteoarthritis
- For the relief of the signs and symptoms of ankylosing spondylitis
- For the relief of the signs and symptoms of juvenile arthritis

Naproxen as naproxen suspension is recommended for juvenile rheumatoid arthritis in order to obtain the maximum dosage flexibility based on the patient's weight.

Naproxen as NAPROSYN, ANAPROX and ANAPROX DS and is also indicated:

EC-NAPROSYN® (naproxen delayed-release tablets), NAPROSYN® (naproxen tablets), ANAPROX®/ANAPROX® DS (naproxen sodium tablets)

- For relief of the signs and symptoms of tendonitis
- For relief of the signs and symptoms of bursitis
- For relief of the signs and symptoms of acute gout
- For the management of pain
- For the management of primary dysmenorrhea

EC-NAPROSYN is not recommended for initial treatment of acute pain because the absorption of naproxen is delayed compared to absorption from other naproxen-containing products (*see CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION*).

CONTRAINDICATIONS

NAPROSYN, EC-NAPROSYN, ANAPROX and ANAPROX DS are contraindicated in the following patients:

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to naproxen, naproxen sodium, or any components of the drug product (*see WARNINGS; Anaphylactic Reactions, Serious Skin Reactions)*.
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients (*see WARNINGS; Anaphylactic Reactions, Exacerbation of Asthma Related to Aspirin Sensitivity)*.
- In the setting of coronary artery bypass graft (CABG) surgery (*see WARNINGS; Cardiovascular Thrombotic Events*).

WARNINGS

Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients

should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as naproxen, increases the risk of serious gastrointestinal (GI) events (*see WARNINGS; Gastrointestinal Bleeding, Ulceration, and Perforation).*

Status Post Coronary Artery Bypass Graft (CABG) Surgery
Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG *(see CONTRAINDICATIONS).*

Post-MI Patients
Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of NAPROSYN, EC-NAPROSYN, ANAPROX and ANAPROX DS in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including naproxen cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation

Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients

treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Strategies to Minimize the GI Risks in NSAID-treated patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding *(see PRECAUTIONS; Drug Interactions)*.

Hepatotoxicity

Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis and hepatic failure have been reported.

Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients taking NSAIDs including naproxen.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS immediately, and perform a clinical evaluation of the patient.

Hypertension

NSAIDs, including NAPROSYN, EC-NAPROSYN, ANAPROX and ANAPROX DS, can lead to new onset of hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs *(see PRECAUTIONS; Drug Interactions)*.

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Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

Heart Failure and Edema

The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalization for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of naproxen may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) *(see PRECAUTIONS; Drug Interactions).*

Avoid the use of NAPROSYN, EC-NAPROSYN, ANAPROX and ANAPROX DS in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

Since each ANAPROX or ANAPROX DS tablet contains 25 mg or 50 mg of sodium (about 1 mEq per each 250 mg of naproxen), this should be considered in patients whose overall intake of sodium must be severely restricted.

Renal Toxicity and Hyperkalemia

Renal Toxicity

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.

Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state

No information is available from controlled clinical studies regarding the use of NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS in patients with advanced renal disease. The renal effects of NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS may hasten the progression of renal dysfunction in patients with preexisting renal disease.

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Correct volume status in dehydrated or hypovolemic patients prior to initiating NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS (*see PRECAUTIONS; Drug Interactions)*. Avoid the use of NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

Hyperkalemia
Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state.

Anaphylactic Reactions

Naproxen has been associated with anaphylactic reactions in patients with and without known hypersensitivity to naproxen and in patients with aspirin-sensitive asthma (*see CONTRAINDICATIONS, WARNINGS; Exacerbation of Asthma Related to Aspirin Sensitivity)*.

Exacerbation of Asthma Related to Aspirin Sensitivity

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, NAPROSYN, EC-NAPROSYN, ANAPROX and ANAPROX DS are contraindicated in patients with this form of aspirin sensitivity (*see CONTRAINDICATIONS)*. When NAPROSYN, EC-NAPROSYN, ANAPROX and ANAPROX DS are used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

Serious Skin Reactions

NSAIDs, including naproxen, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions and to discontinue the use of NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS at the first appearance of skin rash or any other sign of hypersensitivity. NAPROSYN, EC-NAPROSYN, ANAPROX and ANAPROX DS are contraindicated in patients with previous serious skin reactions to NSAIDs *(see CONTRAINDICATIONS)*.

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Premature Closure of Fetal Ductus Arteriosus

Naproxen may cause premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS, in pregnant women starting at 30 weeks of gestation (third trimester) *(see PRECAUTIONS; Pregnancy)*.

Hematologic Toxicity

Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a patient treated with NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders, or concomitant use of warfarin and other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding (*see PRECAUTIONS; Drug Interactions*).

PRECAUTIONS

General

Naproxen-containing products such as NAPROSYN, EC-NAPROSYN, ANAPROX and ANAPROX DS®, and other naproxen products should not be used concomitantly since they all circulate in the plasma as the naproxen anion.

NAPROSYN, EC-NAPROSYN, ANAPROX and ANAPROX DS cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids and the patient should be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of arthritis.

Patients with initial hemoglobin values of 10g or less who are to receive long-term therapy should have hemoglobin values determined periodically.

Because of adverse eye findings in animal studies with drugs of this class, it is recommended that ophthalmic studies be carried out if any change or disturbance in vision occurs.

Information for Patients

Advise the patient to read the FDA-approved patient labeling (Medication Guide) that accompanies each prescription dispensed. Inform patients, families, or their caregivers of

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the following information before initiating therapy with NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS and periodically during the course of ongoing therapy.

Cardiovascular Thrombotic Events
Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately *(see WARNINGS; Cardiovascular Thrombotic Events).*

Gastrointestinal Bleeding, Ulceration, and Perforation
Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for the signs and symptoms of GI bleeding *(see WARNINGS; Gastrointestinal Bleeding, Ulceration, and Perforation).*

Hepatotoxicity
Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, instruct patients to stop NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS and seek immediate medical therapy *(see WARNINGS; Hepatotoxicity).*

Heart Failure and Edema
Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur *(see WARNINGS; Heart Failure and Edema).*

Anaphylactic Reactions
Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur *(see CONTRAINDICATION, WARNINGS; Anaphylactic Reactions).*

Serious Skin Reactions
Advise patients to stop NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS immediately if they develop any type of rash and to contact their healthcare provider as soon as possible *(see WARNINGS; Serious Skin Reactions).*

Female Fertility
Advise females of reproductive potential who desire pregnancy that NSAIDs, including VOLTAREN, may be associated with a reversible delay in ovulation *(see PRECAUTIONS; Carcinogenesis, Mutagenesis, Impairment of Fertility).*

Fetal Toxicity
Inform pregnant women to avoid use of NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS and other NSAIDs starting at 30 weeks gestation because of the risk of

the premature closing of the fetal ductus arteriosus *(see WARNINGS; Premature Closure of Fetal Ductus Arteriosus*).

Avoid Concomitant Use of NSAIDs
Inform patients that the concomitant use of NAPROSYN, EC-NAPROSYN, ANAPROX and ANAPROX DS with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy *(see WARNINGS;: Gastrointestinal Bleeding, Ulceration, and Perforation, PRECAUTIONS; Drug Interactions).* Alert patients that NSAIDs may be present in "over the counter" medications for treatment of colds, fever, or insomnia.

Use of NSAIDS and Low-Dose Aspirin
Inform patients not to use low-dose aspirin concomitantly with NAPROSYN, EC-NAPROSYN, ANAPROX and ANAPROX DS until they talk to their healthcare provider *(see PRECAUTIONS; Drug Interactions).*

Activities Requiring Alertness
Caution should be exercised by patients whose activities require alertness if they experience drowsiness, dizziness, vertigo or depression during therapy with naproxen.

Masking of Inflammation and Fever

The pharmacological activity of NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

Laboratory Monitoring

Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically (see *WARNINGS; Gastrointestinal Bleeding, Ulceration and Perforation, and Hepatotoxicity*).

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Drug Interactions

See Table 1 for clinically significant drug interactions with naproxen.

Table 1: Clinically Significant Drug Interactions with naproxen

Drugs That Interfere with Hemostasis	
Clinical Impact:	• Naproxen and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of naproxen and anticoagulants has an increased risk of serious bleeding compared to the use of either drug alone. • Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding

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	more than an NSAID alone.
Intervention:	Monitor patients with concomitant use of NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding (see *WARNINGS; Hematologic Toxicity).*
Aspirin	
Clinical Impact:	Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone *(see WARNINGS; Gastrointestinal Bleeding, Ulceration and Perforation).*
Intervention:	Concomitant use of NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding (see *WARNINGS; Hematologic Toxicity).* NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS is not a substitute for low dose aspirin for cardiovascular protection.
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers	
Clinical Impact:	• NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol). • In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.
Intervention:	• During concomitant use of NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS and ACE-inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function (see *WARNINGS; Renal Toxicity and Hyperkalemia).* When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.
Diuretics	
Clinical Impact:	Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.
Intervention	During concomitant use of NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects (see

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	WARNINGS; Renal Toxicity and Hyperkalemia).
Digoxin	
Clinical Impact:	The concomitant use of naproxen with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
Intervention:	During concomitant use of NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS and digoxin, monitor serum digoxin levels.
Lithium	
Clinical Impact:	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	
Clinical Impact:	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
Intervention:	During concomitant use of NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	Concomitant use of NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS and cyclosporine may increase cyclosporine's nephrotoxicity.
Intervention:	During concomitant use of NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates	
Clinical Impact:	Concomitant use of naproxen with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy *(see WARNINGS; Gastrointestinal Bleeding, Ulceration and Perforation).*
Intervention:	The concomitant use of naproxen with other NSAIDs or salicylates is not recommended.
Pemetrexed	
Clinical Impact:	Concomitant use of NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
Intervention:	During concomitant use of NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and

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	NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.
Antacids and Sucralfate	
Clinical Impact:	Concomitant administration of some antacids (magnesium oxide or aluminum hydroxide) and sucralfate can delay the absorption of naproxen.
Intervention:	Concomitant administration of antacids such as magnesium oxide or aluminum hydroxide, and sucralfate with NAPROSYN EC-NAPROSYN, ANAPROX or ANAPROX DS is not recommended. Due to the gastric pH elevating effects of H2-blockers, sucralfate and intensive antacid therapy, concomitant administration of EC-NAPROSYN is not recommended.
Cholestyramine	
Clinical Impact:	Concomitant administration of cholestyramine can delay the absorption of naproxen.
Intervention:	Concomitant administration of cholestyramine with NAPROSYN EC-NAPROSYN, ANAPROX or ANAPROX DS is not recommended.
Probenecid	
Clinical Impact:	Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly.
Intervention:	Patients simultaneously receiving NAPROSYN EC-NAPROSYN, ANAPROX or ANAPROX DS and probenecid should be observed for adjustment of dose if required.
Other albumin-bound drugs	
Clinical Impact:	Naproxen is highly bound to plasma albumin; it thus has a theoretical potential for interaction with other albumin-bound drugs such as coumarin-type anticoagulants, sulphonylureas, hydantoins, other NSAIDs, and aspirin.
Intervention:	Patients simultaneously receiving NAPROSYN EC-NAPROSYN, ANAPROX or ANAPROX DS and a hydantoin, sulphonamide or sulphonylurea should be observed for adjustment of dose if required.

Drug/Laboratory Test Interactions

Bleeding times	
Clinical Impact:	Naproxen may decrease platelet aggregation and prolong bleeding time.
Intervention:	This effect should be kept in mind when bleeding times are determined.
Porter-Silber test	
Clinical Impact:	The administration of naproxen may result in increased urinary values for 17-ketogenic steroids because of an interaction between the drug and/or its metabolites with m-di-nitrobenzene used in this assay.
Intervention:	Although 17-hydroxy-corticosteroid measurements (Porter-Silber test) do not appear to be artifactually altered, it is suggested that therapy with naproxen be temporarily discontinued 72 hours before adrenal function tests are performed if the Porter-Silber test is to be used.
Urinary assays of 5-hydroxy indoleacetic acid (5HIAA)	
Clinical Impact:	Naproxen may interfere with some urinary assays of 5-hydroxy indoleacetic acid

	(5HIAA).
Intervention:	This effect should be kept in mind when urinary 5-hydroxy indoleacetic acid is determined.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

A 2-year study was performed in rats to evaluate the carcinogenic potential of naproxen at rat doses of 8, 16, and 24 mg/kg/day (0.05, 0.1, and 0.16 times the maximum recommended human daily dose [MRHD] of 1500 mg/day based on a body surface area comparison). No evidence of tumorigenicity was found.

Mutagenesis

Studies to evaluate the mutagenic potential of Naprosyn, EC-Naprosyn, Anaprox or Anaprox DS tablets have not been completed.

Impairment of fertility

Male rats were treated with 2, 5, 10, and 20 mg/kg naproxen by oral gavage for 60 days prior to mating and female rats were treated with the same doses for 14 days prior to mating and for the first 7 days of pregnancy. There were no adverse effects on fertility noted (up to 0.13 times the MRDH based on body surface area).

Pregnancy

Risk Summary

Use of NSAIDs, including Naprosyn, EC-Naprosyn, Anaprox, and Anaprox DS tablets, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including Naprosyn, in pregnant women starting at 30 weeks of gestation (third trimester) *(see WARNINGS; Premature Closure of Fetal Ductus Arteriosus)*.

There are no adequate and well-controlled studies of Naprosyn, EC-Naprosyn, Anaprox, or Anaprox DS tablets in pregnant women.

Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In the general U.S. population, all clinically recognized pregnancies, regardless of drug exposure, have a background rate of 2-4% for major malformations, and 15-20% for pregnancy loss. In animal reproduction studies in rats, rabbit, and mice no evidence of teratogenicity or fetal harm when naproxen was administered during the period of organogenesis at doses 0.13, 0.26, and 0.6 times the maximum recommended human daily dose of 1500 mg/day, respectively. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as naproxen, resulted in increased pre- and post-implantation loss.

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Data
Human Data
There is some evidence to suggest that when inhibitors of prostaglandin synthesis are used to delay preterm labor there is an increased risk of neonatal complications such as necrotizing enterocolitis, patent ductus arteriosus and intracranial hemorrhage. Naproxen treatment given in late pregnancy to delay parturition has been associated with persistent pulmonary hypertension, renal dysfunction and abnormal prostaglandin E levels in preterm infants. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly starting at 30-weeks of gestation, or third trimester) should be avoided.

Animal Data
Reproduction studies have been performed in rats at 20 mg/kg/day (0.13 times the maximum recommended human daily dose of 1500 mg/day based on body surface area comparison), rabbits at 20 mg/kg/day (0.26 times the maximum recommended human daily dose, based on body surface area comparison), and mice at 170 mg/kg/day (0.6 times the maximum recommended human daily dose based on body surface area comparison) with no evidence of impaired fertility or harm to the fetus due to the drug. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as naproxen, resulted in increased pre- and post-implantation loss.

Labor and Delivery

There are no studies on the effects of Naprosyn, EC-Naprosyn, Anaprox, or Anaprox DS tablets during labor or delivery. In animal studies, NSAIDS, including naproxen, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Nursing Mothers

The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Naprosyn, EC-Naprosyn, Anaprox, or Anaprox DS tablets and any potential adverse effects on the breastfed infant from the Naprosyn, EC-Naprosyn, Anaprox, or Anaprox DS tablets or from the underlying maternal condition.

Females and Males of Reproductive Potential

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including Naprosyn, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin- mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation.

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Consider withdrawal of NSAIDs, including Naprosyn, EC-Naprosyn, Anaprox and Anaprox DS tablets, in women who have difficulties conceiving or who are undergoing investigation of infertility.

Pediatric Use

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 2 years have not been established. Pediatric dosing recommendations for juvenile arthritis are based on well-controlled studies (see **DOSAGE AND ADMINISTRATION**). There are no adequate effectiveness or dose-response data for other pediatric conditions, but the experience in juvenile arthritis and other use experience have established that single doses of 2.5 to 5 mg/kg (as naproxen suspension, see **DOSAGE AND ADMINISTRATION**), with total daily dose not exceeding 15 mg/kg/day, are well tolerated in pediatric patients over 2 years of age. Safety and effectiveness in pediatric patients below the age of 2 years have not been established.

Geriatric Use

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects *(see WARNINGS; Cardiovascular Thrombotic Events, Gastrointestinal Bleeding, Ulceration, and Perforation, Hepatotoxicity, Renal Toxicity and Hyperkalemia, PRECAUTIONS; Laboratory Monitoring).*

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Caution is advised when high doses are required and some adjustment of dosage may be required in elderly patients. As with other drugs used in the elderly, it is prudent to use the lowest effective dose.

Experience indicates that geriatric patients may be particularly sensitive to certain adverse effects of nonsteroidal anti-inflammatory drugs. Elderly or debilitated patients seem to tolerate peptic ulceration or bleeding less well when these events do occur. Most spontaneous reports of fatal GI events are in the geriatric population *(see WARNINGS; Gastrointestinal Bleeding, Ulceration, and Perforation*).

Naproxen is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Geriatric patients may be at a greater risk for the development of a form of renal toxicity precipitated by reduced prostaglandin formation during administration of nonsteroidal anti-inflammatory drugs *(see WARNINGS: Renal Toxicity and Hyperkalemia).*

EC-NAPROSYN® (naproxen delayed-release tablets), NAPROSYN® (naproxen tablets), ANAPROX®/ANAPROX® DS (naproxen sodium tablets)

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Cardiovascular Thrombotic Events (*see WARNINGS)*
- GI Bleeding, Ulceration and Perforation (see *WARNINGS)*
- Hepatotoxicity (see *WARNINGS)*
- Hypertension (see *WARNINGS)*
- Heart Failure and Edema (see *WARNINGS)*
- Renal Toxicity and Hyperkalemia (see *WARNINGS*)
- Anaphylactic Reactions (see *WARNINGS)*
- Serious Skin Reactions (see *WARNINGS)*
- Hematologic Toxicity (see *WARNINGS)*

Adverse reactions reported in controlled clinical trials in 960 patients treated for rheumatoid arthritis or osteoarthritis are listed below. In general, reactions in patients treated chronically were reported 2 to 10 times more frequently than they were in short-term studies in the 962 patients treated for mild to moderate pain or for dysmenorrhea. The most frequent complaints reported related to the gastrointestinal tract.

A clinical study found gastrointestinal reactions to be more frequent and more severe in rheumatoid arthritis patients taking daily doses of 1500 mg naproxen compared to those taking 750 mg naproxen (see *CLINICAL PHARMACOLOGY*).

In controlled clinical trials with about 80 pediatric patients and in well-monitored, open-label studies with about 400 pediatric patients with juvenile arthritis treated with naproxen, the incidence of rash and prolonged bleeding times were increased, the incidence of gastrointestinal and central nervous system reactions were about the same, and the incidence of other reactions were lower in pediatric patients than in adults.

In patients taking naproxen in clinical trials, the most frequently reported adverse experiences in approximately 1% to 10% of patients are:

Gastrointestinal (GI) Experiences, including: heartburn*, abdominal pain*, nausea*, constipation*, diarrhea, dyspepsia, stomatitis

Central Nervous System: headache*, dizziness*, drowsiness*, lightheadedness, vertigo

Dermatologic: pruritus (itching)*, skin eruptions*, ecchymoses*, sweating, purpura

Special Senses: tinnitus*, visual disturbances, hearing disturbances

Cardiovascular: edema*, palpitations

General: dyspnea*, thirst

*Incidence of reported reaction between 3% and 9%. Those reactions occurring in less than 3% of the patients are unmarked.

EC-NAPROSYN® (naproxen delayed-release tablets), NAPROSYN® (naproxen tablets), ANAPROX®/ANAPROX® DS (naproxen sodium tablets)

In patients taking NSAIDs, the following adverse experiences have also been reported in approximately 1% to 10% of patients.

Gastrointestinal (GI) Experiences, including: flatulence, gross bleeding/perforation, GI ulcers (gastric/duodenal), vomiting

General: abnormal renal function, anemia, elevated liver enzymes, increased bleeding time, rashes

The following are additional adverse experiences reported in <1% of patients taking naproxen during clinical trials and through postmarketing reports. Those adverse reactions observed through postmarketing reports are italicized.

Body as a Whole: *anaphylactoid reactions, angioneurotic edema, menstrual disorders, pyrexia (chills and fever)*

Cardiovascular: *congestive heart failure, vasculitis, hypertension, pulmonary edema*

Gastrointestinal: *inflammation, bleeding (sometimes fatal, particularly in the elderly), ulceration, perforation and obstruction of the upper or lower gastrointestinal tract. Esophagitis, stomatitis, hematemesis,* pancreatitis, vomiting, *colitis, exacerbation of inflammatory bowel disease (ulcerative colitis, Crohn's disease).*

Hepatobiliary: jaundice, *abnormal liver function tests, hepatitis (some cases have been fatal)*

Hemic and Lymphatic: *eosinophilia, leucopenia,* melena, thrombocytopenia, agranulocytosis, *granulocytopenia, hemolytic anemia, aplastic anemia*

Metabolic and Nutritional: *hyperglycemia, hypoglycemia*

Nervous System: inability to concentrate, *depression, dream abnormalities, insomnia, malaise, myalgia, muscle weakness, aseptic meningitis, cognitive dysfunction, convulsions*

Respiratory: *eosinophilic pneumonitis, asthma*

Dermatologic: *alopecia, urticaria,* skin rashes, *toxic epidermal necrolysis, erythema multiforme, erythema nodosum, fixed drug eruption, lichen planus, pustular reaction, systemic lupus erythematoses, bullous reactions, including Stevens-Johnson syndrome, photosensitive dermatitis, photosensitivity reactions, including rare cases resembling porphyria cutanea tarda (pseudoporphyria) or epidermolysis bullosa. If skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur, treatment should be discontinued and the patient monitored.*

Special Senses: *hearing impairment, corneal opacity, papillitis, retrobulbar optic neuritis, papilledema*

Urogenital: *glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis, raised serum creatinine*

EC-NAPROSYN® (naproxen delayed-release tablets), NAPROSYN® (naproxen tablets), ANAPROX®/ANAPROX® DS (naproxen sodium tablets)

Reproduction (female): *infertility*

In patients taking NSAIDs, the following adverse experiences have also been reported in <1% of patients.

Body as a Whole: fever, infection, sepsis, anaphylactic reactions, appetite changes, death

Cardiovascular: hypertension, tachycardia, syncope, arrhythmia, hypotension, myocardial infarction

Gastrointestinal: dry mouth, esophagitis, gastric/peptic ulcers, gastritis, glossitis, eructation

Hepatobiliary: hepatitis, liver failure

Hemic and Lymphatic: rectal bleeding, lymphadenopathy, pancytopenia

Metabolic and Nutritional: weight changes

Nervous System: anxiety, asthenia, confusion, nervousness, paresthesia, somnolence, tremors, convulsions, coma, hallucinations

Respiratory: asthma, respiratory depression, pneumonia

Dermatologic: exfoliative dermatitis

Special Senses: blurred vision, conjunctivitis

Urogenital: cystitis, dysuria, oliguria/polyuria, proteinuria

OVERDOSAGE

Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare. Because naproxen sodium may be rapidly absorbed, high and early blood levels should be anticipated. A few patients have experienced convulsions, but it is not clear whether or not these were drug-related. It is not known what dose of the drug would be life threatening. *(see WARNINGS; Cardiovascular Thrombotic Events, Gastrointestinal Bleeding, Ulceration, and Perforation, Hypertension, Renal Toxicity and Hyperkalemia).*

Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding. Consider emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdosage (5 to 10 times the recommended dosage). Forced

diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

For additional information about overdosage treatment contact a poison control center (1-800-222-1222).

DOSAGE AND ADMINISTRATION

Carefully consider the potential benefits and risks of NAPROSYN, EC-NAPROSYN, ANAPROX and ANAPROX DS and other treatment options before deciding to use NAPROSYN, EC-NAPROSYN, ANAPROX and ANAPROX DS. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals *(see WARNINGS; Gastrointestinal Bleeding, Ulceration, and Perforation)*.

After observing the response to initial therapy with NAPROSYN, EC-NAPROSYN, ANAPROX or ANAPROX DS, the dose and frequency should be adjusted to suit an individual patient's needs.

Different dose strengths and formulations (i.e., tablets, suspension) of the drug are not necessarily bioequivalent. This difference should be taken into consideration when changing formulation.

Although NAPROSYN, EC-NAPROSYN, ANAPROX and ANAPROX DS all circulate in the plasma as naproxen, they have pharmacokinetic differences that may affect onset of action. Onset of pain relief can begin within 30 minutes in patients taking naproxen sodium and within 1 hour in patients taking naproxen. Because EC-NAPROSYN dissolves in the small intestine rather than in the stomach, the absorption of the drug is delayed compared to the other naproxen formulations *(see CLINICAL PHARMACOLOGY)*.

The recommended strategy for initiating therapy is to choose a formulation and a starting dose likely to be effective for the patient and then adjust the dosage based on observation of benefit and/or adverse events. A lower dose should be considered in patients with renal or hepatic impairment or in elderly patients *(see WARNINGS; Hepatotoxicity, and Renal Toxicity and Hyperkalemia, and PRECAUTIONS; Geriatric Use)*.

Geriatric Patients

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Caution is advised when high doses are required and some adjustment of dosage may be required in elderly patients. As with other drugs used in the elderly, it is prudent to use the lowest effective dose.

Patients With Moderate to Severe Renal Impairment

Naproxen-containing products are not recommended for use in patients with moderate to severe and severe renal impairment (creatinine clearance <30 mL/min) (see **WARNINGS: Renal Effects**).

EC-NAPROSYN® (naproxen delayed-release tablets), NAPROSYN® (naproxen tablets), ANAPROX®/ANAPROX® DS (naproxen sodium tablets)

Rheumatoid Arthritis, Osteoarthritis and Ankylosing Spondylitis

NAPROSYN	250 mg or 375 mg or 500 mg	twice daily twice daily twice daily
ANAPROX	275 mg (naproxen 250 mg with 25 mg sodium)	twice daily
ANAPROX DS	550 mg (naproxen 500 mg with 50 mg sodium)	twice daily
EC-NAPROSYN	375 mg or 500 mg	twice daily twice daily

To maintain the integrity of the enteric coating, the EC-NAPROSYN tablet should not be broken, crushed or chewed during ingestion.

During long-term administration, the dose of naproxen may be adjusted up or down depending on the clinical response of the patient. A lower daily dose may suffice for long-term administration. The morning and evening doses do not have to be equal in size and the administration of the drug more frequently than twice daily is not necessary.

In patients who tolerate lower doses well, the dose may be increased to naproxen 1500 mg/day for limited periods of up to 6 months when a higher level of anti-inflammatory/analgesic activity is required. When treating such patients with naproxen 1500 mg/day, the physician should observe sufficient increased clinical benefits to offset the potential increased risk. The morning and evening doses do not have to be equal in size and administration of the drug more frequently than twice daily does not generally make a difference in response (see CLINICAL PHARMACOLOGY).

Juvenile Arthritis

Naprosyn Tablets may not allow for the flexible dose titration needed in pediatric patients with juvenile arthritis. A liquid formulation may be more appropriate.

In pediatric patients, doses of 5 mg/kg/day produced plasma levels of naproxen similar to those seen in adults taking 500 mg of naproxen (see Clinical Pharmacology).

The recommended total daily dose of naproxen is approximately 10 mg/kg given in 2 divided doses. One-half of the 250 mg tablet will be needed for dosing lower-weight children. Dosing with Naprosyn Tablets is not appropriate for children weighing less than 25 kilograms.

The recommended total daily dose of naproxen is approximately 10 mg/kg given in 2 divided doses (i.e., 5 mg/kg given twice a day). A measuring cup marked in 1/2 teaspoon and 2.5 milliliter increments is provided with the naproxen suspension. The following table may be used as a guide for dosing of naproxen suspension:

EC-NAPROSYN® (naproxen delayed-release tablets), NAPROSYN® (naproxen tablets), ANAPROX®/ANAPROX® DS (naproxen sodium tablets)

Patient's Weight	Dose	Administered as
13 kg (29 lb)	62.5 mg bid	2.5 mL (1/2 tsp) twice daily
25 kg (55 lb)	125 mg bid	5.0 mL (1 tsp) twice daily
38 kg (84 lb)	187.5 mg bid	7.5 mL (1 1/2 tsp) twice daily

Management of Pain, Primary Dysmenorrhea, and Acute Tendonitis and Bursitis

The recommended starting dose is 550 mg of naproxen sodium as ANAPROX/ANAPROX DS followed by 550 mg every 12 hours or 275 mg every 6 to 8 hours as required. The initial total daily dose should not exceed 1375 mg of naproxen sodium. Thereafter, the total daily dose should not exceed 1100 mg of naproxen sodium. Because the sodium salt of naproxen is more rapidly absorbed, ANAPROX/ANAPROX DS is recommended for the management of acute painful conditions when prompt onset of pain relief is desired. NAPROSYN may also be used but EC-NAPROSYN is not recommended for initial treatment of acute pain because absorption of naproxen is delayed compared to other naproxen-containing products *(see CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE).*

Acute Gout

The recommended starting dose is 750 mg of NAPROSYN followed by 250 mg every 8 hours until the attack has subsided. ANAPROX may also be used at a starting dose of 825 mg followed by 275 mg every 8 hours. EC-NAPROSYN is not recommended because of the delay in absorption *(see CLINICAL PHARMACOLOGY).*

HOW SUPPLIED

NAPROSYN Tablets: 250 mg: round, yellow, biconvex, engraved with NPR LE 250 on one side and scored on the other. Packaged in light-resistant bottles of 100.

100's (bottle): NDC 0004-6313-01.

375 mg: pink, biconvex oval, engraved with NPR LE 375 on one side. Packaged in light-resistant bottles of 100.

100's (bottle): NDC 0004-6314-01.

500 mg: yellow, capsule-shaped, engraved with NPR LE 500 on one side and scored on the other. Packaged in light-resistant bottles of 100.

100's (bottle): NDC 69437-316-01.

Store at 15° to 30°C (59° to 86°F) in well-closed containers; dispense in light-resistant containers.

EC-NAPROSYN Delayed-Release Tablets: 375 mg: white, oval biconvex coated tablets imprinted with NPR EC 375 on one side. Packaged in light-resistant bottles of 100.

EC-NAPROSYN® (naproxen delayed-release tablets), NAPROSYN® (naproxen tablets), ANAPROX®/ANAPROX® DS (naproxen sodium tablets)

100's (bottle): NDC 69437-415-01.

500 mg: white, oblong coated tablets imprinted with NPR EC 500 on one side. Packaged in light-resistant bottles of 100.

100's (bottle): NDC 69437-416-01.

Store at 15° to 30°C (59° to 86°F) in well-closed containers; dispense in light-resistant containers.

ANAPROX Tablets: Naproxen sodium 275 mg: light blue, oval-shaped, engraved with NPS-275 on one side. Packaged in bottles of 100.

100's (bottle): NDC 0004-6202-01.

Store at 15° to 30°C (59° to 86°F) in well-closed containers.

ANAPROX DS Tablets: Naproxen sodium 550 mg: dark blue, oblong-shaped, engraved with NPS 550 on one side and scored on both sides. Packaged in bottles of 100.

100's (bottle): NDC 69437-203-01.

Store at 15° to 30°C (59° to 86°F) in well-closed containers.

Manufactured for:
Atnahs Pharma US Ltd
Miles Gray Road,
Basildon Essex SS14 3FR
United Kingdom

Distributed by:
Canton Laboratories, LLC
Alpharetta, GA 30004-5945
United States

EC-NAPROSYN® (naproxen delayed-release tablets), NAPROSYN® (naproxen tablets), ANAPROX®/ANAPROX® DS (naproxen sodium tablets)

Medication Guide for Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAIDs can cause serious side effects, including:

- **Increased risk of a heart attack or stroke that can lead to death.** This risk may happen early in treatment and may increase:
  - with increasing doses of NSAIDs
  - with longer use of NSAIDs

  Do not take NSAIDs right before or after a heart surgery called a "coronary artery bypass graft (CABG)." Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.
- **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:**
  - any time during use
  - without warning symptoms
  - that may cause death

  The risk of getting an ulcer or bleeding increases with:
  - past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
  - taking medicines called "corticosteroids", "anticoagulants", "SSRIs", or "SNRIs"
  - increasing doses of NSAIDs
  - longer use of NSAIDs
  - smoking
  - drinking alcohol
  - older age
  - poor health
  - advanced liver disease
  - bleeding problems

NSAIDs should only be used:

- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What are NSAIDs?

NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.

Who should not take NSAIDs?

Do not take NSAIDs:

- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

Before taking NSAIDs, tell your healthcare provider about all of your medical conditions, including if you:

- have liver or kidney problems
- have high blood pressure
- have asthma
- are pregnant or plan to become pregnant. Talk to your healthcare provider if you are considering taking NSAIDs during pregnancy. **You should not take NSAIDs after**

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EC-NAPROSYN® (naproxen delayed-release tablets), NAPROSYN® (naproxen tablets), ANAPROX®/ANAPROX® DS (naproxen sodium tablets)

29 weeks of pregnancy.

- are breastfeeding or plan to breastfeed.

Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins or herbal supplements. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Do not start taking any new medicine without talking to your healthcare provider first.**

What are the possible side effects of NSAIDs?

NSAIDs can cause serious side effects, including:

See "What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

- new or worse high blood pressure
- heart failure
- liver problems including liver failure
- kidney problems including kidney failure
- low red blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions
- **Other side effects of NSAIDs include:** stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

Get emergency help right away if you have any of the following symptoms:

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop taking your NSAID and call your healthcare provider right away if you get any of the following symptoms:

- nausea
- more tired or weaker than usual
- diarrhea
- itching
- your skin or eyes look yellow
- indigestion or stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms and legs, hands and feet

If you take too much of your NSAID, call your healthcare provider or get medical help right away.

These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about NSAIDs

- Aspirin is an NSAID medicine but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some NSAIDs are sold in lower doses without a prescription (over-the-counter). Talk to your

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healthcare provider before using over-the-counter NSAIDs for more than 10 days.
General information about the safe and effective use of NSAIDs Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them. If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.
Manufactured for: Atnahs Pharma US Ltd Miles Gray Road, Basildon Essex SS14 3FR United Kingdom Distributed by: Canton Laboratories, LLC Alpharetta, GA 30004-5945 United States

This Medication Guide has been approved by the U.S. Food and Drug Administration.
Revised: Month 2016

Appendix F: Average Pain Intensity over the Last 7 Days

Please describe your average pain intensity over the last 7 days:

- 0=None
- 1=Mild
- 2=Moderate
- 3=Severe

Appendix G: Kellgren - Lawrence Classification

Grade	Description
0: No osteoarthritis	No osteroarthritis
1: Doubtful	Doubtful narrowing of the joint space and possible osteophytic tipping
2: Mild	Definite osteophytes, possible narrowing of the joint space
3: Moderate	Multiple osteophytes, definite narrowing of the joint space, and some sclerosis and possible deformity of bone ends
4: Severe	Large osteophytes, marked narrowing of the joint space, severe sclerosis, and definite deformity of the bone ends

Appendix H: Hospital Anxiety and Depression Scale (HADS)

Hospital Anxiety and Depression Scale (HADS)

This questionnaire is designed to help your doctor to know how you feel. Read each item and check off the box opposite the reply that comes closest to how you have been feeling in the past week.

Don't take too long on your replies; your immediate reaction to each item will probably be more accurate than a long-thought-out response.

		Patient Response	Anxiety Score	Depression Score
1.	**I feel tense or "wound-up"**			
	Most of the time	☐	(3)	
	A lot of the time	☐	(2)	
	From time to time, occasionally	☐	(1)	
	Never	☐	(0)	
2.	**I enjoy the things I used to enjoy**			
	Definitely as much	☐		(0)
	Not quite so much	☐		(1)
	Only a little	☐		(2)
	Hardly at all	☐		(3)
3.	**I get a sort of frightened feeling as if something awful is about to happen**			
	Very definitely and fairly badly	☐	(3)	
	Yes, but not too badly	☐	(2)	
	Sometimes, but it doesn't worry me	☐	(1)	
	Never	☐	(0)	
4.	**I can laugh and see the funny side of things**			
	As much as I always could	☐		(0)
	Not quite so much now	☐		(1)
	Definitely not so much now	☐		(2)
	Never	☐		(3)

5. Worrying thoughts go through my mind

A great deal of the time	□	(3)
A lot of the time	□	(2)
Not too often	□	(1)
Almost never	□	(0)

6. I feel cheerful

Never	□	(3)
Not often	□	(2)
Sometimes	□	(1)
Most of the time	□	(0)

7. I can sit at ease and feel relaxed

Always	□	(0)
Usually	□	(1)
Not often	□	(2)
Never	□	(3)

8. I feel as if I am slowed down

Nearly all the time	□	(3)
Very often	□	(2)
Sometimes	□	(1)
Never	□	(0)

9. I get a sort of anxious feeling like “butterflies” in the stomach

Never	□	(0)
Occasionally	□	(1)
Often	□	(2)
Very often	□	(3)

10. I have lost interest in my appearance

Definitely	□	(3)
Often I don’t take as much care as I should	□	(2)
Sometimes I don’t take as much care as I should	□	(1)
I take just as much care as ever	□	(0)

11. I feel restless as if I have to be on the move

Definitely	☐	(3)
Quite a lot	☐	(2)
Not very much	☐	(1)
Never	☐	(0)

12. I look forward with enjoyment to things

As much as I ever have	☐	(0)
Somewhat less than I used to	☐	(1)
Much less than I used to	☐	(2)
Rarely	☐	(3)

13. I get sudden feelings of panic

Very often	☐	(3)
Often	☐	(2)
Not very often	☐	(1)
Never	☐	(0)

14. I can enjoy a good book, radio or television program

Often	☐	(0)
Sometimes	☐	(1)
Not often	☐	(2)
Very seldom	☐	(3)

Now check that you have answered all questions:

(Note: Subjects do not see scoring.)

HADS Scoring

1. Add up all the odd-numbered questions for the total anxiety score.
2. Add up all the even-numbered questions, for the total depression score.

Appendix I: Modified Brief Pain Inventory-Short Form (mBPI-SF)

1. Please rate your pain by circling the one number that best describes **your pain at its WORST in the last 24 hours**.

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

2. Please rate your pain by circling the one number that best describes **your pain at its LEAST in the last 24 hours**

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

3. Please rate your pain by circling the one number that best describes **your pain on the AVERAGE in the last 24 hours**.

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

4. Please rate your pain by circling the one number that tells **how much pain you have right now.**

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

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

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

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

A. General activity

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

B. Mood

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

C. Walking ability

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

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

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

E. Relations with other people

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

F. Sleep

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

G. Enjoyment of life

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

Appendix J: Western Ontario and McMaster OA Index (WOMAC)

WOMAC OSTEOARTHRITIS INDEX VERSION LK3.1

INSTRUCTIONS TO PATIENTS

In Sections A, B, and C questions are asked in the following format. Please mark your answers by putting an "✗" in one of the boxes.

EXAMPLES:

1. If you put your " ✗ " in the box on the far left as shown below,

none	mild	moderate	severe	extreme
☒	☐	☐	☐	☐

then you are indicating that you feel **no** pain.

2. If you put your " ✗ " in the box on the far right as shown below,

none	mild	moderate	severe	extreme
☐	☐	☐	☐	☒

then you are indicating that you feel **extreme** pain.

3. Please note:
   a) that the further to the right you place your "✗", the **more** pain you feel.
   b) that the further to the left you place your "✗", the **less** pain you feel.
   c) **please do not** place your "✗" **outside any of the boxes**.

You will be asked to indicate on this type of scale the amount of pain, stiffness or disability you have felt during the last 24 hours.

Think about your _____ (study joint) when answering the questions. Indicate the severity of your pain and stiffness and the difficulty you have in doing daily activities that you feel are caused by the arthritis in your _____ (study joint).

Your study joint has been identified for you by your health care professional. If you are unsure which joint is your study joint, please ask before completing the questionnaire.

English for USA - V2

WOMAC LK3.1 QUESTIONNAIRE **WOM**A

Section A

PAIN

Think about the pain you felt in your _____ (study joint) caused by your arthritis during the last 24 hours.

(Please mark your answers with an "✗".)

QUESTION: **How much pain have you had . . .**					Study Coordinator Use Only
1. when walking on a flat surface?	none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PAIN1 _____
2. when going up or down stairs?	none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PAIN2 _____
3. at night while in bed? (that is - pain that disturbs your sleep)	none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PAIN3 _____
4. while sitting or lying down?	none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PAIN4 _____
5. while standing?	none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PAIN5 _____

English for USA - V2

WOMAC LK3.1 QUESTIONNAIRE **WOM$_B$**

Section B

STIFFNESS

Think about the stiffness (not pain) you felt in your _____ (study joint) caused by the arthritis during the last 24 hours.

Stiffness is a sensation of **decreased** ease in moving your joint.

(Please mark your answers with an "✗".)

	Study Coordinator Use Only
6. How **severe** has your stiffness been **after you first woke up** in the morning? none ❑ mild ❑ moderate ❑ severe ❑ extreme ❑	STIFF6 _____
7. How **severe** has your stiffness been **after sitting or lying down or while resting later in the day?** none ❑ mild ❑ moderate ❑ severe ❑ extreme ❑	STIFF7 _____

English for USA - V2

WOMAC LK3.1 QUESTIONNAIRE **WOM**C1-3

Section C

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your _____ (study joint) during the last 24 hours. By this we mean **your ability to move around and take care of yourself.** (Please mark your answers with an "✗".)

QUESTION: **How much difficulty have you had . . .**	none	mild	moderate	severe	extreme	Study Coordinator Use Only
8. when going down the stairs?	❑	❑	❑	❑	❑	PFTN8 _____
9. when going up the stairs?	❑	❑	❑	❑	❑	PFTN9 _____
10. when getting up from a sitting position?	❑	❑	❑	❑	❑	PFTN10 _____
11. while standing?	❑	❑	❑	❑	❑	PFTN11 _____
12. when bending to the floor?	❑	❑	❑	❑	❑	PFTN12 _____
13. when walking on a flat surface?	❑	❑	❑	❑	❑	PFTN13 _____

English for USA - V2

WOMAC LK3.1 QUESTIONNAIRE **WOM**C2-3

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your _____ (study joint) during the last 24 hours. By this we mean **your ability to move around and take care of yourself**. (Please mark your answers with an "✗".)

QUESTION: **How much difficulty have you had . . .**					Study Coordinator Use Only
14. getting in or out of a car, or getting on or off a bus?	none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PFTN14 ____
15. while going shopping?	none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PFTN15 ____
16. when putting on your socks or pantyhose or stockings?	none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PFTN16 ____
17. when getting out of bed?	none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PFTN17 ____
18. when taking off your socks or panty hose or stockings?	none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PFTN18 ____
19. while lying in bed?	none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PFTN19 ____

English for USA - V2

WOMAC LK3.1 QUESTIONNAIRE **WOM**C3-3

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by the arthritis in your _____ (study joint) during the last 24 hours. By this we mean **your ability to move around and take care of yourself**. (Please mark your answers with an "✗".)

QUESTION: **How much difficulty have you had . . .**					Study Coordinator Use Only
20. when getting in or out of the bathtub?					
none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PFTN20 _____
21. while sitting?					
none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PFTN21 _____
22. when getting on or off the toilet?					
none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PFTN22 _____
23. while doing heavy household chores?					
none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PFTN23 _____
24. while doing light household chores?					
none ❑	mild ❑	moderate ❑	severe ❑	extreme ❑	PFTN24 _____

English for USA - V2

Appendix K: EQ-5D

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

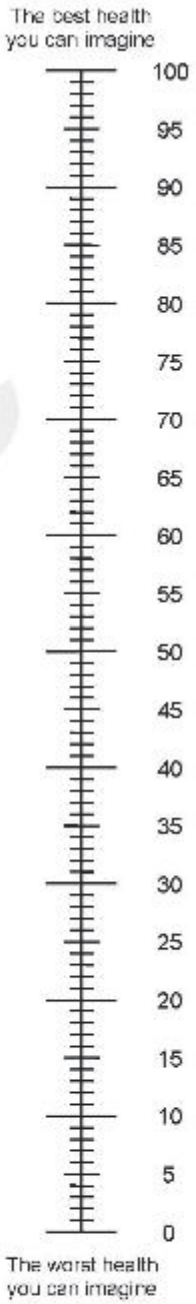
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix L: Medical Outcomes Study 36-item Short-Form (SF-36)

SF-36v2 Health Survey Single-Item Presentation Text Acute, United States (English)

Note: Item SF36v2_BP1 (Item #21) has 6 answers, not 5 answers; see entry for item at end of sheet for more detail.

Item Name	Instructions	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5
	Your Health and Well-Being						
		This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey! For each of the following questions, please select the one box that best describes your answer.					
SF36v2_GH1	None	In general, would you say your health is:	Excellent	Very good	Good	Fair	Poor
SF36v2_HT	None	Compared to one week ago, how would you rate your health in general now?	Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
SF36v2_PF01	The following question is about activities you might do during a typical day.	Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF02	The following question is about activities you might do during a typical day.	Does your health now limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF03	The following question is about activities you might do during a typical day.	Does your health now limit you in lifting or carrying groceries? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF04	The following question is about activities you might do during a typical day.	Does your health now limit you in climbing several flights of stairs? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF05	The following question is about activities you might do during a typical day.	Does your health now limit you in climbing one flight of stairs? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF06	The following question is about activities you might do during a typical day.	Does your health now limit you in bending, kneeling, or stooping? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		

Item Name	Instructions	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5
SF36v2_PF07	The following question is about activities you might do during a typical day.	Does your health now limit you in walking more than a mile? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF08	The following question is about activities you might do during a typical day.	Does your health now limit you in walking several hundred yards? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF09	The following question is about activities you might do during a typical day.	Does your health now limit you in walking one hundred yards? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_PF10	The following question is about activities you might do during a typical day.	Does your health now limit you in bathing or dressing yourself? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all		
SF36v2_RP1	During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities?	Cut down on the amount of time you spent on work or other activities as a result of your physical health	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_RP2	During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities?	Accomplished less than you would like as a result of your physical health	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_RP3	During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities?	Were limited in the kind of work or other activities as a result of your physical health	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_RP4	During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities?	Had difficulty performing the work or other activities as a result of your physical health (for example, it took extra effort)	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_RE1	During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities?	Cut down on the amount of time you spent on work or other activities as a result of any emotional problems (such as feeling depressed or anxious)	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_RE2	During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities?	Accomplished less than you would like as a result of any emotional problems (such as feeling depressed or anxious)	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_RE3	During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities?	Did work or other activities less carefully than usual as a result of any emotional problems (such as feeling depressed or anxious)	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_SF1	None	During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?	Not at all	Slightly	Moderately	Quite a bit	Extremely
SF36v2_BP1	None	How much bodily pain have you had during the past week?	See end of document for answers #1-#6				

Item Name	Instructions	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5
SF36v2_BP2	None	During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?	Not at all	A little bit	Moderately	Quite a bit	Extremely
SF36v2_VT1	This question is about how you feel and how things have been with you during the past week. Please give the one answer that comes closest to the way you have been feeling.	How much of the time during the past week did you feel full of life?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_MH1	This question is about how you feel and how things have been with you during the past week. Please give the one answer that comes closest to the way you have been feeling.	How much of the time during the past week have you been very nervous?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_MH2	This question is about how you feel and how things have been with you during the past week. Please give the one answer that comes closest to the way you have been feeling.	How much of the time during the past week have you felt so down in the dumps that nothing could cheer you up?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_MH3	This question is about how you feel and how things have been with you during the past week. Please give the one answer that comes closest to the way you have been feeling.	How much of the time during the past week have you felt calm and peaceful?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_VT2	This question is about how you feel and how things have been with you during the past week. Please give the one answer that comes closest to the way you have been feeling.	How much of the time during the past week did you have a lot of energy?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_MH4	This question is about how you feel and how things have been with you during the past week. Please give the one answer that comes closest to the way you have been feeling.	How much of the time during the past week have you felt downhearted and depressed?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_VT3	This question is about how you feel and how things have been with you during the past week. Please give the one answer that comes closest to the way you have been feeling.	How much of the time during the past week did you feel worn out?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_MH5	This question is about how you feel and how things have been with you during the past week. Please give the one answer that comes closest to the way you have been feeling.	How much of the time during the past week have you been happy?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_VT4	This question is about how you feel and how things have been with you during the past week. Please give the one answer that comes closest to the way you have been	How much of the time during the past week did you feel tired?	All of the time	Most of the time	Some of the time	A little of the time	None of the time

(SF-36v2® Health Survey Single-Item Presentation Text Acute, United States (English))

Item Name	Instructions	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5
	feeling.						
SF36v2_SF2	None	During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
SF36v2_GH2	How TRUE or FALSE is the following statement for you?	I seem to get sick a little easier than other people.	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
SF36v2_GH3	How TRUE or FALSE is the following statement for you?	I am as healthy as anybody I know.	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
SF36v2_GH4	How TRUE or FALSE is the following statement for you?	I expect my health to get worse.	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
SF36v2_GH5	How TRUE or FALSE is the following statement for you?	My health is excellent.	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
		SF-36v2® Health Survey © 1992, 2000, 2010 Medical Outcomes Trust and QualityMetric Incorporated. All rights reserved. SF-36® is a registered trademark of Medical Outcomes Trust. (SF-36v2® Health Survey Acute, United States (English))					

Data for item SF36v2_BP1 (item #21 in the survey template)

Item Name	Instructions	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5	Answer Text 6
SF36v2_BP1	None	How much bodily pain have you had during the past week?	None	Very mild	Mild	Moderate	Severe	Very severe

Appendix M: Patient Global Impression of Change (PGIC)

Since the start of the study, my overall status is: (Please check only 1 choice)

1. Very much improved
2. Much improved
3. Minimally improved
4. No change
5. Minimally worse
6. Much worse
7. Very much worse

Appendix N: Pain Numerical Rating Scale

Daily Average Pain Over the Last 24 Hours

Choose 1 number that best describes your average pain in the last 24 hours.

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

Pain Right Now (assessments taken before taking supplemental pain medications)

Choose 1 number that best describes the pain you have right now.

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

Appendix O: Columbia Suicide Severity Rating Scale (C-SSRS)

Sample "Baseline/Screening" below:

SUICIDAL IDEATION		
*Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", **ask questions 3, 4 and 5.** If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.*	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., "I want to end my life") without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*) Past X Months - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end/stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end/stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

C-SSRS—Baseline/Screening (Version 1/14/09)
Page 1 of 2

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts ____ Yes ☐ No ☐	Yes ☐ No ☐ Total # of Attempts ____ Yes ☐ No ☐
Has subject engaged in Non-Suicidal Self-Injurious Behavior?		
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted ____	Yes ☐ No ☐ Total # of interrupted ____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted ____	Yes ☐ No ☐ Total # of aborted ____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, [illegible] a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	**Most Recent Attempt Date:**	**Most Lethal Attempt Date:**	**Initial/First Attempt Date:**
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* ____	*Enter Code* ____	*Enter Code* ____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* ____	*Enter Code* ____	*Enter Code* ____

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Sample “Since Last Visit” Questionnaire:

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
Yes ☐ No ☐
If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
Yes ☐ No ☐
If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it and I would never go through with it."*
Have you been thinking about how you might do this?
Yes ☐ No ☐
If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
Yes ☐ No ☐
If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Yes ☐ No ☐
If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: ____ _____
Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or reaction from others and to end/stop the pain
(4) Mostly to end/stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end/stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

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Appendix P: Chemotherapy-induced Taste Alteration Scale (CiTAS)

The following scale will be administered for each subject.[31]

CiTAS

Chemotherapy-induced Taste Alteration Scale

The items below describe various symptoms and problems related to taste change. **Circle the number that most closely fits your condition over the past week.**

I. Changes in sense of taste

	Taste normally	Slightly difficult to taste	Somewhat difficult to taste	Quite difficult to taste	Unable to taste at all
1 Have difficulty tasting food	1	2	3	4	5
2 Have difficulty tasting sweetness	1	2	3	4	5
3 Have difficulty tasting saltiness	1	2	3	4	5
4 Have difficulty tasting sourness	1	2	3	4	5
5 Have difficulty tasting bitterness	1	2	3	4	5
6 Have difficulty tasting *umami* (savoriness: it's like a brothy taste or the taste brought out by adding monosodium glutamate (MSG))	1	2	3	4	5

II. Unpleasant taste change

	No	Slightly	Somewhat	Quite	Very
7 Unable to perceive the smell or flavor of food	1	2	3	4	5
8 Everything tastes bad	1	2	3	4	5
9 Food doesn't taste as it should	1	2	3	4	5
10 Have a bitter taste in the mouth	1	2	3	4	5
11 Have a bad taste in the mouth	1	2	3	4	5
12 Everything tastes bitter	1	2	3	4	5

III. Unpleasant symptoms or problems	No	Slightly	Somewhat	Quite	Very
13 Feel nauseated or queasy	1	2	3	4	5
14 Bothered by the smell of food	1	2	3	4	5
15 Have difficulty eating hot food	1	2	3	4	5
16 Have difficulty eating oily food	1	2	3	4	5
17 Have difficulty eating meat	1	2	3	4	5
18 Have a reduced appetite	1	2	3	4	5

Appendix Q: List of Prohibited Medications and Classification

Source: FDA Guidance: Drug Interaction Studies-Study Design, Data Analysis, and Implications for Dosing and Labeling

If it's unknown whether the medication the patient is taking a moderate to strong CYP3A inhibitor, please contact the medical monitor.

This is a representative list. Please contact the medical monitor if there are any questions.

Medication	Category	Protocol guidance
alfentanil	CYP3A - narrow range	Excluded
aliskiren	P-gp substrate	Excluded
ambrisentan	P-gp substrate	Excluded
amprenavir	CYP3A Moderate inhibitor	Allowed if on stable dose for 1 month prior to start of study drug dosing
aprepitant	CYP3A Sensitive substrate	Excluded
atazanavir	CYP3A Moderate inhibitor	Allowed if on stable dose for 1 month prior to start of study drug dosing
atorvastatin	P-gp substrate	Excluded
avanafil	CYP3A Sensitive substrate	Excluded
azithromycin	P-gp substrate	Excluded
boceprevir	CYP3A Strong inhibitor	Excluded
Bosentan	CYP3A Sensitive substrate	Excluded
budesonide	CYP3A Sensitive substrate	Excluded
Buspirone	CYP3A Sensitive substrate	Excluded
carbamazepine	Strong CYP3A inducer	Excluded
cerivastatin	P-gp substrate	Excluded
chloramphenicol	CYP3A Strong inhibitor	Excluded
ciprofloxacin	CYP3A Moderate inhibitor	Allowed if on stable dose for 1 month prior to start of study drug dosing
clarithromycin	CYP3A Strong inhibitor	Excluded
colchicine	P-gp substrate	Excluded
conivaptan	CYP3A Sensitive substrate & Strong inhibitor	Excluded
cyclosporine	CYP3A - narrow range & P-gp substrate	Excluded
dabigatran	P-gp substrate	Excluded
darifenacin	CYP3A Sensitive substrates	Excluded
darunavir	CYP3A Sensitive substrates	Excluded
darunavir/ritonavir	CYP3A Moderate inhibitor	Allowed if on stable dose for 1 month prior to start of study drug dosing
digoxin	P-gp substrate	Excluded

dihydroergotamine	CYP3A - narrow range	Excluded
diltiazem	CYP3A Moderate inhibitor	Allowed if on stable dose for 1 month prior to start of study drug dosing
domperidone	P-gp substrate	Excluded
dronedarone	CYP3A Sensitive substrates	Excluded
eletriptan	CYP3A Sensitive substrates	Excluded
eplerenone	CYP3A Sensitive substrates	Excluded
ergotamine	CYP3A - narrow range	Excluded
erythromycin	CYP3A Moderate inhibitor	Allowed if on stable dose for 1 month prior to start of study drug dosing
everolimus	CYP3A Sensitive & P-gp substrate	Excluded
felodipine	CYP3A Sensitive substrates	Excluded
fentanyl	CYP3A - narrow range & P-gp substrate	Excluded
fexofenadine	P-gp substrate	Excluded
fluconazole	CYP3A Moderate inhibitor	Allowed if on stable dose for 1 month prior to start of study drug dosing
fluticasone	CYP3A Sensitive substrates	Excluded
grapefruit juice	CYP3A Strong inhibitor	Excluded
indinavir	CYP3A Sensitive substrate & Strong inhibitor	Excluded
itraconazole	CYP3A Strong inhibitor	Excluded
ketoconazole	CYP3A Strong inhibitor	Excluded
linezolid	P-gp substrate	Excluded
lomitapide	CYP3A Sensitive substrates	Excluded
loperamide	P-gp substrate	Excluded
lopinavir	CYP3A Sensitive substrates	Excluded
lopinavir/ritonavir	CYP3A Strong inhibitor	Excluded
lovastatin	CYP3A Sensitive substrates	Excluded
lurasidone	CYP3A Sensitive substrates	Excluded
midazolam	CYP3A Sensitive substrates	Excluded
nefazodone	CYP3A Strong inhibitor	Excluded
nelfinavir	CYP3A Strong inhibitor	Excluded
nisoldipine	CYP3A Sensitive substrates	Excluded
phenytoin	Strong CYP3A inducer	Excluded
pimozide	CYP3A - narrow range	Excluded
posaconazole	CYP3A Strong inhibitor & P-gp subsrate	Excluded
quetiapine	CYP3A Sensitive substrates	Excluded

quinidine	CYP3A - narrow range & P-gp substrate	Excluded
ranolazine	P-gp substrate	Excluded
rifampin	Strong CYP3A inducer	Excluded
riociguat	P-gp substrate	Excluded
ritonavir	CYP3A Strong inhibitor & P-gp subsrate	Excluded
rivaroxaban	P-gp substrate	Excluded
saquinavir	CYP3A Sensitive substrates, strong inhibitor, p-gp substrate	Excluded
saxagliptin	P-gp substrate	Excluded
sildenafil	CYP3A Sensitive substrates	Excluded
simvastatin	CYP3A Sensitive substrates & p-gp substrate	Excluded
sirolimus	CYP3A - narrow range, sensitive substrate, & P-gp substrate	Excluded
sitagliptin	P-gp substrate	Excluded
sofosbuvir	P-gp substrate	Excluded
St. John's wort	Strong CYP3A inducer	Excluded
tacrolimus	CYP3A - narrow range & P-gp substrate	Excluded
talinolol	P-gp substrate	Excluded
telaprevir	CYP3A Strong inhibitor	Excluded
telithromycin	CYP3A Strong inhibitor	Excluded
ticagrelor	P-gp substrate	Excluded
tipranavir	CYP3A Sensitive substrates	Excluded
tolvaptan	CYP3A Sensitive substrate & P-gp substrate	Excluded
triazolam	CYP3A Sensitive substrates	Excluded
vardenafil	CYP3A Sensitive substrates	Excluded
verapamil	CYP3A Moderate inhibitor	Allowed if on stable dose for 1 month prior to start of study drug dosing
voriconazole	CYP3A Strong inhibitor	Excluded

Appendix R: Amendment 1 Summary of Changes

VAN2001

Amendment No. 1

Summary of Changes

1. Date of Amendment: 17-February-2017
2. Replaces Protocol VAN2001 Version 1, dated 14-October-2016
3. The overall rationale for the content changes in Amendment 1 is summarized as follows:
    a. To revise the protocol to align with standard medical practice
        - Increased allowed BMI to 38.0 kg/m^2
        - Excluded monoclonal antibodies for osteoporosis as a concomitant medication
        - Excluded benzodiazepines as concomitant medications
    b. To further clarify protocol requirements
        - Rescreening allowed within certain parameters
        - Clarification to indicate if a meal had been eaten within 2 hours of dosing
        - Extended pain assessment period
        - Clarification of timing of visit 2 related to pain score qualification
        - Clarified Kellgren-Lawrence grade scale
        - Extended period for central ECG provider to report ECG data rate
        - Added predose PK sampling at visit 2 for intensive sampling patients and removed requirement for predose sample at visits 4 and 5
        - Clarified definition of AESI
    c. To correct lettering of appendices to be in sequence
    d. To correct minor typos, formatting errors and inconsistencies

4. Changes, additions, and deletions are described below, with in-text changes represented in red. Changes that appear in more than 1 section of the protocol are presented as a single entry with references to the other sections where the changes occur. When the changed text affects multiple sections, the wording may be slightly different depending on the context, eg, the visit. Those sentences and paragraphs that do not have design changes, but rather have only minor stylistic changes, eg, changing

"Visit" to "visit" and adding periods, will not be presented in this summary of changes document. The list of abbreviations was updated when needed.

5. Summary of changes, additions, and deletions

a. Synopsis and Section 9.1, Study Design schematic

i. Footnote b

Changed from:

69 subjects/treatment arm
[…]
Subjects who do not take any medications for pain will record their "average pain over last 24 hours" scores for 3 to 5 days. Subjects who take medications for pain will record their "average pain over last 24 hours" scores for 3 to 7 days after all incoming pain medications have been stopped. All subjects may return to the study clinic for visit 2 as soon as they recorded "average pain over last 24 hours" scores ≥ 4 for 3 consecutive days.

Changed to:

Approximately 69 subjects/treatment arm

[…]

Subjects who do not take any medications for pain will record their "average pain over last 24 hours" scores for 3 to 7 days. Subjects who take medications for pain will record their "average pain over last 24 hours" scores for 3 to 9 days after all incoming pain medications have been stopped. All subjects may return to the study clinic for visit 2 as soon as they recorded "average pain over last 24 hours" scores ≥ 4 and ≤ 9 for ≥ 3 consecutive days. All subjects must return to the study clinic for visit 2 within 96 hours of the latest qualifying pain score entry within the pain assessment period.

b. Synopsis and Section 9.3.1, Inclusion criteria

i. Inclusion criteria #3, revised to increase BMI range

Changed from:

Subjects with body mass index ranging from 18 to 34 (kg/m^2), inclusive

Changed to:

Subjects with body mass index ranging from 18.0 to 38.0 (kg/m^2)

ii. Inclusion criteria #5, revised to allow patients to come in for randomization/visit 2 within 96 hours after qualification met

Changed from:

The subjects must have "average pain over the last 24 hours" scores ≥ 4 and ≤ 9 on an 11-point NRS for the index knee on ≥ 3 consecutive days during the

screening period and come in for randomization within 96 hours after qualification is met.

Changed to:

The subjects must have “average pain over the last 24 hours” scores ≥ 4 and ≤ 9 on an 11-point NRS for the index knee on ≥ 3 consecutive days during the pain assessment period and come in for visit 2 within 96 hours after the latest qualifying pain score entry.

c. Synopsis and Section 9.3.2, Exclusion criteria
   i. Exclusion criteria #1, clarified Kellgren-Lawrence grade scale

Changed from:

Subjects with radiographic evidence of OA with Kellgren-Lawrence (K-L) grade 1 or 4;

Changed to:

Subjects with radiographic evidence of OA with Kellgren-Lawrence (K-L) grade 0, 1 or 4;

   ii. Exclusion criteria #22 & 23, added reference to appendix

Changed from:

Subjects taking strong CYP3A inhibitors, inducers, sensitive substrates, substrates with narrow therapeutic range, or P-gp substrates;

Subjects taking moderate CYP3A inhibitors if the dose has not been stable for at least 1 month prior to start of study drug dosing;

Changed to:

Subjects taking strong CYP3A inhibitors, inducers, sensitive substrates, substrates with narrow therapeutic range, or P-gp substrates (see Appendix Q);

Subjects taking moderate CYP3A inhibitors if the dose has not been stable for at least 1 month prior to start of study drug dosing (see Appendix Q);

d. Synopsis and Section 9.4.8 Concomitant Medication:
   i. Added restriction of benzodiazepines and monoclonal antibodies for osteoporosis

Changed from:

Other prohibited concomitant treatments include methotrexate, any local OA treatments for the knee(s), including topical anesthetics or NSAIDs; topical, intra-articular, or systemic corticosteroids; or any OA injection in the knee(s), antidepressants (other than SSRIs), warfarin or anticoagulants, and cyclosporine (except ophthalmic emulsion).

Changed to:

Other prohibited concomitant treatments include benzodiazepines, monoclonal antibodies for osteoporosis, methotrexate, any local OA treatments for the knee(s), including topical anesthetics or NSAIDs; topical, intra-articular, or systemic corticosteroids; or any OA injection in the knee(s), antidepressants (other than SSRIs), warfarin or anticoagulants, and cyclosporine (except ophthalmic emulsion).

e. Synopsis and Section 9.1, Study Procedures:

i. Revised washout period

Changed from:

Telephone Contact and Washout Period

As soon as the laboratory results, ECG results, and radiograph results are available, the site staff will contact the subjects by telephone to inform them of the results and whether they are qualified to continue in the study. Subjects who do not meet the initial entry criteria will be considered screen failures. For subjects who meet the initial entry criteria and:

- Who do not take any analgesic medications for their pain, the site staff will instruct them to record in the diary their "average pain over the last 24 hours" scores for their index knee at approximately 8 PM every day for 3 to 5 days; these subjects will return to the study clinic for visit 2 as soon as they have "average pain over the last 24 hours" scores ≥ 4 for 3 consecutive days.
- Who are on topical and/or oral analgesics (including opioids, antidepressants, anticonvulsants, or other medications for OA), the site staff will instruct them to discontinue from these medications in accordance with accepted medical practice. Once all medications used for pain have been discontinued, the subjects will undergo an analgesic washout period of up to 7 days. During this period, the subjects will record in the diary their "average pain over the last 24 hours" scores for the index knee at approximately 8 PM every day. These subjects will return to the study clinic for visit 2 as soon as they reported "average pain over the last 24 hours" scores of ≥ 4 for 3 consecutive days.

Changed to:

Telephone Contact and Washout Period

As soon as the laboratory results, ECG results, and radiograph results are available, the site staff will contact the subjects by telephone to inform them of the results and whether they are qualified to continue in the study. Subjects who do not meet the initial entry criteria will be considered screen failures. For subjects who meet the initial entry criteria and:

- Who do not take any analgesic medications for their pain, the site staff will instruct them to record in the diary their "average pain over the last 24 hours" scores for their index knee at approximately 8 PM every evening for 3 to 7 days; these subjects may return to the study clinic for visit 2 as soon as they have

"average pain over the last 24 hours" scores ≥ 4 and ≤ 9 for ≥ 3 consecutive days. All subjects must return to the study clinic for visit 2 within 96 hours of the latest qualifying pain score entry within the pain assessment period.

- Who are on topical and/or oral analgesics (including opioids, antidepressants, anticonvulsants, or other medications for OA), the site staff will instruct them to discontinue from these medications in accordance with accepted medical practice. Once all medications used for pain have been discontinued, the subjects will undergo an analgesic washout period of up to 9 days. During this period, the subjects will record in the diary their "average pain over the last 24 hours" scores for the index knee at approximately 8 PM every evening for 3 to 9 days. These subjects may return to the study clinic for visit 2 as soon as they have "average pain over the last 24 hours" scores ≥ 4 and ≤ 9 for ≥ 3 consecutive days. All subjects must return to the study clinic for visit 2 within 96 hours of the latest qualifying pain score entry within the pain assessment period.

f. Synopsis and Section 9.1 Overall Study Design

i. Rescreening language added

Rescreening of subjects who previously failed screening is allowed only with the permission of the medical monitor on a case by case basis.
Subjects may be considered for rescreening if they failed screening previously due to eligibility criteria that are now allowed under the current amended protocol; delay of acquiring records; out of window issues (eg, lost or delayed labs); timing of exclusionary procedures; or other reasons approved by the medical monitor.

Subjects with positive hepatitis B, hepatitis C, or human immunodeficiency results, subjects with a positive urine drug test (UDT) for illicit drugs or non-prescribed opioids; and/or subjects who previously received study drug in a V120083 trial will not be permitted to be rescreened.

X-rays for rescreened subjects do not need to be repeated provided they were originally collected as part of this study and occurred within 1 month of rescreening.

All rescreening must be approved in advance by the medical monitor.

g. Synopsis and Section 9.1 Overall Study Design and Plan Description

i. Clarified period when eligibility is assessed and clarified PK sampling

Changed from:

Prior to entering the double-blind period, the subjects' "average pain over the last 24 hours" scores will be assessed to determine the subjects' eligibility to continue in the double-blind period. To qualify for entry into the double-blind period, subjects must have "average pain over the last 24 hours" scores of ≥ 4 and ≤ 9

for ≥ 3 consecutive days during the screening. Subjects who do not qualify for the double-blind period will be discontinued from the study as screen failures.

Subjects who are eligible for the double-blind period will have visit 2 (Day 1) scheduled in the morning. At this visit, all qualified subjects will be randomized to receive the double-blind treatments. The first dose of study drug will be administered at the study clinic. For subjects in the intensive PK subgroup, blood samples for pharmacokinetic (PK) analysis will be collected postdose at 1, 2, 4, 6, and 8 hours. These subjects will remain at the study clinic until the PK samples are collected.
Clinic visits during the double-blind period will occur at week 1 (visit 3), week 2 (visit 4), and week 4 (visit 5) visits. All clinic visits should occur in the morning. During these visits, PK samples will be collected at visits 3 (predose, 1 and 2 hours postdose), 4 (predose), and 5 (predose) during the treatment period. Supplemental analgesic medication is APAP/acetaminophen 500 mg. No more than 4 tablets/24 hours (ie, no more than 2 g/24 hours), as needed, will be permitted during the double-blind period. All subjects will be instructed to refrain from taking any supplemental analgesic medication for at least 24 hours prior to the weeks 1, 2, and 4 visits (visits 3, 4, and 5, respectively) of the double-blind period and to refrain from taking study drug dose on the morning of clinic visits to allow for predose PK sampling.

Changed to:

Prior to entering the double-blind period, the subjects' "average pain over the last 24 hours" scores will be assessed to determine the subjects' eligibility to continue in the double-blind period. To qualify for entry into the double-blind period, subjects must have "average pain over the last 24 hours" scores of ≥ 4 and ≤ 9 for ≥ 3 consecutive days during the pain assessment period. Subjects who do not qualify for the double-blind period will be discontinued from the study as screen failures.
Subjects who are eligible for the double-blind period will have visit 2 (Day 1) scheduled in the morning. At this visit, all qualified subjects will be randomized to receive the double-blind treatments. The first dose of study drug will be administered at the study clinic. For subjects in the intensive PK subgroup, blood samples for pharmacokinetic (PK) analysis will be collected predose and postdose at 1, 2, 4, 6, and 8 hours. These subjects will remain at the study clinic until the PK samples are collected.
Clinic visits during the double-blind period will occur at week 1 (visit 3), week 2 (visit 4), and week 4 (visit 5) visits. All clinic visits should occur in the morning. During these visits, PK samples will be collected at visits 3 (predose, 1 and 2 hours postdose), 4 (predose or postdose), and 5 (predose or postdose) during the treatment period. Supplemental analgesic medication is APAP/acetaminophen 500 mg. No more than 4 tablets/24 hours (ie, no more than 2 g/24 hours), as needed, will be permitted during the double-blind period. All subjects will be instructed to refrain from taking any supplemental analgesic medication for at least 24 hours prior to the weeks 1, 2, and 4 visits (visits 3, 4, and 5, respectively) of the double-blind period and to refrain from taking study drug dose on the morning of clinic visits to allow for predose PK sampling.

h. Synopsis – Study design section and Drug Concentration Measurements and Section 9.1 Overall Study Design

i. Clarified PK sampling

Changed from:

Blood samples for pharmacokinetic (PK) analysis will be collected at visits 2, 3, 4, and 5. The PK evaluation will involve two components: intense PK sampling and sparse PK sampling. Sparse PK sampling will be conducted for all subjects enrolled (276 subjects), with samples collected at visits 3 (predose, 1 and 2 hours postdose), 4 (predose), and 5 (predose) during the treatment period. Intense PK sampling will be conducted for 24 subjects, consisting of the sparse PK schedule and visit 2 postdose sampling at 1, 2, 4, 6, and 8 hours (day 1 of dosing). A single sample of blood (6 mL) will be taken for each time point. The date and time of dosing and sampling will be documented on the case report forms (CRFs).

Changed to:

Blood samples for pharmacokinetic (PK) analysis will be collected at visits 2, 3, 4, and 5. The PK evaluation will involve two components: intense PK sampling and sparse PK sampling. Sparse PK sampling will be conducted for all subjects enrolled (276 subjects), with samples collected at visits 3 (predose, 1 and 2 hours postdose), 4 (predose or postdose), and 5 (predose or postdose) during the treatment period. Intense PK sampling will be conducted for 24 subjects, consisting of the sparse PK schedule and visit 2 predose sample and postdose sampling at 1, 2, 4, 6, and 8 hours (day 1 of dosing). A single sample of blood (6 mL) will be taken for each time point. The date and time of dosing and sampling will be documented on the case report forms (CRFs).

i. Section 9.4.8 Prior and Concomitant Therapy

i. Addition of text directing investigator to contact the medical monitor with questions or concerns

- The investigator should contact the medical monitor if there are any questions or concerns.

ii. Clarified the language for inclusion of aspirin

Changed from:

Aspirin is permitted only for conditions other than chronic pain, including headache, fever, and cardiovascular disease prophylaxis. Aspirin dose of 81 mg per day is allowed to be taken for cardiovascular disease prophylaxis. Note: Subjects will be requested not to take any aspirin for at least 24 hours before each clinic visit.

Changed to:

Aspirin dose of 81 mg per day is allowed to be taken for cardiovascular disease prophylaxis.

j. Section 9.5.1 Schedule of activities,

i. Footnote a revised

Changed from:

[a] The washout period (at least 3 days) is required only for subjects who take analgesic medications for pain. Subjects who do not take any medications for pain will record their "average pain over last 24 hours" scores for 3 to 5 days. Subjects who take medications for pain will record their "average pain over last 24 hours" scores for at least 3 days once all medication used for pain has been discontinued in accordance with acceptable medical practice. Subjects may return to the study clinic for visit 2 as soon as they recorded "average pain over last 24 hours" scores ≥ 4 and ≤ 9 for ≥ 3 consecutive days.

Changed to:

[a] The washout period is required only for subjects who take analgesic medications for pain. Subjects who do not take any medications for pain will record their "average pain over last 24 hours" scores for 3 to 7 days. Subjects who take medications for pain will record their "average pain over last 24 hours" scores for at least 3 days once all medication used for pain has been discontinued in accordance with acceptable medical practice. Subjects may return to the study clinic for visit 2 as soon as they recorded "average pain over last 24 hours" scores ≥ 4 and ≤ 9 for ≥ 3 consecutive days. All subjects must return to the study clinic for visit 2 within 96 hours of the latest qualifying pain score entry within the pain assessment period.

ii. Footnote j and k - revised to clarify PK sampling time points and remove recording of food intake

Changed from:

[J] For subjects in the intense PK sampling population, PK samples will be collected at Visit 2 (5 time points; 1, 2 [+/- 10 min], 4, 6 and 8 hrs [+/- 20 min] postdose). The actual time of food intake, dosing and sampling should be recorded.

[k] For all subjects, PK samples will be collected at visit 3 (predose, 1 and 2 hours post-dose); visit 4 (predose) and 5 (predose). The actual time of dosing and sampling should be recorded. Visit 3 sample must contain a predose PK sample collection. If the subject took a morning dose of study medication at home on day of visit 3, subject should be instructed to return the following day.

Changed to:

[J] For subjects in the intense PK sampling population, PK samples will be collected at Visit 2 (6 time points; predose and 1, 2 [+/- 10 min], 4, 6 and 8 hrs [+/- 20 min] postdose). The actual time of dosing and sampling should be recorded.

[k] For all subjects, PK samples will be collected at visit 3 (predose, 1 and 2 hours postdose); visit 4 (predose or postdose) and 5 (predose or postdose). The actual time of dosing and sampling should be recorded.

k. Sections 9.5.2.1 – Visit 1 (screening)

i. Clarified consent for PK sampling

Changed from:

The following information will be obtained and procedures performed for all potential subjects at a screening visit conducted within 7 to 14 days after the ICF is signed:

- Obtain ICF
- Obtain PG consent form (optional)
- Contact IVRS/IWRS to obtain subject number which will be retained throughout the study. Instructions for contacting the IWRS are provided in the study manual

Changed to:

The following information will be obtained and procedures performed for all potential subjects at a screening visit conducted within 7 to 14 days after the ICF is signed:

- Obtain ICF
- Obtain PG consent form (optional)
- Obtain intense PK consent form (optional)
- Contact IVRS/IWRS to obtain subject number which will be retained throughout the study. Instructions for contacting the IWRS are provided in the study manual

l. Sections 9.5.2.1, 9.5.4 and 9.5.5

i. Extended period for central ECG provider to provide data to site

Changed from:

ECG reports from the central ECG provider will be sent to the clinical site within 24 hours of receipt of ECG transmission. The investigator/designee must review and sign the ECG report from the central ECG provider.

Changed to:

ECG reports from the central ECG provider will be sent to the clinical site within 72 hours of receipt of ECG transmission. The investigator/designee must review and sign the ECG report from the central ECG provider.

m. Section 9.5.2.1 Rescreening language added:

Rescreening of subjects who previously failed screening is allowed only with the permission of the medical monitor on a case by case basis.

Subjects may be considered for rescreening if they failed screening previously due to eligibility criteria that are now allowed under the current amended protocol; delay of acquiring records; out of window issues (eg, lost or delayed labs); timing of exclusionary procedures; or other reasons approved by the medical monitor.

Subjects with a positive hepatitis B, hepatitis C, or human immunodeficiency virus test results; subjects with positive urine drug test (UDT) for illicit drugs or non-prescribed opioids and/or subjects who previously received study drug in a V120083 trial will not be permitted to be rescreened.

All rescreening must be approved in advance by the medical monitor.

n. Section 9.5.2.2. Telephone Contact/ Washout Period

i. Changed from:

- Instruct the subject to record his/her daily "average pain over the last 24 hours" scores for the index knee at approximately 8 PM every day for:
  - Up to 5 days (or until instructed to stop) if the subject is not taking any medications for pain
  - Up to 7 days (or until instructed to stop) after all analgesic medications have been discontinued (applicable only to subjects taking medications for pain)

During the remaining screening period, the site personnel will monitor daily the subjects' daily "average pain over the last 24 hours" scores in the diaries. The subjects may return to the study clinic as soon as he/she recorded "average pain over the last 24 hours" scores of ≥ 4 and ≤ 9 for ≥ 3 consecutive days or until the pain score recording period (5 days for subjects not taking any medications; 7 days for subjects who were on pain medication prior to screening) is completed.

[…]

- Schedule visit 2 to occur in the morning as soon as possible

Changed to:

- Instruct the subject to record his/her daily "average pain over the last 24 hours" scores for the index knee at approximately 8 PM every day for:
  - Up to 7 days (or until instructed to stop) if the subject is not taking any medications for pain

- Up to 9 days (or until instructed to stop) after all analgesic medications have been discontinued (applicable only to subjects taking medications for pain)

During the remaining screening period, the site personnel will monitor daily the subjects' daily "average pain over the last 24 hours" scores in the diaries. The subjects may return to the study clinic as soon as he/she recorded "average pain over the last 24 hours" scores of ≥ 4 and ≤ 9 for ≥ 3 consecutive days or until the pain score recording period (7 days for subjects not taking any medications; 9 days for subjects who were on pain medication prior to screening) is completed. The subjects must return for visit 2 within 96 hours of the latest qualifying pain score entry within the pain assessment period.

[…]

- Schedule visit 2 to occur in the morning as soon as possible (within 96 hours of the latest qualifying score within the pain assessment period)

o. Section 9.5.3 Visit 2 – Randomization

i. Clarified consent for PK sampling

Changed from:

The following procedures will be performed for subjects who are eligible for randomization:

- Contact IVRS/IWRS to indicate that the subject is entering the double-blind period.
- Have the subject record his/her responses to the mBPI-SF WOMAC, EQ-5D, and SF-36
- Perform CiTAS rating
- Collect optional PG sample (for subjects who provide additional consent)
- Dispense study drug as instructed by IWRS

ii. Changed to:

The following procedures will be performed for subjects who are eligible for randomization:

- Contact IVRS/IWRS to indicate that the subject is entering the double-blind period.
- Have the subject record his/her responses to the mBPI-SF WOMAC, EQ-5D, and SF-36
- Perform CiTAS rating
- Collect optional PG sample (for subjects who provide additional consent)

- Collect optional PK sample (for subject who provide additional consent)
- Dispense study drug as instructed by IWRS

p. Section 9.5.3 Visit 2 – Randomization and Section 9.5.4 Visits 3 (week 1) and 4 (week 2) – Double-blind Period

i. Revised requirement for recording of date/time of meals to indication if a meal had been eaten within 2 hours of dosing.

Changed from:

- Supplemental analgesic medication dosing information (date/time/amount taken)
- Date/time of meals
- The "pain right now" scores for the index knee immediately prior to taking supplemental analgesic medication (Appendix P).

Changed to:

- Supplemental analgesic medication dosing information (date/time/amount taken)
- Indicate if meal eaten within ± 2 hours of dosing
- The "pain right now" scores for the index knee immediately prior to taking supplemental analgesic medication (Appendix N).

Note: Updated assessment in Table 3 to reflect this change.

q. Section 9.5.3 Visit 2 – Randomization

i. Clarified time points for PK sampling

Changed from:

- For subjects in the intensive PK subgroup, collect PK blood samples for pharmacokinetic (PK) analysis at the following time points and record time of collection:
  - 1, 2, 4, 6, and 8 hours after the first dose of the study drug
- Schedule the next visit to occur in the morning approximately 1 week later

Changed to:

- For subjects in the intensive PK subgroup, collect PK blood samples for pharmacokinetic (PK) analysis at the following time points and record time of collection:

- Predose and 1, 2, 4, 6, and 8 hours after the first dose of the study drug

- Schedule the next visit to occur in the morning approximately 1 week later

r. Section 9.5.4 Visits 3 (week 1) and 4 (week 2) – Double-blind Period and Section 9.5.5 Visit 5- End of Study or Early Discontinuation

i. Clarified time points for PK sampling

Changed from:

- Collect pre-dose PK sample, noting time of sample collection [at visit 4, conduct the ECG prior to any PK sampling]

[…]

- Instruct the subject to record his/her daily "average pain over the last 24 hours" scores for the index knee at approximately 8 PM every day

- At visit 3 only, collect PK blood sample 1 and 2 hours post-dose, noting time of sample collection.

[…]

9.5.5 Visit 5 - End of Study or Early Discontinuation

At approximately 1 to 2 days before the scheduled clinic visits, the site personnel will contact the subject to remind subjects to refrain from taking any supplemental analgesic medications for at least 24 hours prior to the clinic visit. Remind subject to hold morning dose of study drug to allow for pre-dose PK sampling during clinic visit.

[…]

- Collect predose PK blood sample and record time of collection

Changed to:

- Collect pre-dose PK sample at visit 3, noting time of sample collection [at visit 4, conduct the ECG prior to any PK sampling and PK sample could be pre- or postdose]

[…]

- At visit 3 only, collect PK blood sample at predose and at 1 and 2 hours postdose, noting time of sample collection. Collect pre- and postdose sample at visit 4.

[…]

9.5.5 Visit 5 - End of Study or Early Discontinuation

At approximately 1 to 2 days before the scheduled clinic visits, the site personnel will contact the subject to remind subjects to refrain from taking any supplemental

analgesic medications for at least 24 hours prior to the clinic visit. Remind subject to hold morning dose of study drug to allow for predose PK sampling during clinic visit.

[…]

- Collect predose or postdose PK blood sample and record time of collection

s. Section 9.5.7 Follow-up
   i. Clarified the recording of adverse events

   Changed from

   - Record all adverse events

   Changed to

   - Record all adverse events, including outcomes of previously reported unresolved adverse events

t. Section 9.5.4 Visit 3 (week 1) and 4 (week 2) - Double-blind Period
   i. Clarified PK sampling relative to ECG measurements

   Changed from:

   - At visit 4 only,
     - Perform a 12-lead ECG after 5 minutes' rest [prior to predose PK sampling]

   Changed to:

   - At visit 4 only,
     - Perform a 12-lead ECG after 5 minutes' rest [prior to predose or postdose PK sampling]

u. Section 9.5.4 Visit 3 (week 1) and 4 (week 2) - Double-blind Period and Section 9.5.5 Visit 5 - End of Study or Early Discontinuation
   i. Added text regarding missing subject diary entries

   - Instruct the subject to complete last missed diary(ies) if not completed.

v. Section 9.5.5 Visit 5 - End of Study or Early Discontinuation
   i. Revised requirement for recording of date/time of meals to indication if a meal had been eaten within 2 hours of dosing.

   Changed from:

   - Supplemental analgesic medication dosing information (date/time/amount taken)
   - Date/time of meals

   Changed to:

- Supplemental analgesic medication dosing information (date/time/amount taken)
- Indicate if meal eaten within ± 2 hours of dosing

w. Section 9.6.3 Drug Concentration Measurements
   i. Clarified PK sampling

Changed from:

Samples of blood will be taken to determine plasma concentrations of V120083 in this study. For subjects in the intensive PK subgroup, blood samples will be collected at visit 2 (day 1 of dosing) postdose at 1, 2, 4, 6, and 8 hours. All subjects will have PK samples collected a visit 3 (week 1; predose, 1 and 2 hours postdose); visit 4 (week 2; predose); and visit 5 (week 4; predose). The site will obtain one (6 mL) blood sample during the visit and confirm the time of the subject's last 2 doses of study drug. The actual time when the samples are taken should be recorded. See Appendix C for information on collection, processing, storage, and shipment of PK samples.

Changed to:

Samples of blood will be taken to determine plasma concentrations of V120083 in this study. For subjects in the intensive PK subgroup, blood samples will be collected at visit 2 (day 1 of dosing) predose and postdose at 1, 2, 4, 6, and 8 hours. All subjects will have PK samples collected a visit 3 (week 1; predose, 1 and 2 hours postdose); visit 4 (week 2; predose or postdose); and visit 5 (week 4; predose or postdose). The site will obtain one (6 mL) blood sample during the visit and confirm the time of the subject's last 2 doses of study drug. The actual time when the samples are taken should be recorded. See Appendix C for information on collection, processing, storage, and shipment of PK samples.

x. Section 9.6.5.2. Pharmacogenomics
   i. Clarified pharmacogenomics sampling schedule at visit 5

Changed from:

Three samples of blood, totaling approximately 20 mL, will be collected from each subject during the treatment period:

- 1 sample for DNA at visit 2 predose
- 2 samples for protein: 1 sample at visit 2 predose, and 1 sample at visit 5 postdose.

Changed to:

Three samples of blood, totaling approximately 20 mL, will be collected from each subject during the treatment period:

- 1 sample for DNA at visit 2 predose

- 2 samples for protein: 1 sample at visit 2 predose, and 1 sample at visit 5.

y. Section 10.3.2 Additional Reporting Requirements for Adverse Events of Special Interest

i. Clarified description of AESI

Changed from:

Thermal burns/heat sensitivity Inhibition of thermal sensation and associated AEs Taste disturbance (as evaluated by the CiTAS)

Changed to:

- Disturbances in thermal sensation, which may include:
  - inhibition of thermal sensation and associated AEs such as thermal burns
  - heat sensitivity
- Taste disturbance

z. Appendices

i. Re-lettered or corrected formatting of appendices titles so falls sequentially. Corrected in-text references accordingly.

ii. Appendix Q - List of Prohibited Medications and Classification

Add the following language for clarity.

This is a representative list. Please contact the medical monitor if there are any questions.